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Lymphocyte Proliferation to a Cross-Reactive Gut Commensal Candidate in Antiphospholipid Syndrome. William Ruff1, Silvio M. Vieira1, Cassyane Aguilar1, John Sterpka1, Andrew Goodman1, Donuk Erkan1 and Martin Kriegel2. 1Yale School of Medicine, New Haven, CT, 2New York Presbyterian/Weill Cornell Medical Center, New York, NY. 3Yale School of Medicine, Microbial Diversity Institute, New Haven, CT.

Background/Purpose: Antiphospholipid syndrome (APS) is an autoimmune, clotting disorder of unknown etiology targeting a major autoantigen, β2-glycoprotein 1 (β2GPI). Infectious triggers have been implicated in transient autoantibody production, but the persistent stimuli for anti-β2GPI antibodies remain unknown. Given the vast antigenic potential of the gut microbiota, we hypothesize that human gut commensal bacteria induce and sustain autoreactivity via cross-reactivity. To this end, we characterized APS antibodies in silico candidates and determined fecal autoantibody production.

Methods: Protein BLAST and Clustal Omega were used to identify commensal protein sequences with high homology to β2GPI-dominant epitopes. Using anaerobic cultures, we grew isolated candidate and control strains. Blood and stool samples were obtained from anti-β2GPI-positive patients, non-autoimmune thrombophilia patients, and healthy controls. Stool DNA was isolated using the MoBio extraction kit. A novel species-specific real-time PCR strategy was developed and validated using isolated strains and defined fecal microbiomes. In vitro proliferation of PBMC to bacterial protein extracts was assessed by [3H]-thymidine incorporation. An in-house ELISA was established with high-binding plates to analyze anti-β2GPI levels in plasma and fecal supernatants.

Results: Systematic in silico searches revealed Roseburia intestinalis as a major candidate for cross-reactivity. R. intestinalis is a common colonic gram-positive, flagellated, mucus adhering commensal containing high homology to the main B and T cell epitopes of β2GPI. R. intestinalis colonization load was semi-quantified in patients and controls using real-time PCR. APS PBMC proliferated significantly more to protein extracts from R. intestinalis versus control subjects (n = 5–6; p = 0.0005), and also compared to the closely phylogenetically related, but mimic-deficient gut commensal Eubacterium rectale (n = 6, p = 0.020). Importantly, we were also able to detect anti-β2GPI IgA antibodies in APS fecal supernatants, which differed significantly compared to controls (n = 14–15; p = 0.0019).

Conclusion: We have identified a major cross-reactive commensal candidate in silico with high homology to dominant β2GPI epitopes and developed a highly sensitive and specific real-time PCR screening strategy. APS PBMCs proliferated significantly more to candidate protein extracts compared to controls. Furthermore, we report, to our knowledge, for the first time fecal autoantibody production in a non-gut autoimmune disease. Production of fecal anti-β2GPI IgA in patients with peripheral blood anti-β2GPI IgG supports our hypothesis of a gut mucosal, cross-reactive trigger in APS, which we are actively pursuing.

Disclosure: W. Ruff, None; S. M. Vieira, None; C. Aguilar, None; J. Sterpka, None; A. Goodman, None; D. Erkan, None; M. Kriegel, None.

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Thrombocytopenia in Primary Antiphospholipid Syndrome Is Related to Arterial Thrombosis. Ikuma Nakagawa, Kenji Oku, Olga Amengual, Ryo Hisada, Eri Sugawara, Kazumasa Ohmura, Tomoko Fujii, Sanae Shimamura, Haruki Shida, Toshiyuki Watanabe, Yuka Shimizu, Michihito Kono, Takashi Kurita, Toshiyuki Bohgaki, Tetsuya Horita, ShinSuke Yasuda and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Antiphospholipid-associated syndrome refers to organ dysfunctions developed in the existence of antiphospholipid antibodies (aPL), apart from the typical manifestations of antiphospholipid syndrome (APS) such as thromboembolism and pregnancy morbidities. Thrombocytopenia is one of the aPL-associated manifestations and is reported in 20–40% of APS patients. Patients with thrombocytopenia and aPL are at risk of both bleeding and thrombosis. The evaluation of the coagulation status in patients with thrombocytopenia is particularly difficult and the clinical profile of APS patients with thrombocytopenia has not been fully elucidated. The purpose of this study is to analyze the clinical profile of patients with primary APS and thrombocytopenia and to examine the relation between the risk of thrombosis and thrombocytopenia.

Methods: This study comprised of 57 consecutive patients with primary APS and 72 autoimmune disease control patients (non-systemic lupus erythematosus) who visited Hokkaido University Hospital Rheumatology Clinic between January 2000 and May 2014. Thrombocytopenia was defined as a platelet count less than 100,000 per microliter, persistent on two occasions more than 12 weeks apart and without any underlying causes besides aPL. Primary APS patients were retrospectively followed-up for the incidence of thrombosis. Kaplan-Meier survival probability estimate was performed to analyze the occurrence of thrombotic events in primary APS patients with and without thrombocytopenia.

Results: The median age of patients was 41 years (IQR 32–50) in primary APS patients and 50 years (IQR 31–59) in the control group. Thrombocytopenia was more frequently diagnosed in patients with primary APS (17/57(30%) than in the control group 4/72(6%), p < 0.001.

In primary APS group, arterial thrombosis was developed in 9 patients (16%) throughout the follow-up period (106 months [IQR 36–142]); 8 patients had cerebral infarctions and 1 myocardial infarction. Arterial thrombosis was more frequently developed in patients with thrombocytopenia than in those without (6/17(35%) vs. 3/40(8%), p = 0.014), while no correlation was found between venous thrombosis and thrombocytopenia. There was no statistically significant difference in the rate of hemorrhagic event between APS patients with and without thrombocytopenia (1/17(6%) vs. 0/40 (0%), p = 0.298). Kaplan-Meier curve revealed that the inferior survival was associated with thrombocytopenia (6/9(67%) vs. 11/48(23%), p = 0.047 log-rank test; Figure 1).

Conclusion: Thrombocytopenia in APS patients represents a risk factor for arterial thrombosis and not for bleeding. The risk of thrombosis associated with thrombocytopenia in primary APS must be carefully evaluated and, if necessary, appropriate antithrombotic therapy administered.

Disclosure: I. Nakagawa, None; K. Oku, None; O. Amengual, None; R. Hisada, None; E. Sugawara, None; K. Ohmura, None; T. Fukui, None; S. Shimamura, None; H. Shida, None; T. Watanabe, None; Y. Shimizu, None; M. Kono, None; T. Kurita, None; T. Bohgaki, None; T. Horita, None; S. Yasuda, None; T. Atsumi, None.

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Is There an Association Between Persistently High Positive Antiphospholipid Antibody Profile and Organ Damage Accrual in Lupus Patients? Donuk Erkan1, Lisa G. Criscione-Schreiber2, Maria Dall’era3, Olga Dvorkina4, Russell Griffin5, Galina Marler6, Maureen A. McMahon7, Jorge Sanchez-Guerrero8, Amit Saxena9 and Robert Roubey1. 1Hospital for Special Surgery, New York, NY, 2Duke University School of Medicine, Durham, NC, 3University of California, San Francisco, San Francisco, CA, 4SUNY Health Science Center at Brooklyn, Brooklyn, NY, 5University of Alabama at Birmingham, Birmingham, AL, 6North Shore Long Island Health System, Great Neck, NY, 7UCLA David Geffen School of Medicine, Los Angeles, CA, 8UHN Toronto Western Hospital, Toronto, ON, 9New York University School of Medicine, New York, NY. 10University of North Carolina at Chapel Hill, Chapel Hill, NC.
Background/Purpose: Few studies assessed the impact of antiphospholipid antibodies (aPL) on organ damage in lupus with conflicting results. Our objective was to determine if persistently high positive aPL profiles are associated with organ damage in lupus patients.

Methods: The Lupus Clinical Trials Consortium Inc. (LCTC) Lupus Data Registry consists of consecutively enrolled adults with lupus from 16 US and Canada centers, each contributing ~100 patients. Patients with at least 1 follow-up (fu) visit who were tested for aPL were analyzed. We investigated the SLICC/ACR Damage Index (SDI) (baseline [BL] and fu) and the aPL profile (lupus anticoagulant [LA]), anticardiolipin antibody [aCL], IgG/M/A, and anti-B2GPI-I antibody [aB2GPI] (historically, BL, and fu). “High Positive [HP] aPL” profile was defined as positive LA, aCL IgG/M/A≥40U, and/or aB2GPI-I IgG/M/A≥40U. “Low Positive [LP] aPL” profile was negative LA, and aCL or aB2GPI-I IgG/M/A above the laboratory range but <40U. “Negative aPL” was negative LA, and aCL and aB2GPI-I IgG/M/A below the laboratory range. “Persistent aPL” was based on threshold levels at least of 50%, 60%, or 75% of the tests reported in HP or LP groups (based on ≥2 tests ≥12 weeks apart). A logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals for the association between an increase in SDI (first to last) and aPL profile and SDI accrual points and aPL profiles.

Results: Among 1506 patients, 1417 (94%) had at least 1 fu visit, 1392/1417 (98%) had at least 1 aPL result, 1310/1392 (94%) had analyzable aPL (82 excluded; missing aCL/aB2GPI levels), and 816/1310 (62%) had ≥2 tests ≥12 weeks apart, or at least 1 triple negative aPL result. Tables demonstrate the crude and adjusted odds ratios for SDI increase based on different SDI accrual points and aPL profiles.

Table 1 Odds ratios* and 95% confidence intervals for the association between aPL profile and SDI accrual of ≥1 points from baseline

| Persistence threshold | HP (n=610) | LP (n=742) | Negative (n=254) | p-value
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<tbody>
<tr>
<td>N (with damage)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>1.69 (0.78)</td>
<td>1.98 (0.64)</td>
<td>1.65 (0.81)</td>
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</tr>
<tr>
<td>Crude</td>
<td>0.95 (0.47–1.74)</td>
<td>0.46 (0.24–0.86)</td>
<td>Referent</td>
<td>0.2535</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>0.91 (0.47–1.74)</td>
<td>0.52 (0.27–0.99)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>≥50%</td>
<td>≥60%</td>
<td>≥75%</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>50%</td>
<td>60%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>1.42 (0.71)</td>
<td>2.01 (0.52)</td>
<td>1.66 (0.81)</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.25 (0.39–4.03)</td>
<td>0.44 (0.21–0.90)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.02 (0.30–3.39)</td>
<td>0.49 (0.24–1.03)</td>
<td>Referent</td>
<td>0.1903</td>
</tr>
<tr>
<td>N (%)</td>
<td>≥12 (0.23)</td>
<td>≥30 (0.29)</td>
<td>≥70 (0.12)</td>
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</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>1.38 (0.70)</td>
<td>2.00 (0.63)</td>
<td>1.67 (0.80)</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.57 (0.47–5.29)</td>
<td>0.46 (0.23–0.96)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Adjusted†</td>
<td>1.38 (0.40–4.80)</td>
<td>0.52 (0.25–1.08)</td>
<td>Referent</td>
<td>0.3458</td>
</tr>
</tbody>
</table>

Results: Out of 400 samples, 71 (14.5%) were positive for a-B2GPI IgG by either ELISA or CIA, 48 (10%) by ELISA, and 23 (5.7%) by CIA. This evidence comes from case-control studies with clinically defined APS patients and disease and healthy controls. This study aims to investigate the performance of a-B2GPI-D1 in a cohort of consecutive, clinically characterized samples derived from a routine diagnostic workup for the detection of antiphospholipid antibodies (aPL). A total of 400 samples with a complete aPL panel (aCL IgG/IgM and a-B2GPI-D1 IgG by in-house ELISA, Lupus Anticoagulant and LA- tested with a DRVVT and aPTT based method) were collected. All the samples were tested for aCL IgG/IgM, anti-B2GPI IgG/IgM, and anti-B2GPI-D1 IgG by QUANTA Flash CIA (INOVA). The clinical diagnosis/reason for aPL detection was retrieved from hospital records. The classification of APS was based on the Sapporo revised criteria. Systemic Lupus Erythematosus (SLE) was defined according to ACR criteria. Undifferentiated Connective Tissue Disease (UCTD) was classified using international criteria.

Results: Out of 400 samples, 71 (14.5%) were positive for a-B2GPI IgG by either ELISA or CIA. Eighteen samples (4.5%) were positive for both a-B2GPI-D1 and a-B2GPI IgG by either ELISA or CIA assay, with the exception of 2 samples which were positive at low titer for a-B2GPI-D1 only (one positive also for aCL IgG CIA at low titer). These 2 sample derived from one patient with stroke and from one patient with recurrent pregnancy loss, both under investigation. Ten patients displayed a triple aPL positive profile (LA, aCL and anti-B2GPI positive at both ELISA and CIA). A significant association was found between the presence a-B2GPI-D1 (especially at medium-high titer) and triple aPL positivity (Chi Squared=195,468, p< 0.0001). Among 55 patients with positive a-B2GPI IgG (45 at low titer, 10 at medium-high titer) and negative a-B2GPI-D1 IgG, 47 (85.5%) had clinical features compatible with either APS (n=20) and/or systemic autoimmune rheumatic disease (SARD) (n=27).
Conclusion: In a diagnostic routine setting for aPL, medium-high titer a-B2GPI-D1 were found to cluster in patients with triple aPL positivity. a-B2GPI-D1 were present mainly in patients with APS-related clinical manifestations and in patients with SARD. Nearly 80% of sample positive for a-B2GPI IgG did not display any reactivity toward D1 and the majority of these patients had a diagnosis of APS/SARD, suggesting that clinically significant a-B2GPI IgG antibodies can be also directed against other epitopes of the B2GPI molecule.

Disclosure: L. Andreoli, None; A. Zanola, None; C. Nalli, None; F. Allegri, None; M. Mahler, Employee ofINOVA Diagnostics, 3; G. Norman, Employee ofINOVA Diagnostics, 3; A. Tincani, None.

5

Antiphospholipid-Associated Nephropathy Is a Risk for Developing Arterial Thromboses in Patients with Systemic Lupus Erythematosus.

Tomoko Fukui, Shinsuke Yasuda, Toshiyuki Watanabe, Kazumasa Ohmura, Sanae Shimamura, Bunna Nakagawa, Atsushi Noguchi, Haruki Shida, Yuka Shimizu, Michihito Kono, Takashi Kurita, Kenji Oku, Toshiyuki Bohgaki, Olga Amengual, Tetsuya Horita and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Antiphospholipid-associated nephropathy (APLN) is characterized by coexistence of antiphospholipid antibodies (aPLs) and renal small-vascular vasculopathy/chronic renal ischemia. Consequences of APLN to thrombosis have yet to be known. We aimed in this study to clarify the characteristics and thrombotic risk of APLN in patients with lupus nephritis (LN).

Methods: Patients with LN proven by renal biopsy from January 2000 to February 2014 were included. A total of 90 patients were histologically diagnosed as having LN according to the ISN/RPS classification. APLN was diagnosed when both aPLs and at least one of the following pathological features were present, thrombotic microangiopathy (TMA), fibrinous intimal hyperplasia (FIH), fibrocellular arterial occlusion (FAO), focal cortical atrophy (FCA) or tubular thyroidization (TUB) according to the criteria (Miyakos S et al. J Thromb Haemost 2009). Patients with antiphospholipid syndrome were excluded. aPLs including lupus anticoagulant, IgG/M anticardiolipin, IgG/M anti-b2-glycoprotein I antibody and IgG/M phosphatidylserine dependent antiprothrombin antibody were measured. Clinical features of APLN patients were retrospectively analyzed. Development of arterial thrombosis was retrospectively observed. Log-rank test was introduced for the comparison between those with APLN and without.

Results: Among 90 patients with biopsy-proven LN, 21 were excluded (10 with APS, 5 without tests for aPLs and 6 for other reasons) and the rest 69 patients were recruited in the study. The median age and mean disease duration was 33 years old and 4.8 years, respectively. Twelve patients (17.4%) were diagnosed as APLN (9 FCA, 5 FIH, 1 FAO and 3 TUB) and 10 as APLN-like disease without aPL and with pathological features. Patients with APLN had higher frequency of hypertension (p-value by chi-square test = 0.002). APLN patients more frequently developed arterial thrombosis during the median observation period of 53 months (p-value by log-rank test = 0.018) compared with patients without APLN. Among patients positive for aPLs, patients with APLN had higher frequency of hypertension (p-value < 0.001) and developing arterial thrombosis (p-value=0.046) than patients without APLN. (Figure)

Conclusion: APLN was found in 17% of LN and associated with hypertension. APLN with LN is a possible risk for developing arterial thrombosis, although prospective study in a larger cohort would be necessary.
assessment in APS patients with regards to pregnancy morbidity and thrombotic manifestations. It has encouraging clinical value and potential to be part of the diagnostic criteria for APS.

| Table 1: ROC Analysis: AUC, Sensitivity, Specificity and LR+ of Assays for Predicting Thrombosis |
|-------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Any Thrombosis AUC AUC p-value Sensitivity (%) Specificity (%) PPV (%) NPV (%) LR+ | | | | | | | |
| APHI-lgM 0.558 0.004 13.8 93.8 40.2 78.3 2.2 | | | | | | | |
| APHI-lgG 0.531 0.131 6.3 96.2 34.6 77.3 1.8 | | | | | | | |
| ACl-lgG 0.477 0.253 25.8 80.1 28.2 78.1 1.3 | | | | | | | |
| ACl-lgM 0.377 <0.0001 16.6 75.5 17 74.9 0.8 | | | | | | | |
| B2GPl-lgM 0.594 <0.0001 8.9 95.9 39.3 77.7 2.1 | | | | | | | |
| B2GPl-lgM 0.578 0.0001 4.1 97.5 33.3 77.1 1.7 | | | | | | | |

Disclosure: C. Lopez-Pedrera, None; C. Perez-Sanchez, None; Aguirre Zamorano, None; N. Barbarroja, None; P. Ruiz-Limon, None; Y. Jimenez Gomez, None; M. A. Khamashita, None; A. Rodriguez-Ariza, None; J. A. Gonzalez-Reyes, None; J. M. Villalba, None; E. Collantes-Estevez, None; M. J. Cuadrado, None.


Background/Purpose: Long term anticoagulation is recommended in antiphospholipid syndrome with thrombosis in order to prevent recurrences. While the current mainstay relies on vitamin K antagonists, their long term maintenance may remain challenging. Our aim was to report on the safety and the efficacy of new oral direct inhibitors of thrombin and factor Xa (ODIs) in antiphospholipid syndrome (APS).

Methods: Descriptive analysis of patients with APS enrolled in a French multicentre observational cohort between January 2012 and March 2014 and receiving ODIs. Clinical, biological, and therapeutic data were retrospectively analyzed. The main primary outcome was the occurrence of a thrombotic recurrence. Secondary outcomes included adverse effects – notably hemorrhagic episodes, and biological tolerance. Kaplan-Meier survival analyses were performed to take into account censored data, using therapeutic interruptions/modifications as events.

Results: Twenty-four patients with APS (primary in 11) received ODIs. The median (IQR) age at APS diagnosis was 41 (23–50) years, and the median duration of disease was 3 [1–11] years at introduction of the anti-thrombotic agent. Antiphospholipid antibodies (Abs) included anticardiolipin Abs (n=21/24, IgG isotype in 20), lupus anticoagulant (n=16/22), and IgG anti-b2glycoprotein I Abs (n=6/24).

ODIs included dabigatran (n=11), and rivaroxaban (n=13). Nineteen patients had been previously treated with VKA (n=18), or fondaparinux (n=1) for a median duration of 3 years. ODIs were introduced as second-line therapy because of INR lability/therapeutic simplification (n=16), recurrent thrombosis (n=1), VKA’s associated bleeding event (n=1), atrial fibrillation (n=1). Five patients received ODIs as first-line therapy. After a median follow-up of 15 [8–21] months, one relapse of arterial thrombosis, two bleeding events (hypermennorrhea and rectal bleeding under Rivaroxaban) and one recurrent migraine were reported, leading to discontinuation of therapy in these patients. Overall, the event-free survival rate was of 86.6% at 12 months using Kaplan-Meier curve analysis.

Conclusion: ODIs might be an alternative therapeutic option in APS, especially for patients with INR lability. Prospective studies are warranted to evaluate their safety in this condition.
9 A Risk-Stratified Perioperative Management Strategy for Antiphospholipid Antibody Positive Patients Undergoing Kidney Transplantation

Vicenzo Domingues, Darshana Dadhaniya, Choi Hartono, Raymond Pastor and Doruk Erkan

The objective of this study was to analyze the outcomes of aPL-positive patients who were managed by a risk-stratified perioperative “standard of care” protocol while undergoing kidney Tx.

Methods: We designed a “standard of care” protocol based on patient’s immunological and aPL risk profiles. Low Immunological and aPL Risk (IR) was defined as negative donor flow crossmatch (T and B cell XM) with/without donor specific antibodies; Moderate IR was defined as positive donor flow crossmatch (T and/or B cell XM) with positive donor specific antibodies; and High IR defined as was ABO incompatibility OR positive donor CDC T cell crossmatch with positive donor specific antibodies. Low aPL Risk was defined as anticardiolipin antibody (aCL) or anti-b2Glycoprotein-I (a2GPI) IgG/M/A 20–39U at least twice ≥ 12w apart and negative lupus anticoagulant (LA) test; High aPL Risk was aCL/a2GPI GPI IgG/M/A 40U OR a positive LA test twice ≥ 12w apart. We categorized patients into 6 groups and assigned different management strategies to each group (Table). For this descriptive preliminary analysis, we retrospectively reviewed the charts for perioperative and 6-month follow-up thrombosis, graft failure, and glomerular filtration rate (GFR).

Results: Eight patients (mean age: 49.2 ± 19.3; female: 4) underwent kidney transplantation (4 low IR/aPL risk; 2 low IR and high aPL risk; and 2 moderate IR and high aPL risk). Reasons for kidney Tx were lupus nephritis (5), polycystic kidney disease (2), and focal segmental glomerulosclerosis (1). No delayed graft function, thrombosis, or thrombotic microangiopathy were defined as was ABO incompatibility OR positive donor CDC T cell crossmatch with positive donor specific antibodies. Low aPL Risk was defined as anticardiolipin antibody (aCL) or anti-b2Glycoprotein-I (a2GPI) IgG/M/A 20–39U at least twice ≥ 12w apart and negative lupus anticoagulant (LA) test; High aPL Risk was aCL/a2GPI GPI IgG/M/A 40U OR a positive LA test twice ≥ 12w apart. We categorized patients into 6 groups and assigned different management strategies to each group (Table). For this descriptive preliminary analysis, we retrospectively reviewed the charts for perioperative and 6-month follow-up thrombosis, graft failure, and glomerular filtration rate (GFR).

Background/Purpose: Antiphospholipid antibody (aPL) positive patients undergoing kidney transplantation (Tx) are at increased risk for perioperative complications. The objective of this study was to analyze the outcomes of aPL-positive patients who were managed by a risk-stratified perioperative “standard of care” protocol while undergoing kidney Tx.

Methods: We designed a “standard of care” protocol based on patient’s immunological and aPL risk profiles. Low Immunological and aPL Risk (IR) was defined as negative donor flow crossmatch (T and B cell XM) with/without donor specific antibodies; Moderate IR was defined as positive donor flow crossmatch (T and/or B cell XM) with positive donor specific antibodies; and High IR defined as was ABO incompatibility OR positive donor CDC T cell crossmatch with positive donor specific antibodies. Low aPL Risk was defined as anticardiolipin antibody (aCL) or anti-b2Glycoprotein-I (a2GPI) IgG/M/A 20–39U at least twice ≥ 12w apart and negative lupus anticoagulant (LA) test; High aPL Risk was aCL/a2GPI GPI IgG/M/A 40U OR a positive LA test twice ≥ 12w apart. We categorized patients into 6 groups and assigned different management strategies to each group (Table). For this descriptive preliminary analysis, we retrospectively reviewed the charts for perioperative and 6-month follow-up thrombosis, graft failure, and glomerular filtration rate (GFR).

Disclosure: Disclosure: V. Domingues, None; D. Dadhaniya, None; C. Hartono, None; R. Pastor, None; D. Erkan, None.

11 Sustained Moderate Intensity Levels of Oral Anticoagulant Therapy and the Rate of Recurrent Thrombosis in Patients with Primary Antiphospholipid Syndrome

Luis M. Buckley, None;

The current recommended anti-thrombotic therapy for patients with anti-phospholipid syndrome (APS) is oral anticoagulants with an INR intensity of 2.0–3.0. This recommendation has been mostly derived from retrospective and prospective randomized studies based on INRs determined at time of thrombosis or the closest available one. The current recommended anti-thrombotic therapy for patients with anti-phospholipid syndrome (APS) is oral anticoagulants with an INR intensity between 2.3–3.5. This recommendation has been most frequently derived from prospective and retrospective randomized studies based on INRs determined at time of thrombosis or the closest available one.

Objective: To evaluate the rate of re-thrombosis in patients with primary APS (PAPS) during a defined anticoagulation index period.

Methods: We studied patients attending a Tertiary Referral Care Center according to the following inclusion criteria: PAPS (Sydney Criteria), a history of one or more episodes of thrombosis, oral anticoagulants and ≥ 2 INR determinations per year. Index period was defined as either the time elapsed between the first available INR and the next thrombotic event or the time between the first and last available INRs in rethrombosis-free patients. We also analyzed the number of thrombotic episodes before the index period.

Statistical analysis: We used X2 test, U-Mann Whitney test and Cox survival analysis.

Background/Purpose: The aims of our prospective study were to determine the prevalence of non-criteria aPL and their clinical relevance in a seronegative population with pregnancy morbidity according to Sapporo criteria.

Methods: We included 118 women: 73 with history of pregnancy morbidity according to clinical Sapporo’s criteria (SN-APS), 38 patients with confirmed obstetrical APS (SP-APS) and 45 with pregnancy without any obstetrical complication (Controls). Other than APS thrombophilia screening was negative in all women (protein C, S, ATIII, V and II mutations).

The IgG/IgM anti-phosphatidylethanolamine antibodies (aPE), IgG/IgM anti- phosphatidylserin/prothrombin antibodies (aPS/PT) and IgG anti-annexin 5 antibodies (aANX) were measured by commercial ELISAs (Theradiag, Instrumentation laboratory).

Results: Among the SN-APS group, 47% women presented ≥ 3 early miscarriages, 43% mid-to-late pregnancy loss and 22% premature birth ≤34 weeks of gestation related to placental insufficiency.

Non-criteria aPL were detected in 32% of SN-APS and 72% SP-APS and 13% controls (p<0.05). Among the non-criteria aPL antibodies, only the aPE IgG were more frequent in SN-APS patients than controls (18% vs 2%; p<0.05) and the levels of IgG aPE and IgG aANX were higher in SN-APS patients (median titres 6 U/mL and 8 U/mL, respectively), than in controls (2 U/mL and 2 U/mL, respectively; p<0.0001)(figures 2–3). Non-criteria aPL antibodies were present in 74% SP-APS versus 33% of SN-APS (p<0.05). APS/PT antibodies were more frequent in the SP-APS group: 48% vs 4.4% in controls and 2.2% in SN-APS (p<0.001). IgA anti-β2GPI antibodies were negative in SN-APS vs 23% SP-APS. Antibodies to anti-domain I of β2GPI were absent in SN-APS vs 30% of SP-APS. None of the five aPL antibodies was associated with specific obstetrical feature in SN-APS.

Conclusion: Our results suggest that non-criteria antibodies can be detected in 33% of women with obstetrical complications suggestive of APS with negative aPL.

Figure 1. The prevalence of non-criteria APL in SN-APS, SP-APS and controls.

Figure 2. The frequency of different non-criteria APS prevalence in SN-APS, SP-APS and controls.

Figure 3. Anti-PE IgG titres in different groups.

Disclosure: A. Turrent, None; G. Hernandez-Molina, None; A. R. Cabrál, None.

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Background/Purpose: Antiphospholipid syndrome (APS) is defined as the occurrence of venous or arterial thrombosis and/or pregnancy morbidity, in the presence of serological evidence of antiphospholipid antibodies (including IgM and IgG anticardiolipin antibodies, IgM and IgG anti-beta2-glycoprotein I antibodies, or the lupus anticoagulant). Whereas most patients with focal thrombotic events respond to anticoagulation, occasional patients are refractory to standard therapeutic interventions and continue to have either focal or multifocal occlusive disease. For those with recurrent disease or those with the catastrophic antiphospholipid syndrome (CAPS), physicians resort to the addition of anti-platelet agents, steroids, immunosuppressives, IVIG, rituximab, or plasma exchange.
Complement inhibition may be an effective way to prevent thrombosis associated with APS. Eculizumab, a monoclonal antibody that binds to complement protein C5 and prevents the conversion of C5 to C5a and C5b, may potentially be an effective treatment for patients with APS. First studied in patients with systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and idiopathic membranous nephropathy in the early 2000’s, development of the drug for rheumatic diseases was abandoned in favor of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Given the experience of complement inhibition in animal models of APS as well as prior use of eculizumab several years ago in one of our refractory APS patients, we administered eculizumab to three patients with severe refractory APS.

**Methods:** Two patients with APS, unresponsive to conventional anticoagulant therapy, were treated with a loading dose of eculizumab followed by dosing every other week (Atypical Hemolytic Uremic Syndrome dosing schedule). At the time of submission, the third patient has only received a loading dose. It has been suggested that the platelet count may be used as a surrogate marker of APS activity. During therapy, the patients’ platelet counts were monitored and any new thrombotic events documented.

**Results:** At their lowest values, the patients had platelet counts of 35,000, 22,000 and 18,000 (K/mL). One of the patients was steroid-dependent in order to maintain her platelet count. After initiation of eculizumab, the patient was able to taper steroids as the platelet count had risen from a low of 35,000 to average counts of 100,000. The second patient’s platelet count rose to over 200,000 from 22,000 within 10 days of receipt of eculizumab. After receiving one dose of eculizumab, the third patient’s platelet count rose from 18,000 to 50,000 within 4 days. For the first two patients, the increases in platelet counts were sustained other than during brief periods when therapy was delayed. During the treatment period (4–8 months), there were no new thrombotic events. We will report additional data on the third patient as he proceeds with treatment.

**Conclusion:** Eculizumab has shown promising results in our patients with refractory APS. Longer follow-up of these patients will be needed in order to discern the effect on thrombosis. Controlled studies are needed to further assess the efficacy of eculizumab in this condition as are mechanistic studies.

**Disclosure:** E. Zapantis, None; R. Furie, None; D. Horowitz, None.

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**Rivaroxaban Use in Patients with Antiphospholipid Syndrome Patients and Previous Poor Anticoagulation Control with Vitamin K Antagonists.** Savino Sciascia1, and Beverley Hunt2. 1Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, 2Thrombosis and Thrombophilia Center (St Thomas Hospital, London, UK), London, United Kingdom.

**Background/Purpose:** Management of antiphospholipid syndrome (APS) centres on attenuating the procoagulant state whilst balancing the bleeding risks of anticoagulant therapy. In a minority of APS patients treated with vitamin K antagonists (VKA) maintaining the INR within the target therapeutic range is still a matter of concern.

**Methods:** Data from consecutive APS patients attending the Thrombosis and Thrombophilia Center (St Thomas Hospital, London, UK) with poor anticoagulation control with VKA were collected. Inclusion criteria included 1) APS patients treated with VKA with INR target 2–3 for secondary prevention of venous thromboembolism (VTE) 2) Poor Anticoagulation Control, defined as ‘erratic’ pattern (where more time is spent both above and below INR target) or unidirectional pattern (where time out of range is predominantly in one direction-low or high). Time in therapeutic range (TTR) was assed in all the included patients. Included patients were switched to rivaroxaban 20 mg od for secondary thromboprophylaxis.

**Results:** 18 APS patients were included (13 female, mean age 45.2 ± 10.4 yrs, mean disease duration 8.8 ± 6.7 yrs, mean age at onset of disease 35.1 ± 9.7 yrs). Thirteen had a history of deep vein thrombosis, 5 had both deep vein thrombosis and pulmonary embolism. In all the included patients TTR was 65% or lower. Indication for switching to rivaroxaban was erratic INR control (mean 15 [11–21] INR tests within the last 6 months) in 13 patients and INR control in sub-therapeutic range in three patients, respectively. Patients were followed for a mean of 12.9 months [6–24] after starting rivaroxaban. No further VTE or major bleeding events were observed. In two women there was a worsening of menorrhagia, which was serving. In two women there was a worsening of menorrhagia, which was starting rivaroxaban. No further VTE or major bleeding events were observed. No significant difference was found in the rate of group A patients in the two subgroups of discrepant samples (ELISA pos – CIA neg and viceversa) (Chi squared test).

**Results:** The two assays displayed a good overall agreement for both IgG and IgM detection (81% and 84% respectively). Such agreement can be estimated to be higher after reconciliation of discrepant results using clinical features and degree of aPL positivity. The majority of discrepant results for both IgG and IgM assays were due to low tier values. No significant difference was found in the rate of group A patients in the two subgroups of discrepant samples (ELISA pos – CIA neg and viceversa) (Chi squared test).

**Conclusion:** In this study, the use of rivaroxaban therapy for secondary thromboprophylaxis for VTE appears safe in APS. A larger trial RAPS (Rivaroxaban in Antiphospholipid Syndrome, IRScTN 68222801) is ongoing and results will be available next year. In the interim, rivaroxaban may be considered cautiously as an alternative anticoagulant in APS patients with poor anticoagulant control with VKA.

**Disclosure:** S. Sciascia, None; B. Hunt, None.

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**Performance of an Automated Chemiluminescence Assay for Anti-cardiolipin and Anti-beta2glycoprotein I Antibodies Detection in a Cohort of 400 Clinically Characterized Consecutive Routine Samples.** Alessandra Zanol1, Laura Andreoli2, Cecilia Nalli3, Flavio Allegri1, Michael Mahler4, Gary Norman5 and Angela Tincani6. 1Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, 2INOVA Diagnostics, San Diego, CA.

**Background/Purpose:** Several immunoassays are available for the detection of anti-cardiolipin (aCL) and anti-beta2glycoprotein I antibodies (anti-beta2GPI), but standardization and harmonization of these tests is an ongoing process. Here we aimed to comparing the performance of an automated chemiluminescence assay with a validated in-house ELISA method, using clinically characterized samples derived from a routine diagnostic workup for the detection of antiphospholipid antibodies (aPL).

**Methods:** A total of 400 samples with a complete aPL panel (aCL IgG/IgM and anti-beta2GPI IgG/IgM determined by an in-house ELISA, Lupus Anticoagulant (LA) tested with DRVVT and aPTT based method) were collected. All the samples were tested for aCL IgG/IgM and anti-beta2GPI IgG/IgM by QUANTA Flash CIA (INOVA). The two assays were compared using a definition of aPL profile for each isotype (single vs double positive samples). The clinical diagnosis/ration for aPL detection was retrieved. Subjects were grouped upon the clinical situation: A) clinical features compatible with Antiphospholipid Syndrome (APS) and/or other systemic autoimmune rheumatic diseases (SARD) (patients considered at risk of aPL-related manifestations); B) clinical features other than A; C) unresolved clinical picture.

**Results:** The two assays showed a good overall agreement for both IgG and IgM detection (81% and 84% respectively). Such agreement can be estimated to be higher after reconciliation of discrepant results using clinical features and degree of aPL positivity. The majority of discrepant results for both IgG and IgM assays were due to low tier values. No significant difference was found in the rate of group A patients in the two subgroups of discrepant samples (ELISA pos – CIA neg and viceversa) (Chi squared test).

**Conclusion:** In this study, the use of rivaroxaban therapy for secondary thromboprophylaxis for VTE appears safe in APS. A larger trial RAPS (Rivaroxaban in Antiphospholipid Syndrome, IRScTN 68222801) is ongoing and results will be available next year. In the interim, rivaroxaban may be considered cautiously as an alternative anticoagulant in APS patients with poor anticoagulant control with VKA.

**Disclosure:** S. Sciascia, None; B. Hunt, None.

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**Methods:** Data from consecutive APS patients attending the Thrombosis and Thrombophilia Center (St Thomas Hospital, London, UK) with poor anticoagulation control with VKA.

**Results:** The two assays showed a good overall agreement for both IgG and IgM detection (81% and 84% respectively). Such agreement can be estimated to be higher after reconciliation of discrepant results using clinical features and degree of aPL positivity. The majority of discrepant results for both IgG and IgM assays were due to low tier values. No significant difference was found in the rate of group A patients in the two subgroups of discrepant samples (ELISA pos – CIA neg and viceversa) (Chi squared test).

**Conclusion:** In this study, the use of rivaroxaban therapy for secondary thromboprophylaxis for VTE appears safe in APS. A larger trial RAPS (Rivaroxaban in Antiphospholipid Syndrome, IRScTN 68222801) is ongoing and results will be available next year. In the interim, rivaroxaban may be considered cautiously as an alternative anticoagulant in APS patients with poor anticoagulant control with VKA.

**Disclosure:** S. Sciascia, None; B. Hunt, None.
Conclusion: In-house ELISA assays and the CIA assays displayed a comparable performance in the detection of aCL and anti-beta2GPI. Discrepant results were mostly due to values in the low positive range. The clinical features of the subjects are crucial information to interpret results when comparing different assays for aPL detection.

Disclosure: A. Zanola, None; L. Andreoli, None; C. Nalli, None; F. Allegri, None; M. Mahler, Inova Diagnostics, Inc., San Diego, CA, 3; G. Norman, Employee of INOVA Diagnostics, 3; A. Tincani, None.


Background/Purpose: IgA anti-beta2Glycoprotein I (aβ2GPI) antibodies remain controversial in the assessment of thrombotic risk in spite of several studies indicating an association with thromboembolic events in SLE and antiphospholipid syndrome (APS) patients. In addition, recent proficiency testing revealed widely discrepant results between 2 commonly used IgA aβ2GPI ELISAs on SLE and catastrophic APS samples. This controversy may have contributed to exclusion of IgA aCL and aβ2GPI antibodies from the current classification criteria for APS. One hypothesis is that coated β2GPI of one assay displayed the open (reactive) β2GPI configuration while the other had the closed (non-reactive) configuration.

Methods: Four sera selected from positive SLE and APS patients having discrepant IgA aβ2GPI reactivity; strongly positive in assay A (144–388 A units) and negative in assay B (9.9–18.6 A units). Cut-off was <20 A units in both assays. These samples were also strong IgG aβ2GPI (143–237 G units in assay A). A negative serum was used as control. IgA antibodies were affinity purified (Peptide M, Invivogen, Inc) to investigate β2GPI reactivity. Column wash-through and eluents were tested on both IgA aβ2GPI assays.

Results: were normalized to total protein. To determine the nature of differential reactivity, assay conjugates and controls/calibrators from assay A and B were interchanged.< Results: IgA eluents from IgA aβ2GPI positive samples reacted 10× stronger on assay A compared to assay B (graph). ODs of assay B were within the negative range (<0.200). When normalized to protein content, the eluents showed no cross-reactivity for IgG or IgM aβ2GPI antibodies confirming IgA isotype specificity. IgG aβ2GPI antibodies were detected in the wash-through. Conjugate from assay A reacts with reagents from both assays. However, conjugate from assay B reacts only with assay B reagents. This confirms that β2GPI coated plates of assay B bind IgA aβ2GPI antibodies, questioning the open/closed hypothesis. When both conjugates were compared in assay B, conjugate from assay A was 4× more reactive, suggesting that the ability of assay A to detect IgA aβ2GPI antibodies is partially dependent on the anti-IgA conjugate and calibration.

Conclusion: These results confirm not only the presence of IgA aβ2GPI antibodies in the selected patient samples but highlight an IgA conjugate reactivity issue for assay B, causing an underestimation of IgA aβ2GPI. This finding may assist in ongoing standardization efforts of APS antibody testing. In addition, conclusions from published clinical studies may need to be revised as some assays may understate IgA significance.

defined as: positive lupus anticoagulant test, anticardiolipin antibody IgG/M/ A > 40U, and/or anti-β2-Glycoprotein-I IgG/M/A > 40U on two or more occasions, at least 12 weeks apart, within ± 1 year of registry entry. The outcome variable was any increase of SDI at 5 years of follow-up (time 0 was defined as registry entry). For univariate analysis the demographic and clinical characteristics of patients with and without SDI increase at 5 years were compared (Chi square or Fisher’s exact test for categorical data, Student t test or Mann-Whitney for continuous data as appropriate). The Generalized Estimated Equation (GEE) model was used in a multivariate analysis to detect significant factors for increased SDI at 5 years.

**Results:** Of 394 patients with less than 10 years of disease duration, 112 (28%) had at least 5 years of prospective follow-up and a complete aPL profile (44% Caucasian, 19% African-American, 15% Asian, and 89% female). Mean age at diagnosis was 32 years (±13) and mean age at registry entry was 35 years (±13) with mean disease duration of 3.5 years (±2). Twenty-one (19%) patients had clinically significant aPL profile (isolated IgA positivity only in 5 patients, 4%). Damage was present (SDI ≥ 1) in 18/112 (16%) of patients with a mean SDI of 1.9 (±1.7) at the registry entry, and in 27/112 (24%) at 5 years follow-up with a mean of 2.4 (±2.0). An increase of SDI (range: 1–5 points) after 5 years of follow-up was observed in 16/112 (14%) of patients. On a univariate analysis, no significant associations were found between any increase of SDI at 5 years and aPL profile, race, gender, age at diagnosis, and disease duration. The GEE model confirmed the lack of an association between the aPL profile and organ damage; African-American (Odds Ratio, [OR]: 7.58, 95% Confidence Interval, [CI]: 1:54–37.27, p: 0.013) and Asian (OR: 8.1, 95% CI: 1:49–44.16, p: 0.016) patients had significantly higher risk of increased SDI at 5 years.

**Conclusion:** Our preliminary data demonstrate that: a) approximately 15% of SLE patients have new organ damage in 5 years; b) one-fifth of SLE patients have clinically significant aPL profiles; and c) there is no association between organ damage and clinically significant aPL-profile.

**Disclosure:** M. Taraborelli, None; L. Leuenberger, None; W. Zhang, None; A. Tincan, None; J. Salmon, None; D. Erkan, None.

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**ACR Poster Session A**

**Biology and Pathology of Bone and Joint: Osteoclasts, Osteoblasts and Bone Remodeling**

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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**Adenosine Receptors Stimulate Bone Remodeling.** Aranzazu Mediero1, Tuere Wilder2, and Bruce N. Cronstein3. NYU School of Medicine, New York, NY. NYU School of Medicine, Division of Rheumatology, New York, NY.

**Background/Purpose:** Such orthopedic procedures as spinal fusion and repair of bone defects due to trauma, infection or metastatic disease, require formation of new bone. Adenosine, acting via stimulation of the A2AR receptor (A2AR), inhibits osteoclast differentiation. Here we determined whether direct A2AR stimulation or enhancing adenosine concentrations via blockade of purine transport into cells via ent1 with dipyridamole regulates bone formation in a murine calvarial model.

**Methods:** 6–8 wk male C57Bl/6 mice (WT) or A2AR KO were anesthetized, a 3mm trephine defect was formed and covered with a collagen scaffold soaked in saline or CGS21680 (A2AR agonist) or dipyridamole (1mM each) alone or in the presence of ZM241385 1mM (A2AR antagonist). Animals received appropriate treatment daily until sacrifice. Bone Morphogenetic Protein 2 (BMP-2) 200ng was used as a bone formation control. At 0, 2, 4, 6 and 8 weeks calvarias were harvested and prepared for microCT and histology, XenoLight Rediject Bone Probe 680 was injected intravenously at different time points and used to probe bone formation (fluorescence). At 8 weeks after surgery microCT examination of WT mouse calvaria demonstrated that both CGS21680 and dipyridamole markedly enhanced bone generation as well as BMP-2 (60±2%, 79±2% and 75±1% bone regeneration, respectively, vs. 32±2% in control, p<0.001, n=5 mice per condition). Both CGS21680 and dipyridamole effects were abrogated by ZM241385 20±3% and 26±4% bone regeneration, respectively, vs. 32±2% in control, p<0.05, n=5 mice per condition). Neither CGS21680 nor dipyridamole-treated WT mice there was increased immunostaining for bone formation markers in the bony defects (Alkaline Phosphatase positive cells/hpf increased from 15±1 for control to 21±1 for CGS21680 and 24±1 for dipyridamole, p<0.001). TRAP staining revealed fewer osteoclasts in CGS21680- and dipyridamole-treated defects (17±1 and 16±1 osteoclast/hpf respectively vs. 24±1 Osteoclast/hpf for control, p<0.001) 8 weeks after defect formation, an effect blocked by ZM241385 or absent in A2AR KO mice. In vivo imaging with Xenolight Rediject Bone Probe 680 (a marker of bone formation) reveals a markedly increased fluorescent signal in treated animals, equivalent to BMP-2, when compared to control as soon as one week after bone defect formation and which lasts for at least 7 weeks.

**Conclusion:** Stimulation of A2AR increases the rate of new bone formation at sites of surgical bone defects as well as BMP2, a finding which suggests that targeting A2AR may be an effective way to increase bone formation following orthopedic procedures.

**Disclosure:** A. Mediero, None; T. Wilder, None; B. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 1, Cellione, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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**High Systemic LDL Cholesterol Levels during Experimental Osteoarthritis Lead to Increased Synovial Activation and Ectopic Bone Formation at End-Stage Osteoarthritis, While Excessive Levels Accelerate Development of Joint Pathology Already at Early-Stage Osteoarthritis.** Wouter de Munter, Martijn H. van den Bosch, Annet W. Sloetjes, Peter M. van der Kraan, Wim B. van den Berg and Peter L. van Lent. Radboud university medical center, Nijmegen, Netherlands.

**Background/Purpose:** A relation between osteoarthritis (OA) and the metabolic syndrome has long been established. One of the characteristics of the metabolic syndrome is increased cholesterol levels. In a recent study, we showed that LDL accumulation by LDL receptor deficient mice resulted in increased ectopic bone formation during experimental osteoarthritis.

In the present study we investigate OA pathology in ApoE deficient (ApoE−/−) mice with and without a cholesterol-rich diet, which is a model for extremely high systemic LDL cholesterol levels.

**Methods:** Wild type (WT) and ApoE−/− mice received a normal or cholesterol-rich diet for 54 days. At day 18, experimental OA was induced by intra-articular injection of collagenase and animals were sacrificed at day 28 and 54. Joint pathology was investigated by histology. LDL levels were measured in serum and synovial wash-outs.

**Results:** ApoE−/− mice on a normal diet showed markedly higher LDL levels than WT mice (8.90 mmol/L and 0.40 mmol/L, respectively; p<0.001). While no differences between the two groups were found at the early time point (day 28), end point OA (day 54) in ApoE−/− mice showed a strong increase of ectopic bone formation, mainly at the medial collateral ligament (fold increase 5.4; p<0.001) compared to WT mice. No significant differences in cartilage damage were found between the two groups; a slight increase in synovial thickening, however, was found in ApoE−/− mice (arbitrary score 1.9 versus 1.1 in WT mice; p<0.05). Furthermore, synovial gene expression of both S100A8 and S100A9 (fold increase 1.8 and 1.4, respectively; p<0.05) and S100A8/S100A9 protein levels of synovial wash-outs were increased in ApoE−/− mice (fold increase 5.8; p<0.05), suggesting an activated status of synovial lining cells.

In addition, we investigated whether a cholesterol-rich diet could increase joint pathology after induction of OA. The diet increased LDL levels even more in ApoE−/− mice (fold increase 2.1, compared to ApoE−/− mice on a normal diet; p<0.001). In both ApoE−/− and WT mice on a cholesterol-rich diet, excessive bone formation was found in the medial collateral ligament at day 54, however, no significant difference was found between the two groups. Interestingly, at the early time point (day 28; 10 days after OA induction), histological differences between the two groups were observed. Synovial thickening was four times increased (p<0.001) in ApoE−/− mice on a cholesterol-rich diet and also ectopic cartilage formation in the medial collateral ligament was strongly increased (fold increase 2.7; p<0.01) compared to WT mice on a cholesterol-rich diet.

**Conclusion:** LDL cholesterol accumulation by ApoE deficiency or a cholesterol-rich diet resulted in increased synovial activation and ectopic bone formation in experimental OA. Excessive LDL levels induced by a combination of ApoE deficiency and a cholesterol-rich diet did not affect joint pathology at end-stage OA, but rather accelerates synovial activation and ectopic bone formation, resulting in early pathology.

**Disclosure:** W. de Munter, None; M. H. van den Bosch, None; A. W. Sloetjes, None; P. M. van der Kraan, None; W. B. van den Berg, None; P. L. van Lent, None.
Mendelian Randomization Analysis to Examine for Causal Relationships Between Serum Urate Levels and Bone Mineral Density. Nicola Dalbeth1, Rith Topless2, Tonya Flynn, Murray Cadzow2, Mark Beaulieu1, and Tony R. Merriman2. 1University of Auckland, Auckland, New Zealand, 2University of Otago, Dunedin, New Zealand.

Background/Purpose: In observational studies, serum urate is positively associated with bone mineral density (BMD) and reduced risk of fracture. However, the possibility of unmeasured confounding means that it is uncertain whether urate is a direct mediator of bone density. Mendelian randomization analysis assumes that inherited genetic risk variants for one phenotype are naturally randomized with respect to a second unrelated phenotype, and allows disentangling of cause and effect in the presence of potential confounding. We used Mendelian randomization analysis to examine whether there is a causal relationship between serum urate and BMD.

Methods: We analysed data from the Generation 3 cohort in the Framingham Heart Study (FHS). Inclusion criteria were availability of serum urate, BMD, body mass index (BMI) and genotype data. Exclusion criteria were cGFR<30, and any of the following medications: diuretics, bisphosphonates, oral glucocorticoids and hormone replacement therapy. A weighted urate genetic risk score (GRS) was calculated using SNPs for uric acid metabolism, such as ABCG2, SLC17A1, SLC22A11. The GRS did not demonstrate evidence for reverse causation (data not shown).

Conclusion: Serum urate is strongly associated with BMD. However, controlling for confounders by Mendelian randomization does not provide evidence that serum urate is causal in increased BMD.

Reference:

Table: Mendelian randomization analysis with BMD as the outcome of interest for all eligible participants.

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Disclosure: N. Dalbeth, Areda, 5, AstraZeneca, 5, Takeda, 5, Metabolix, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Areda, 2, Fonterra, 9, R. Topless, None; T. Flynn, None; M. Cadzow, None; M. Bolland, None; T. R. Merriman, None.

Adenosine A2a Receptor (A2AR) Stimulation Inhibits Osteoclast Differentiation and Promotes Osteoblast Formation By Regulation of Axon Guidance Proteins. Aranazua Mediero1, Miguel Perez-Aso2 and Bruce N. Cronstein3. 1NYU School of Medicine, New York, NY, 2New York University, New York City, NY, 3NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Semaphorins (Sema), axonal guidance proteins, play a role in communication between osteoclast and osteoblast. Thus, sema4D, secreted by osteoclasts, binds to its receptor PlexinB1 on osteoblasts to inhibit osteoclast differentiation and function whereas sema3A, produced by osteoblasts, binds to PlexinA1/Neuropilin-1 to both inhibit RANKL-induced osteoclast differentiation and stimulate osteoblast differentiation and function. Because stimulation of A2AR diminishes osteolysis we asked whether A2aR activation regulates bone homeostasis by regulating osteoclast and osteoblast expression of semaphorins.

Methods: Osteoclast and osteoblast differentiation were studied in primary murine bone marrow culture as the number of TRAP-positive or Alizarin Red-positive cells, respectively, after challenge in the presence/absence of CGS21680 (A2aR agonist) 1µM and ZM241385 (A2aR antagonist) 1µM together with recombinant Sema4D or Sema3A 10ng/ml each. Sema3A/PlexinA1/Neuropilin-1 and Sema4D/PlexinB1 expression were studied by RT-PCR and Western Blot in bone marrow-derived osteoclasts and osteoblasts in the presence/absence of CGS21680 and ZM241385 1µM each. RANKL and Osteoprotegerin (OPG) levels were studied by RT-PCR.

β-catenin activation was studied in primary osteoblast culture. Cytoskeleton changes were studied in osteoclasts.

Results: RANKL induced a 2.5±0.1 fold increase in Sema4D mRNA (p<0.001,n=4) in osteoclasts which was blocked by CGS21680 (1.3±0.3 fold change, p<0.001,n=4). In contrast, PlexinA1 mRNA was enhanced by CGS21680 (9.3±2.0 fold increase vs 4.9±0.6 for RANKL, p<0.001,n=4) but Neuropilin-1 mRNA was unchanged. Sema3A mRNA increased 3.5±0.5 fold during osteoblast differentiation and CGS21680 enhanced this increase by 7.7±0.6 fold, p<0.001,n=4. PlexinB1 mRNA was increased 2 fold during osteoclast differentiation and was not altered by CGS21680. Similar changes were observed at the protein level. CGS21680 decreased RANKL expression and increased OPG expression in osteoblasts. Total and nuclear β-catenin expression were increased in osteoclasts after CGS21680 treatment and this increase was abolished by ZM241385. Sema4D increased Rhoa phosphorylation and FAK activation in osteoclast precursors and these effectswere reversed in the presence of CGS21680.

Conclusion: A2AR activation diminishes secretion of Sema4D by osteoclasts and enhances secretion of Sema3A by osteoblasts leading to an increase in osteoblast differentiation and function, and, in combination with the suppressive effects of A2aR on osteoclast differentiation and function, diminishes bone osteolysis.

Disclosure: A. Mediero, None; M. Perez-Aso, None; R. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

Activation of EPAC1/2 Is Essential for Osteoclast Formation By Modulating NFKB Nuclear Translocation and Actin Cytoskeleton Rearrangement. Aranazua Mediero1, Miguel Perez-Aso2 and Bruce N. Cronstein3. 1NYU School of Medicine, New York, NY, 2New York University, New York City, NY, 3NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Bisphosphonates inhibit osteoclast differentiation/function via inhibition of Rap1A isoprenylation and cytoskeletal assembly. As Rap1 is the effector of EPAC proteins (exchange protein directly activated by cAMP), we determined the role of EPAC in osteoclast differentiation.

Methods: Osteoclast differentiation was studied as the number of TRAP+ multinucleated cells following M-CSF/RANKL stimulation of either primary murine or human bone marrow precursors in the presence of the EPAC-selective cAMP analog 8-CPT-cAMP (100nM) and the EPAC inhibitor BFA (10µM). Rap1 activity assay was performed. Signaling events were studied by Western Blot in EPAC1/2 knockdown (lentiviral shRNA for EPAC1 or EPAC2 or scrambled shRNA) RAW264.7 cells. Osteoclast marker

S10
expression was studied by RT-PCR. Osteoclast morphological characterization was studied by phallolidin staining.

**Results:** 8-CPT-cAMP significantly increased osteoclast differentiation whereas BFA inhibited differentiation (113 ± 3% (p < 0.05) and 42 ± 2% (p < 0.001) of control, respectively, n = 6). Rap1 activation was maximal 15 min after RANKL stimulation (136 ± 3% of basal, p < 0.001, n = 4) whereas silencing of EPAC1/2 diminished activated Rap1 (43 ± 2% and 30 ± 5% of control respectively, p < 0.01, n = 4) and NFκB translocation. TRAP staining revealed no osteoclast differentiation in EPAC1/2 KO cells. Cathepsin K, NFATc1 and Osteopontin mRNA expression decreased in EPAC1/2 KO cells when compared to control. Activation of Rhoa, cd42, Rac1 and FAK were observed in an EPAC1/2 dependent manner and there was diminished cytokineskeletal assembly in EPAC1/2 KO cells.

**Conclusion:** EPAC1/2 are critical signaling intermediates in osteoclast differentiation that permit RANKL-stimulated NFκB nuclear translocation and actin reorganization. Targeting this signaling intermediate may mitigate bone destruction in inflammatory arthritis.

**Disclosure:** A. Mediero, None; M. Perez-Aso, None; B. N. Cronstein, Canplie Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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**Netrin Is Highly Expressed and Required in Inflammatory Infiltrates in Wear Particle-Induced Osteolysis.** Aranzazu Mediero1, Bhama Ramkhalawan1, Ed Purdue5, Steven R. Goldring2, Kathryn Moore1 and Bruce N. Cronstein3. 1NYU School of Medicine, New York, NY, 2Hospital for Special Surgery, New York, NY, 3NYU School of Medicine, Division of Rheumatology, New York, NY.

**Background/Purpose:** Osteoclasts play a critical role in homeostatic bone turnover and pathologic bone destruction. Netrin-1, expressed in the marrow only by osteoclast precursors, acts in an autocrine manner via its receptor Unc5b (but not its receptor DCC) to stimulate osteoclast differentiation *in vitro*. Here we tested the hypothesis that blockade of Netrin-1 or Unc5b diminishes wear particle-induced osteolysis in a mouse model.

**Methods:** A 1-cm midline sagittal incision was made over the anterior calvarium to the line connecting both ears in anesthetized 6–8 wk-old male C57BL/6 mice. 3mg of dried UHMWPE particles were implanted and animals were treated with either 0.9% saline, Netrin-1 antibody, Unc5b antibody or DCC antibody (Rabbit polyclonal for all). 100 μg antibodies were injected intraperitoneal the day of surgery and then once a week. Animals were sacrificed after 14 days and calvaria were removed, fixed, and prepared for microCT and histology. Netrin-1 immunostaining was performed in human tissue obtained following primary prosthetic implantation or after prosthesis re-implant osteolysis and aseptic implant loosening.

**Results:** Weekly ip injection of anti-Netrin-1 or anti-Unc5b antibodies significantly reduced the area of particle-induced bone pitting in calvaria exposed to UHMPE (46±4 and 49±5% bone pitting, respectively, compared to control, p < 0.001, n = 5) but anti-DCC receptor antibody did not affect UHMPE-induced pitting and resorption (80±7% bone pitting, p = ns vs control). MicroCT also revealed a significant increase in bone volume (BV) and bone volume/total volume ratio (BV/TV) in both Netrin-1 and Unc5b antibody treated mice. Anti-Netrin-1 or anti-Unc5b antibody treatment markedly reduced both the inflammatory infiltrate and the number of TRAP-positive osteoclasts in affected bone (7±1 and 4±1 cells/μm² respectively vs. 12±1 for control, p < 0.001). In contrast, treatment with anti-DCC antibody did not significantly reduce the number of osteoclasts in affected bone. There were no significant changes in Alkaline Phosphatase positive osteoblasts on bone forming surfaces in any antibody-treated group compared to control (8±1, 10±2 and 10±2 cells/μm² vs. 10±1 for control, p = ns). The peri-implant tissues of patients undergoing prosthesis revision surgery show a similar increase in Netrin-1 expression whereas there is little Netrin-1 expression by cells in soft tissues removed at the time of primary joint replacement.

**Conclusion:** These results demonstrate a unique role for netrin-1 in osteoclast biology; netrin-1 is an autocrine and paracrine regulator of osteoblast biology; netrin-1 is an autocrine and paracrine regulator of osteoblasts on bone forming surfaces in any antibody-treated group compared to control. There were no significant changes in Alkaline Phosphatase positive osteoblasts on bone forming surfaces in any antibody-treated group compared to control. Activation of Rhoa, cd42, Rac1 and FAK were observed in an EPAC1/2 dependent manner and there was diminished cytokineskeletal assembly in EPAC1/2 KO cells.

**Disclosure:** A. Mediero, None; B. Ramkhalawan, None; E. Purdue, None; S. R. Goldring, K. Moore, None; B. N. Cronstein, Canplie Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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**Functional Osteoclasts Differentiate Spontaneously from the Rheumatoid Joint.** Stinne Greisen1, Halldó尔 Bjarki Einarsson1, Malene Hvid2, Ellen Margrethe Haage1, Bent Deleuran3 and Tue Kragstrup1. 1Aarhus University, Aarhus, Denmark, 2Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, 3Aarhus University Hospital, Aarhus, Denmark.

**Background/Purpose:** Osteoimmunology is a field of emerging interest in which bone formation and resorption are understood in the context of the immune system. In rheumatoid arthritis (RA) uncontrolled joint inflammation alters the balance between osteoclasts and osteoblasts resulting in bone resorption. The inflamed joint in RA contains multiple factors contributing to the activation of osteoclasts, among these RANKL, M-CSF, TNFα and IL-17 secreted from activated fibroblast-like cells and T-cells. In this study, we...
aimed to investigate the potential of synovial fluid mononuclear cells (SFMCs) to develop into functional osteoclasts in vitro.

**Methods:** Synovial fluid was collected from inflamed joints of chronic RA patients at the outpatient clinic at Aarhus University Hospital. SFMCs were isolated using ficoll paque and cultured in DMEM (+10% FCS + 2% penicillin/streptomycin + 1% glutamin) at a concentration of 0.5 × 10⁶ cells/cm² (n=5). Following 21 days in culture, cells were TRAP stained and examined in light microscopy or lysed for qPCR for the common osteoclast genes calcitoninR, cathepsinK and beta3 integrin. To investigate functionality, SFMCs were also cultured on dentin plates for 21 days. To potentially increase the osteoclast differentiation in the SFMC cultures, culture medium was supplemented with RANKL (50ng/ml) and M-CSF (25ng/ml). As a control, conventional osteoclasts where cultured from healthy control monocytes with RANKL (50ng/ml) and M-CSF (25ng/ml).

**Results:** SFMCs cultured for 21 days differentiate into both multinucleated TRAP positive osteoclasts (6.7%, SD 4.8%) and mononuclear TRAP positive pre-osteoclasts (43.2%, SD 0.45%) (Fig 1). These cells expressed the common osteoclast genes calcitonin receptor, cathepsin K and beta3 integrin. Both the percentage of TRAP positive multinucleated cells (8.3%) and gene expression were comparable with conventional osteoclasts. Adding RANKL and M-CSF to SFMC cultures increased the percentage of multinucleated TRAP positive cells to 15.3% (SD 1.5%). SFMCs cultured on dentin plates finally confirmed the osteoclast phenotype of these cells, as the dentin was digested in the same manner as observed with conventional osteoclasts cultured on dentin plates.

**Conclusion:** Here we provide a new and simple method for generating functional osteoclasts from RA SFMCs. This spontaneous differentiation of osteoclasts from cells of the arthritic joint provides a new understanding of the inflamed joint and could explain the increased bone resorption observed in RA. Because osteoclasts are one of the ultimate effector cells in RA, this method could be a new tool to evaluate the effect of novel signaling molecules or the effectiveness of new drugs.

SHAPE * MERGEFORMAT

**Fig 1:** TRAP+ multinucleated cells differentiated from RA SFMCs.

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**Background/Purpose:** Bone erosions and systemic bone loss in rheumatoid arthritis patients result from an increased activity of osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about the mechanisms regulating the formation and activation of mature osteoclasts, the identity of an osteoclast precursor population in and its regulation by inflammatory cytokines during arthritis is poorly understood.

**Methods:** HTNFtg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. IL/IL-6 were crossed into HTNFtg mice and blood was also analyzed. K/BxN Arthritis was induced in wild type mice, blood and spleen were collected 14 days after disease induction. Different monocyte subsets were Fscs-scored and cultured in the presence of RANKL and MCSF to induce osteoclasts.

**Results:** We show that during TNF-driven arthritis CD11b+ CD115+ macrophages are elevated in blood before the onset of clinical symptoms and remain elevated throughout. In particular, a certain subset of CD11b+ myeloid cells that express intermediate levels of Ly6G expand in blood, spleen and bone marrow during arthritis. Of these, 89% express CD115, the MCSF-receptor. The increase of this population is not only observed in TNF-driven arthritis, but also in K/BxN arthritis. IL-1 and IL-6 importantly regulate the expansion of these cells as in IL/IL-6 double deficient HTNFtg we did not detect an elevation of this subset. After sorting this cells both subsets were able to form mature osteoclasts in vitro.

**Conclusion:** CD115+ CD11b+ cells with osteoclastogenic potential increase during inflammatory arthritis. This process, at least in TNF-driven arthritis is regulated by proinflammatory cytokines IL-1 and IL-6. Elevated numbers of these cells can be detected before clinical onset of disease and therefore may provide a biomarker for inflammatory arthritis.

**Disclosure:** A. Pucher, None; V. Saferding, None; E. Goncalves-Alves, None; S. Hayer, None; H. Leiss, None; J. S. Smolen, None; K. Redlich, None; S. Blüml, None.

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Evidence for Receptor Activator of NF-Kb (RANK)-Independent Bone Erosion in the Cherubism Mouse Model of Inflammatory Arthritis

**Background/Purpose:** A gain-of-function mutation in the adaptor Src Homology 3 Binding Protein 2 (SH3BP2) causes Cherubism, a rare pediatric disease marked by aggressive bone remodeling in the mandible and maxilla. Mice homozygous for the most common Cherubism mutation (Sh3bp2KI/KI) display TNF-dependent osteopenia and inflammatory arthritis with periarticular bone erosions. We sought to investigate whether bone-resorbing osteoclasts are key cellular mediators of the systemic bone loss and local inflammatory erosion observed in this model. To this end, Sh3bp2KI/KI mice with an inducible mutation in RANK, encoding a master regulator of osteoclast differentiation, were generated.

**Methods:** We generated Sh3bp2KI/KI RANK-deficient mice using Mx1-Cre driven deletion of floxed Rank alleles after intra-peritoneal injection of poly-IC at 10 days of age (wild type) or as Sh3bp2KI/KI Rankfl/fl. Control mice, also treated with poly-IC, included Sh3bp2KI/KI Rankfl/fl without the Mx1-Cre transgene, Sh3bp2KI/KI Rankfl/fl and Sh3bp2KI/KI Rankfl/fl. Bone mass, periarticular erosions and synovitis were assessed by a combination of micro-computed tomography (mCT) and histology at 12 weeks of age.

**Results:** Neither Sh3bp2KI/KI Rankfl/fl nor Sh3bp2KI/KI Rankfl/fl displayed inflammatory arthritis or bone erosion. Sh3bp2KI/KI Rankfl/fl developed severe osteopetrosis, consistent with osteoclast-deficiency. As previously reported, Sh3bp2KI/KI sufficient for RANK (Sh3bp2KI/KI Rankfl/fl) developed osteopenia and inflammatory arthritis at the elbow joint with marked peri-articular erosions. Depletion of osteoclasts by genetic deletion of Rank reversed the systemic osteopenia observed in Sh3bp2KI/KI mice but had no effect on synovitis at the elbow. Unexpectedly, peri-articular erosions at the elbow joints were not ameliorated in Sh3bp2KI/KI Rankfl/fl mice despite a significant reduction in tartrate-resistant acid phosphatase (TRAP) positive osteoclasts.

**Conclusion:** Deletion of Rank inhibits osteoclastogenesis and reverses systemic osteopenia in Sh3bp2KI/KI mice. In contrast, while the loss Rank reduces classic TRAP-positive osteoclasts at the inflamed elbow joints of Sh3bp2KI/KI mice, it does not reduce local bone erosion. These intriguing findings suggest an alternative pathway to bone erosion exists in the Sh3bp2KI/KI model of inflammatory arthritis that is independent of RANK.

**Disclosure:** W. R. O’Brien, None; J. F. Charles, None; K. Tsang, None; A. O. Aliprantis, None.
Impaired Bone Healing in Patients Suffering from Rheumatoid Arthritis - Anti-Inflammatory Therapy as Confounder. Ammemarie Lang1, Sarah Fuegener1, Paula Hoff1, Anastasia Rakow1, Manuela Jakstadt1, Timo Gaber1, Gerd Burmester1, Carsten Perka2 and Frank Buttgereit1. 1Berlin-Brandenburg Center of Regenerative Therapies (BRCRT), Berlin, Germany, 2Berlin-Brandenburg Center of Regenerative Therapies (BRCRT), Berlin, Germany, 3Charité University Medicine, Berlin, Germany, 4Berlin-Brandenburg Center of Regenerative Therapies (BRCRT), Berlin, Germany.

Background/Purpose: Anti-inflammatory treatment of rheumatoid arthritis (RA) with glucocorticoids (GC) and/or non-steroidal anti-inflammatory drugs (NSAIDs) is supposed to negatively influence bone metabolism and healing. However, both RA itself and treatment thereof are closely related to bone healing complications. However, studies addressing the number of afflicted patients and/or quantifying the negative impact of preexisting comorbidities and treatment with GC and/or NSAIDs on the bone fracture healing process are scarce. Thus, we hypothesized that both (i) suffering from RA and (ii) treatment with either GC or NSAIDs represent risk factors of bone healing disorders.

Methods: To test our hypothesis, we performed a single-center retrospective study based on the database of the Center for Musculoskeletal Surgery at Charité University Hospital Berlin to measure the impact of RA, GC and NSAID on bone healing complications. All patients who underwent surgery at our institution for treating fracture healing complications in 2012 were included. Exclusion criteria were patients with an age below 18 years at initial fracture, open fracture, and metastases close to fracture location. A control group matched for age and type of fracture at the ratio of two was considered for controls. In total, we conducted 24 retrospective case studies analyzing the impact of GC and NSAID on osteogenic differentiation of mesenchymal stromal cells (MSC) and the counteracting ability of hypoxia and the hypoxia-inducible factor (HIF) stabilizer deferoxamine (DFO). To this end, human bone marrow derived MSC were cultured, characterized and differentiated into osteoblasts under normoxic (37°C, 5% CO2) and hypoxic (37°C, 5% CO2, 1% O2) conditions using varying doses of dexamethasone (10-3 - 10-6 M), ibuprofen (5x10-3 - 5x10-4 M) and deferoxamine (DFO; 125-500µM). The calcification process during osteogenesis was analyzed using a quantifiable alizarin red staining method.

Results: Retrospective analysis included 93 patients with fracture-healing complications and 193 controls; both groups equally represented both sexes. We found a 10.6% higher probability (p<0.036) of fracture healing disorders in RA patients compared to the controls with a higher rate of these patients being treated with GC and NSAID, respectively. In our in vitro studies, we could demonstrate a concentration-dependent significant inhibitory effect of dexamethasone and ibuprofen on the osteogenic capacity of MSC which could be considerably antagonized by either hypoxia or DFO.

Conclusion: The results we have obtained so far support the hypothesis that both RA and GC medication have a negative impact on the outcome of fracture healing. Our results also demonstrate that GC and NSAID inhibit MSC differentiation which could contribute to explain impaired fracture healing. In addition, we demonstrated a positive effect of (chemically induced) hypoxia promoting osteogenic differentiation and being a promising tool to overcome bone healing disorders which result from anti-inflammatory treatment.

Disclosure: L. A. Jordan, None; F. L. Collins, None; S. A. Jones, None; E. H. Choy, None; A. K. Harvey, None; A. S. Williams, None.

31 Interaction of FGF-8 and TNF-α in the Regulation of BMP-Induced Osteoblast Differentiation. Takayuki Katsuyama, Fumio Otsuka, Mariko Narazaki, Ken-ei Sada, Kenichi Inagaki, Jun Wada and Hirofumi Makino. Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background/Purpose: Osteoblasts and osteoclasts play important roles in the bone remodeling. When the balance between these cells is disrupted, bone loss or aberrant bone formation occur. In rheumatoid arthritis (RA), pro-inflammatory cytokines such as TNF-α play a predominant role in joint destruction. We earlier reported that TNF-α inhibits bone morphogenetic protein (BMP)-induced osteoblast differentiation via activation of JNK and NF-κB pathways.

The fibroblast growth factor (FGF) family constitutes of at least 25 structurally related proteins and known to be involved in various biological processes including cell migration, differentiation, growth and survival. In particular, FGF-2, -8 and -18 have been implicated as key factors for the bone and cartilage homeostasis. It has also been reported that joint destruction of RA patients is involved in the increase of endogenous FGF-2 in synovial fluids. Among the FGF family, FGF-8 is known to be a key regulator for limb development and cranial formation. However, functional relationship between FGF-8 and BMPs in the osteoblast differentiation and the signal interaction of FGF-8 and proinflammatory cytokines remain unclear. Here we studied the effects of FGF-8’s interaction to TNF-α actions on BMP-2-induced osteoblast differentiation.

Methods: Mouse myoblast cell line C2C12, osteoblast precursor cell line MC3T3-E1 and rat primary osteoblast were used to clarify the effects of FGF-8 and TNF-α on BMP-induced osteogenesis. Quantitative real-time PCR was performed to evaluate mRNA levels of osteoblast differentiation markers. Immunoblot analysis for the phosphorylation of Smads and MAPKs was performed to analyze the signal interaction induced by FGF-8, TNF-α and BMP-2.

Results: We found that FGF-8 inhibited BMP-2-induced expression of osteoblast markers in a concentration-dependent manner. The efficacy of...
FGF-8 was smaller than that of TNF-α in the experiments using myoblast C2C12, MC3T3-E1 and rat osteoblasts. Of note, the inhibitory effects of FGF-8 on BMP-induced osteoblastic differentiation and Smad1/5/8 activation were enhanced under the co-treatment with TNF-α. FGF-8 also inhibited BMP-2-induced expression of Wnt5a, a non-canonical Wnt signaling, which is known to be involved in Smad-independent signaling induced by BMPs. FGF-8 had no influence on the expression levels of TNFRs, whereas FGF-8 increased the expression levels of ALK3 (BMPR1A) and reduced inhibitory Smad5, demonstrating possible feedback activity of FGF to BMP signaling. Moreover, a MEK inhibitor, but not JNK or NF-κB inhibitors, suppressed the FGF-8 actions on BMP-induced osteoblast differentiation.

**Conclusion:** Collectively, it was uncovered that FGF-8 inhibits induced osteoblast differentiation via ERK pathway and the effects were amplified by TNF-α activity. This FGF-BMP interaction may be involved in the regulatory process of inflammatory bone damages as shown in RA.

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**32 Regulation of Senescence and Inflammatory Mediators By N- and C-Termal Parathyroid Hormone-Related Protein in Osteoarthritic Human Osteoblasts.** Maria Isabel Guillén1, Julia Platas1, Sergio Portal-Nuñez2, Pedro Esbrit2 and M.J. Alcaraz1.

1 University of Valencia, Burjasot, Valencia, Spain, 2Fundación Jimenez Diaz, Madrid, Spain.

**Background/Purpose:** In osteoarthritis (OA), there is an abnormal remodeling process in subchondral bone associated with an altered osteoblast metabolism. Inflammatory mediators participate in bone remodeling and cartilage degradation during OA progression. Parathyroid hormone (PTH) and its bone counterpart, PTH-related protein (PTHrP), increase bone turnover through interaction of their N-terminal domain with the PTH type 1 receptor in osteoblasts. PTHrP peptides may be a novel approach to treat bone metabolic alterations. The aim of this study was to investigate the effects of different PTHrP peptides, PTHrP(1-36), PTHrP(1-37), and the C-terminal peptides PTHrP(107-139) and PTHrP(107-111) (osteostatin), on osteoblast senescence and the production of inflammatory mediators and degradative enzymes in osteoarthritic human osteoblasts stimulated with interleukin-1β (IL-1β).

**Methods:** Osteoblasts were obtained from 8 patients undergoing total knee joint replacement. Subchondral bone tissue obtained from tibial plateau was minced into small portions and digested with collagenase under agitation. Collected tissue was seeded in osteogenic medium to obtain osteoblastic cells according to a standard protocol. At first passage, osteoblastic cells were treated with PTHrP (1-37), PTHrP (107-139) and osteostatin (each at 100 nM) with or without IL-1β (10 ng/ml) for 1, 3 and 6 days. Senescence-associated β-galactosidase activity (SA-β-gal) was assessed by cytochemistry. mRNA expression of matrix metalloproteinases (MMPs) and senescence markers was determined by qPCR. Prostaglandin E2 (PGE2), COX-2 and cyclooxygenase-2 (COX-2) expression was determined by immunocytochemistry.

**Results:** IL-1β increased senescence features and the secretion of inflammatory mediators in osteoarthritic osteoblasts. Increased production of cytokines, MMPs and PGE2 may contribute to bone sclerosis and degradative processes in the joint. The three PTHrP peptides tested significantly downregulated mouse and human COX-2, p21, p53, MMP-1 and MMP-3. In addition, these peptides reduced the release of tumor necrosis factor-α into the culture medium. PGE2 production was significantly decreased by PTHrP (1-37) on days 1, 3 and 6, and also by each C-terminal PTHrP peptide on day 6. This effect on PGE2 was dependent on the downregulation of IL-1β-induced COX-2 overexpression.

**Conclusion:** These findings show that both N- and C-terminal PTHrP peptides counteract the effects of IL-1β on the induction of cell senescence and the production of inflammatory and degradative mediators in osteoarthritic human osteoblasts, suggesting a beneficial effect of these peptides in osteoarthritic subchondral bone.

**Disclosure:** M. I. Guillen, None; J. Platas, None; S. Portal-Nuñez, None; P. Esbrit, None; M. J. Alcaraz, None.
**Results:** microCT revealed an increase in cortical and trabecular bone in proNGF/+ mice when compared to WT. This change correlated with a decrease in osteoclast differentiation in cells from proNGF/+ mice (30 ± 3% decrease, p < 0.001, n = 4) and increased osteoblast differentiation in proNGF/+ (46 ± 5% increase, p < 0.5, n = 4). Treatment with proNGF markedly inhibits osteoclast differentiation (60 ± 2% decrease, p < 0.001, n = 5) without affecting osteoblast differentiation (10 ± 5% increase, p = ns, n = 5). In contrast, recombinant NGF increased osteoclast differentiation (17 ± 2% increase, p = 0.05, n = 5) with a decrease in osteoblast formation (62 ± 3% decrease, p < 0.001, n = 5). P75, Sortilin and Sorcs2 receptors were expressed in osteoclasts and osteoblasts.

**Conclusion:** These results indicate that the rapid bone destruction seen in patients treated with anti-NGF antibodies is most likely due to reduction of pro-NGF levels required for maintenance of bone homeostasis. Moreover, our results suggest that administering a therapeutically effective amount of proNGF may provide a novel therapeutic approach to promote bone growth and prevent Charcot’s arthropathy, a common problem in patients, such as diabetics, with peripheral neuropathy.

**Disclosure:** A. Mediero, None; B. Hempstead, None; B. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

35 Hydrogen Sulfide Inhibits Human Osteoclast Differentiation in Vitro By Triggering Sustained Antioxidant Response and Inhibiting the RANKL/OPG Ratio. Francesco Grassi, Laura Gambardi, Andrea Facchini and Gina Lisiognoli. ISTITUTO ORTOPEDICO RIZZOLI, BOLOGNA, Italy.

**Background/Purpose:** Hydrogen sulfide (H2S) has been recently appreciated as a novel gasotransmitter with an important role in the regulation of tissues and organs. H2S is produced endogenously in mammalian cells from L-cysteine mainly by the enzymes cystathionine-β-synthase or psoriatic arthritis, and a potential pharmacological target.

**Conclusion:** This study suggests that administering a therapeutically effective amount of H2S may provide a novel therapeutic approach to promote bone growth and prevent Charcot’s arthropathy, a common problem in patients, such as diabetics, with peripheral neuropathy.

**Disclosure:** F. Grassi, None; B. Hempstead, None; B. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.

36 The Use of Three-Dimensionally Printed β-Tri Calcium Phosphate/ Hydroxyapatite to Further Understand the Regulation of Adenosine Receptors in Osteoclast Formation and Promotion of Bone Regeneration. Stephanie Ishack1, Aranazhu Mediero1, John Ricci2 and Bruce N. Cronstein. 1NYU School of Medicine, New York, NY, 2NYU Dental School, New York, NY. 3NYU School of Medicine, Division of Rheumatology, New York, NY.

**Background/Purpose:** Bone defects resulting from trauma or infection need timely and effective treatments to restore damaged bone. Using specialized three-dimensional (3-D) printing technology, combined with osteostimulants, we can design custom 3-D scaffolds for bone repair. The Hydroxyapatite (HA)/Beta-Tri Calcium Phosphate (B-TCP) scaffold components provide mechanical strength, conduct bone throughout the scaffold and remodel over time. Dipyridamole (DIPY) increases local adenosine levels by blocking cellular uptake of adenosine and stimulates bone regeneration. Because DIPY, adenosine and adenosine A2A receptor-specific agonists stimulate bone regeneration in mice as well as BMP-2, a growth factor currently used to promote bone regeneration, we tested the capacity of DIPY-coated matrices could promote successful bone regeneration.

**Methods:** 15% HA:85% B-TCP scaffolds were designed using Robocad software, fabricated using a 3-D Robocasting system, and sintered at 1100°C for 4h. Scanning electron microscopy (SEM), micro-computed tomography (micro-CT), x-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and inductive coupled plasma (ICP) were used for material characterization. Vehicle, BMP-2 and DIPY drug scaffolds (scaffold + PBS, scaffold + DIPY or BMP-2, scaffold + collagen + DIPY or DIPY) were implanted in C57B6 (wild type, WT) and A2AKO mice with 3mm critical size defect for 2, 4 and 8 weeks. DIPY release from scaffold was assayed spectrophotometrically over time. microCT and histological analysis were conducted to determine the degree of new bone formation and remodeling.

**Results:** Quantitative and qualitative results from microCT showed similar significant and bone formation and remodeling in HA/B-TCP-DIPY and HA/B-TCP-BMP-2 scaffolds when compared to vehicle at 2, 4 and 8 weeks in WT mice (55% bone formation for in HA/B-TCP-DIPY and HA/B-TCP-BMP-2 vs 41% for vehicle, N=5 per group; P=0.01). Dipyridamole did not enhance bone formation in A2AKO mice 4 weeks after trephination (31% for HA/B-TCP-DIPY vs 27% for vehicle, N=5, p=ns). Histological analysis of WT mice showed increased bone formation and a trend toward increased remodeling in HA/B-TCP-DIPY and HA/B-TCP-BMP-2 scaffolds. Histologic examination of Dipyridamole treated scaffold in A2AKO mice showed no significant differences in bone formation when compared to vehicle treated scaffolds. Dipyridamole release from collagen coated scaffolds, maintain a constant concentration (10-6M) for up to 10 days.

**Conclusion:** Dipyridamole increases adenosine levels and targeting osteoclasts and osteoblasts via activation of the adenosine A2A receptor leads to increased bone regeneration in a murine model. Delivery of Dipyridamole in the 3-D ceramic scaffolds is an effective approach for bone regeneration following orthopedic, dental and craniofacial procedures.

**Disclosure:** S. Ishack, None; A. Mediero, None; J. Ricci, None; B. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.
Angiopoietin-like 4 Is over-Expressed in Rheumatoid Arthritis: A Potential Role in Pathological Bone Resorption. Catherine Swales, Nick Athanasou and Helen Knowles. 1The Botnar Research Centre, Oxford, United Kingdom, 2Department of Pathology, Oxford, United Kingdom, 3Botnar Research Centre, Oxford, United Kingdom.

Background/Purpose: In contrast to normal synovial tissue, rheumatoid synovium is hypoxic, and expresses the hypoxia-inducible transcription factors HIF-1α and HIF-2α which allow the transcription of genes involved in angiogenesis, inflammation, apoptosis and regulation of immune function. Hypoxia also stimulates osteoclast differentiation and causes a HIF-1α-dependent 3-fold increase in bone resorption. Angiopoietin-like 4 (ANGPTL4) is a hypoxia- and HIF-inducible pro-angiogenic adipokine that is induced in fibroblast-like synoviocytes in rheumatoid arthritis. This study sought to investigate whether ANGPTL4 is expressed in osteoclasts and other cells within rheumatoid synovial tissue, and to compare serum and synovial fluid levels of ANGPTL4 with those in normal controls and patients with osteoarthritis.

Methods: Serum, synovial fluid and synovial tissue samples were derived from patients with osteoarthritis (OA) and rheumatoid arthritis (RA); serum was obtained from aged-matched normal controls. All donors were recruited from the Nuffield Orthopaedic Centre, Oxford, UK and gave written informed consent. ANGPTL4 and HIF-1α expression was assessed in OA and RA synovial sections by immunohistochemistry and immunofluorescence. Serum and synovial fluid levels of ANGPTL4 were measured by ELISA. Osteoclasts were differentiated from circulating RA monocytes using M-CSF and RANKL, and hypoxic induction of ANGPTL4 mRNA was measured by real-time PCR.

Results: Bone-apposing osteoclasts within the rheumatoid synovium expressed ANGPTL4 and its regulating transcription factor HIF-1α. ANGPTL4 was strongly expressed in synovial lining cells, endothelial cells, stromal cells, CD68+ macrophages and plasma cells within the RA synovium. Little ANGPTL4 was evident in normal synovium, mirroring the expression pattern of HIF-1α in rheumatoid versus normal synovial tissue. ANGPTL4 concentrations were higher in the serum and synovial fluid of RA patients than in OA patients or normal controls. High serum ANGPTL4 correlated with elevated levels of the serum bone resorption marker sRANKL. Finally, ANGPTL4 mRNA was induced 5.5-fold by hypoxia in monocyte-derived osteoclasts from RA patients.

Conclusion: ANGPTL4 is over-expressed in both the serum and the synovial fluid and tissue of RA patients. Expression of ANGPTL4 in bone-apposing osteoclasts and correlation of high serum ANGPTL4 with circulating sRANKL suggests ANGPTL4 as a marker for bone destruction, and a potential target for inhibition of osteoclast-mediated bone resorption in RA.

Disclosure: C. Swales, None; N. Athanasou, None; H. Knowles, None.

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Human CD14+ Monocytes Stimulated with a Combination of TNFα and IL-6 Differentiate into Osteoclast-like Cells with Bone-Resorption Activity. Kazuhiro Yokota, Kojiro Sato, Yoshimi Aizaki, Yuji Akiyama and Toshihide Mimura. Saitama Medical University, Saitama, Japan.

Background/Purpose: Proinflammatory cytokines play an important role in bone destruction in rheumatoid arthritis (RA), as inferred by the efficacy of biologics. Previously, we reported that mouse osteoclast-like cells were induced, both in vitro and in vivo, by a combination of TNFα and IL-6 from bone marrow-derived monocytes/macrophages. Herein, we examined the differentiation, function, and regulation of osteoclast-like cells that were induced by the combination of TNFα and IL-6 from human CD14+ monocytes.

Methods: Human CD14+ monocytes were cultured with IL-6, TNFα, or TNFα plus IL-6. Pit formation assay on dentine slices was performed to assess the bone-resorbing activity. The expression of nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), which is the master regulatory transcription factor for osteoclast differentiation, was detected by a western blot analysis. The effects of osteoprotegerin (OPG), a decoy receptor for RANKL, NFAT inhibitor tacrolimus, or JAK inhibitor tofacitinib were examined.

Results: The tartrate-resistant acid phosphatase positive multinucleated osteoclast-like cells were induced by the combination of TNFα and IL-6 from human CD14+ monocytes in a dose-dependent manner. These osteoclast-like cells had bone resorption activity on dentin slices. The differentiation of conventional osteoclasts induced by RANKL from CD14+ monocytes was inhibited by OPG, whereas that of our osteoclast-like cells was not. Expression of NFATc1 was upregulated by the combination of TNFα and IL-6 compared with TNFα or IL-6 alone. In addition, differentiation of the osteoclast-like cells from CD14+ monocytes was completely inhibited by tacrolimus. On the other hand, tofacitinib blocked the differentiation of the osteoclast-like cells through the JAK signaling pathway.

Conclusion: Osteoclast-like cells with bone resorption activity were induced by culturing human CD14+ monocytes with the combination of TNFα and IL-6. These results indicate that not only osteoclasts, but also osteoclast-like cells may be involved in the pathogenic mechanism of inflammatory bone destruction, such as RA.

Disclosure: K. Yokota, None; K. Sato, None; Y. Aizaki, None; Y. Akiyama, None; T. Mimura, None.

ACR Poster Session A

Epidemiology and Public Health: Osteoporosis, Non-Inflammatory Arthritis and More

Sunday, November 16, 2014, 8:30 AM–4:30 PM

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Prevalence of Spondyloarthritis (ASAS Criteria) in First-Degree Relatives of Patients with Ankylosing Spondylitis. Raül Menor Almagro1, Carmen Ordesa2, Carlos Montuilla1, José Luis Alvarez-Vega1, Íñigo Hernández-Rodríguez2, Montserrat Corteguera3, Santiago MiNoz Fernandez2, Claudia Urrego1, Rafael Ariza-Ariza4, Mireia Moreno15, Xavier Juanola11, María Isabel Tévar12, Eduardo Collantes-Estevez13, Juan Muler-Mendoza13 and Ana Ruiz-Zorrilla15. 1Hospital de Jerez, Jerez de la Frontera, Spain, 2Hospital de Cabueñas, Gijón, Spain, 3Hospital Clínico Universitario de Salamanca, Salamanca, Spain, 4H. de Salamanca, Salamanca, Spain, 5University Hospital Complex of Vigo, Vigo, Spain, 6Hospital N S Sonsoles, Avila, Spain, 7Sección de Reumatología, Hospital Universitario infantia Sofia, San Sebastian de los Reyes, Madrid, Spain, 8Hospital G. Segovia, Segovia, Spain, 9University Hospital Virgen Macarena, Sevilla, Spain, 10Hospital University Parc Taulí, Sabadell, Spain, 11University Hospital Bellvitge, Barcelona, Spain, 12Hospital Reina Sofia, Córdoba, Spain, 13Hospital Puerta de Hierro, Madrid, Spain, 14Abbvie, Madrid, Spain.
Background/Purpose: Spondyloarthritis (SpA), a group of inflammatory diseases which exhibit similar genetic background, clinical features and symptoms, has an estimated prevalence of 0.5–1% in Spain. However, in first-degree relatives positive for the HLA-B27 antigen, this prevalence may reach up to 24%.

Methods: A multicentre, cross-sectional prevalence study was designed in first-degree relatives of patients with AS. Relatives agreeing to participate in the study completed a screening questionnaire to identify the presence of specific SpA characteristics. Relatives whose responses indicated the presence of SpA features were referred to a rheumatologist to collect their medical history and an assessment of disease activity, which included a blood test for the HLA-B27 antigen and C-reactive protein (CRP), a simple pelvic X-ray (Rx) and a pelvic magnetic resonance image (MRI). All the imaging tests were assessed by an expert radiologist.

Results: Of the 486 participants, 290 first-degree relatives were classified as positive for SpA features after the screening questionnaire, and 299 continued in the study. After a rheumatologist's evaluation using the ASAS criteria (table 1), 55 participants had no apparent signs of SpA and 214 were considered to be evaluable by the rheumatologist. Supplementary tests were performed in 195 relatives. Approximately 10.9% (n=53/486) of all the relatives met the criteria for SpA, of whom 60% (n=32) and 40% (n=21) were diagnosed as having axial SpA and peripheral SpA, respectively. Of the relatives assessed for diagnosis (n=250), 21.2% (n=53) met the criteria for SpA; 12.8% (n=32) were diagnosed with axial SpA, 8.4% (n=21) with peripheral SpA (table 2).

Conclusion: The incidence of SpA in first-degree relatives of Spanish patients with AS was 10.9%, which is consistent with the published literature.

Table 1: Assessed ASAS criteria rates

<table>
<thead>
<tr>
<th>Relatives Screening</th>
<th>N</th>
<th>%</th>
<th>Inflammatory back pain</th>
<th>Arthritis</th>
<th>Enthesitis of the heel</th>
<th>Uveitis</th>
<th>Dactylitis</th>
<th>Psoriasis</th>
<th>Crohn's disease/colitis</th>
<th>Good response to NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td></td>
<td>39.70%</td>
<td>486</td>
<td>37</td>
<td>7.60%</td>
<td>486</td>
<td>5</td>
<td>13</td>
<td>14</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 2: Distribution of relatives evaluated for SpA diagnosis

<table>
<thead>
<tr>
<th>Relative screening + assessed for diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not meet spondyloarthrits criteria</td>
<td>197</td>
<td>78.80%</td>
</tr>
<tr>
<td>Meet spondyloarthrits criteria</td>
<td>53</td>
<td>21.20%</td>
</tr>
<tr>
<td>- Axial spondyloarthrits</td>
<td>32</td>
<td>12.8%</td>
</tr>
<tr>
<td>- Peripheral spondyloarthrits</td>
<td>21</td>
<td>8.4%</td>
</tr>
<tr>
<td>Axial SpA</td>
<td>32</td>
<td>100%</td>
</tr>
<tr>
<td>Only HLA B27+</td>
<td>20</td>
<td>62.5%</td>
</tr>
<tr>
<td>Only MRI</td>
<td>5</td>
<td>15.6%</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

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The Impact of Ankylosing Spondylitis on Work Impairment: Data from the Scotland Registry for Ankylosing Spondylitis. Linda E. Dean, Alan G. MacDonald, Roger D. Sturrock, John Hunter, David Marshall, Gary J. Macfarlane and Gareth T. Jones. 1University of Aberdeen, Aberdeen, United Kingdom; 2Aberdeen Royal Infirmary, Aberdeen, United Kingdom; 3Glasgow Royal Infirmary, Glasgow, United Kingdom; 4Gartnavel General Hospital, Glasgow, United Kingdom; 5Inverclyde Royal Hospital, Greenock, United Kingdom.

Background/Purpose: The impact of ankylosing spondylitis (AS) on work status is substantial. While the majority of studies focus on the prevalence of absenteeism in this group, impairment (i.e. presenteeism) whilst at work is also an important factor when assessing the impact of disease on work-life yet remains relatively understudied. The aim of the current study was therefore to describe the prevalence of, and factors associated with, work impairment in AS.

Methods: SIRAS collects data on clinically diagnosed AS patients in Scotland. Clinical measures recorded from medical records include disease activity (BASDAI) and physical function (BASFI), while postal questionnaires provide patient-reported data including pain and fatigue (Chalder Fatigue Scale). Work impairment ‘during the past 7 days’ was assessed using the Work Productivity and Activity Impairment questionnaire – Specific Health Problem. Logistic regression was used to identify potential clinical and patient-reported factors associated with work impairment. These were assessed further using forward stepwise logistic models to identify independent risk factors. Results: are given as odds ratios with 95% confidence intervals. Additionally, the population attributable risks associated with independent risk factors were calculated.

Results: SIRAS contains both clinical and patient-reported information on 959 patients (male 73%, mean age 52yrs). Of those who answered items on employment (n=946), 55% were currently working, and only 10% of workers had missed work (during the past 7 days) due to their AS. However, 71% of workers reported some impairment during this time (any versus none). Factors independently associated with work impairment were: moderate/severe fatigue (4.8; 2.4–9.4), poor physical function (BASFI≥4; 2.6, 1.2–5.6) and chronic widespread pain (3.7, 1.9–7.3). The population attributable risks associated with these factors were 19%, 9% and 13% respectively.

Conclusion: The majority of employed AS patients did not report missing any work, in the previous week, due to their AS. However, many experienced impairment whilst working, the key identifiable drivers of which were fatigue, pain and poor physical function. Targeting non-pharmacological treatments, such as cognitive behavioural therapy, in addition to traditional therapeutic targets, may help to improve overall work productivity. This may reduce the economic impact of the disease and, ultimately, could improve overall work retention.

Disclosure: L. E. Dean, None; A. G. MacDonald, None; R. D. Sturrock, None; J. Hunter, None; D. Marshall, Abbvie, 5, Chugai-Roche, 5, MSD, 5, Chugai-Roche, 8, Celgene, 8, Novartis Pharmaceutical Corporation, 8; G. J. Macfarlane, Pfizer Inc, 2, Abbvie Ltd., 2, Pfizer Inc, 5, G. T. Jones, Pfizer Inc, 2, Abbvie Ltd, 2.

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The Prevalence of Ankylosing Spondylitis in Sweden – a Nationwide Register Study. Sofia Exarchou1, Ulf Lindström2, Johan Askling3, Jonas Eriksson4, Helena Forsblad-D’Elia5, Lars Erik Kristensen6, Martin Neovius1, Carl Turesson1 and Lennart T. Jacobsson1. 1Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden; 2Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; 3Clinical Epidemiology Unit, Rheumatology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; 4Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; 5Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; 6Lund University, Malmö, Sweden.

Background/Purpose: Reported Ankylosing Spondylitis (AS) prevalence estimates vary considerably, and there is a lack of nationwide estimates. Previous studies by our group support the validity of WHO International Classification of Disease codes (ICD-codes) for AS in the Swedish National Patient Register (NPR) and indicate that the mean diagnostic delay is about 10 years. This study aims to describe the national prevalence of diagnosed AS in
Deaths Associated with Ankylosing Spondylitis in France from 1969 to 2009.

Clement Prati1, Daniel Wendling2 and Xavier Guillot3. 1Hopital Jean Minjoz, Besancon, France, 2CHU J Minjoz, Besancon, France, 3rheumatology, Besancon, France.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that can lead to chronic pain in the axial and peripheral joints and to functional impairments. AS is a systemic disease that can cause extraarticular manifestations which could participate to excess mortality. The aim of the study is to describe characteristics of deaths for which AS was mentioned on the death certificate as either the underlying cause or anywhere on the death certificate and to analyze trends in AS related mortality from 1969 to 2009 in France.

Methods: Data were obtained from the Centre of Epidemiology on the Medical Causes of Death (CépiDc) for individuals aged 18 years and over died in France. Owing to implementation of International Classification of Diseases (ICD) 8, ICD-9 and ICD-10 for recording causes of deaths, three separate periods were analyzed (1969–78; 1979–99 and 2000–09). Initial, terminal and associated causes of deaths were analyzed. Initial Causes of deaths were compared with deaths of French general population in the same periods (CIM9 and 10).

Results: In the global period (1969–2009), AS appeared in 2942 deaths certificates, 2292 men (mean age of death 68.7 years) and 650 women (mean age of 75.8, 601 between 1969-78 (ICD8), 1471 between 1979–1999 (ICD9) and 867 between 2000 and 2009 (ICD10). There is a trend that AS decreases life expectancy in men compared with general population. The number of deaths with AS on the death certificates is increasing due to change of ICD and increase of diagnosis. AS is mentioned as initial cause in 38% in 1969–1978, 33% in 1979–1999 and 5% in 2000–2009. Apart from AS, most frequent initial causes are diseases of the circulatory system (28.5% in ICD8, 23.1% in ICD9 and 26.5% in ICD10; neoplasms (7.8%, 10.2% and 16.3%); diseases of the respiratory system (7.5%, 11.1% and 9.4%) and external causes of mortality (3.5%, 7.8% and 13.1%). Compared to general population there is less deaths caused by neoplasms, but more caused by infectious, genitourinary diseases and external causes of mortality. Most frequent associated causes are diseases of the circulatory system (22.2%, 34.4% and 23.7%).

Conclusion: The manner of death coding varies according to ICD. Our study is the first to analyze data from deaths certificate. Diseases of the circulatory system are the most frequent initial and associated causes of death. But compared to general population, infectious, genitourinary diseases and external causes of mortality are more frequent in AS.

Disclosure: C. Prati, None; D. Wendling, None; X. Guillot, None.

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Physical Function, Hyperuricemia and Gout in Older Adults.

Mara McAdams-DeMarco1, Bridget Burke2, Andrew Law3, Anna Kottingen4, Alan N. Baer5 and Josef Coresh1. 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD, 3University Hospital Freiburg, Freiburg, Germany, 5Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: The prevalence of gout is higher in older adults than in younger adults and these patients are at risk of physical disability. We sought to determine the prevalence of and risk factors for impaired physical function in relation to gout status and hyperuricemia.

Methods: We studied gout, hyperuricemia, and function in 5,819 older adults (age >65) using the Atherosclerosis Risk in Communities cohort, a prospective US population-based cohort study of middle-aged adults enrolled between 1987–1989 with ongoing annual follow-up through 2012. Differences in lower (Short Physical Performance Battery (SPPB) and 4 meter walk test, measured in 2011–2013) and upper extremity function (grip strength) by gout status and by hyperuricemia prevalence were estimated: adjusted ordinal logistic regression for SPPB and modified Poisson regression for 4 meter walk test and grip strength. The risk of poor physical function (lowest quartile of grip strength, lowest quartile of SPPB and highest quartile of 4 meter walk test) was estimated using modified Poisson regression. Characteristics of gout participants with poor physical function were identified using modified Poisson regression.

Results: There were 595 (10.2%; women: 7.1% and men: 14.6%) participants with gout and 1,242 (21.3%; women: 16.2% and men: 28.4%) with hyperuricemia. There was no difference in grip strength by history of gout (mean difference = -0.29, 95% CI: -0.90, 0.32; P = 0.36) nor risk of poor grip strength by history of gout (RR = 1.07, 95% CI: 0.95–1.21; P = 0.27). Participants with gout had 0.70-times (95% CI: 0.60, 0.82; P < 0.001) the odds of a 1-unit increase in the SPPB score, such that those with gout had worse performance on the SPPB and participants with gout were 1.28-times (95% CI: 1.15–1.42; P < 0.001) more likely to have poor SPPB performance. Participants with gout had slower 4 meter walk test by history of gout (mean difference = -0.23, 95% CI: 0.12, 0.33; P < 0.001) and were at 1.24-fold (95% CI: 1.10–1.41; P = 0.001) increased risk of poor 4 meter walk test performance. Results were similar when comparing grip strength, SPPB and 4 meter walk test by hyperuricemia (Table). Among participants with gout, older participants (for every 5 year increase in age, RR = 1.42, 95% CI: 1.28, 1.59), black participants (RR = 1.58, 95% CI: 1.25, 2.00), participants with higher BMI (for every 5 kg/m² increase in BMI, RR = 1.18, 95% CI: 1.07, 1.29) and participants who were current smokers (RR = 1.65, 95% CI: 1.14, 2.38) were at highest risk of poor 4 meter walk test; similar results were observed for poor SPPB score.

Conclusion: Older adults with gout and hyperuricemia are more likely to have poor lower but not upper body function. Additionally, we identified a
group of gout participants with high risk of poor lower extremity function, namely, older age, men, with higher BMIs, and current smokers.

Table: Independent association of physical function in older adults, by gout and hyperuricemia status

<table>
<thead>
<tr>
<th>BMI at age 35 years</th>
<th>n</th>
<th>Incident rate of gout</th>
<th>Cumulative incidence at specified age (%)</th>
<th>Unadjusted HR</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No gout (n = 5,224)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference (n = 2,442)</td>
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<td></td>
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</tr>
<tr>
<td>Gout (n = 2,782)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No hyperuricemia (n = 4,577)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference (n = 2,242)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia (n = 1,242)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.36</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Poor physical function</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No gout (n = 5,224)</td>
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<tr>
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</tr>
<tr>
<td>P-value</td>
<td>0.27</td>
<td>&lt;0.001</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

Ordinal logistic regression was used for SPPP score 5,548 with available 4 meter walk test: lower time is indicative of better function.

Low physical function was defined as the lowest quartile for grip strength (≥22 kg) and SPPP (≥7) as well as the highest quartile for normal walking pace (≥5.2 seconds).

Disclosure: R. M. McAdams-DeMarco, None; B. Burke, None; A. Law, None; A. Kottgen, None; A. N. Baer, None; J. Coresh, None.

45 Body Mass Index Across the Lifespan and Lifetime Incidence of Gout in Men

Allan C. Gelber, Lucy Meoni, Michael Klag and Joseph Gallo. Johns Hopkins University, Baltimore, MD.

Background/Purpose: Gout is the leading cause of inflammatory arthritis in men and is linked to higher levels of body weight and obesity in mid-adult life. However, few, if any, observational cohorts have examined the association of body weight across the life span with incident gout. We sought to determine whether weight, assessed in young, mid and late-adult life, predicts the subsequent development of gout.

Methods: Body mass index [BMI] was first calculated at a mean age of 23 (± 2) years among 1040 male former medical students who graduated from 1948–1964. Thereafter, BMI was re-assessed in each decade of adult life. Incident gout was ascertained during follow-up using self-administered questionnaires and confirmed in a subset of participants according to American College of Rheumatology criteria. Survival analysis techniques were used to examine the association of BMI in each age interval with incidence of gout, with adjustment for comorbid hypertension at time of BMI, cholesterol level and alcohol consumption at cohort entry.

Results: In this prospective cohort study, the mean weight at cohort entry was 75.6 (±9.8) kilograms, height was 1.81 (± 0.06) meters, corresponding to mean BMI of 23.1 (±2.6) kg/m². During a median follow-up of 45 years, a total of 158 men developed gout. Notably, the youngest age at which gout first occurred was 28 years. Thereafter, 6 men developed gout by age 35 years, an additional 36 developed gout by age 50 years, 36 more between ages 50–65 years, and finally, 70 men developed gout between 65 to 88 years of age. The cumulative incidence of gout by age 45 years was 2.2%, by 55 years was 5.4%, by 65 years was 8.5%, by age 75 years was 14.4%, and the cumulative incidence of gout by 85 years was 21.0%. Further, at each period in the adult life spectrum, a dose-response association was observed between successively higher tertiles of BMI and gout incidence (Table; each logrank p<0.006). Moreover, those men in the highest tertile of BMI (at ages 35, 50 and 65) experienced a heightened risk to develop gout over the next 15–20 year period (between ages 35–50, 50–65, and 65–85, respectively) compared to those in the lowest BMI tertile, an association largely explained in the late adult period by comorbid hypertension.

Conclusion: The incidence of gout in men rises during each decade of the lifespan. Body weight in young, mid and late adult life, each predicted gout incidence during the subsequent age period. These findings imply that across the lifespan, overweight and obesity are potential modifiable targets in the primary prevention of gout.

46 Xanthine Oxidase Inhibitors and Risk of Type 2 Diabetes in Patients with Gout

Seoyoung C. Kim1, John D. Seeger2, Jun Liu1 and Daniel H. Solomon1. 1Brigham and Women’s Hospital, Boston, MA. 2Brigham and Women’s Hospital/Harvard Medical School, Boston, MA.

Background/Purpose: Hyperuricemia and gout are associated with an increased risk of type 2 diabetes (T2D). Xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are the main therapy to treat gout patients with hyperuricemia. Little is known whether treating hyperuricemia with a XOI has any effect on future risk of T2D. We examined the risk of T2D in gout patients initiating a XOI versus untreated patients with hyperuricemia.

Methods: We conducted a cohort study using a U.S. commercial insurance claims database. Patients aged ≥40 years with gout and hyperuricemia (≥ 6.8mg/dl) who had an enrollment period for ≥ 365 days were eligible. Propensity score (PS) matching was used to simultaneously control for baseline demographic factors, comorbidities, medications, health care utilization, and time trend. From January 2004 to December 2012, XOI initiators and non-initiators matched on a PS were identified with a 1:2 ratio in each calendar month (a total of 108 calendar months). The first day of each month was the index date for both groups. We excluded patients with diabetes, use of XOI or anti-diabetic drugs, end-stage renal disease and renal transplantation prior to the index date. Follow-up continued until the outcome occurrence, discontinuation or initiation of XOI, disenrollment, or administrative censoring. We calculated incidence rates (IR) of T2D based on a new diagnosis of T2D and a receipt of anti-diabetic medication. Due to violation of the proportional hazards assumption, Cox proportional hazards models stratified by treatment duration compared the risk of T2D in XOI initiators versus non-initiators.

Results: There were 4,045 XOI initiators and 8,090 non-initiators. Baseline characteristics were well-balanced between the matched groups. Mean age was 54 years and 89% male in both groups. Common comorbidities include hypertension (64%), hyperlipidemia (61%), CVD (10%), obesity (10%) and chronic kidney disease (8%). Use of systemic steroids at baseline was common (33%). The mean serum uric acid level at baseline was 8.9 mg/dl in XOI initiators and 8.3 mg/dl in non-initiators. The mean HgbA1c level at baseline was 5.9% in XOI initiators and 5.8% in non-initiators. The IR of T2D per 100 person-years was 1.88 (95% CI 1.41–2.51) in XOI initiators and 1.57 (95% CI 1.36–1.81) in non-initiators. XOI treatment for 0–90 days was associated with an increased risk of T2D versus non-initiators, whereas the use of XOI for longer than 360 days may be associated with a decreased risk of T2D (Table).

Conclusion: Nearly 2% of gout patients were newly diagnosed with T2D during follow-up. Short-term use of XOI was associated with a greater risk of T2D in gout patients compared to non-initiators, but a potential long-term beneficial effect of XOI on T2D cannot be excluded. Future research such as a randomized clinical trial ensuring treatment adherence may be needed to examine the long-term effect of XOI on T2D.

Table: Risk of type 2 diabetes by the duration of xanthine oxidase inhibitor treatment in gout patients: PS-matched analysis

<table>
<thead>
<tr>
<th>Follow-up time (days)</th>
<th>Xanthine oxidase inhibitor initiators (n = 4,045)</th>
<th>Non-initiators (n = 8,090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>Incident rate</td>
<td>Cumulative incidence at specified age (%)</td>
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<tr>
<td>----------------</td>
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<td>----------------------------------------</td>
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<tr>
<td>0-365</td>
<td>1,988</td>
<td>1.15 (0.64–2.06)</td>
</tr>
<tr>
<td>Person-years</td>
<td>Incident rate</td>
<td>Cumulative incidence at specified age (%)</td>
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<tr>
<td>0-90</td>
<td>220</td>
<td>4.40 (1.10–1.88)</td>
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<tr>
<td>90–180</td>
<td>5</td>
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</tr>
<tr>
<td>Person-years</td>
<td>Incident rate</td>
<td>Cumulative incidence at specified age (%)</td>
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<tr>
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<td>5</td>
<td>4.40 (1.10–1.88)</td>
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</tbody>
</table>
The Risk of Aplastic Anemia and Pancytopenia with Colchicine: A Retrospective Study of Integrated Health System Database. Jasvinder Singh1, Shuo Yang2 and Jeff Foster3. 1University of Alabama at Birmingham, Birmingham, AL, 2The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Colchicine is a commonly used medication, sometimes associated with bone marrow toxicity. The objective of this study was to examine the risk of severe hematologic side effects including pancytopenia and aplastic anemia with colchicine.

Methods: This retrospective study utilized the Veterans Affairs (VA) administrative and clinical databases from fiscal year 2001 to 2012. Colchicine use was defined as at least 30-day filled prescription. Prevalent gout was defined as the presence of ≥1 International classification of diseases, ninth revision (ICD-9) codes for gout during an inpatient visit or during ≥2 codes during outpatient visits. Aplastic anemia was captured with an ICD-9 code of 284.9 and Pancytopenia with a code of 284.1. We used Cox proportional hazards models that assessed hazards of aplastic anemia or pancytopenia adjusted for the following factors: Model 1: drug exposure, age, gender, body mass index, race, marital status, region; Model 2: variables in model 1, plus baseline Charlson comorbidities.

Results: 198 gout patients had aplastic anemia, of which 59 occurred in patients exposed to colchicine. 2047 gout patients had pancytopenia, of which 582 occurred in patients exposed to colchicine. The incidence rate of aplastic anemia was 0.5/1000 person years and of pancytopenia was xx/ in patients exposed to colchicine. 2047 gout patients had pancytopenia, of which 284.9 occurred in patients exposed to colchicine. The incidence rate of aplastic

Table 1  Association of colchicine with severe hematologic side effects

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (demographics)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
<th>Model 2 (demographics + comorbidity)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>3.72 (2.61, 5.31)</td>
<td>&lt;0.0001</td>
<td></td>
<td>3.32 (2.32, 4.76)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2.88 (2.58, 3.22)</td>
<td>&lt;0.0001</td>
<td></td>
<td>2.26 (2.02, 2.53)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>


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Osteoporotic Women at High Risk for Fractures Despite Two Years of Oral Bisphosphonate Therapy: Analysis Using the Canadian Multicentre Osteoporosis Study. Jonathan D. Adachi1, David Goltzman2, Ankita Modi1, Jackson Tang2, Chun-Po S. Fan3 and Jessica Weaver1. 1Division of Rheumatology, McMaster University, Hamilton, ON, 2McGill University, Montreal, QC, 3Merck & Co., Inc., Whitehouse Station, NJ, 4Asclepius Analytics, New York, NY.

Background/Purpose: Individuals with osteoporosis (OP) have an increased susceptibility to fractures. Prevention and treatment of postmenopausal OP is critical to decreasing the risk of non-traumatic bone fractures. These fractures cause medical and personal hardships, particularly among older individuals, and are a burden on health care systems (Adachi 2003). The objective of this study was to quantify the number of osteoporotic women 55 years of age or older that remain at high risk of fracture despite benefits of prior oral bisphosphonate (BIS) therapy.

Methods: This study retrospectively analyzed a subset of participants in The Canadian Multicentre Osteoporosis Study (CaMos). CaMos is a prospective cohort study of 9,423 selected from community dwelling men and women older than 25 years of age. A subset of women from the CaMos database that were studied was 55 years of age or older with OP, who did not have Paget’s disease and who reported receiving BIS therapy for at least two consecutive years. Additionally, patients must have had at least three years of follow-up data from the index date (start of 2 years of BIS therapy), and be considered osteoporotic at baseline for inclusion. Patients with lumbar spine or hip BMD of < -2.5 at baseline, or with prior vertebral or hip fractures, were classified as osteoporotic. Two consecutive years of BIS therapy was utilized as a proxy for adherence to BIS therapy, and was based on annual self-reported patient questionnaire responses regarding BIS therapy. High risk for fracture was determined by the following three criteria: 1) Fractures during the first year following the BIS treatment period. 2) Any decline in BMD at the hip (femoral neck) or lumbar spine (L1-L4) from baseline BMD (the most recent BMD prior to the treatment period) to the “study BMD” (i.e., the closest BMD after the 2-year treatment period). 3) A “study BMD” less than -2.5 at the hip (femoral neck) or lumbar (L1-L4) spine. Descriptive analysis was conducted to characterize the fracture risk profile in this patient population.

Results: 628 women with a mean age of 71.6 years met the eligibility criteria. 24 participants (3.8%) experienced fractures during the first year following the two consecutive years of BIS therapy. Of the 24 patients with fractures during this time, 3 had fractures during the two years of BIS therapy. Almost two thirds (59.2%) of participants (372) experienced a decline in BMD from baseline following two years of therapy. Additionally, 71.3% of patients (448) were classified as osteoporotic after two years of OP therapy.

Conclusion: This study demonstrates that despite the benefits of OP treatment with BIS, a considerable proportion of women represented in the CaMos database who reported taking oral BIS therapy for two years remained at high-risk for OP fractures. In light of this finding, alternative treatments should be considered for many osteoporotic women who remain at high risk for OP or non-traumatic fractures.

Disclosure: J. D. Adachi, Actavis, Amgen, Eli Lilly, Merck, 2; D. Goltzman, Amgen, Lilly, Merck, 2; A. Modi, Employee of Merck and hold stock options, 3; J. Tang, None; C. P. S. Fan, Merck Pharmaceuticals, Alkermes, 5; J. Weaver, Merck Pharmaceuticals, 3.

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Long-Term Oral Bisphosphonate Use for Osteoporosis Among Older Women – US and Canadian Perspective. Nicole C. Wright1, Wilson Smith2, Amy H. Warriner3, Jeff Foster4, Ruth McConnell2, Huiying Yun2, Mary H Melton3, Jeffrey R. Curtis1 and Kenneth G. Saag3. 1The University of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL, 3University of Alabama at Birmingham School of Public Health, Birmingham, AL.

Background/Purpose: Bisphosphonates (BPs) have been widely used for the treatment and prevention of osteoporosis for two decades. Although new parenteral preparations have been introduced, oral BPs still represent the vast majority of osteoporosis treatments. Little is known about the characteristics of or regional differences in long-term oral BP users.

Methods: We evaluated the long-term use of oral BPs in the national US Medicare and Ontario (ON) Canada data systems. The US Medicare cohort consisted of women aged ≥65 years with an osteoporosis or fracture diagnosis code, or BP prescription fill. The ON data consisted of women aged ≥66 years who were new users of BPs. We identified women with three years of continuous medical and pharmacy coverage. Long-term BP users were those with exposure to an oral BP (alendronate, risedronate, ibandronate, and etidronate) in each of the three most recent years of available data (2009–2011). We evaluated demographic and BP utilization data including, BP exclusivity (no exposure to another BP agent in three year period) and compliance to therapy using proportion of days covered (PDC) (days of drug supplied in 3 years/3*365.25). Users with a PDC of ≥70% were considered compliant.

Results: We identified 888,704 US and 99,530 ON women meeting the inclusion criteria with at least one oral BP prescription in the most recent data. We then identified 698,012 US and 54,656 ON long-term oral BP users (Table). Alendronate was primarily used by Medicare patients (78.0%), whereas risedronate was the primary oral BP in ON (56%). Based on the available data, the mean duration of use among the long-term BP users was five years in both US (SD: 1.1) and ON (SD: 2.2). In the US, risedronate users were more likely to be exclusive users (83%) compared to alendronate users; whereas in ON, a higher proportion of alendronate users were considered exclusive users than risedronate users. All ibandronate users were exclusive
users in US data. Compliance was higher in ON (80% alendronate, 78% risedronate) than in US (63% alendronate, 63% risedronate).

**Conclusion:** Although alternative preparations of BPs and new non-BP drugs have emerged in the market, the prevalence of oral BP use is high. In the data evaluated, the prevalence of long-term use (≥3 years) was also high in both countries. However, compliance differed by country. Evaluations in more recent data would determine if and how drug holidays have altered these characteristics.

### Table. Characteristics of Long-Term Oral Bisphosphonate Users

<table>
<thead>
<tr>
<th></th>
<th>US, 2009–2011 (n = 696,012)</th>
<th>ON, 2009–2011 (n = 54,656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>79.3 (7.4)</td>
<td>74.0 (6.4)</td>
</tr>
<tr>
<td>Mean BP duration*, yrs (SD)</td>
<td>5.0 (1.1)</td>
<td>4.9 (2.2)</td>
</tr>
<tr>
<td>Most recent BP, (n,%)</td>
<td>354,656 (78.0)</td>
<td>24,056 (44.0)</td>
</tr>
<tr>
<td>Alendronate</td>
<td>96,795 (13.9)</td>
<td>30,600 (56.0)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>56,561 (8.1)</td>
<td>–</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Exclusive BP users**, (n,%)</td>
<td>419,496 (77.2)</td>
<td>22,596 (93.9)</td>
</tr>
<tr>
<td>Alendronate</td>
<td>80,314 (83.0)</td>
<td>26,981 (88.2)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>56,561 (100.0)</td>
<td>–</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Mean duration based on first BP dispensed in each data system. US = 2006–2011; ON: 2002–2011

**Exclusive users are those who only filled a prescription for each oral BP among most recent BP users

Compliance estimated at proportion of days covered (PDC) of ≥70% among exclusive BP users.

### Disclosure: N. C. Wright, None; W. Smith, None; A. H. Warriner, None; J. Foster, None; R. McConnell, None; H. Yun, None; M. H. Melton, None; J. R. Curtis, None; K. G. Saug, None.

### 50 Incidence and Risk Factors for Osteoporotic Vertebral Fracture in Low-Income Community-Dwelling Elderly: A Population-Based Prospective Cohort Study in Brazil, the São Paulo Ageing & Health (SAPH) Study.

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### Background/Purpose:

Vertebral fractures are associated with increased future fracture risk and mortality. No data on incidence of osteoporotic vertebral fracture have been reported in low-income countries where the population’s aging has been faster. Thus, we sought to describe the incidence and predictors of radiographic vertebral fracture in a longitudinal prospective Brazilian population-based elderly cohort - the São Paulo Ageing & Health (SAPH) Study.

### Methods:

From 2005–2007, all residents ≥65 years living in the Butantã community, located in the Western part of the city of São Paulo, were identified through census records. In total, 1,023 subjects were included in the fracture prevalence study. Until 2012, 132 individuals had died during follow-up, and 725 subjects agreed to take part in this longitudinal evaluation (response rate in surviving subjects, 81.2%). Eighteen subjects were excluded due to cancer; thus, 449 women and 258 men were evaluated. A new vertebral fracture was considered as a distinct alteration in morphology of vertebral resulting in a higher grade of deformity when the second radiograph was compared to the same vertebra on the baseline radiograph. Clinical questionnaire, bone mineral density (BMD) and laboratory tests were performed at baseline. Multivariate Poisson regression models were used to identify independent predictors of vertebral fracture.

### Results:

After a mean follow-up of 4.3±0.8 years, the age-standardized incidence of vertebral fracture was 40.3/1000 person-years in women and 30.6/1000 in men. In women, three possible models of risk factors for fracture were fitted: 1. age (RR: 2.46, 95% CI 1.66–3.65), previous osteoporotic fracture (RR: 1.65, 95% CI 1.00–2.71) and lumbar spine BMD (RR: 1.21, 95% CI 1.03–1.41); 2. age (RR: 2.25, 95% CI 1.52–3.34) and femoral neck BMD (RR: 1.42, 95% CI 1.11–1.81); 3. age (RR: 2.11, 95% CI 1.41–3.15) and total hip BMD (RR: 1.56, 95% CI 1.21–2.0). In men, the highest quartile of serum type I collagen C-telopeptide (CTX) (RR: 1.96, 95% CI 0.98–3.91) and prior fracture (RR: 2.10, 95% CI 1.00–4.39) were predictors of new vertebral fracture.

### Conclusion:

This is the first population-based study to ascertain the incidence of vertebral fracture in elderly Latin Americans, confirming the high frequency of the disorder. Age, prior fracture, BMD and bone turnover were predictors of the short-term incidence of vertebral fracture.

### Disclosure: D. S. Domiciano, None; L. G. Machado, None; J. B. Lopes, None; V. Caparbo, None; L. Takayama, None; R. M. Oliveira, None; R. M. R. Pereira, None.

### 51 High Incidence of Non-Vertebral Osteoporotic Fracture and Hip Fracture in Brazilian Low-Income Community-Dwelling Elderly: A Population-Based Prospective Cohort Analysis from the São Paulo Ageing & Health (SAPH) Study.

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### Background/Purpose:

There is considerable variability in the incidence of hip fracture among countries, even among different geographical areas within the same country. In Brazil, population differences in occurrence of hip fracture are probably related to the huge size of the country, the substantial ethnic miscegenation and distinct lifestyle habits within the Brazilian territory. Longitudinal studies on incidence of hip fracture in the Brazilian population are scarce and the results are hampered by incomplete capture of cases and short follow-up time. Moreover, there is no prospective study on incidence of non-vertebral fractures beyond the hip. Thus, our aim was to describe the incidence of hip and non-vertebral fracture in elderly community from a prospective population-based study.

### Methods:

Incidence of hip and non-vertebral fracture were determined in 707 women and men from community, aged 65 years or older. Specific questionnaire (clinical and anthropometric data), including personal history of fragility fracture in non-vertebral osteoporotic sites (hip, humerus, wrist, rib) was performed at baseline and after an average of 4.3 years. All incident fractures during the study period were confirmed by radiograph of the affected site.

### Results:

449 women (mean age 72.9±4.8 years) and 258 men (mean age 72.3±4.7 years) were included in the study. The age-adjusted incidence of non-vertebral fracture was 171/100,000 person-years in women and 63/100,000 person-years in men (female/male ratio: 2.6). The age-adjusted incidence of hip fracture was 420/100,000 person-years in women and 90/100,000 person-years in men (female/male ratio: 4.7). The incidence increases with age, particularly in women.

### Conclusion:

The incidence of non-vertebral osteoporotic fracture in the Brazilian elderly population was high, especially among women. Concerning hip fracture, these results emphasize that the incidence in the southern and southeastern regions of the country seems to be higher than the rates in the northern/northeastern population. Furthermore, our results reinforce the notion that the incidence of hip fracture in Brazilian older adults, particularly in women, is higher than in other Latin American populations, except Argentina.

### Disclosure: D. S. Domiciano, None; L. G. Machado, None; J. B. Lopes, None; C. P. Figueiredo, None; V. Caparbo, None; L. Takayama, None; R. Oliveira, None; P. R. Menezes, None; R. M. R. Pereira, None.

### 52 Visceral Fat Measured By Dual-Energy X-Ray Absorptiometry Is Associated With Increased Risk of Non-Spine Fractures in Nonobese Elderly Women: A Population-Based Prospective Cohort Analysis from the São Paulo Ageing & Health (SAPH) Study.

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### Background/Purpose:

The protective role of obesity on bone health has currently been questioned, since it has been demonstrated that visceral fat have a deleterious effect on bone. However, there are no studies evaluating the association between visceral fat measured by DXA with fracture risk. The aim of this study was to investigate the association of visceral fat with incident non-spine fractures in community-dwelling elderly women.

### Disclosure: D. S. Domiciano, None; L. G. Machado, None; J. B. Lopes, None; C. P. Figueiredo, None; V. Caparbo, None; L. Takayama, None; R. Oliveira, None; P. R. Menezes, None; R. M. R. Pereira, None.
Methods: This is a longitudinal prospective population-based cohort study evaluating 433 community-dwelling women aged 65 years or older. Specific questionnaire (clinical and anthropometric data), including personal history of fragility fracture in non-spine osteoporotic sites (hip, humerus, wrist, rib), was performed at baseline and after an average of 4.3 years. All incident fractures during the study period were confirmed by affected site radiography. Bone mineral density (BMD) and laboratory tests were also performed at baseline. Visceral fat was measured by a new software of dual-energy X-ray absorptiometry (DXA) in the android region of a total body DXA scan. Logistic regression models were used to estimate the relationship between visceral fat and non-spine fractures.

Results: The mean age was 72.8 ± 4.7 years and 28 incident non-spine osteoporotic fractures were identified after a mean follow-up time of 4.3 ± 0.8 years. According the Lipschitz classification for nutritional status in elderly, 61.4% of women were considered obese/overweight (BMI > 27 kg/m²) and 38.6% were nonobese (7.4% underweight- BMI < 22 kg/m² and 31.2% normal weight- BMI = 22 and ≤ 27 kg/m²). After adjusting for age, previous fracture and BMD (parameters with significance at univariate analysis), visceral fat area had a significant association with incident non-spine fractures in nonobese (BMI = 27 kg/m²) elderly women (p = 0.009).

Conclusion: Higher visceral fat was associated with the risk for non-spine fractures in nonobese elderly women. This study supports a potential negative effect of visceral adiposity on bone health.

Disclosure: L. G. Machado, None; D. S. Domicianno, None; C. F. Figueiredo, None; J. B. Lopes, None; V. Caparbo, None; L. Takayama, None; R. M. Oliveira, None; R. M. R. Pereira, None.

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Background/Purpose: Diagnostic discordance for osteoporosis is the presence of different T-scores in two skeletal sites in the same subject leading to different WHO diagnostic categories. Discordance is defined as minor when the difference between two sites is no more than one WHO diagnostic class and major when one site is osteoporotic and the other is normal. This study examines to determine the percentage of minor and major diagnostic discordance and identify associated factors in patients undertaking osteoporosis screening.

Methods: Details of the first Dual-X-Ray-Absorptiometry test (DXA) during 2011–2013 were extracted, including weight, height, T score at lumbar spine (LS, Lumbar Spine), LTH, Left Total Hip, RTH, Right Total Hip. Only complete data for individuals over 18 years old, with nationality of North Africa Middle East (as per WHO definition) were analysed. Differences in T scores and degree of discordance between sites were calculated. Age and BMI were analysed as contributing factors.

Results: One thousand, four hundred and forty four patients with complete data were identified. The mean age was 59.1 (±13.2 SD) and 86.3% were females. Diagnostic agreement among all skeletal sites was found in 415 (28.7%) patients, while 631 (43.7%) and 398 (27.6%) showed at least one major or minor discordance, respectively. Maximum concordance was found between right total hip and left total hip (RFN, RTH) and left side (LFN, LTH) and T score at lumbar spine (LS). Only complete data for individuals over 18 years old, with nationality of North Africa Middle East (as per WHO definition) were analysed. Differences in T scores and degree of discordance between sites were calculated. Age and BMI were analysed as contributing factors.

Conclusion: Results show a high level of major diagnostic discordance, higher than previously reported in published studies. This high prevalence of discordance could produce some problems for the physicians in decision-making regarding these patients. This reiterates the understanding that multiple site measurements are mandatory for osteoporosis diagnosis, including BMD measurements at both hips. High prevalence of discordance between lumbar spine and hip T-scores suggests some defects in the cut-off values for the definition of osteoporosis and osteopenia proposed by the WHO. BMD should be used as only one of the factors in making therapeutic decisions when evaluating patients with osteoporosis.

Table 1. Number (percentage) of cases categorised as normal, minor and major discordance and the directional trend and weight between the different skeletal sites

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Normal</th>
<th>Minor</th>
<th>Discordance</th>
<th>Major</th>
<th>Trend</th>
<th>Direction</th>
<th>Number of comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-LTH</td>
<td>n (%)</td>
<td>581 (41.2)</td>
<td>544 (38.5)</td>
<td>285 (20.2)</td>
<td>93.30%</td>
<td>LS lower</td>
<td>1410</td>
</tr>
<tr>
<td>LS-LFN</td>
<td>n (%)</td>
<td>570 (40.7)</td>
<td>532 (38)</td>
<td>298 (21.3)</td>
<td>93.70%</td>
<td>LS lower</td>
<td>1400</td>
</tr>
<tr>
<td>LS-RFN</td>
<td>n (%)</td>
<td>579 (40.9)</td>
<td>561 (39)</td>
<td>270 (19.2)</td>
<td>92.10%</td>
<td>LS lower</td>
<td>1407</td>
</tr>
<tr>
<td>LS-LFN</td>
<td>n (%)</td>
<td>575 (41.2)</td>
<td>469 (40.8)</td>
<td>242 (20.1)</td>
<td>89.50%</td>
<td>LS lower</td>
<td>1396</td>
</tr>
<tr>
<td>RFN-LFN</td>
<td>n (%)</td>
<td>1150 (80.9)</td>
<td>260 (18.2)</td>
<td>12 (0.9)</td>
<td>56.90%</td>
<td>RFN Lower</td>
<td>1422</td>
</tr>
<tr>
<td>LTH-LFN</td>
<td>n (%)</td>
<td>1097 (77.8)</td>
<td>297 (21)</td>
<td>16 (1.2)</td>
<td>67.90%</td>
<td>LFN Lower</td>
<td>1410</td>
</tr>
<tr>
<td>RTH-LHN</td>
<td>n (%)</td>
<td>1219 (86.6)</td>
<td>177 (12.6)</td>
<td>11 (0.8)</td>
<td>51.60%</td>
<td>RTH Lower</td>
<td>1407</td>
</tr>
<tr>
<td>RFN-LFN</td>
<td>n (%)</td>
<td>1121 (80)</td>
<td>261 (18.6)</td>
<td>19 (1.2)</td>
<td>62.40%</td>
<td>LFN lower</td>
<td>1401</td>
</tr>
<tr>
<td>RTH-LFN</td>
<td>n (%)</td>
<td>1058 (75.4)</td>
<td>26 (1.9)</td>
<td>26 (1.9)</td>
<td>56.80%</td>
<td>RFN lower</td>
<td>1401</td>
</tr>
<tr>
<td>LTH-LFN</td>
<td>n (%)</td>
<td>1085 (77.2)</td>
<td>297 (21.3)</td>
<td>23 (1.7)</td>
<td>56.50%</td>
<td>LFN Lower</td>
<td>1405</td>
</tr>
</tbody>
</table>

Conclusion: Higher visceral fat was associated with the risk for non-spine fractures in nonobese elderly women. This study supports a potential negative effect of visceral adiposity on bone health.

Disclosure: N. Wilson, None; L. Sanchez Riera, None; I. Hobeldin, None; S. Waheeduddin, None; N. Ibrahim, None; S. Gonuguntla, None; T. Khan, None; R. Anjela, None; S. Nuhaily, None; M. Al Maini, None.

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Concordance with the National Osteoporosis Foundation Treatment Guidelines. Nicole Wright1, Xin Lu2, Stephanie Edmonds3, Fredric Wolin4, Detha G. Roblin5 and Kenneth G. Saag4. 1Department of Clinical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, 2University of Iowa, Iowa City, IA, 3Kaiser Permanente Georgia, Atlanta, GA, 4University of Toronto, Toronto, ON, 5The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The National Osteoporosis Foundation (NOF) published treatment guidelines to help guide clinicians on which patients should be considered for osteoporosis (OP) therapy. We examined patient factors associated with non-concordance among older adults participating in the PAADRN study.

Methods: The PAADRN study (NCT01507662) is a large, NIH funded, randomized trial currently being conducted in the Iowa City, IA, Birmingham, AL, and Atlanta, GA metro areas. Immediately following DXA, participants ≥50 years of age are recruited and randomized. We used data from the control arm, usual care group, (n=2,711 as of 6/14/14) for our analyses. We defined guideline concordant OP therapy as the report of any FDA approved OP therapy at the 12-week post-DXA survey along with one of the following criteria: 1) baseline self-report of fracture after the age of 40, 2) T-score at or below the OP threshold (≤-2.5), or 3) T-score within the low bone mass range (≥1.5 to -2.5) and a FRAX score ≥20%. Non-concordance was examined among participants who 1) were indicated for OP therapy who did not report OP therapy at 12 weeks (N=1,170), and 2) were not indicated for OP therapy who reported OP therapy at 12 weeks (N=540). We used logistic regression to assess the association of baseline demographic and comorbidity factors with non-concordance in both groups.

Results: Our study population was 85% female, 20% from minority backgrounds, and 60% ≥ 65 years of age. At baseline, 760 (28%) reported having a fracture after 40 years of age, 576 (21%) had DXA defined OP, and 188 (7%) had low bone mass with a FRAX ≥ 20%. At the 12-week survey, 35% of patients with indications for OP therapy reported medication use, and 15% of patients without indications for OP therapy reported medication use. When treatment was indicated, we found that being Black was associated with higher odds of treatment non-concordance in the crude analyses (Table). Factors associated with higher odds of non-concordance among those not indicated for treatment included: being a woman, Hispanic, having comorbidities related to secondary OP, being a pre-menopausal woman, the self-report of low bone mass and OP, calcium and multi-vitamin supplementation use, and having spoken to provider by 12-week survey (Table).

Conclusion: In this study of usual OP treatment, 38% of those indicated for OP treatment reported medication use, and 15% of those not indicated for treatment reported medication use. We found that race was associated with non-concordance when treatment was indicated. When treatment was not indicated, non-concordance was associated with conditions related to low BMD, potentially being used as preventative therapy. However, demographic and lifestyle factors were also associated with high non-concordance in this group, suggesting that additional education on the benefits and risks of OP therapies for both patients and providers is needed.

Disclosure: N. Wilson, None; L. Sanchez Riera, None; I. Hobeldin, None; S. Waheeduddin, None; N. Ibrahim, None; S. Gonuguntla, None; T. Khan, None; R. Anjela, None; S. Nuhaily, None; M. Al Maini, None.

S22
Women vs. Men 0.75 (0.52, 1.08) 0.117 4.13 (2.32, 7.34) 0.001
Hispanic vs. Non-Hispanic 0.79 (0.52, 1.21) 0.239 3.35 (1.91, 5.86) 0.001
Black vs. White 1.71 (1.14, 2.56) 0.001 0.40 (0.27, 0.60) 0.001
Site A vs. Site C 0.74 (0.55, 0.99) 0.044 1.39 (0.98, 1.95) 0.062
Site B vs. Site C 1.32 (0.95, 1.83) 0.099 0.55 (0.38, 0.81) 0.003
Self-report of BMD 0.45 (0.35, 0.57) <0.001 1.35 (2.50, 4.48) <0.001
Self-report of osteoporosis 0.33 (0.26, 0.43) <0.001 0.33 (0.26, 0.43) <0.001
Pre-menopausal 0.67 (0.51, 0.89) 0.006 1.43 (1.02, 2.00) 0.038
Secondary Osteoporosis 0.47 (0.37, 0.60) 0.022 1.59 (1.17, 2.17) 0.005
Calcium Supplementation 0.53 (0.41, 0.69) <0.001 3.07 (2.19, 4.19) <0.001
Self-report of LBM 0.45 (0.35, 0.57) <0.001 3.07 (2.19, 4.19) <0.001
Vitamin D Supplementation 0.52 (0.39, 0.69) <0.001 3.02 (2.10, 4.34) <0.001
DXA defined Low vs. Normal BMD 0.23 (0.12, 0.47) <0.001 2.34 (1.69, 3.25) <0.001
*Crude associations from logistic regression models

Disclosure: N. Wright, None; X. Lu, None; S. Edmonds, None; F. Wolinsky, None; D. Roblin, None; P. Cram, None; K. G. Saag, Amgen, 2; Merck Pharmaceuticals, 2; Takeda, 2; Aredea, 2; Abbott Immunology Pharmaceuticals, 5; AbbVie, 5; Amgen, 5; Aredea, 5; BioCryst, 5; Bristol-Myers Squibb, 5; Eli Lilly and Company, 5; Crescendo, 5; Iroko, 5; Merck Pharmaceuticals, 5; Roche Pharmaceuticals, 5; NOV VP Board of Trustees, 6; ACR Board of Directors, 6.

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Validation of the Diagnosis of Avascular Necrosis of Bone in Administrative Data. Medha Barbhaiya,1 Yan Dong,2 Jeffrey A. Sparks,3 Elena Losina2, Karen H. Costenbader,4 and Jeffrey N. Katz5. 1Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: Avascular necrosis (AVN) of bone is a painful, disabling condition. Studies aimed at improving the diagnosis or treatment of AVN require accurate case-finding methods. We examined the sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (LR+) of alternative algorithms that use claims data to identify cases of AVN of the upper and lower extremities.

Methods: Using a centralized clinical data database from a large academic hospital, we identified all adults aged ≥18 years who underwent MRI of an upper or lower extremity joint for any indication between January 1, 2010 and June 1, 2011. We examined the performance characteristics (sensitivity, specificity, PPV, and LR+) of four algorithms (A – D) using International Classification of Diseases, 9th edition (ICD-9) codes for AVN (ICD-9, 733.4X) (Table). The algorithms ranged from least stringent (Algorithm A, requiring ≥1 ICD-9 code) to most stringent (Algorithm D, requiring ≥3 ICD-9 codes at least 30 days apart). Only ICD-9 codes within 6 months of MRI enrolment were included. We compared cases identified by each algorithm to the gold standard of a clinical MRI reading by a radiologist confirming “avascular necrosis” or “osteonecrosis.” We calculated 95% confidence intervals (CI) using the normal approximation of the binomial distribution.

Results: A total of 11,878 patients who underwent MRI of the upper and lower extremities during the 1.5 year period were included in this study. The prevalence of AVN using the gold standard of MRI was 0.7%, with 83 total cases of AVN. Algorithm A had a sensitivity of 81.9% (95% CI 71.9–89.5), with a PPV of 48.6% (95% CI 40.0–57.2) and a LR+ of 134 (95% CI 104–173). The PPV of Algorithm D increased to 61.4% (95% CI 47.6–74.0) with a LR+ of 226 (95% CI 139–368), although the sensitivity decreased to 42.2% (95% CI 31.4–53.5) (Table). The specificity of all four algorithms ranged from 99.0 to 99.8%.

Conclusion: In this study, we demonstrated that the PPV for AVN among patients who underwent MRI ranged from 49–61% in different ICD-9 code-based algorithms. Given its high sensitivity, Algorithm A (requiring at least 1 ICD-9 code for AVN) appears best suited for situations in which it would be problematic to miss AVN cases, and confirming cases to exclude false positives with further chart review is feasible. Algorithm B, requiring ≥2 ICD-9 codes at least 7 days apart, had the highest PPV and might be recommended when further validation is not feasible, although misclassification may occur. These algorithms provide an efficient way to identify AVN cases in administrative data, and the PPVs will be greater in populations with higher disease prevalence such as SLE or orthopedic cohorts. Of note, since all patients in this study underwent MRI, cases of asymptomatic or mild AVN that did not prompt MRI evaluation would not be detected with these methods.

Disclosure: M. Khraishi, Research grants, 2; R. Aslanov, None; S. Khraishi, None.

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High Prevalence of Cervical Malignant and Premalignant Lesions Among Women with Rheumatoid and Psoriatic Arthritis. Majed Khraiishi1, Rana Aslanov2 and Sarah Khraishi3. 1Nexus Clinical Research, St John’s, NF, 2Memorial University of Newfoundland, St John’s, NF, 3NL Research Technologies (NLRT), St John’s, NF.

Background/Purpose: Rheumatic diseases have been associated with an increased prevalence of malignancy. We aimed to examine the prevalence of premalignant lesions and malignancies in the published literature that included patients with inflammatory Arthritis. We aimed to compare the prevalence of malignancy between Rheumatoid (RA) and Psoriatic (PsA) Arthritis patients and to investigate correlations that may explain the high prevalence of cervical lesions that we noted.

Methods: Patients were recruited prospectively from a rheumatology clinic specializing in treating patients with arthritis and followed from January 2011 to December 2013. The prevalence of premalignant lesions and malignancy was evaluated and compared to the data provided by Statistics Canada, Canadian and Provincial Cancer Registries. Disease severity was assessed using the TJC/SJC, CRP, ESR, DAS28, and CDAI scores.

Results: A cohort of 700 (67.9% females) patients with Inflammatory Arthritis was included in this study with mean (SD) age 55.0 (12.4) years and mean (SD) duration of disease 8.4 (8.3) years. Overall, 116 (16.6%) precancerous lesions and cancers were analysed. Hundred and ten patients (15.7%) had at least one malignancy; three patients had a history of 2 malignancies. The most frequently observed cancers were: Cervical (37-7.8% of female population; OR (95%CI)=2.5 (1.0–6.2); P=0.042), Breast (20-4.2% of female population; OR (95%CI)=1.1 (1.0–1.1); p=0.001), Bowel (11-1.6%), and Lung Cancer (10-1.4%). We identified 37 cases with cervical lesions. Of them, six females had a history of cervical cancer (SCC), 18- High Grade Squamous Intraepithelial Lesions (HSIL), 3- Low Grade SIL cannot exclude HSIL, and in 5 cases it was impossible to trace the type of cervical dysplasia. Six cases belonged to women aged 49 years and younger, 31 cases of dysplasia and cancer belonged to women aged 50 years and older. All of them underwent hysterectomy prior to enrolment in the study. Prevalence of cervical lesions was strongly correlated with: females’ age (R=0.151, p=0.033), Health Assessment Questionnaire (HAQ: R=0.140, P=0.023), Tender Joint Count (TJC: R=0.108, p=0.016), and Clinical Disease Activity Index (CDAI: R=0.140, p=0.002) in RA cohort; and with: females’ age vs. 30%, respectively. Our data suggested their possible correlation with disease activity. Closer surveillance will be warranted if the reported increased prevalence is confirmed in larger cohorts.

Disclosure: M. Khraishi, Research grants, 2; R. Aslanov, None; S. Khraishi, None.
**Risk of Hospitalized Infection in a Psoriasis/Psoriatic Arthritis Cohort.**

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**Background/Purpose:** Psoriasis (PsO)/Psoriatic arthritis (PsA) often requires treatment with systemic immunosuppressive agents, some of which may increase hospitalized infection risk. Few population-based studies to date have evaluated the incidence of hospitalized infections in these populations.

**Methods:** We used the US Medicare data from 2006–2011 to identify a large cohort of PsA and PsO patients. We defined PsA and PsO patients as those with >1 rheumatologist-diagnosis code for psoriatic arthritis (ICD 9 696.0), or >1 dermatologist-diagnosis code for psoriasis (ICD 9 696.1) respectively, followed by a prescription for etanercept (ETA), cyclosporine (CIC), ustekinumab (UST), adalimumab (ADA), methotrexate (MTX) or ultraviolet light (UV) therapy. Patients had at least 6 months of continuous Medicare enrollment prior to the first date of exposure to these therapies. We excluded patients with organ transplantation, human immunodeficiency virus infection, advanced kidney and liver disease, or cancer with a 183-day period prior to cohort inception. We used validated-claims based algorithms to identify hospitalized infections among all exposure groups. Patient exposures were censored at time of serious infection, death, end of study, loss of coverage, or 90 days following end of treatment exposure whichever came first. Pairwise propensity scores (PS) were calculated and used to control for potential differences between comparator treatments. We calculated crude incidence rates for exposure groups, and used Cox-proportional hazard regression models to calculate hazard ratios for hospitalized infection between exposure groups while adjusting for PS quintile.

**Results:** We identified 10,261 PsA individuals and 31,052 PsO individuals. Within the PsA cohort, we identified 185 hospitalized infections for an overall incidence rate of 36.2 (95% CI 31.1–41.8) per 1,000 py. The rate of hospitalized infections ranged from 13.2 (95% CI 4.3–41.0) per 1,000 py for the UV group to 38.7 (95% CI 28.8–52.0) per 1,000 py for the ETA group. In Cox modeling, incidence rates were similar between exposure groups, with the exception of patients starting ETA as compared to UV therapy (HR 3.1 [95% CI 0.9–1.9]) where a non-statistically significant trend was noted. Within the PsO cohort, there were 1,198 hospitalized infections for an overall incidence rate of 36.9 (95% CI 31.6–44.5) per 1,000 py for the MTX group. After adjustment for confounders, patients on ADA had higher incidence rates as compared to CIC (HR 1.4 [95% CI 1.0, 2.0]), or UV therapy (HR 1.5 [95% CI 1.1, 1.9], respectively. Patients on ETA were at higher risk for infection than those using UV therapy (HR 1.3 [95% CI 1.1, 1.6]). Incidence rates between all other exposure comparisons were similar.

**Conclusion:** Among Medicare enrollees with PsA or PsO, rates of hospitalized infections varied across therapies but were largely similar. PsA patients were at similar risk no matter their therapy, although PsO patients starting ADA or MTX were at higher risk for infection than those using UV therapy.

**Disclosure:** K. L. Winthrop, Pfizer Inc, 5, Pfizer Inc, 2, Ismed, 2, Ismed, 5, UCBB, 5, Roche Pharmaceuticals, 5, Abbvie, 5, L. Chen, None, J. Baddiley, BMS, 2, Merck, Astellas, Pfizer, 5, A. Taylor, None, B. Chan, None, H. Yun, Angen, 2, S. Siegel, None, J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Angen, Pfizer, BMS, Crescendo, Abbvie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Angen, Pfizer, BMS, Crescendo, Abbvie, 5.

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**58 What Does the Patient Global Assessment (PGA) Mean for Patients with Psoriatic Arthritis?**

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**Background/Purpose:** Patient global assessment (PGA) is one of the most widely used patient reported outcomes (PROs) in psoriatic arthritis (PsA). PGA should reflect the global impact of the disease from the patient’s point of view, however we lack information on the concepts encompassed in PGA. In addition the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed to use also two specific (joints, skin) patient assessments but their scope is also unclear. (1) Recently the European League Against Rheumatism (EULAR) developed the PsAID (Psoriatic Arthritis Impact of the Disease) which includes 12 domains of health important for patients. (2)

Objective: to explore PGA in PsA from the patient’s point of view by comparing it to the PsAID domains of health and also to explore the two specific (joints, skin) patient assessments in relation to PGA.

**Methods:** Post-hoc analysis of the cross-sectional PsAID study (2) for patients with definite PsA (according to the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria). Data collection included PGA (“Considering all the ways PsA has affected you during the last week, circle the number that best describes how you have been doing”), skin and joint patient assessments (patient global assessments of these 2 aspects) and PsAID questions covering physical (including joints and skin), psychological and social impact of PsA. The concepts covered by PGA were explored by univariate (Spearman correlation coefficient) and multivariate linear regression, and intra-class correlation between PGA and joint and skin patient assessments was calculated.

**Results:** Among 223 patients (mean age 51.0 (standard deviation, ±13.3) years, mean disease duration 9.9 (±10.1) years, mean swollen joint count 4.1 (±5.1), 84.3% with current psoriasis (mainly of less than 5% body surface area)), 51.1% were females. Mean patient assessment values were for PGA 4.8 (±2.7), joint patient assessment 5.6 (±2.5) and skin patient assessment 4.1 (±3.0). Multivariate linear regression indicated that PGA was well explained (R2 of model 0.754) by (β = 0.287); pain (β = 0.240); work and/or leisure activities (β = 0.141); and anxiety (β = 0.109). Intra-class correlation between PGA and joint or skin patient assessment was respectively 0.71 [95% confidence interval, 0.64–0.77] and 0.52 [95% confidence interval, 0.42–0.60].

**Conclusion:** PGA in PsA is explained by coping, then as expected physical aspects of impact which may reflect joint involvement: pain and work/leisure activities; and psychological impact: anxiety. In this population, skin related issues were not additional explanatory elements of PGA in multivariate analysis. Finally, joint patient assessment may be redundant with PGA whereas skin patient assessment gives additional information in characterizing the disease and its impact.

**References**


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**59 Assessing Dietary Habits in a Large Cohort of Rheumatoid Arthritis and Psoriatic Arthritis Patients: Results of the Spanish Imid Consortium.**

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be also interesting to study if these factors could contribute to disease. Consumption of several foods have been observed. Fruit, fish, pasta, rice, potatoes, dairy products, sausage and sweets. Certain foods: fresh fruit, meat, fish, legumes, vegetables, pasta, rice, bread, dairy products, sausage and sweets.

**Results:** From a total number of 3,941 patients surveyed n=3,229 patients were included in the present study: n=1,128 (65%) had Rheumatoid arthritis and n=1,128 (35%) Psoriatic arthritis. The proportion of women was 77% in RA patients and 47% in PsA patients. We observed that the mean number of days per week eating fish and fruit was significantly higher in RA patients (3.41 vs 3.22; P=7x10E-3). In this group, the mean of vegetable weekly intake was 4.23 days and in PsA group was 3.97 days (P=6x10E-4). Dairy products consumption was also significantly higher in RA than in PsA patients (5.89 vs 5.62; P=3x10E-5). Among PsA patients the mean number of days per week of intake meat, sausage and sweets was significantly higher comparing to RA patients (3.17 vs 2.72; P=3x10E-13, 2.02 vs 1.58; P=9x10E-10), (2.56 vs 2.72; P=5x10E-3).

**Conclusion:** In our large cohort of patients we describe for the first time the dietary habits differences between rheumatoid arthritis and psoriatic arthritis patients in Spanish population. Significant differences in the consumption of several foods have been observed. Fruit, fish, pasta, rice, potatoes and vegetables were the group of ingredients that RA patients intake more days per week; while meat, sausage and sweets are eaten more often in PsA patients. Our findings could provide insights about the possible implication of dietary factors in the development and progress of these diseases. It will be also interesting to study if these factors could contribute to disease prevention strategies.


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**Epidemiology of Polymyalgia Rheumatica in Korea.** In young Kim, Seulee Lee, Hemin Jeong, Hyungmin Kim, Jiwon Hwang, Jaejoon Lee, Eun-Mi Koh and Hoon-Suk Cha. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

**Background/Preparation:** Polymyalgia Rheumatica (PMR) is a chronic inflammatory disease affecting people older than 50 years. Diagnosis is made based on clinical features and the current standard of treatment is low-dose glucocorticoids. PMR is known to be more frequent in Caucasian ethnicity and females. But up to date, there has been a scant epidemiologic study of PMR in Asian countries including Korea. We aimed to estimate incidence and prevalence rates of PMR and current treatment state in Korea.

**Methods:** We performed nationwide retrospective review of PMR using the Korean National Health Insurance (NHI) and Health Insurance Review and Assessment (HIRA) database from 2007 to 2012. NHI is the sole public medical insurance system in Korea, which covers 100% of the Korean population and HIRA is a government incorporated organization to build an accurate claims review and quality assessment system for the NHI. We defined PMR cases by both diagnostic codes and medication codes simultaneously, in other words, by proper ICD code (M 35.3) and concurrent appropriate prescription codes (glucocorticoids).

**Results:** We identified total 1,463 newly diagnosed cases of PMR for the 5 years. The annual incidence rate of PMR per 100,000 Korean individuals was estimated as 2.06 (1.45 in male, 2.59 in female), and the prevalence rate was 3.92 (2.65 in male, 5.10 in female). Among the 1,463 cases, 992 (67.8%) were female and 471 (32.2%) were male and the median age at the time of diagnosis was 67 years old. The incidence rate according to age appeared to increase with advancing age peaking 70 years old, as similar as previous reports of western studies. The most frequently prescribed agent was prednisolone, and the starting daily dosage of glucocorticoids as prednisolone equivalent was between 5 to 15 mg daily in 74.5 % of the patients.

**Conclusion:** This is the first study that evaluated epidemiologic data of PMR in Korea, and included population was the largest among those of studies published in East Asia so far. The incidence and prevalence rates of PMR are estimated considerably lower than that of Western populations. And this result supports that both genetic and environmental factor would play important roles in pathogenesis of PMR.

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**Advocating for Pediatric Rheumatology Care in the Mid-Canadian Provinces: Large Geographic Area, Large Pediatric Population, Low Number of Pediatric Rheumatologists and Allied Health Workers Identification as Unique Challenges.** Paivi Miettinen, Nadia Luca, Susanne Benseler, Janet Ellsworth, Tommy Gershman, Nicole Johnson, Henriette Schmeling and Natalie J. Shiff.

**Background/Purpose:** Protecting the health and well-being of children with rheumatologic disease is the responsibility of pediatric rheumatologists (PRs) and allied health workers (AHWs). The considerable geographic and clinical distances in the Mid-Canadian provinces (MC) provide a unique challenge for this practice. Our objective was to collect and report data for pediatric population, number of pediatric rheumatologists, patient diagnoses, wait times, allied health support and pediatric rheumatologists’ work-life balance in MC provinces.

**Methods:** Canadian 2012 Statistical data was used to identify population between 0–14 years (Defined as “children” by Statistics Canada) in MC provinces. A survey monkey was sent to each MC pediatric rheumatology center to identify 1) the number of pediatric rheumatology full time equiva-
lents (FTEs) per province for clinical care, education, research and adminis-
tration; 2) Distribution of pediatric rheumatology diagnoses and wait times, and 3) perceived work-life balance of participants.

**Results:** All 3 currently active pediatric rheumatology centers in MC provinces responded (2 in Alberta and 1 in Saskatchewan). Total pediatric
MC population aged 0–14 years (% of all Canadian) was 1.1 million (21.4%). There were a total of 7.7 FTEs pediatric rheumatologists: 5.7 in Alberta (0.7 at one center, 5 at the other), 2 in Saskatchewan and 0 in Manitoba, Nunavut and Northwest Territories. Out of 7.7 FTEs, 4.74 were devoted to for clinical care, 1.08 for education, 3.58 for research and 0.8 for administration. Night-time on-call service frequency varied from “not mandatory” to 1.5. Allied health support was variable: nursing, physiotherapy and occupational therapy were available at 23 centers, 1/3 center had a social worker and a pharmacist, and 0/3 center had a psychologist. Individual outpatient data was available for Alberta and Saskatchewan and included 1225 active outpatients. The most common diagnoses (% total) were juvenile idiopathic arthritis (65–82%), systemic lupus erythematosus (4–6%), auto-inflammatory disorders (3–7%) and vasculitis (2–4%). Wait time data was available for Saskatchewan and Alberta and ranged from 1 to 8 weeks for patients classified as “urgent” and from 2 weeks to 6 months for “semi-urgent”. One center was not able to schedule routine patients. Regarding wellness, 30% of responders reported their work and personal lives were “well balanced”, 50% “struggled occasionally”, 40% reported adverse impact on personal life and non-clinical work activities, and 60% reported their family/friends had commented on their “stress levels”.

**Conclusion:** The MC provinces provide a unique challenge for provision of pediatric rheumatology care due to the vast geographic area and high proportion of children and low numbers of pediatric rheumatologists. Currently 3 out of 5 provinces are without a pediatric rheumatologist. The small number of residents in some centers resulted in unequal wait-times, and had an adverse impact on physician wellness. Our results underline a need for a network/collaboration to help address pediatric rheumatology care in these provinces.

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### Severe Spine Osteoarthritis in Older Men Is Associated with the Risk of Incident Fragility Fracture

Roland Chapurlat1, Charline Estublier2 and Pawel Szulc3.

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**Background/Purpose:** Data on the association of osteoarthritis (OA) with bone fragility are limited. In particular, data on the fracture risk in older men with spine OA are scarce. Our aim was to study the association of baseline severity of spine OA with bone mineral density (BMD), bone loss and risk of fragility fracture in a prospective study of a cohort of older men.

**Methods:** Men aged >50 (n=766) had lateral spine radiographs at baseline. Spine OA was assessed by Lane’s score (J Rheumatol, 1993). We calculated the total osteophyte score by adding up osteophyte scores for 6 intervertebral levels. We calculated total disc narrowing score (DSN) and total overall grade score similarly. BMD was measured by DXA using a Hologic QDR1500 device. Abdominal aortic calcification (AAC) was assessed by Kauppi’s semiquantitative score (Atherosclerosis, 1997). Men were followed-up for 7.5 yr to assess bone loss (every 18 mo) and incident vertebral fractures. Incidence peripheral fractures were assessed for 10 yr.

**Results:** Moderate and severe osteophytes were found in 85% of men, 72% of men had DSN. After adjustment for age and weight, BMD (hip, forearm, whole body) was 2–7% higher (p<0.05 to <0.001) in men with severe spine OA in comparison with men with or without mild spine OA. For instance, men with severe DSN (total score >4, highest quartile) had 5% (0.4SD, p<0.001) higher total hip BMD compared with men without DSN. The rate of bone loss did not differ according to the severity of spine OA regardless of the measure of the spine OA (DSN, osteophytosis) and regardless of the skeletal site (p>0.4).

During the follow-up, 27 men sustained radiographic vertebral fractures. After adjustment for age, BMI, lumbar spine BMD, AAC, prior falls and fractures, risk of vertebral fracture increased with the DSN severity (HR: 1.15 per increase by 1 unit, 95%CI: 1.01–1.31, p<0.05). In this multivariable model, the risk of vertebral fracture was higher in the highest quartile of total DSN score vs. the three lower quartiles combined (HR=2.47, 95%CI: 1.04–5.86, p<0.05). During the follow-up, 61 men sustained non-vertebral fragility fractures. The incidence of non-vertebral fracture was lower above the median of total DSN score (4.6 vs 10.2%, p<0.005). After adjustment for the confounders (including hip BMD and leg disability), the risk of peripheral fracture was lower in men above the median total DSN score vs. below the median (HR=0.44, 95%CI: 0.24–0.80, p<0.01). Other measures of spine OA were not associated with the risk of fracture.

**Conclusion:** Men with severe spine OA have fewer non vertebral fractures but more vertebral fractures. This may be due to better bone quality but abnormal spine biomechanics.

Disclosure: R. Chapurlat, None; C. Estublier, None; P. Szulc, None.

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### Spine Osteoarthritis Is Associated with All Cause Mortality in Older Men

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**Background/Purpose:** Hip and knee osteoarthritis (OA) was associated with higher cardiovascular morbidity and mortality. Data on the cardiovascular status in men with spine OA are scarce. We assessed the association of spine OA with all cause mortality and with abdominal aortic calcification (AAC) severity and its progression rate in older men.

**Methods:** Men aged ≥50 (n=766) had lateral spine radiographs and blood collection and were followed-up prospectively. Spine OA was assessed by Lane’s score (Lane et al., J Rheumatol, 1993). We calculated the total osteophyte score by adding up osteophyte scores for 6 intervertebral levels. We calculated total disc narrowing score (DSN) and total overall grade score similarly. AAC was assessed by Kauppi’s semiquantitative score (Atherosclerosis, 1997). We assessed the association of spine OA with all cause mortality (10 years), AAC severity and AAC progression (7.5 years).

**Results:** Moderate and severe osteophytes were found in 85% of men, 72% of men had DSN. During the follow-up, 176 men died. After adjustment for confounders, men who had both severe AAC (AAC ≥2) and severe OA (total overall grade score >8, highest tertile) had higher mortality than the reference group (AAC score ≤2 and total overall grade score ≤8): 51.8 vs 10.3 /1000 person-years; HR=2.30, 95%CI: 1.34–3.96, p<0.005).

After adjustment for confounders, the odds of severe AAC (AAC >5) increased with total DSN score (HR= 1.44 per SD increase, 95% CI: 1.11–1.87, p<0.05). The highest tertile of total DSN score was associated with higher odds of severe AAC (adjusted HR = 2.42 versus two lower tertiles combined, i.e. >3 vs 0–3, 95% CI: 1.24–4.73, p<0.005). Finally, probability of long-term AAC stability decreased with increasing total osteophyte score (adjusted HR = 0.66 per SD, 95% CI: 0.49–0.88, p<0.05). The highest tertile of total osteophyte score ( >10) was associated with lower probability of AAC stability (adjusted HR = 0.35 versus the lowest tertile, i.e. 0–6, 95% CI: 0.18–0.71, p<0.01).

OA therapy (non-steroidal anti-inflammatory drugs, analgesics) had no impact on the results of all the above analyses.

**Conclusion:** Older men with severe spine OA have greater AAC severity, faster AAC progression and higher all-cause mortality. Higher mortality may be partly mediated by lower physical activity and metabolic abnormalities.

Disclosure: C. Estublier, None; R. Chapurlat, None; P. Szulc, None.

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### Effect of Family Support on Short- and Intermediate Term Pain and Function Outcomes after Knee or Hip Replacement

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**Background/Purpose:** Patients who undergo total knee replacement (TKR) and total hip replacement (THR) need significant help in the immediate post-operative period, when discharged to home. Limited or no data are available regarding the impact of family support on short and intermediate term pain and function outcomes after THR or TKR.

**Methods:** A subset of patients from a national joint registry undergoing primary TJR between 5/2013 and 6/2014 were queried patients at 2- and 8-weeks regarding pain severity and level of family support, assessed with validated single-item (0–10; 10= highest family support) and dichotomized, as previously into deficient (scores 5 or less) or non-deficient family support.
Frequency distributions were used to describe the cohort; bivariate statistical tests to compare groups included the chi-square, Fisher’s exact, t tests and Wilcoxon-Mann-Whitney test.

**Results:** There were 1,502 primary TKR or primary THR respondents at 2-weeks and 1,514 respondents at 8-weeks. 1,416 patients reported good level of family support and 86 reported deficient family support (level 5 or less; 5.7%) on the 2-week survey, 1,418 reported good family support 96 reported deficient family support (6.3%) on the 8 week survey. Patients with higher family support were more likely to be males (41% vs. 31%), and less likely to have income <$45K (25% vs. 43%).

At 2-weeks, compared to patients with non-deficient family support (scores 6–10), those with deficient family support had significantly higher levels of pain severity (3.9 vs. 3.2), pain frequency (4.6 vs. 3.2) and lower levels of satisfaction with pain control (0.68 vs. 0.83), treatment satisfaction (5.6 vs. 6.0) and participation in decision-making (6.9 vs. 8.1). At 8-weeks, similar differences were noted; significantly higher levels of pain severity (2.5 vs. 1.8), pain frequency (4.4 vs. 2.9) and lower levels of current satisfaction with pain control (0.71 vs. 0.83), treatment satisfaction (5.4 vs. 6.0) and participation in decision making (6.9 vs. 8.4).

**Conclusion:** To our knowledge, this is the first study examining the association of family support with pain and other outcomes after TKR and THR. A positive association of non-deficient family support with better pain and satisfaction outcomes is a novel finding. Further research into how to translate these findings into improved outcomes after TKR/THR for those with deficient family support are needed.

**Disclosure:** J. Singh, Savi dent, 2. Takeda, 2. Degen eron, 5. Allergan, 5. K. G. Saag, None; C. Lemay, None; J. Allison, None; P. D. Franklin, None.

### 65 Impact of Dropout and Total Knee Replacement on Joint Space Narrowing Estimation: Data from Osteoarthritis Initiative

#### Background/Purpose:
Structural progression in knee osteoarthritis (OA) is often measured by Joint Space Narrowing (JSN). In longitudinal studies, it is common for subjects to drop out by the end of follow-up. In OA, subjects might undergo total knee replacement (TKR), and consequently drop out of a study evaluating structural progression. Our objective was to estimate the impact of dropout due to TKR on estimates of structural progression in OA and investigate whether information about TKR could be used to improve these estimates.

#### Methods:
We used data from the Osteoarthritis Initiative (OAI), a multicenter, longitudinal, observational study of knee OA. We selected knees with radiographic, symptomatic OA at baseline (KL ≥ 2, WOMAC Pain >0), selecting the knee with the worst pain for subjects with two knees with OA. We compared the estimate of change in JSN over time in persons who did and who did not undergo TKR. Further, we estimated JSN without taking into account dropout and compared to the model that took into consideration time of the dropout and timing of TKR among those that underwent TKR.

#### Results:
We used data from 2,058 subjects with radiographic, symptomatic knee OA at baseline. 377 subjects (18%) dropped out before the 48 month visit; 231 dropped out and did not undergo TKR while 146 underwent TKR. Among those who had TKR, they were distributed evenly between 24, 36 and 48 months visits. The estimates of annual joint space narrowing ranged from 0.116 mm for those who completed the 48 month follow up to 0.28 among those who had TKR between baseline and 24 months visit (Table). Additional analyses showed that not accounting for dropout and TKRs led to underestimation of JSN (0.46 mm over 4 years) compared to the estimated of joint space narrowing using the model that took into consideration both timing of dropout and timing of TKR (0.276 mm over 4 years).

#### Conclusion:
In longitudinal studies restricting analysis to ‘completers’ may lead to underestimation of structural changes. Subjects with OA who drop out of the study to undergo TKR tend to have much more pronounced structural progression. Investigators studying disease progression in OA should consider the potential impact of dropout due to TKR, particularly when a large proportion of subjects undergo the procedure.

**Table.** Annual JSN stratified by dropout and timing of TKR

<table>
<thead>
<tr>
<th>Group</th>
<th>Annual JSN/mm</th>
<th>% of cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dropout/No TKR</td>
<td>−0.116</td>
<td>82.0%</td>
</tr>
<tr>
<td>Dropout/No TKR</td>
<td>−0.129</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

### 66 Association of Knee Osteoarthritis and Limitations in Physical Function in a Rural Chinese Population: The Wuchuan OA Study

#### Background/Purpose:
To our knowledge, this is the first study examining the association of knee osteoarthritis (OA) causes more limitations in physical function than other chronic conditions in Caucasians. Knee OA is known to be more prevalent among Chinese than among Caucasians. However, little is known about the effect of knee OA on physical function among Chinese living in rural areas.

#### Methods:
Wuchuan OA Study was a population-based cohort study conducted in the rural areas of Wuchuan, Inner Mongolia of China. Subjects completed a baseline home-interview in 2005, including knee symptoms and 8 physical function questions on daily-living activities (e.g., walking, going up or down stairs, bending or kneeling, chair standing, preparing meals, cleaning house, making beds, getting up bed) with 1: no difficulty, 2: some difficulty, 3: very difficult, and 4: unable to do. Subjects had bilateral weight-bearing posterior-anterior and patellar skyline radiographs taken. Whole radiographic knee OA (ROA) was defined as either tibiofemoral KL score ≥2 or presence of patellofemoral OA. Symptomatic OA (SxOA) was defined as presence of both ROA and knee pain for most days in the last month. We identified distinct groups of limitation in physical function based on subject’s response to each of 8 physical function questions using a latent class model (SAS PROC LCA) and examined the relation of ROA and SxOA to the latent groups of limitation in physical function adjusting for potential confounders.

#### Results:
Among 1025 subjects of Wuchuan OA study (men: 49.3%, mean age: 56.4 years, mean BMI: 22.4 kg/m²), prevalence of knee ROA and SxOA was 17.7% and 6.2%, respectively, at baseline. For KL grading, the weighted kappa for inter-rater reliability was 0.80 (95% confidence interval (CI): 0.72–0.88) and the intra-rater reliability was 0.92 (95% CI: 0.86–0.99). We identified 4 distinct physical function groups: no limitation (n=543, 53.0%), mild limitation (n=252, 24.6%), moderate limitation (n=128, 12.5%), and severe limitation (n=102, 9.9%). Worse limitation was characterized by increasing difficulty in performing 8 daily-living activities. The mean posterior probability of subgroup assignment was 0.90, suggesting a good-fit of model Compared with those without knee ROA, multivariable adjusted odds ratios (OR) of no, mild, moderate and severe limitation in physical function among subjects with ROA was 1.6 (1.0, 2.5), 1.9 (1.1, 3.3) and 3.3 (1.9, 5.7), respectively. Association of SxOA with limitation in physical function was even stronger, with ORs being 1.0, 2.7, 3.6, and 11.3, respectively, for each increasing difficulty on activity limitations.

#### Conclusion:
Knee OA was strongly associated with limitation in physical function among people in rural areas of China. Knee OA is likely to become a major public health problem given the limitation in physical function associated with this disease among Chinese elderly.

**Table.** Knee OA Status by Physical Function

<table>
<thead>
<tr>
<th>Knee OA Status</th>
<th>No</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ROA (N=844)</td>
<td>57.2</td>
<td>24.2</td>
<td>11.6</td>
<td>7.0</td>
</tr>
<tr>
<td>ROA (N=181)</td>
<td>33.2</td>
<td>26.5</td>
<td>16.7</td>
<td>23.8</td>
</tr>
<tr>
<td>OR (95% CI)*</td>
<td>1.0</td>
<td>1.6 (1.0, 2.5)</td>
<td>1.9 (1.1, 3.3)</td>
<td>3.3 (1.9, 5.7)</td>
</tr>
<tr>
<td>No SxOA (N=962)</td>
<td>55.4</td>
<td>24.7</td>
<td>12.2</td>
<td>7.7</td>
</tr>
<tr>
<td>SxOA</td>
<td>15.9</td>
<td>22.2</td>
<td>17.5</td>
<td>44.4</td>
</tr>
<tr>
<td>OR (95% CI)*</td>
<td>1.0</td>
<td>2.7 (1.2, 6.3)</td>
<td>3.6 (1.5, 8.9)</td>
<td>11.3 (4.9, 25.7)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, years of education, annual income, physical activity, and number of comorbidities

**Disclosure:** J. E. Collins, None; E. Losina, None.

**Acknowledgement:** This research was supported by grants from National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR064138), and the National Rheumatism Research Council of China (T201102). The authors would like to thank the staff and participants of the Wuchuan OA Study for their contributions. The authors would also like to thank the staff of the Osteoarthritis Initiative for their assistance with data collection and management.
Effects of Exercise on Depressive Symptoms in Adults with Arthritis: A Systematic Review with Meta-Analysis. George A. Kelley1, Kristi S. Kelley2 and Jennifer Hootman3. 1West Virginia University, Morgantown, WV, 2Centers for Disease Control and Prevention, Atlanta, GA.

Background/Purpose: Previous randomized controlled trials have led to conflicting findings regarding the effects of exercise on depressive symptoms in adults with arthritis and other rheumatic diseases (AORD). The purpose of this study was to use the meta-analytic approach to try and reach some general conclusions regarding these discrepancies.

Methods: The a priori inclusion criteria were: (1) randomized controlled trials, (2) aerobic (aerobic strength training, or both) (>7 days per week), (3) comparative control group, (4) adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus, (5) published and unpublished studies in any language since January 1, 1981, (6) depressive symptoms assessed. Studies were located by searching 10 electronic databases, cross-referencing, hand searching and expert review. Dual selection of studies and data abstraction were performed. Hedge’s standardized effect size (g) was calculated for each result and pooled using random-effects models, an approach that accounts for heterogeneity. Non-overlapping 95% confidence intervals (CIs) were considered statistically significant. Heterogeneity based on fixed-effect models was estimated using Q and I² with alpha values <=0.10 for Q considered statistically significant. Small-study effects were examined using funnel plots and Egger’s regression test, with adjustment for statistically significant results (non-overlapping one-tailed 95% confidence intervals). In addition, a meta-regression models were performed on small-study effects, improving the NNT. The NNT was increased to 15 while percentile improvements were reduced to 7.4%. All studies were considered to be at high risk of bias with respect to blinding of participants and personnel to group assignment. Given the lack of information provided, greater than 15% of the studies were at an unclear risk of bias with respect to (1) incomplete outcome reporting (86%), (2) allocation concealment (86%), (3) blinding of participant and personnel to group assignment. None of the 565 adults who were inactive at baseline, 141 (25%) became active (but insufficient to meet guidelines) while 15 (2.7%) became active enough to meet activity guidelines. Over two years, this group of adults characterized by baseline inactivity on average had worse function compared to baseline levels. However, people who became more active over two years compared to those who remained inactive lost gait speed (2.6 versus 6.1 loss in feet/second), had improved chair stand (0.6 gain versus 1.0 loss repetitions/minute) and had less decrease in WOMAC function (0.7 versus 1.0 loss). This functional benefit remained after accounting for other modifiable and descriptive covariates. All results were calculated using the Cochrane Risk of Bias Assessment Instrument. Training program characteristics were reported as mean +/- standard deviation.

Results: Of the 500 studies screened, 2,449 participants (1,470 exercise, 979 control) from 29 studies met the criteria for inclusion. Length of training averaged 19.1 +/- 16.0 weeks, frequency 3.6 +/- 2 times per week and duration 33.6 +/- 16.9 minutes per session. Overall, statistically significant exercise minus control group improvements were found for depressive symptoms (g = -0.41, 95% CI, -0.58, -0.24, Q = 196.2, p<0.0001, I² = 82.7%). The NNT was 8 with percentile improvements of 16.0%. Overlapping 95% PI (1.33, 0.50) were observed. When adjusted for statistically significant small-study effects, improvements were reduced by 54.7% but remained statistically significant (g = -0.19, 95% CI, 0.37, -0.003). The NNT increased to 15 while percentile improvements were reduced to 7.4%. All studies were considered to be at high risk of bias with respect to blinding of participants and personnel to group assignment. Given the lack of information provided, greater than 30% of the studies were at an unclear risk of bias with respect to (1) incomplete outcome reporting (86%), (2) allocation concealment (86%), (3) blinding of participant and personnel to group assignment. None of the 565 adults who were inactive at baseline, 141 (25%) became active (but insufficient to meet guidelines) while 15 (2.7%) became active enough to meet activity guidelines. Over two years, this group of adults characterized by baseline inactivity on average had worse function compared to baseline levels. However, people who became more active over two years compared to those who remained inactive lost gait speed (2.6 versus 6.1 loss in feet/second), had improved chair stand (0.6 gain versus 1.0 loss repetitions/minute) and had less decrease in WOMAC function (0.7 versus 1.0 loss). This functional benefit remained after accounting for other modifiable and descriptive covariates. All results were calculated using the Cochrane Risk of Bias Assessment Instrument. Training program characteristics were reported as mean +/- standard deviation.

Conclusion: While this inactive group of individuals on average lost function over two years, those who increased their activity lost less function compared to those who remained inactive. Promoting increased physical activity, even to levels not meeting DHHS guidelines, may help inactive persons with arthritis minimize loss of function.

Table: Increased activity versus remaining inactive two-year function loss among adults with/ at high risk for knee OA who were inactive at baseline

Disclosure: G. A. Kelley, None; K. S. Kelley, None; J. Hootman, None.

Physical Inactivity to Activity Associated with Less Decline in Physical Function. Abigail Gilbert1, Jing Song2, Pamela A. Semanik1, Rowland W. Chang1 and Dorothy D. Dunlop6. 1Northwestern University, Chicago, IL, 2Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Regular physical activity has been demonstrated to improve quality of life for adults with chronic disease including osteoarthritis. Despite these benefits, half of adults with arthritis are inactive. An inactive lifestyle is associated with disability, loss of motion, pain, and stiffness. We analyzed longitudinal data from the Osteoarthritis Initiative (OAI) to evaluate the effect of transitioning from inactive to activity on changes in function over a 2-year follow-up to assess the benefit of increasing physical activity in persons at high risk for disability.

Methods: The Osteoarthritis Initiative enrolled adults who had or were at risk of developing knee osteoarthritis. Longitudinal physical activity accelerometer data were collected on a subgroup at baseline (48 month OAI visit) and at 2 years (72 month OAI visit). We evaluated two-year activity transitions on 565 individuals identified as being inactive at baseline (zero 10 minute bouts of moderate-to-vigorous [MV] intensity physical activity during a week). We examined the relationship of becoming active (that is, a transition from inactive to insufficient activity or inactive to meeting guideline levels [meeting DHHS Guidelines of at least 150 minutes/week MV activity]) versus remaining inactive in relationship to change in function as measured by gait speed, chair stand rate, and WOMAC function. Analyses used multiple regression analysis controlling for baseline modifiable factors (smoking, knee pain, depressive symptoms, and overweight/obesity), and descriptive factors (age, gender, race/ethnicity, education, income, arthritis severity as measured by K-L grade, knee injury, medical comorbidities, hip pain, foot or ankle pain, and chronic knee symptoms).

Results: Of the 565 adults who were inactive at baseline, 141 (25%) became active (but insufficient to meet guidelines) while 15 (2.7%) became active enough to meet activity guidelines. Over two years, this group of adults characterized by baseline inactivity on average had worse function compared to baseline levels. However, people who became more active over two years compared to those who remained inactive lost gait speed (2.6 versus 6.1 loss in feet/second), had improved chair stand (0.6 gain versus 1.0 loss repetitions/minute) and had less decrease in WOMAC function (0.7 versus 1.0 loss). This functional benefit remained after accounting for other modifiable and descriptive covariates. All results were calculated using the Cochrane Risk of Bias Assessment Instrument. Training program characteristics were reported as mean +/- standard deviation.

Conclusion: Exercise may improve depressive symptoms in selected adults with AORD. However, a need exists for additional, well-designed, randomized controlled trials on this topic.

Disclosure: G. A. Kelley, None; K. S. Kelley, None; J. Hootman, None.

Assessment of Exercise Status in Routine Care Using Patient Reported Outcomes: Initiating Exercise Is Associated with Better Outcomes Than No Exercise. Isabel Castro-Rojas1, Selda Celik7, Theodore Pincus7 and Yusuf Yazici7. 1Rush University Medical Center, Chicago, IL, 2NYU School of Medicine, New York, NY, 3New York University School of Medicine, New York, NY.

Background/Purpose: Extensive evidence indicates major benefits of exercise in rheumatoid arthritis7 and many other rheumatic diseases,7 not only for cardiovascular and general fitness, but also for better rheumatologic clinical status. Most reported exercise data are derived from structured research studies rather than from usual care. A multidimensional health assessment questionnaire (MDHAQ) designed for usual care includes a query concerning exercise status for the rheumatologist to analyze possible associations with clinical outcomes. The objective of this study was to compare baseline demographic and clinical data and changes in status over 1 year, in patients classified into 4 categories according to the level of exercise.

Methods: Each patient seen at an academic rheumatology setting completes an MDHAQ at each visit while waiting to see the rheumatologist. The MDHAQ includes scores for physical function, pain, patient global estimate (PAGTL), and RAPID3 (Routine Assessment of Patient Index Data), an index of these 3 measures, each scored 0–10; total = 30. Patients were classified into 4 groups according to exercise 3 times a week at baseline and 1 year: EX at baseline & 1 year later, no EX at baseline but EX 1 yr later, EX at baseline but no 1 yr later and no EX at baseline or 1 yr later. Mean baseline data and percentage change from baseline to 1 year were analyzed and compared by analysis of variance (ANOVA), with multivariate adjustment
Results: 795 patients, including 221 with RA, were classified into 4 exercise groups: EX at baseline & 1 year later, no EX at baseline but EX 1 yr later, EX at baseline but no 1 yr later and no EX at baseline or 1 yr later. Patients doing exercise at baseline were younger with a higher level of education than the NO exercise group (data not shown). Patients reporting no exercise at baseline and exercise 1 year later had greater improvement in scores than those in all other groups. Patients reporting exercise at baseline but not 1 yr later were the only group with poorer status. A potential limitation for our study is that it was unknown if change in exercise status preceded or resulted from change in clinical status.

RAPID3 (0–10) participants who reported exercise at baseline but not at year later had significantly higher MDHAQ-PN scores than those in all other groups. Patients reporting exercise at baseline but not at year later had significantly higher MDHAQ-PN scores than those in all other groups. Patients reporting exercise at baseline but not at year later had significantly higher MDHAQ-PN scores than those in all other groups.

Conclusion: Exercise 3 times a week is associated with better clinical status. The best status was seen for patients who report no EX at baseline but performing EX 1yr later while poorest status was seen in patients reporting exercise at baseline but no 1 yr later. Regular exercise may be of therapeutic relevance in the management of rheumatic diseases by reducing pain and improving physical function. This clinically relevant information concerning exercise is available on MDHAQ for routine care settings.

References:

Disclosure: I. Castrejon, None; S. Celli, None; T. Pincus, None; Y. Yazici, Celgen, BMS, genentech, 2.

The Odds of Work Disability, Unemployment and Depending on Living Allowances Are More Influenced By the Number of Morbidities Than By the Presence of a Musculoskeletal Disease. Antje van der Zee-Neuen, Polina Putrik*, Sofia Ramiro, Andreas Keszei, Rob de Bie, Astrid M. Chorus* and Annelies Boonen*, 1Maastricht University, Maastricht, Netherlands, 2Aarhus University Clinical Center, Aarhus, Denmark, 3University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: The prevalence of multimorbidity (≥2 chronic morbidities in 1 person), is increasingly common also in patients at working age. Musculoskeletal diseases (MSKD) are among the most frequently occurring chronic diseases and comorbidities. However, little is known about the association of multimorbidity with official work disability and even less about its association with economic unemployment or dependence on living allowances (LA). Also, the additional influence of MSKD as comorbidity is unclear. We aimed to explore 1) whether an increasing number of morbidities is associated with increased odds to be work disabled (WD), unemployed or depending on LA & 2) whether presence of MSKD is associated with these outcomes or has an important additional contribution when combined with other morbidities.

Methods: In a Dutch epidemiological study, 8904 subjects (≥18 years old) completed a questionnaire on socio-demographic and lifestyle factors, self-reported physician-diagnosed diseases & work status. Persons at working age (18–65 years) who were either employed, formally WD, economically unemployed or receiving LA were included in the analyses (n=5396). Two multimonial regression models were computed with work status (i.e. employed, WD, unemployed or LA) as outcome and adjusted for age, gender, education, body mass index and smoking status. In model 1 the number of morbidities was the independent variable of interest and in model 2 either the single diseases (distinguishing MSKD from all other single diseases) or combinations of 2 or ≥3 diseases, including and excluding MSKD. Paid employment was used as reference outcome and estimates were compared to the healthy.

Results: MSKD occurred in 925 cases (17%) of the sample. Multimorbidity was present in 755 cases (14%). Of all cases with 2 morbidities 265/490 (54%) reported a MSKD. In cases with ≥3 morbidities 198/265 (75%) reported a MSKD. The odds to be WD increased steeply with every additional morbidity and the same trend but less pronounced was seen for unemployment and dependence on a LA (Table 1). Small (but no significant) increments were seen when looking the role of MSKD in multimorbidity (e.g. the odds to be WD were 9.2 times higher than to be employed for persons suffering from 2 morbidities including MSKD and these odds were somewhat lower (8.8) when none of the 2 morbidities was MSKD). The odds to be unemployed or to receive a LA were slightly (but not significantly) higher for persons suffering from 2 co-occurring morbidities when 1 of these was a MSKD compared to 2 co-occurring morbidities without MSKD. (Table 1)

Conclusion: An increasing number of morbidities is associated with increased odds of WD, and to a lesser extent also with unemployment and dependence on a LA. There is a small additional adverse influence of the co-occurrence of MSKD in those suffering from 2 morbidities on all work outcomes. Multimorbidity requires more attention in considering patients’ work outcome.

Table 1 Association of multimorbidity and combinations with and without MSKD with employment status

<table>
<thead>
<tr>
<th>Number of morbidities</th>
<th>OR [95% CI]</th>
<th>Type of morbidities</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 morbidities (no MSKD)</td>
<td>1.36 (0.91; 2.02)</td>
<td>1 morbidity (MSKD)</td>
<td>1.32 (0.73; 2.31)</td>
</tr>
<tr>
<td>≥3 morbidities (no MSKD)</td>
<td>2.43 (1.31; 4.51)</td>
<td>2 morbidities (MSKD)</td>
<td>2.00 (0.83; 4.79)</td>
</tr>
<tr>
<td>≥4 morbidities (no MSKD)</td>
<td>3.08 (1.81; 5.14)</td>
<td>≥3 morbidities (MSKD)</td>
<td>2.31 (1.62; 3.25)</td>
</tr>
</tbody>
</table>

Disclosure: A. van der Zee-Neuen, None; P. Putrik, None; S. Ramiro, None; A. Keszei, None; R. de Bie, None; A. M. Chorus, None; A. Boonen, None.

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Background/Purpose: Very large epidemiological studies designed to investigate genetic and environmental influences on disease, known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes. Known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes. Known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes. Known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes. Known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes. Known as ‘biobanks’ can be used to look at associations between rare exposures and health outcomes.

Methods: UK Biobank recruited 0.5 million people across Great Britain. Participants attended assessment centers and answered questions on health and lifestyle by touch-screen questionnaire. They were asked “In the last month have you experienced any of the following that interfered with your usual activities?” and could indicate: headache, face pain, neck/shoulder pain, back pain, abdominal pain, hip pain, knee pain, or pain all over. For each positive answer, participants were asked if the pain had lasted at least 3 months, which was defined as chronic. Questions were also asked on gender, age, ethnicity, income, employment status, adverse life events and mental health. Self-reported ethnicity was classed as white, mixed, south Asian, south East Asian, south west Asian, middle east Asian, north west Asian, African, mixed, black African, Indian, Pakistani, Bangladeshi, Chinese, East Asian, south east Asian, south east Asian, south east Asian.
black, Asian (Chinese), or other. Life events recorded were: serious illness, injury, or death to a partner or close relative, marital separation, and financial difficulties. Mental health included mood swings, feelings of guilt and loneliness, and being tense. Prevalence of any pain, chronic pain, and regional pain was calculated for each ethnic group, standardized to age/gender structure in the UK 2011 Census. Risk ratios adjusted for age and sex with 99% confidence intervals were calculated using white as the referent group. Risk ratios for any pain and chronic pain were adjusted for income, employment status, life events, and mental health.

**Results:** Pain questions were answered by 498,071 participants between the ages of 40 and 69. Compared to the white group (prevalence 60.3%), persons identified as mixed (66.3%), south Asian (71.8%), black (70.2%), or other (71.5%) were more likely to report pain (see table). Relationships were similar for chronic pain, although less strong. Asian (Chinese) were more likely to report pain (61.0%) and less likely to report chronic pain. After adjustment for potential confounders differences to groups remained but were smaller. Excess prevalence of regional pains was observed for all groups compared to whites apart from Asian (Chinese), who were more likely than whites to report neck or shoulder pain, and less likely to report hip and facial pain.

**Conclusion:** This study has shown differences in pain reporting according to self-reported ethnicity. These are partly explained by socio-economic and psychosocial factors, and adverse life events. The large numbers of centers in this study means the results are more generalizable compared to those from single center studies. Difference in pain prevalence between groups has implications for allocation of healthcare resources where populations differ.

**Disclosure:** M. Beasley, None; L. Murphy, None; K. A. Theis, None; C. G. Helmick, None; J. Hootman, None; J. A. Stevens, None.

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**Frequency and Risk Factors for Recurrent Falls in Community-Dwelling Elderly: A Population-Based Prospective Cohort Study in Brazil.** Ketty LLI, Machado1, Diogo S. Domiciano, Luana G. Machado, Camille P. Figueredo, Jaquequine B. Lopes, Valéria Caparbo, Lúcia Taubay, Ricardo de H. R. de Carvalho, and Rosa Maria Pereira. 1Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, 2Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 3RDO Diagnosticos Medicos, Sao Paulo, Brazil.

**Background:** Falls are among the leading external causes of mortality and the elderly while their prevalence acquires substantial importance in low-income countries where the population’s aging has been faster. Several clinical factors (including age, drugs and previous fracture) have been identified with increased fall risk. However, few studies performed a concomitant evaluation of clinical data, laboratory bone exams and bone mineral density (BMD) to determine more accurately the contribution of each of these variables to fall risk in community-dwelling elderly. Our aim was to identify the association between bone parameters and falls in a population-based prospective cohort of community-dwelling older adults.

**Methods:** Risk factors for recurrent falls were determined in 705 community-dwelling individuals (448 women and 257 men) aged ≥65 years. Specific questionnaire (clinical data), BMD and laboratory tests — including 25-hydroxyvitamin D (25(OH)D), intact PTH (iPTH) and serum cross-linked C-telopeptide (CTX) were performed at baseline and after a mean follow-up of 4.3±0.8 years. Individuals with recurrent falls (2 or more falls in the last year from the date of the second evaluation) were considered chronic fallers. Potential risk factors for recurrent falls were compared between fallers and non-fallers. Logistic regression models were used to identify independent predictors of recurrent falls.

**Results:** The frequency of chronic fallers was 16.5% (95% CI: 13.8–19.2). In multivariate analysis, independent risk factors for recurrent falls were visual impairment (OR = 2.49, 95% CI 1.10–4.87, p = 0.006), chronic use of hypnotic drugs (OR = 2.47, 95% CI 1.37–4.49, p = 0.003), previous fracture (OR = 2.78, 95% CI 1.48–5.20, p = 0.001), persistently low serum 25(OH)D (<20ng/mL) (OR = 1.71, 95% CI 1.10–2.64, p = 0.020) and other risk factors included sex, age, body mass index (BMI), self-rated health status, physical activity, heart disease, and stroke.

**Disclosure:** K. E. Barbour, None; L. Murphy, None; K. A. Theis, None; C. G. Helmick, None; J. Hootman, None; J. A. Stevens, None.

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**The Association Between Doctor-Diagnosed Arthritis and Falls and Fall Injuries Among Middle-Aged and Older Adults.** Kamil E. Barbour1, Louise Murphy2, Kristina A. Theis3, Charles G. Helmick2, Jennifer Hootman2, and Judy A. Stevens. 1CDC, Atlanta, GA, 2Centers for Disease Control and Prevention, Atlanta, GA, 3Centers for Disease Control and Prevention, Atlanta, GA.

**Background/Purpose:** Falls are the leading cause of injury-related morbidity and mortality among older adults (age ≥65 years), with more than one in three falling each year, resulting in direct medical costs of nearly $30 billion. Arthritis can lead to poor neuromuscular function (i.e., gait speed and balance), a major risk factor for falling. Although the association between arthritis and increased falls risk among older adults is well documented, little is known about arthritis and falls among middle-aged adults (45–64 years).

**Methods:** We analyzed data from the 2012 Behavioral Risk Factor Surveillance System (BRFSS), an annual, random-digit-dialed landline and cellphone survey representative of the noninstitutionalized adult population aged ≥18 years from the 50 states, DC, Puerto Rico, and Guam (n=338,734 respondents age ≥45 years). Respondents were considered to have arthritis if they answered “yes” to, “Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?” They were considered to have fallen if they answered one or more to, “In the past 12 months, how many times have you fallen?” Those reporting one or more falls were also asked, “How many of these falls caused an injury?” By an injury, we mean the fall caused you to limit your regular activity for at least a day or to go see a doctor.” We analyzed number of falls as a categorical (zero, one, or two or more) and binary variable (no falls, one or more falls). Fall injury was categorized as a binary variable (yes or no). Prevalence ratios (PRs) and 95% confidence intervals (CIs) were estimated in log binomial and multinomial regression models which adjusted for age, sex, race, education, body mass index (BMI), self-rated health status, physical activity, heart disease, and stroke.

**Results:** Among middle-aged adults, the prevalence of arthritis, falls, and fall injuries was 33.8%, 25.6%, and 9.7%, respectively, whereas the prevalence among older adults was 53.4%, 27.1%, and 9.6%, respectively. Among middle-aged adults with arthritis, the prevalence of one or more falls, two or more falls, and fall injuries was 1.58 (95% CI: 1.53, 1.63), 1.92 (95% CI: 1.82, 2.02), and 2.10 (95% CI: 1.97, 2.23) times higher compared with middle-aged adults without arthritis. Among older adults with arthritis, the prevalence one or more falls, two or more falls, and fall injuries was 1.38 (95% CI: 1.34, 1.45), 1.69 (95% CI: 1.59, 1.80), and 1.63 (95% CI: 1.52, 1.75) times higher compared with older adults with arthritis.

**Conclusion:** These findings establish the significant relationship between arthritis and falls and fall injuries among middle-aged adults and demonstrate these associations are similar in magnitude to those already recognized among older adults. Rising awareness of falls and fall injuries among middle-aged adults is an important first step in mitigating negative fall consequences in this population. The high burden of falls and fall injuries among middle-aged and older adults with arthritis can be addressed through greater dissemination of arthritis management and fall prevention programs in clinical and community practice.

**Disclosure:** M. Beasley, None; G. T. Jones, None; T. Macfarlane, None; G. J. Macfarlane, None.
and loss of total hip BMD between the two assessments (OR = 1.21, 95% CI 1.17–1.25, p = 0.03 for each 5% decrease).

**Conclusion:** In addition to traditional clinical risk factors for falls, significant loss of total hip BMD and persistently hypovitaminosis D were associated with recurrent falls in Brazilian community-dwelling elderly. In this way, recognizing these factors is essential to recommend preventive actions to reduce recurrence of falls and might improve the health outcomes in this population.

Disclosure: K. L. Machado, None; D. S. Domiciano, None; L. G. Machado, None; C. P. Figueiredo, None; J. B. Lopes, None; V. Caparbo, None; L. Takayama, None; R. M. Oliveira, None; R. M. Pereira, None.

### Table 1.

<table>
<thead>
<tr>
<th>IL1β (−511 A/C)</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 G/G</td>
<td>2.09 (1.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>G/A</td>
<td>1.49 (1.56)</td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>1.45 (1.50)</td>
<td></td>
</tr>
<tr>
<td>DAS≥3.2 Yes</td>
<td>20/31</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>7/43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td>IL6 (−174 G/C)</td>
<td>Patients</td>
<td></td>
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<td>AXIAL G/G</td>
<td>6</td>
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</tr>
<tr>
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<td>MIXED G/G</td>
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<tr>
<td></td>
<td>GC/C/CC</td>
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<tr>
<td>IL1B27 G/G</td>
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<td>46</td>
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<tr>
<td></td>
<td>GC/C/CC</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>0.003</td>
<td></td>
</tr>
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Disclosure: T. Carranco, None; N. Cubino, None; C. Cieza-Borrela, None; I. Calero, None; M. D. Sanchez, None; C. Hidalgo-Calleja, None; A. Quesada, None; A. Plata, None; A. Diaz Alvarez, None; R. Usategui, None; R. Gonzalez, None; C. A. Montilla-Morales, None; J. Del Pino-Montes, None.

### Discussion

- **Influence of the Polymorphism IL1β (−511 A/C) and IL6 (−174 G/C) on the Activity, Radiographic Damage and Clinical Forms of Patients with Psoriatic Arthritis (PSA).**
  - Tatiana Carranco1, Noelia Cubino1, Clara Cieza-Borrela1, Isabel Calero1, Maria Dolores Sanchez1, C. Hidalgo-Calleja1, Alba Quesada1, Agustín Daz Alvarez2, Ricardo Usategui2, Rogelio Gonzalez3, Ca. Montilla-Morales2 and J. Del Pino-Montes2. 1HOSPITAL CLINICO UNIVERSITARIO DE SALAMANCA, SALAMANCA, Spain, 2University of Salamanca Hospital, Salamanca, Spain, 3IBSAL, SALAMANCA, Spain.

  **Background/Purpose:** PSA is a chronic inflammatory disease associated with psoriasis which affects the joints, vertebrae and enthesis. Interleukin-1 is an inflammatory cytokine. A higher expression of IL-1 has been observed in the synovial fluid of patients with PSA. Interleukin-6 promotes synovitis and enhances bone resorption. No studies have analyzed the relation between PSA patients with polymorphisms of IL-1β (−511 A/C) and IL-6 (−174 G/C) and the activity, the presence of erosions or the clinical form of presentation. We relate the polymorphisms of IL-1β (−511 G/A) and IL-6 (−174 G/C) with inflammatory activity, radiographic damage and clinical forms in a group of PSA patients.

  **Methods:** We studied 125 patients diagnosed with PSA according to the CASPAR criteria. The patients were classified depending on whether they presented peripheral, axial or mixed. The activity in the peripheral or mixed forms was measured according to the number of swollen, painful joints, visual analogue scale, ESR and CRP. The DAS 28 index was calculated. For the axial and mixed forms, the BASDAI index, Ankylosing spondylitis and the modified mSASSS were used. In the assessment of radiographic damage we used the sH and mSASSS. All patients underwent an assessment of the polymorphism in the promoter region of IL-1β (−511 G/A) and IL-6 (−174 G/C).

  **Results:** 59.2% of the patients were men. 13 patients showed axial involvement (10.4%), 38 a mixed involvement (30.4%), and 74 a peripheral involvement (59.2%). The distribution and genotype of the polymorphism of IL-1β (−511 G/A), with regard to the number of swollen joints and DAS >3.2 are included in Table 1. In the logistic regression model: DAS >3.2 (p=0.018; OR = 3.46). In the allele analysis, 30.92% of the carriers of the G allele showed DAS over 3.2, compared with 12.5% of the patients with the A allele (OR: 3.13; p=0.0004; 95% CI: 1.43–6.82; adjusted p<0.008). No differences were found regarding the distribution of the polymorphism in the different clinical forms of the disease or the radiographic damage. With regard to the polymorphism of IL-6 (−174 G/C) in the group of G/A homozygous patients, compared with the combined group of G/A and A/A patients, we found differences in the clinical forms of PSA and in the frequency of appearance of HLA-B27 antigen (Table 1). In the logistic regression analysis:

  - types of disease (p=0.007; OR =2.741) and HLA-B27 (p=0.001; OR=0.103). The G allele was not more frequently found in peripheral forms (70.86%) than in mixed forms (57.42%) (OR =1.89; p<0.03; 95% CI: 1.06–3.39; adjusted p<0.05). We did find a lower association of the G allele with HLA-B27 (15.78%) compared with the C allele (28.57%) (OR = 0.469; p=0.02; 95% CI: 0.238–0.923; adjusted p<0.03).

  **Conclusion:** The G allele of polymorphism IL-1β (−511 A/C) was associated with the presence of more inflammatory activity. We found a trend in patients who carried the G allele of the polymorphism IL-6 (−174 G/C) to present with a peripheral form of the disease.

### Methods

- **Four published gene expression data sets containing a total of 91 patients were used to train a classifier to identify anti-TNF non-responders.**
  - Ty Thomson, Reynolds Lescarbeau, David Drubin, David Fryburg, David de Graaf, Renée Deehan, Daphne Lainefield and Aaron Van Hooser. Selvента, Cambridge, MA.

  **Background/Purpose:** The number of biologic therapies approved for use in treating rheumatoid arthritis (RA) has grown steadily over the past 15 years. While many patients are treated with anti-TNF therapies, 30–40% of these patients fail to respond adequately as their disease progressively worsens. Tools to guide disease management and identify a priory which patients are likely to be non-responsive to anti-TNF therapies would allow these patients to seek alternative therapies to achieve faster relief from symptoms, avoid unnecessary treatment side effects, and avoid further disease progression.

  **Methods:** Four published gene expression data sets containing a total of 91 patients were used to train a classifier to identify anti-TNF non-responders. Gene expression measurements, collected prior to patient treatment with the anti-TNF infliximab, were grouped into disease-relevant biological signaling mechanisms to provide a stable, quantitative representation of biological state. Regularized logistic regression was used to train a classifier to identify non-responders, and a classifier score threshold was selected to optimize for detection of non-responders with high specificity.

  **Results:** Repeated 10-fold cross-validation resulted in highly-specific prediction of non-response (specificity = 92%; likelihood ratio = 5.53; area under the receiver operator characteristic curve (AUROC) = 78%; p-value<0.0001; Figure 1), while still correctly identifying a significant fraction of non-responders (sensitivity = 45%). Prediction of non-response on independent infliximab treated cohorts, consisting of an independent 27 patient cohort as well as each of the four training when left out in turn from training, resulted in AUROCs between 63% and 80% and associated p-values between 0.029 and 0.15. Specificity of the classifier for infliximab and its therapeutic target TNF was supported by a lack of association with responses in small rituximab (anti-CD20) and tocilizumab (anti-IL6R) treated cohorts.

  **Conclusion:** The classifier developed in this study identifies RA patients who are unlikely to respond to infliximab, and thus are good candidates for other therapeutic options.
alternative biologic therapies. The test robustly predicts non-response across multiple patient cohorts. Future iterations of the test could include additional training cohorts and expansion to include complementary prediction of response to other RA therapies.

Disclosure: T. Thomson, Selventa, 1, Selventa, 3; R. Lescarbeau, Selventa, 1, Selventa, 3; D. Druhin, Selventa, 1, Selventa, 3; D. Fryburg, Selventa, 1, Selventa, 3; D. de Graaf, Selventa, 1, Selventa, 3; R. Deban, Selventa, 1, Selventa, 3; D. Laffenfeld, Selventa, 1, Selventa, 3; A. Van Hoozer, Selventa, 1, Selventa, 3.

Identification of Synovial Genes and Pathways Associated with Disease Progression in a Cohort of Early Symptomatic Osteoarthritis Using a Transcriptomic Approach. Argen B. Blom1, Peter L. van Lent1, Martijn H. van den Bosch1, Hans Cats2, Frank H.I. van den Hoogen1, Floris P.J.G. Lafeber4, Wim B. van den Berg5 and Peter M. van der Kraan6, 1Radboud university medical center, Nijmegen, Netherlands, 2Sint Maartenskliniek, Utrecht, Netherlands, 3Rheumatology Centre Sint Maartenskliniek and Radboud university medical center, Utrecht (Nijmegen), Netherlands, 4University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: If and how the synovial activation that is observed in over 50% of osteoarthritis (OA) patients contributes to irreversible joint pathology, is not known. The purpose of this study was to identify pathways that may determine progression of cartilage damage in this disease.

Methods: From 25 patients with knee OA that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and 6 controls, synovial biopsies were collected at baseline. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints initiated by the Dutch Arthritis Association. Progression was determined based on change of joint space width (JSW) and osteophyte formation in radiographs, as analyzed using the KIDA (Knee Image Digital Analysis) system. Synovial samples from baseline were studied using histology and affymetrix U133-plus-2.0 chips, which were analyzed using Partek Genomics Suite software and DAVID.

Results: Histologically, lining thickness and synovitis were enhanced in the CHECK biopsies compared to control synovia. Next we compared synovial tissue of CHECK-patients with radiological damage with CHECK-patients without joint damage at baseline. Among the genes that were strongest associated with cartilage damage were MMP1 (18-fold), MMP3 (10-fold), and S100A8 (6-fold). Immunohistochemical staining revealed that expression of MMP-1 and MMP-3 was highest in the synovial lining layer. Enrichment analysis showed that chemotaxis, innate immune response and MMPs were significantly associated with joint damage at baseline. To determine whether any of the regulated genes and pathways were predictive for progression of joint damage between baseline and t=5 yrs, we identified 13 patients that were marked progressors and 8 non-progressors, based on JSW and osteophyte size. At baseline, neither minimum JSW nor osteophyte size differed between the groups. Approximately 200 genes were expressed more than 2-fold higher in synovium of progressors compared to non-progressors. Among these genes were genes from the wnt-signaling pathway: WISP1, FZD1, FZD8 and FZD10, whereas FRZB was downregulated. In addition, pro-inflammatory factors like IL1, IL6, S100A9 and MMP1 were increased. Macrophage markers like CD14, MHC class II genes, scavenger receptor A3 and CXCR2 were positively associated with progression. This indicates that expression of these factors may predict, or even be involved in, progression of joint damage in OA patients. Using DAVID we identified inflammatory response, macrophage differentiation, blood vessel formation, ossification, and cell migration to be enriched in patients that show progression of damage 5 yrs later. Histologically, the progressors showed a higher thickness of the lining layer at baseline compared to non-progressors, 2.0 vs 1.2 respectively on an arbitrary scale from 0–3.

Conclusion: These data suggest an active role for the synovium in OA pathology, and identify pathways that may be involved. From histology and the expression data, it appears that presence of macrophages is associated with progression of joint damage in OA. In addition, synovial expression of wnt-signaling genes seems important in progression of damage.

Disclosure: A. B. Blom, None; P. L. van Lent, None; M. H. van den Bosch, None; H. Cats, None; F. H. J. van den Hoogen, None; F. P. J. G. Lafeber, None; W. B. van den Berg, None; P. M. van der Kraan, None.
Conclusion: We characterized the DNA methylome in lupus neutrophils for the first time and showed a pattern of robust demethylation of interferon signature genes in lupus patients supporting a pathogenic role for neutrophils in lupus.

Disclosure: P. Coit, None; S. Yadavarti, None; W. Zhao, None; M. J. Kaplan, None; A. H. Sawalha, None.

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a HPLC-SRM-MS Based Method for the Detection and Quantification of Methotrexate Used at Doses in Clinical Practice for Patients with Rheumatological Disease in Urine. James Bluet1, Isabel Riba-Garcia2, Richard Linney2, Suzanne Verstappen4 and Anne Barton4. 1Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom, 2Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, 3Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, 4Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Methotrexate (MTX) is a recommended first-line therapy in 2013 EULAR guidelines for active rheumatoid arthritis (RA). Despite this, up to 54% do not adequately respond to MTX. Non-adherence rates vary depending on the method used to measure adherence. Currently there is no gold standard for measurement of MTX adherence. Whilst an ELISA is routinely used to detect MTX levels at the doses used for chemotherapy regimens, this is not sensitive enough for the low dose MTX used to treat patients with rheumatological conditions. Detection of MTX and its major metabolite 7-OH-MTX in urine may be an improved method to detect adherence in routine practice, when used in the lower dose range (7.5 – 30 mg/wk). The aim, therefore, was to develop a liquid chromatography-selected reaction monitoring mass spectrometry (HPLC-SRM-MS) method to determine the presence of low levels of MTX and 7-OH-MTX in urine.

Methods: Donated drug-free samples from RA patients were frozen at ~80°C after collection. Samples were thawed at room temperature and then prepared by spiking purchased MTX, 7-OH-MTX and the internal standard (IS) with low levels of IS. Supernatant was subsequently analysed using HPLC with a reversed-phase column on line to a triple quadrupole mass spectrometer operated in positive ionization mode. Analytes were measured in selected reaction monitoring mode for the following mass transitions: 455.1 → 111.1 for MTX, 458.1 → 311.1 for 7-OH-MTX and 308.1 → 311.1 for IS. Method validation consisted of accuracy, lower limit of quantification, recovery, linearity, precision and stability at room temperature and ~80°C. All samples were measured in triplicate.

Results: For MTX and 7-OH-MTX respectively, average recovery of analyte following sample preparations was 118% ± 8.9% and 86% ± 18.6%. The lower limit of quantification (LLOQ) was 2.5 and 5.0 ng/mL. The coefficient of variance for intraday run was 3.0% and 2.5% respectively. The method was linear from the LLOQ up to 1000 ng/mL (r² = 0.99, 1.00 respectively). Stability testing revealed no loss at 7 days when samples were stored at ~80°C, although storage at room temperature produced an average loss of 27% ± 6% and 10% ± 3.9% respectively within 24 hours.

Conclusion: We have developed a rapid, simple and cost effective HPLC-SRM-MS method to measure MTX and 7-OH-MTX concentrations in urine, which is sensitive to the low doses used to treat RA and other musculoskeletal diseases. The method requires limited sample preparation and may be a novel biochemical assay for measurement of adherence to MTX therapy.

Disclosure: J. Bluet, None; I. Riba-Garcia, None; R. Unwin, None; S. Verstappen, None; A. Barton, None.

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PECOM-1 GENE Polymorphisms and Soluble PEcom-1 LEVEL in Rheumatoid Arthritis and Systemic LUPUS Erythematosus Patients Is There a Link with Clinical Atherosclerotic Events? Omer Nuri Pamuk1, Hilmi Tözükk2, Mehmet Svetki Uyanik1, Hakan Gurkan2, Julide Duymaz2, Salim Donmez2, Metin Yazarc and Gulsum Pamuk1. 1Trakya University Medical Faculty, Edirne, Turkey, 2Trakya University Medical Faculty, EDIRNE, Turkey, 3Trakya University School of Medicine, Edirne, Turkey.

Background/Purpose: Platelet-endothelial cell adhesion molecule-1 (PECAM-1/CD31) which plays a role in the transmigration of leucocytes into tissues is a member of the immunoglobulin (Ig) superfamily. It was reported that the expression of PECAM-1 on synovial tissue in inflammatory arthritis is enhanced. The genetic polymorphisms of PECAM-1 were found to play roles in atherosclerotic events. We determined PECAM-1 polymorphisms, soluble PECAM-1 and CD40L levels in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE); and evaluated their associations with clinical atherosclerotic complications.

Methods: We included 100 RA and 81 SLE patients and 94 healthy controls into the study. The clinical features about patients were obtained from medical records. Past cardiovascular complications were recorded. The most frequent gene polymorphisms of PECAM-1 were studied in our genetics laboratory. Soluble PECAM-1 and CD40L levels in serum were determined with ELISA.

Results: The frequencies of 373C (rs668) and 1688A (rs12953) alleles were higher in RA patients when compared to controls (p values, 0.03 and 0.023), RA and SLE patients had significantly higher allele frequencies for 2008A (rs1131012) when compared to controls (p values, 0.021 and 0.001), SLE patients had significantly more frequent AA genotype for rs1131012 polymorphism than RA patients and controls (p values, 0.007 and <0.001). Soluble PECAM-1 level was significantly higher in RA patients than in SLE patients and healthy controls (p values <0.001). The CD40L level was also significantly higher in RA group than in SLE and control groups (p values, 0.006 and 0.047). The levels of sPECAM-1 and sCD40L were significantly higher in RA patients with AA genotype (rs1131012) than in patients with AG genotype (p values, 0.046 and 0.008). Atherosclerotic complications were more frequent in SLE patients with AG genotype (rs12953) than those with AA genotype (p value, 0.021). SLE patients with AG genotype (rs668) had a significantly lower frequency of atherosclerotic complications than those with CG genotype (p = 0.045).

Conclusion: We found associations between various PECAM-1 polymorphisms and RA, SLE; PECAM-1 and CD40L levels were significantly higher in RA patients than in SLE and control groups. Soluble PECAM-1 level in RA was found to be linked to a certain genotype; PECAM-1 polymorphisms in SLE were protective against atherosclerotic complications.

Disclosure: O. N. Pamuk, None; H. Tözükk, None; M. S. Uyanik, None; H. Gurkan, None; J. Duymaz, None; S. Donmez, None; M. Yazarc, None; G. Pamuk, None.

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Cellular Responses of IL6 Inhibition (Tocilizumab) in Rheumatoid Arthritis Using High-Accuracy Tandem Mass Spectrometry. Michael Kruse Meyer1, Marlene Andersen2, Grethe N. Andersen3 and Allan Stensballe3. 1Hospital of Vendsyssel/Aalborg University, Hjørring, Denmark, 2Aalborg University, Hjørring, Denmark, 3Aalborg University, Aalborg, Denmark.

Background/Purpose: In this study we are analyzing leukocyte subtype responses from patients with rheumatoid arthritis (RA) to IL6 inhibition. A large contribution to RA immunopathogenesis is caused by the pleiotropic effects of interleukin 6 (IL6), which we are investigating directly on the biological active constituents of the cell, i.e. the proteins, using state-of-the-art mass spectrometry. This has enabled us to quantify changes in protein expression of thousands of proteins as a result of biologic treatment, and mapping of post-translational modifications such as citrullination, and phosphorylation.

Methods: 10 ACA positive RA patients fulfilling the ACR criteria (being enrolled prior to monotherapy IL6 inhibition) and 4 months after compared to 10 healthy controls. PBMC were isolated and past cardiovascular complications from medical records. Inflammatory IL6 inhibition and 4 months were being enrolled prior to monotherapy IL6 inhibition (Tocilizumab) with ELISA. We found associations between various PECAM-1 polymorphisms and RA, SLE; PECAM-1 and CD40L levels were significantly higher in RA patients than in SLE and control groups. Soluble PECAM-1 level in RA was found to be linked to a certain genotype; PECAM-1 polymorphisms in SLE were protective against atherosclerotic complications.

Disclosure: O. N. Pamuk, None; H. Tözükk, None; M. S. Uyanik, None; H. Gurkan, None; J. Duymaz, None; S. Donmez, None; M. Yazarc, None; G. Pamuk, None.

80

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Methods: 10 ACA positive RA patients fulfilling the ACR criteria (being enrolled prior to monotherapy IL6 inhibition) and 4 months after compared to 10 healthy controls. PBMC were isolated and subdivided into CD14+, CD4+, CD8+, C19+, and CD56+ cells using immunoaffinity Dynabeads. Each cell type was prepared for mass spectrometry analysis (Thermo Q Exactive Plus), by a filter-aided sample preparation (FASP) method. MS data was searched against a human isof orm database derived from UNIPROT using the Matrix science MASCOT, and MaxQuant search engines. Differentially expressed proteins were filtered by requiring 2 peptides pr. protein, ANOVA (P-value) cutoff 0.05, q-value (false discovery adjusted p-value using multiple hypothesis testing) cutoff 0.05, and a power of at least 80%. The method was validated using known expression responses to IL6 inhibition. While responses have been shown via array and RT-qPCR, we obtained a broader quantitative differential protein expression profile.

Results: The initial results provided the identification of 4258 different proteins obtained by combining 3 technical replicates of the
Elevated Peripheral Blood Leukocyte Inflammatory Gene Expression in Radiographic Progressors with Symptomatic Knee Osteoarthritis: NYU and OAI Cohorts. Mukundan Attur¹, Alexander Statnikov², Svetlana Krasnokutsky Samuels³, Virginia B. Kraus⁴, Joanne Jordan⁵, Braxton D. Mitchell⁶, Michelle Yau⁷, Jyoti Patel⁸, Constantfin F. Alifiris⁹, Marc C. Hochberg⁶, Jonathan Samuels⁶ and Steven B. Abramson⁸. ¹NYU Langone Medical Center, New York, NY, ²Duke University Medical Center, Durham, NC, ³The University of North Carolina at Chapel Hill, Chapel Hill, NC, ⁴University of Maryland School of Medicine, Baltimore, MD, ⁵University of Maryland, Baltimore, MD.

Background/Purpose: We and others have demonstrated low grade inflammation exists in OA joint tissues, where it may contribute to disease pathogenesis. In the current studies we assessed whether inflammatory events occurring within joint tissues were reported in the peripheral blood leukocytes (PBLs) of patients with symptomatic knee OA (SKOA).

Methods: PBL inflammatory gene expression (IL-1, TNFα, COX-2) was assessed in two independent cohorts of patients with SKOA, and a cohort of healthy control subjects: 1) 111 patients with tibiofemoral medial OA and 21 healthy volunteers from the NYUHJD Cohort, and 2) 200 patients from the OAI progression cohort who had “high quality radiographs”, at both baseline and 24 months, and had KL2 or 3 in the signal knee at baseline. Radiographic progression was defined as narrowing of medial joint space width (JSW) in the signal knee between baseline and 24-months in each cohort. Fast progression were defined as subjects who had JSN >0.5mm over 24 months. For measuring predictive performance, we used the area under the curve (AUC) of a receiver operating characteristics (ROC). OAI SKOA subjects were dichotomized as radiographic non-progressors (JSN <0.0 mm) and progressors (JSN >0.0mm) for association studies.

Results: Elevated PBL expression of IL-1, TNFα or COX-2 at baseline identified SKOA patients who were “fast progressors” (mean JSN 0.71, 0.75 and 0.71 mm / 24 months, respectively) compared to patients with levels below the median (mean JSN 0.34, 0.34 and 0.34 mm / 24 months, respectively). In a multivariable model, anthropometric traits alone (BMI, gender, age) did not predict progression, whereas addition of PBL gene expressions improved prediction of fast progressors (JSN >0.5mm). We next examined inflammatory gene expression in PBLs of radiographic progressors in the OAI cohort. Similar to the NYUHJD cohort, elevated expression of IL-1β, TNFα and COX-2 mRNA at baseline distinguished radiographic progressors from non-progressors (Table 2).

Conclusion: We identified, and confirmed in two cohorts, increased inflammatory gene expression (IL-1β, TNFα or COX-2) by PBLs that predict radiographic progression in patients with SKOA. The data indicate that inflammatory events within joint tissues of patients with SKOA are reported in the peripheral blood. These PBL transcriptome signals of local joint inflammation merit further study as potential biomarkers for OA disease progression.

Table 1: Association of PBL transcriptome IL-1β, TNFα and COX-2 (relative gene expression levels were dichotomized by median), with joint space narrowing (JSN) at 24 months in NYUHJD cohort.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Baseline JSW</th>
<th>AUC</th>
<th>CI</th>
<th>p Value</th>
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<tr>
<td>IL-1β</td>
<td>0.781</td>
<td>0.71–0.85</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>TNFα</td>
<td>0.692</td>
<td>0.61–0.77</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>COX-2</td>
<td>0.664</td>
<td>0.58–0.75</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Area under the curve (AUC) of a receiver operating characteristics (ROC) of PBL inflammatory gene expression for distinguishing radiographic progressors from non-progressors in the OAI cohort. For multivariable models, we used 10-fold stratified cross-validation repeated with 100 different splits of data into 10-folds.

<table>
<thead>
<tr>
<th>Progressors (JSN&gt;0.0mm) vs. non-progressors (JSN&lt;0.0mm)</th>
<th>AUC</th>
<th>CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0.781</td>
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<td>&lt;0.0001</td>
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<tr>
<td>TNFα</td>
<td>0.692</td>
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</tr>
<tr>
<td>COX-2</td>
<td>0.664</td>
<td>0.58–0.75</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Disclosure: M. Attur, Patent, 9; A. Statnikov, None; S. Krasnokutsky Samuels, None; V. B. Kraus, NIAMS-NIH, 2, J. Jordan, NIAMS-NIH, 2; M. Yau, None; J. Patel, None; C. F. Alifiris, None; M. C. Hochberg, NIH, 2; J. Samuel, None; S. B. Abramson, NIAMS-NIH, 2, Patent, 9.
P = 0.031, odds ratio [OR] 0.53), and more strikingly in MPO-ANCA positive AAV (P = 0.0026, OR 0.44). DBP1*05:01 was also decreased in MPA (allelic model, P = 0.0063, OR 0.72). On the other hand, DBP1*04:01 was increased in PR3-ANCA positive AAV (allelic model, P = 0.010, OR 2.38). Interestingly, although significant association was not detected in GPA as a whole, DBP1*04:01 was significantly increased when only PR3-ANCA positive GPA was examined (P = 5.7E-4, OR 3.18), but not in MPO-ANCA positive GPA.

Conclusion: This study demonstrated that DBP1*04:01 is a risk allele to PR3-ANCA positive AAV also in the Japanese population. In contrast, DBP1*04:01 wasprotective against MPO-ANCA positive AAV. In view of the population difference in the DBP1*04:01 allele frequency in the Japanese (6.1%) and in the European populations (42.5% in USA, The Allele Frequency Net Database), DBP1*04:01 may in part account for the epidemiological difference in the prevalence of MPO-ANCA and PR3-ANCA positive AAV, in addition to the DBR1*09:01-DQB1*03:03 haplotype.

Table 1 Association of DBP1*04:01 with AAV in a Japanese population

<table>
<thead>
<tr>
<th>Allele frequency</th>
<th>Carrier frequency</th>
<th>OR (95% CI)</th>
<th>Allele frequency</th>
<th>Carrier frequency</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>MPA</td>
<td>0.050</td>
<td>0.58 (0.33–1.00)</td>
<td>0.016</td>
<td>0.53 (0.30–0.95)</td>
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<tr>
<td>GPA</td>
<td>0.69 (0.037)</td>
<td>0.24 (0.07–0.76)</td>
<td>0.145</td>
<td>0.56 (0.30–0.92)</td>
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<tr>
<td>MPO+ GPA</td>
<td>0.32 (0.026)</td>
<td>0.40 (0.10–1.68)</td>
<td>0.051</td>
<td>0.30 (0.09–0.67)</td>
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</tr>
<tr>
<td>PR3+ GPA</td>
<td>0.11 (0.172)</td>
<td>3.18 (1.65–6.15)</td>
<td>0.281</td>
<td>0.0884 2.85 (1.31–6.21)</td>
<td></td>
</tr>
<tr>
<td>MPO+ AAV</td>
<td>0.030</td>
<td>0.0046 0.47 (0.28–0.79)</td>
<td>0.017</td>
<td>0.0264 0.24 (0.16–0.75)</td>
<td></td>
</tr>
<tr>
<td>PR3+ AAV</td>
<td>0.11 (0.134)</td>
<td>0.0101 2.38 (1.25–4.69)</td>
<td>0.220</td>
<td>0.0606 2.05 (0.95–4.41)</td>
<td></td>
</tr>
<tr>
<td>Healthy control</td>
<td>0.58 (0.061)</td>
<td>0.70 (0.121)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Disclosure: A. Kawasaki, None; M. Hidaka, None; N. Hasebe, None; K. E. Sada, None; S. Kobayashi, None; H. Yamada, None; H. Furukawa, None; K. Yamagata, None; T. Sumida, None; N. Miyasaka, None; S. Tohina, None; O. Azaki, None; S. Matsuo, None; H. Hashimoto, None; H. Makino, None; M. Harigat, None; N. Tsuchiya, None.

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Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Cincinnati Children’s Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH; PRCSG, Cincinnati, OH; Cincinnati Children’s Hospital Medical Center and the University of Cincinnati, Cincinnati, OH.

Background/Purpose: Fibroblastic Rheumatism is a rare disease, first described in 1980 with almost 30 cases reported thus far. One-third of the patients are children. The disease is characterized by sudden and rapidly progressive symmetric arthritis in large and small joints with cutaneous nodules over hands and para-articular sites. Sclerodactyly with thickened palmar fascia and Raynaud’s phenomenon can also be seen. Laboratory tests are usually normal and the diagnosis is based on the histology of the nodules. The etiology of the disease is unknown and no genetic testing has been published on patients with fibroblastic rheumatism to date.

The objective of this study was to identify possible causative candidate genes for this disease using whole exome sequencing.

Methods: We performed exome sequencing analysis on the DNA of a 14 year old patient with biopsy-proven fibroblastic rheumatism and her unaffected brother. It was performed at Perkin Elmer DNA Sequencing and Analysis Branford, CT. Target enrichment was performed using Illumina TruSeq Exome capture. Sequencing was performed on an Illumina HiSeq 2000. Alignment and variant calls were made using the Broad Institute’s Genome Analysis Toolkit (GATK). Variant calls were analyzed using Golden Helix SNP and Variation Suite ver 7.7.5.

We focused on candidate variations that altered the amino-acid sequence of a protein and followed either a recessive homozygous, compound heterozygous or dominant model. Genotypes common with the unaffected sibling were removed as candidates.

Results: After quality control filtering and requiring a minor allele frequency of >1% in the general population, we identified 191 different candidate variations. Of those, 156 mutations fit a dominant model in which the patient was heterozygous for the polymorphism; 6 were recessive homozygous and 29 were compound heterozygous variants in 14 genes.

Several interesting candidate genes causing variants in the dominant model were identified (Table).

Conclusion: Although we did not identify one strong candidate gene, these results will form a basis for comparison to variants identified in other patients. If this is, indeed, a disorder with genetic etiology, we believe the identification of one responsible gene can assist in future genetic research of other arthritis syndromes.

Table: 570660710 Stoppel BDG1/TTF1N1 [Protein Tyrosine Phosphatase, Non-Receptor Type 1B] Glu12 The protein encoded by this gene is a member of the protein tyrosine phosphatase family. The encoded protein localizes to aggregates in the nucleus, and is required for transcription from all three types of promoters.
Protective Association of HLA-DRB1*13:02 Against MPO-ANCA Positive ANCA-Associated Vasculitis in a Japanese Population. Naoyuki Tsuchiya1, Narumi Hasebe1, Ken-etsu Sada1, Shigeto Kobayashi2, Hidehiro Yamada1, Hiroshi Furukawa2, Kenichiro Yamagata1, Takayuki Sumida1, Nobuyuki Miyasaka1, Seichi Matsuo1, Shigeto Tohma1, Shoichi Ozaki2, Hiroshi Hashimoto3, Hirofumi Makio4, Makio Kusaoi4, Hirofumi Amano4, Akiko Suda5, Keigo Setoguchi6, Tatsuo Nagai7, Kota Shimada5, Shoji Sugii5, Shinichi Sato7, Kazuhiro Takehara1 and Naoyuki Tsuchiya1. 1Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, 2School of Pharmaceutical Sciences, Fujita Health University, Toyoake, Japan, 3Second Department of Internal Medicine, National Hospital Organization, Yamagata Medical Center, Yamagata, Japan, 4Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, 5Second Department of Internal Medicine, National Hospital Organization, Yamagata Medical Center, Yamagata, Japan, 6Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, 7Faculty of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan.

Background/Purpose: Epidemiology of antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV) is substantially different between European and Asian populations. In the Japanese population, the majority of AAV patients are positive for myeloperoxidase (MPO) – ANCA. In studies with a small sample size, we previously reported significant association of HLA-DRB1*09:01-DQB1*03:03, a haplotype common in Asians but rare in other populations, with MPO-ANCA positive AAV (Tsuchiya et al., 2003; Tsuchiya et al., 2006). In the present study, we substantially increased the sample size, and compared HLA-DRB1 associations among AAV subgroups, and also made an attempt to detect other DRB1 alleles associated with risk or protection.

Methods: HLA-DRB1 genotypes were determined by using WAK Flow HLA-typing kit (Wakunaga, Hiroshima, Japan) in 356 Japanese AAV and 596 healthy controls. Among the patients, 220 were classified as microscopic polyangiitis (MPA), 69 as granulomatosis with polyangiitis (GPA), 35 as eosinophilic granulomatosis with polyangiitis (EGPA), and 32 were unclassifiable, according to the European Medicines Agency algorithm. Among all patients, 301 were positive for myeloperoxidase (MPO)-ANCA and 41 for proteinase 3 (PR3)-ANCA. The second risk allele and protective allele were examined by relative predispositional effects (RPE) method. Bonferroni correction was employed to correct for the number of compared alleles.

Results: Positive association of DRB1*09:01 carrier frequency was confirmed in MPA (P = 0.0036, OR = 0.877, odds ratio [OR] 1.81). In addition, significant negative association with DRB1*13:02 was detected in MPA (P = 0.001, OR = 0.65, OR 2.56) and negative association in DRB1*13:02 (P = 0.037, OR = 0.77, OR 0.38). The associations were more striking when the patients were classified according to the specificity of ANCA. In MPO-ANCA positive patients, DRB1*09:01 was increased (P = 2.3x10^-5, OR 4.8x10^-5, OR 1.89), while DRB1*13:02 was decreased (P = 3.7x10^-3, OR 7.8x10^-3, OR 0.38). RPE method confirmed negative association of DRB1*13:02 (OR = 7.3x10^-2, OR = 0.47), and also supported DRB1*09:01 as the second risk allele (OR = 0.25, OR 1.82). In PR3-ANCA positive patients, suggestive association was observed in DRB1*13:02 (P = 0.021, OR = 0.65, OR 3.80), but not for DRB1*09:01 (P = 0.06, OR 1.02). Genotype comparison suggested that carriage of DRB1*13:02 cancels the risk of DRB1*09:01 to MPO-ANCA positive AAV in *09:01*13:02 heterozygotes.

Conclusion: DRB1*09:01 is associated with MPO-ANCA positive, but not with PR3-ANCA positive, AAV. Because DRB1*09:01 is a very common HLA-DRB1 allele in East Asian but rare in European populations, such a difference in the genetic background may be associated with the difference in the prevalence of MPO-positive and PR3-positive AAV in both populations. In addition, DRB1*13:02 was identified as a protective allele against MPO-ANCA positive AAV.

Disclosure: N. Tsuchiya, None; N. Hasebe, None; K. E. Sada, None; S. Kobayashi, None; H. Yamada, None; H. Furukawa, None; K. Yamagata, None; T. Sumida, None; N. Miyasaka, None; S. Matsu, None; S. Tohma, None; S. Ozaki, None; H. Hashimoto, None; H. Makino, None; M. Harigai, None; A. Kawasaki, None.

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Association of Leukocyte Immunoglobulin-like Receptor A3 (LILRA3) with Systemic Sclerosis. Yuki Hachida1, Aya Kawashita2, Takashi Matsuura1, Hiroshi Furukawa1, Shouhei Nagaoka1, Kota Shimada1, Shoji Sugii1, Takayuki Sumida1, Shigeto Tohma1, Minori Hasegawa1, Manabu Fujimoto1, Naoyuki Tsuchiya1.

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Association of TRIM21 (RO52) Polymorphisms with Systemic Lupus Erythematosus in a Japanese Population. Misaki Hidaka1, Aya Kawasai1, Hiroshi Furukawa1, Yuya Kondo1, Satoshi Ito1, Isao Masumoto1, Makio Kusaoi2, Hirofumi Amano1, Akiko Suda1, Keigo Setoguchi1, Tatsuo Nagai1, Kota Shimada1, Shoji Sugii1, Akira Okamoto1, Noriyuki Chiba2.
Background/Purpose: Aortitis may occur in the context of multifocal large and medium-sized vessel diseases such as giant cell arteritis (GCA) or Takayasu arteritis (TAK) and as an isolated focal finding (focal idiopathic aortitis, FIA). In each setting, the aortic root and arch are the most common locations for aortic injury that is presumed to be autoimmune. It is not clear whether the propensity to affect the proximal aorta in these diseases suggests common pathways in pathogenesis that could include infection, abnormalities in immune tolerance or response, presence of neo-antigens, or alterations in substrates of the aortic wall. A better understanding of the pathogenesis may lead to new therapies and improved outcomes. Thus, we sought to describe the microbiome of inflammatory and non-inflammatory thoracic aortic aneurysms (TAA).

Methods: Patients with TAA who underwent surgical reconstruction were prospectively enrolled over a period of 3 years. TAA specimens were sterilely collected and snap frozen. Clinicopathologic data were gathered on all patients. Patients who had histologic evidence of inflamed aortas and diagnoses of GCA, TAK or who were found at surgery to have FIA were matched by age, gender and race to patients with non-inflammatory lesions including bicuspid aortic valves, chronic hypertension, Marfan syndrome and other causes of cystic medial degeneration. Total DNA, including human and bacterial, was isolated from TAA. V1–4 regions of the gene encoding bacteria-specific 16S rRNA were amplified and Sanger sequenced. Principal-coordinate analysis (PCoA) plots were created based on de novo operational taxonomic unit classification via the MacQIIME 1.7 toolkit. Hierarchical taxonomic composition of sequences was performed using a custom pipeline and visualized with Krona.

Results: Twenty-seven TAA were analyzed: 7 GCA, 5 FIA, 2 TAK, and 13 non-inflammatory. Hypertension and hyperlipidemia were the most common comorbidities, and were not significantly different between inflammatory and non-inflammatory TAA. TAA microbiomes varied widely in abundance. Autoimmune-associated TAA microbiomes on PCoA plots according to type of aortitis, with the clearest separation seen between FIA and TAK samples. GCA and non-inflammatory TAA microbiomes overlap on PCoA plots, but are separate from FIA and TAK. Both GCA and non-inflammatory TAA microbiomes appear to contain sub-group clusters. Gross visualization of taxonomic composition using Krona plots shows differences between GCA specimens compared to non-inflammatory samples at the phyla level, with a tendency toward increased Proteobacteria, decreased Actinobacteria, and minimal Bacteroidetes in GCA. Overall, TAA microbiomes did not show clustering by age, sex, or prednisone use. Some clustering was seen with tobacco use.

Conclusion: TAA are not sterile. Specimens from patients with different disease associations host distinct microbial communities. Further analysis is needed to assess whether differences in microbial communities play etiologic roles or are secondary results of different types of aortic injury.

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Global miRNA Expression Profiling in Peripheral Blood and Synovial Fluid Mononuclear Cells of Patients with Enthesitis Related Arthritis.
Sushma Singh, Ramnath Misra and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Enthesitis related arthritis (ERA) is the most common category of JIA in India. MicroRNA dysregulation has been associated with arthritis and autoimmune diseases. In rheumatoid arthritis (RA) over-expression of miR-146a, miR-155 miR-132 and miR-16 has been found in PBMC. Data on miRNA profiling in serum of patients with systemic lupus erythematosus (SLE) shows over-expression of miR-142-3p and miR-181a whereas miR-106a, miR-17, miR-20a, miR-203, and miR-92a were found to be down-regulated. No such data is available in case of ERA. Thus we studied global miRNA expression profile of ERA patients using peripheral blood mononuclear cells and synovial fluid mononuclear cells (PBMCs and SFMCs). PBMCs from healthy subjects were used as controls.

Methods: Total RNA was isolated from PBMCs and SFMCs of ERA patients (n= 8 each) and PBMCs of healthy controls (n= 8). miRNA profiling was done using Agilent Human miRNA Microarray G4470A chips. Log-transformed expression values of miRNAs were analysed using RNA algorithms. Differential expression analyses were done using Empirical Bayes moderated t statistics. Highly dysregulated miRNAs were validated by quantitative RT-PCR by comparing fold change (in relation to Let-7a as internal control) in 13 PBMCs with 11 SFMCs from ERA patients. Targets of
disregulated miRNAs were predicted by computational analysis using databases like DIANA LAB, miR Base, Target Scan, etc. Results: The miRNAs profiling of ERA PBMCs were not significantly different from healthy controls. While comparing ERA SFMCs 38 miRNAs were down-regulated and 52 were up-regulated at cut-offs of 0.05 as compared to ERA PBMCs. Among them miR-34a, miR-210, miR-29b, miR-155, miR-21, miR-27a, miR-132, miR-140-5p, miR-15a, and miR-660 were upregulated and miR-146a, miR-126, miR-130a, miR-150, miR-26a, miR-23b, miR-199a, miR-451, miR-151 and miR-221 were down-regulated in SFMCs. Among these 5 down-regulated and 5 up-regulated miRNAs were validated by RT-PCR using 11 ERA SFMCs and 13 ERA PBMCs. The comparison of fold change between ERA SFMCs and ERA PBMCs (p-value) of dysregulated miRNAs showed: miR-34a (p = 0.035), miR-210 (p = 0.424), miR-29b (p = 0.865), miR-155 (p = 0.072), miR-21 (p = 0.047), miR-146a (p = 0.006), miR-126 (p = 0.001), miR-130a (p = 0.001), miR-150 (p = 0.150) and miR-221 (p = 0.011). The targets of dysregulated miRNAs formed a part of multiple immune pathways like MAPK signaling pathways, TLR signaling pathways, T cell receptor signaling pathways, mTOR signaling pathways, Wnt signaling pathways, etc.

Conclusion: ERA SFMC has a distinct miRNA gene expression profile compared to ERA PBMCs. miR-34a and miR-21 are significantly upregulated whereas miR-146a, miR-126, miR-130a and miR-26a are significantly down-regulated in ERA SFMCs and all these dysregulated miRNAs are involved in multiple immune pathways. This difference in SFMC may be related to difference in composition of cells, cytokine milieu that modulates miRNA expression as well as differential expression of miRNAs as they have related to difference in composition of cells, cytokine milieu that modulates pathways, T cell receptor signaling pathways, mTOR signaling pathways, etc.

Disclosure: S. Singh, None; R. Misra, None; A. Aggarwal, None.

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Genetic Variants in IL-6, IL-10, C5-TRAFl and FCRL3 and Progression of Joint Damage in Rheumatoid Arthritis; A Study on Six Cohorts. H.W. van Steenbergen1, L. Rodriguez-Rodriguez2, E. Berglin3, A. Zhermakova4, R. Knexel5, J. Ivorra-Cortes5, T.W.J. Huizinga1, B. Fernandez-Gutierrez6, P.K. Gregersen7, S. Rantapaa-Dahlqvist8 and A.H.M. van der Manhasset-van Mil8.

Background/Purpose: Understanding the mechanisms underlying the inter-individual differences in radiographic progression is relevant and hertiability studies have shown that genetic factors explain part of these inter-individual differences. Indeed, some genetic variants have been identified and replicated in independent studies or found significant in meta-analyses. The literature on genetic variants and joint destruction in RA was systematically reviewed recently; for genetic variants in IL-6, IL-10, C5-TRAFl, and FCRL3 the existing literature was indefinite on whether these variants are associated with joint destruction. We aimed to clarify associations of genetic variants in IL-6, IL-10, C5-TRAFl and FCRL3 with radiographic progression by evaluating six independent cohorts.

Methods: In total 5,895 sets of radiographs of 2,493 RA patients included in the Leiden EAC, Umeå, HCSC-RAC, Wichita, NDB and NARAC cohorts were studied in relation to rs1800795 (IL-6), rs1800896 (IL-10), rs2001180 (C5-TRAFl) and rs7528684 (FCRL3). Associations with radiographic progression rates were tested per cohort using an additive model, adjusting for age, gender and treatment when appropriate. The results on yearly radiographic progression rates were combined in inverse variance weighted meta-analyses. Analyses were done on the total RA population and after stratification for anti-citrullinated peptide antibodies (ACPA). Furthermore, the associated region C5-TRAFl was fine-mapped.

Results: No associations were found for rs1800795 (IL-6), rs1800896 (IL-10) and rs7528684 (FCRL3) in the total RA population and after stratification for ACPA. Also the directionality of the effects was diverse. Although for rs2900180 in C5-TRAFl no significance was obtained in the total population or in ACPA-positive RA, an association was observed in ACPA-negative RA (p value meta-analysis 5.85x10^-7). In all data sets with ACPA-negative RA, the minor allele was associated with more radiographic progression. Fine-mapping revealed a region of 66 Kb that was associated with radiographic progression; the lowest p-value was for rs7021880 In Traf1. The p-value for rs7021880 in meta-analysis was 6.35x10^-8. Previous studies indicate that the region of rs7021880 was associated with RNA expression of Traf1 in monocyes after lipopolysaccharide stimulation.

Conclusion: In contrast to initial reports, variants in IL-6, IL-10 and FCRL3 were not associated with radiographic progression in the present large meta-analyses. Although an association between rs2900180 in C5-TRAFl and joint destruction was initially identified in the total RA population, we here replicated an association of rs2900180 in C5-TRAFl and linked variants in a 66 Kb region with radiographic progression in ACPA-negative RA.

Disclosure: H. W. van Steenbergen, None; L. Rodriguez-Rodriguez, None; E. Berglin, None; A. Zhermakova, None; R. Knexel, None; J. Ivorra-Cortes, None; T. W. J. Huizinga, None; B. Fernandez-Gutierrez, None; P. K. Gregersen, None; S. Rantapaa-Dahlqvist, None; A. H. M. van der Helm-van Mil, None.

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Background/Purpose: Lupus nephritis (LN) progresses from mild focal inflammation, to diffuse proliferative nephritis, to fibrosis and end-stage renal disease. Though the understanding of LN has progressed, there is a need to use global, data-driven research methodologies to elucidate its molecular pathogenesis. As a foundation for this goal, we aimed to develop a quantitative proteomics workflow that can directly study formalin-fixed, paraffin-embodied (FFPE) archived clinical tissues. This applicable workflow could therefore provide a powerful tool to study the progression of LN, albeit if we can trust that data obtained are without substantial sample processing bias.

Methods: To obviate the need for large pieces of human LN tissue, we used kidney tissues from lupus-susceptible NZM.2328 mice that develop glomerulonephritis that mimics LN in humans. Identical transverse kidney tissue cuts from 10-month-old female NZM-2328 mice with high-grade proteinuria were processed as FFPE and fresh frozen tissue (FFT). FFPE and FFT sections were digested with trypsin and stable isotope labeled for protein identification and quantification. Our workflow includes a combination of methodologies including filter aided sample preparation (FASP), in-solution dimethyl isotope labeling, strong cation exchange StageTip fractionation, along with nano-LC MS/MS through an Orbitrap XL mass spectrometer. Two separate experiments were run where three conditions were studied in each: two exact technical replicate FFT conditions and one FFPE condition. Within our workflow, combining FASP and in-solution dimethyl isotope labeling, relative quantitative values were obtained via direct comparison of each pair of conditions within each experiment.

Results: We developed and validated a workflow that allows for a direct comparison of FFPE tissue to FFT. Through our workflow validation experiments, we observed an almost 100% protein identification overlap between FFPE and FFT from a LN kidney. A consistent identification of over 1400 proteins in both FFPE and FFT indicate no selection bias with tissue processing. Although, quantification differences did exist when comparing FFPE-to-FFT, the quantitative changes (quantification ratios) of proteins in FFPE tissues were consistent across replicate experiments. This reliability is seen with global hierarchical clustering as well as with specific protein categories such as TGFβ signaling, the KEGG SLE annotated pathway, the GSEA annotated lupus CD4 T cell vs. myeloid function upregulation, and B cell function related proteins, which have been implicated in LN pathogenesis.

Conclusion: Our methodology is the first to directly compare FFT and FFPE tissue in a manner that can be readily applied to archived clinical samples. Our results demonstrate the utility of this workflow by its ability to equally identify proteins between FFPE and FFT, minimizing sample processing bias, and by providing consistent protein quantification values of FFPE tissue between technical replicates and across separate experiments. We conclude that this clinically oriented proteomics workflow, when applied to archived, FFPE tissue can be reliably utilized to study LN pathogenesis.

Disclosure: A. Amarnani, None; J. Capri, None; P. Souda, None; D. Elashoff, None; I. Lopez, None; J. Whitelegg, None; R. Singh, None.
Long Noncoding RNA Nron Regulates the Activity of NFAT5 through Ubiquitin-Independent Proteasome Pathway in Rheumatoid Arthritis. Kamihiko Umekita1, Michelle Trenkmann1, Christoph Kolling1, Akiko Okayama1, Renate Gay1, Steffen Gay1 and Moja Frank Bertonec1. 1Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland. 2Schulthess Clinic, Zurich, Switzerland. 3University of Miyazaki, Miyazaki, Japan. 4Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Long noncoding RNAs (lncRNAs) are increasingly recognized as master regulators of gene expression. The lncRNA NRON, noncoding repressor of nuclear factor of activated T cells (NFAT) can repress the cytoplasmic-nuclear translocation and function of NFAT1–4 transcriptional factors. Recently, we have reported that NRON regulates also the activity of NFAT5, affecting thereby the function of rheumatoid arthritis synovial fibroblasts (RASF). In addition, the ubiquitin-independent proteasome system has been shown to play an important role in regulating the cellular levels of NFAT5. Our objective was to investigate the regulation of NRON levels in RASF and to explore the role of NRON in protein turnover of NFAT5.

Methods: The levels and subcellular localization of NFAT5 protein in RASF were analyzed by Western blotting using a-ubulin for normalization. RASF were transfected with siRNA targeting NRON or scrambled siRNA using Lipofectamine 2000. RASF were treated with TNF (10 ng/ml), p38MAPK inhibitor (p38i, 10 μM) SB202190, and/or proteasome inhibitor MG132 (1.0 μM). Gene expression was measured by quantitative real-time PCR with normalization to GAPDH or β2-microglobulin. ELISA was used to measure IL-6 secretion from RASF.

Results: The levels of NRON were significantly decreased and the levels of NFAT5 protein were increased in RASF after 2 hr of TNF stimulation, while the levels of NFAT5 mRNA were not changed. Down regulation of NRON after silencing or TNF stimulation was accompanied by the translocation of NFAT5 from the cytoplasm to the nucleus of RASF, increasing the transcription of known NFAT5 target genes, such as IL-6 (x-fold change: 3.0 ± 2.2, p = 0.03, n = 4) and MMP13 (x-fold change: 4.7 ± 2.0, p = 0.03, n = 4). The secretion of IL-6 in the culture medium of RASF was also significantly increased (mean ± SEM: 167.6 ± 479 vs. 2433 ± 504 pg/mL, p = 0.007, n = 5). The treatment of RASF with p38i significantly repressed not only the TNFα-induced up regulation of IL-6 but also the TNFα-induced down regulation of NRON (p = 0.001 and p = 0.04, n = 5, respectively). Additionally, the proteasome-dependent degradation of NFAT5 was significantly enhanced by p38i (p = 0.01, n = 5). Blocking the proteasome activity by MG132 inhibited the p38i-induced degradation of NFAT5. Furthermore, the p38i-induced degradation of NFAT5 was inhibited also after silencing of NRON in RASF.

Conclusion: Our data show that TNFα down regulates the expression of lncRNA NRON in RASF by enhancing the activity of p38MAPK. Down regulation of NRON not only enhances the nuclear translocation and transcriptional activity of NFAT5 but also increases the total amount of NFAT5 in RASF by influencing the turnover of NFAT5 via ubiquitin-independent proteasome system. This novel data show the complex and multilevel capacities of the lncRNA NRON in regulating the function of NFAT5, thereby promoting proinflammatory and matrix-destructive responses of RASF.

Disclosure: K. Umekita, IMI BTCure, EuroTEAM, IAR, 2; M. Trenkmann, None; C. Kolling, None; A. Okayama, None; R. Gay, None; S. Gay, None; M. Frank Bertonec, IMI BTCure, EuroTEAM, IAR, 2.


Background/Purpose: Osteoarthritis (OA) is characterized by the progressive loss of cartilage structural extracellular matrix (ECM) components. The release of these proteins from the tissue can vary according to the stage of the disease and the specific joint affected. The aim of this study was to perform a quantitative proteomics approach to identify and quantify those proteins released from normal (N) and OA human articular cartilages capable of predicting the early stage of hip and knee OA.

Methods: Tissue explants were obtained from the dissection of 4 N and 4 OA cartilages, both from 2 femoral heads and 2 tibial condyles. Among the OA samples, we differentiated the wounded zones (WZOA) from those corresponding to the area adjacent to the lesion, or unwounded zones (UWOA). Cartilage shavings from each donor were cut into 6 mm discs and these discs/donors were placed into 96-well plates and cultured during 6 days. The conditioned media from each condition (N, WZOA and UWOA) were collected and their proteins were digested with trypsin. The resulting peptides were labelled with different isobaric tags using the iTRAQ reagents (ABSciex). Then, labelled peptides from the different conditions were mixed, desalted and separated by liquid chromatography (LC). The resulting fractions were grouped and resolved by reversed-phase nano-LC coupled to mass spectrometry (MS). The identification and relative quantification of the proteins was carried out with Protein Pilot 3.0 software.

Results: Globally we were able to identify 186 proteins released from the cartilage explants. After statistical analysis we found secreted proteins showing differences in abundance (0.75 ± ratio ≥ 1.3, p ≤ 0.05) between the different OA zones (WZOA and UWOA) and N samples from the different joints. We classified them into 3 sets of proteins: a first group of proteins modulated specifically in UWOA sample (early OA biomarkers); a second group of proteins altered only in WZOA samples (late OA biomarkers), and finally a third group modified in both OA zones (progression biomarkers). Some of these modulated proteins are common early and progression biomarkers for both hip and knee OA (Table 1). Furthermore, we also identified that the release of cartilage intermediate layer protein 1 (CILP1), a protein involved in cartilage scaffolding, is increased in UWOA from hip OA cartilage but not in UWOA from knee OA, being a possible early specific biomarker for hip OA. This specific modulation was confirmed by Real-time PCR and western blot in other human cartilage samples (n = 3).

Conclusion: We describe a novel panel of cartilage-secreted proteins with potential biomarker value. Interestingly, we have identified a specific protein, which specifically indicates hip OA onset. This protein is now being explored in biological fluids (synovial fluid and serum) for the development of early diagnosis and/or anti-OA therapy monitoring strategies.

Table 1: A panel of different types of potential protein biomarkers of hip (H) or knee (K) OA is listed in the table. Proteins showing a gradual increase among OA samples (UWOA and WZOA) compared to normal cartilage (N) are indicated as early and progression biomarkers. CILP1 specifically indicates hip OA onset.

<table>
<thead>
<tr>
<th>Protein Name</th>
<th>Uniprot symbol</th>
<th>Joint peptide</th>
<th>Peptide (%)</th>
<th>Ratio UWOA/N</th>
<th>Ratio WZOA/N</th>
<th>p value OA biomarker type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigment epithelium-derived factor</td>
<td>PEDF</td>
<td>H</td>
<td>25</td>
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<tr>
<td>Cartilage intermediate layer protein I</td>
<td>CILP1 H</td>
<td>142</td>
<td>2.27</td>
<td>0.00</td>
<td>1.02</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Disclosure: L. Lourido, None; V. Calamia, None; P. Fernandez-Puente, None; J. Mateos, None; F. J. Blanco Garcia, None; B. Rocha, None; C. Fernandez-Costa, None; C. Fernandez-Lopez, None; N. Oreiro, None; C. Ruiz-Romero, None.
Background/Purpose: Biologics, a relatively new widely used class of medication that can substantially improve the course of RA, are expensive and their use is not reimbursed by all insurance providers. The aim of this study was to determine whether there was a difference in the usage of biologics between RA patients with only Medicare or Medicare-Medicaid and those who had other insurance coverage.

Methods: Demographic and clinical information, medication history, and insurance data were extracted from the electronic records of all patients with a diagnosis of RA managed at the Dallas Arthritis Center (DAC) for at least 3 months in 2013. Patients were then stratified into the following categories, based on their type of insurance coverage: (1) Medicare only: Medicare coverage with no supplemental insurance of any kind, and no medication-specific financial support from charitable organizations; (2) Medicare-Medicaid: both Medicare and Medicaid coverage; (3) Medicare integrated: supplemental insurance in addition to Medicare (private or public insurances or Medicare part D); and (4) Private only: private insurance only. Unadjusted odds ratio was used to determine the likelihood of patients with different types of insurance coverage as compared to patients covered exclusively by Medicare. This latter group was arbitrarily assigned an Odds Ratio of 1.

Results: Our research yielded 529 unique patients (median age 62 years, range 19 to 91; 79% female) with a confirmed diagnosis of RA; 13 patients who received financial support from private foundations to purchase the needed medications were excluded from the analysis. The remaining 516 patients represent our study group. Table 1 depicts the distribution of the insurance coverage amongst the study patients:

<table>
<thead>
<tr>
<th>Insurance Type</th>
<th>Total Patients</th>
<th>Median Age</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare only</td>
<td>118</td>
<td>70 (41–88)</td>
<td>91 (77.1)</td>
</tr>
<tr>
<td>Medicare-Medicaid</td>
<td>67</td>
<td>66 (28–91)</td>
<td>56 (83.6)</td>
</tr>
<tr>
<td>Medicare Integrated</td>
<td>52</td>
<td>68 (36–87)</td>
<td>40 (76.9)</td>
</tr>
<tr>
<td>Private only</td>
<td>279</td>
<td>56 (19–91)</td>
<td>231 (82.8)</td>
</tr>
</tbody>
</table>

Table 2 shows the relative usage of biologics amongst the different groups:

<table>
<thead>
<tr>
<th>Insurance Type</th>
<th>Total RA Patients</th>
<th>RA Patients on any biologic</th>
<th>% of RA Patients on any biologic</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare only</td>
<td>118</td>
<td>22</td>
<td>20%</td>
<td>1</td>
<td>0.1241</td>
</tr>
<tr>
<td>Medicare-Medicaid</td>
<td>67</td>
<td>25</td>
<td>37%</td>
<td>2.44 (1.23–4.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>Medicare Integrated</td>
<td>52</td>
<td>20</td>
<td>38%</td>
<td>2.56 (1.24–5.29)</td>
<td>0.005</td>
</tr>
<tr>
<td>Private only</td>
<td>279</td>
<td>102</td>
<td>37%</td>
<td>2.36 (1.39–3.99)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusion: Patients with Medicare only coverage who received no assistance from private foundations were significantly less likely to be treated with biologics than patients with any other type of coverage. In this study, we did not evaluate each patient’s disease activity. Therefore, the possibility that fewer Medicare-only patients needed biologics than patients with other types of coverage must be considered. A study designed to include disease activity as a variable is currently under way. If confirmed, these results suggest that efforts are needed to increase Medicare patients’ access to medications that can significantly improve the course of their disease and quality of life.

Disclosure: M. Genta. None.

Comparison of Patient Characteristics, Healthcare Costs, and Biologic Persistence Between Patients with Rheumatoid Arthritis Initiating First- or Second-Line Subcutaneous Abatacept, Adalimumab, or Etanercept.

| Table | First-line initiators used only one biologic pre-index; second-line initiators used only one biologic pre-index. Patient characteristics were measured at baseline. Biologic persistence (follow-up) was defined as the period extending from index until the first occurrence of switch to another biologic, censoring at disenrollment from health insurance, or 12/31/2012. Total healthcare costs (medical and pharmacy) were measured during baseline and follow-up on a per-patient-per-month basis. Changes in healthcare costs from baseline to end of available follow-up were compared using multivariable regression (difference-in-difference method). Biologic persistence was compared using multivariable survival analyses.

| Table | The study results are shown in the Table. Patients treated with SC abatacept had baseline characteristics indicative of the poorest health status (e.g., higher baseline number of unique diagnoses and baseline costs). In all analyses, SC abatacept had the numerically lowest increase from baseline in healthcare costs and hazards of non-persistence, with differences often being statistically significant.

Table: Comparison of Cardiovascular Risk Factor Management in Patients with RA and Matched Non-RA Patients. H Cawston,1 E Alema2, F Bourhis3, T Le4, M Al2, M Rutten-van Molken5, KP Liao1 and DH Solomon.1 OptumInsight, Nanterre, France,1 Bristol-Myers Squibb, Princeton, NJ,2 Bristol-Myers Squibb, Hobepol, NJ,2 Erasmus University, Rotterdam,3 Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: The relative risk of acute myocardial infarction in RA patients (pts) has been shown to range from 1.5 to 2.0, with a 1.4–2.7-fold higher risk of stroke. This study aimed to compare management of traditional cardiovascular (CV) risk factors such as lipids and blood pressure in pts with and without RA.

Methods: A retrospective cohort study was conducted from 1987 to 2010, using the GOLD database from the Clinical Practice Research Datalink. Pts presenting with ≥1 RA read diagnosis code after January 1 1988 (index code), with no RA or juvenile RA codes before the RA index code with ≥12 months of data reported before the first RA code, and without any psoriatic arthritis-related codes over the entire period were included. Pts with RA were matched 1:4 to non-RA pts, based on their year of entry in the database, CV risk category (National Cholesterol Education Program classification), CV treatment status and a risk score measuring the probability of having RA.

The index code of non-RA pts was defined as the closest health encounter to the index code of their match. Prescriptions for antihypertensive, hyperlipidemic and diabetic treatments were evaluated for up to 5 years post index code. The percentage of pts attaining UK CV targets was also evaluated.

Results: Between 1987 and 2010, 24,859 RA pts were identified and matched to 87,304 non-RA pts. RA pts were followed for an average (SD) of
5.8 (4.4) years, were 60.0 (15.1) years old; 69% were female, 39% were hypertensive and 27% dyslipidemic at index date, based on diagnoses, prescriptions and tests. Similarly, non-RA pts were followed for an average of 5.7 (4.4) years, were 60.2 (15.9) years old; 66% were females, 38% hypertensive and 28% dyslipidemic. The percentage of RA pts prescribed antihypertensives increased from 38.2% at diagnosis to 45.7% at 5 years, from 14.0% to 20.6% for antidyplidemics, and from 5.1% to 6.4% for antidiabetics (Table). Index rates and changes over time were similar in non-RA pts, although slightly lower for antihypertensives. There was no difference between RA and non-RA pts reaching hypertension targets at 1 year (25.8% vs 26.9%, p = 0.50) although there was for dyslipidemia and diabetes (16.4% vs 18.5%, p < 0.01; and 48.7% vs 44.3%, p = 0.01, respectively). Blood pressure, lipids and diabetes-related testing were similar in both groups over time since diagnosis, although CRP and ESR were higher in RA pts at diagnosis (24.6 mg/L and 31.9 mm/hr, respectively), decreasing over time. These values were lower and did not vary over time in non-RA pts.

**Conclusion:** There were no differences between RA and non-RA patients in the frequency of prescriptions and testing, although there was a modest 2% lower achievement in lipid targets. Based on this analysis, it seems the higher CV risk in RA patients is unlikely to be driven by differences in traditional CV risk factor management alone.

**Table** Summary of treatment received, by time since index

<table>
<thead>
<tr>
<th>Time point</th>
<th>Antihypertensive treatment</th>
<th>Lipid-lowering treatment</th>
<th>Antidiabetic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>At index date</td>
<td>38.2% (24,885)</td>
<td>14.0% (959)</td>
<td>5.1% (324)</td>
</tr>
<tr>
<td>At 5 years</td>
<td>45.7% (25,653)</td>
<td>20.6% (1,624)</td>
<td>6.4% (413)</td>
</tr>
<tr>
<td>Absolute increase (95%CI)</td>
<td>+7.5% (6.5%; 8.6%)</td>
<td>+6.7% (5.8%; 7.5%)</td>
<td>+1.3% (0.8%; 1.8%)</td>
</tr>
</tbody>
</table>

**Disclosure:** H. Cavston, OptumInsight, 3, Bristol Myers-Squibb, 5; E. Alemao, BMS, 3, BMS, 5; F. Arthritis, None; T. Le, BMS; 5; M. Al, None; M. Ruten-van Molken, None; K. Liao, None; D. Solomon, None.

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**Background/Purpose:** Medical care costs have been a major concern for public policy for a generation. Concern about costs of musculoskeletal conditions (MUSC) has been fueled by the aging of the population which puts a growing fraction of the population at risk for these conditions. We document the growth in medical care costs of MUSC from 1996–2011 and analyze the role that aging of the population, age-specific prevalence of the conditions, increased medical care utilization, and increased prices for services play in this growth.

**Methods:** We analyzed the 1996–1998 and 2009–2011 Medical Expenditure Panel Survey (MEPS). Using three-year periods provides more stable estimates of long-term trends. In MEPS, persons self-report conditions causing utilization, disability, or symptoms. Responses are coded to ICD-9-CM 3-digit codes; musculoskeletal codes included arthritis and joint pain, spine conditions, osteoporosis, musculoskeletal injuries, and other musculoskeletal conditions. We calculated per person and aggregate costs in constant dollars, adjusted for inflation.

**Results:** Between 1996–1998 and 2009–2011 prevalence of musculoskeletal conditions rose by 35%, from 76.0 to 102.5 million while costs rose 117%, from $367.2 to $796.2 billion (Table 1). The increased costs resulted from larger populations aged 45–64 and ≥ 65, increased prevalence of MUSC in these age groups, higher unit prices for ambulatory care, hospital admissions, and prescriptions as well as increased numbers of prescriptions used (Table 2). Hospital admissions and ambulatory care utilization did not increase appreciably during this time.

**Conclusion:** The aging of the baby boom generation will lead to short term increases in the population at greatest risk for MUSC. Reducing costs of these conditions will require public health approaches to reduce the prevalence of MUSC through such mechanisms as weight control and exercise programs as well as change in the organization of health care to attenuate the increases in the unit prices of services, especially of prescription medications.

**Table** Number and Percent of US Population with Musculoskeletal Conditions and Mean and Aggregate Health Care Costs in 1996–1998 and 2009–2011

<table>
<thead>
<tr>
<th>Years</th>
<th>MUSC. Conditions</th>
<th>% of Pop.</th>
<th>Mean</th>
<th>Agg</th>
<th>Mean</th>
<th>Agg</th>
<th>Mean</th>
<th>Agg</th>
<th>Other</th>
<th>Mean</th>
<th>Agg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-1998</td>
<td>76.0</td>
<td>28.0</td>
<td>1,522</td>
<td>115.7</td>
<td>1,738</td>
<td>133.6</td>
<td>665</td>
<td>50.8</td>
<td>887</td>
<td>67.4</td>
<td>4,832</td>
<td>367.2</td>
</tr>
<tr>
<td>2009-2011</td>
<td>102.5</td>
<td>33.2</td>
<td>2,614</td>
<td>207.9</td>
<td>2,237</td>
<td>192.5</td>
<td>1,278</td>
<td>241.5</td>
<td>1,258</td>
<td>351.6</td>
<td>7,768</td>
<td>796.2</td>
</tr>
</tbody>
</table>

**Disclosure:** T. Simon, Bristol-Myers Squibb, 3; N. Lin, None; N. Baker, Bristol-Myers Squibb, 3; N. Lin, Bristol-Myers Squibb, 2; V. Hoffman, Optum Epidemiology, 3.
### Table 2: Percent Change in US Population at Risk for Musc. Conditions, Prevalence of Musc. Conditions by Age, and Utilization and Unit Price of Ambulatory Visits, Hospital Admissions, and Prescription Medications

<table>
<thead>
<tr>
<th>Population and Prevalence Factors</th>
<th>Health Care Utilization and Prices</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US Population</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Pet Change</td>
<td>% 45-64</td>
</tr>
<tr>
<td>Pet Change</td>
<td>47%</td>
</tr>
</tbody>
</table>

### Impact of Comorbidities on Health Resource Utilization in Patients with SpA

Mariano Andrés1, Francisa Sivera2, Sabina Pérez-Vicente3, Loreto Carmona4 and Paloma Vela1. 1Hospital General Universitario de Alicante, Alicante, Spain, 2Hospital General Universitario de Elda, Alicante, Spain, 3Unidad de Investigación de la Sociedad Española de Reumatología, Madrid, Spain, 4Instituto de Salud Musculosquelética, Madrid, Spain.

**Background/Purpose:** Similar to other rheumatic disorders, patients with spondyloarthritis (SpA) show an increased prevalence of comorbidities compared to the general population [1]. Comorbidities influence management, prognosis and quality of life in SpA patients [2], but their impact on the utilization of health resources has been scantily explored so far.

**Methods:** The emAR II was a descriptive, multi-center, cross-sectional study, performed in Spain between 2009 and 2010. The results of patients with a SpA diagnosis as a first visit to the Rheumatology department within the previous two years were selected using an equiprobabilistic method. Health care utilization was collected during the previous 2-year period as: a) hospital admissions; b) visits to the rheumatology clinic; c) referrals to other medical specialists by the rheumatologist; and d) diagnostic procedures ordered due to SpA. The following comorbidities were registered: hypertension, diabetes, coronary heart disease, chronic heart failure, stroke, neoplasms, infections, peptic ulcer disease, chronic kidney disease, liver disease, and anticoagulation therapy. Additional descriptive and confounding variables were collected. Association between use of resources and comorbidities was assessed by linear regression for continuous variables and logistic regression for binary variables, accounting for Poisson distribution.

**Results:** 1,168 patients’ records from 45 centres were reviewed in detail (recruitment rate: 73%), mean (±SD) age 50.1 (±13.8) years. 68% males. Main SpA forms were ankylosing spondylitis and psoriatic arthritis. The use of resources was as follows: 248 admissions in 196 patients (19.2%), rate 12.1 per 100 patient-years, 5908 visits to rheumatology clinics (median (IQR) 4 visits per patient (3–6), rate 254 per 100 patient-years), 844 referrals to other specialists (rate 200 per 100 patient-years), and 85560 diagnostic procedures (rate 1753 per 100 patient-years), 254 referrals to other specialists (rate 200 per 100 patient-years), and 844 referrals to other specialists (rate 200 per 100 patient-years). Health care utilization was collected during the previous 2-year period as: a) hospital admissions; b) visits to the rheumatology clinic; c) referrals to other medical specialists by the rheumatologist; and d) diagnostic procedures ordered due to SpA. The following comorbidities were registered: hypertension, diabetes, coronary heart disease, chronic heart failure, stroke, neoplasms, infections, peptic ulcer disease, chronic kidney disease, liver disease, and anticoagulation therapy. Additional descriptive and confounding variables were collected. Association between use of resources and comorbidities was assessed by linear regression for continuous variables and logistic regression for binary variables, accounting for Poisson distribution.

**Conclusion:** Comorbidities in SpA influence health resources utilization, except for referrals to other specialties. This finding, added to the known impact in other areas of the disease, makes the identification of comorbidities advisable.

**References:**

1. J. Rheumatol; 33:2167.

### Table 1. Association between comorbidities and health resources utilization (univariate analysis).

<table>
<thead>
<tr>
<th>Chronic kidney disease</th>
<th>Liver disease</th>
<th>Infections</th>
<th>Anticoagulation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 (2.1)</td>
<td>5.096 (2.452–14.223)</td>
<td>0.822 (2.865,1.001)</td>
<td>1.579 (0.808–1.434)</td>
</tr>
</tbody>
</table>

### Disclosure: E. H. Yelin. None; M. G. Cistermans, None; L. Trupin, None; S. Gansky, None.

### Background/Purpose:


**Background/Purpose:** Non-biologic (NB) disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX) are commonly used to treat rheumatoid arthritis (RA). However, NB-DMARD can have adverse events or inadequate response that lead to premature discontinuation. Up to 50% of patients initiating MTX may discontinue at 2 years.1–3 The objective of this exploratory analysis was to evaluate real world treatment patterns and impact on healthcare resource use (HCRU) among patients whose first DMARD regimen was select NB-DMARD as monotherapy or in combination with other NB-DMARD.

**Methods:** This retrospective cohort study evaluated patients aged ≥18 years with ≥3 physician visits ≥30 days apart for RA (ICD-9 code: 714.xx) who were newly prescribed/administered a select NB-DMARD (MTX, leflunomide, sulfasalazine, hydroxychloroquine) from 2007–2011 in a de-identified electronic health record (EHR) database (Humedica). The index date was the date of the first select NB-DMARD prescription/administration in the EHR (ie, no DMARD in ≥6 months pre-index), and patients were followed for ≥1 year. Patients were categorized by initial treatment with NB-DMARD monotherapy (NBmono) or ≥2 select NB-DMARD at index (NBcombo). Patient baseline characteristics, 1-year-post index treatment patterns and HCRU were evaluated in EHR. RA-related costs were evaluated for a subset of patients with clinical information linked to healthcare claims (Optum) of commercial and Medicare Advantage health plans.

**Results:** Of 10,338 RA patients receiving any DMARD therapy, 73% received NBmono and 6% NBcombo; patient characteristics are presented in the Table. NBcombo patients tended to have a lower DCCI score, fewer were treated by a rheumatologist, and tended to have more NSAIDS/steroids/opioids at index; <1% of patients had other NB-DMARDs within 30 days of index. During the 1-year follow-up, NBcombo patients were less likely than NBmono patients to continue their index NB-DMARD treatment regimen; treatment patterns are presented in the Table. NBcombo patients had fewer RA-related emergency room (mean difference: -0.01) and office (0.46) visits but more prescriptions (1.1), other outpatient visits (0.04), and inpatient admissions (0.01) in the post-index period. In 204 NB-DMARD patients with claims data, the mean monthly cost was $267 (49% attributed to prescriptions, 42% to office/outpatient visits); costs for NBcombo were 6% higher vs NBmono.

**Conclusion:** Among RA patients treated with DMARDs, 79% received NB-DMARD (92% initiated as monotherapy). Approximately one third of NB-DMARD pts did not continue with any DMARD therapy in the 1-year follow up. NBcombo pts were less likely to continue their index treatment regimen, and only 14% initiated a biologic DMARD.

Deyo-Charlson Comorbidity index, mean (SD) 0.93 (1.2) 0.77 (1.0)
Index prescriber (if known), n (%) 0.43 (0.5) 0.37 (0.5)
Primary care physician 1288 (17) 85 (14)
Rheumatologist 4385 (58) 270 (43)
Other 1002 (13) 165 (27)
RA medication use on Day 0, n (%) 744 (11) 25 (4)
NSAIDs 1114 (15) 180 (29)
Corticosteroids 2265 (30) 235 (38)
Opoids 961 (13) 117 (19)

**Treatment patterns**

| Continued index regimen, n/N (%) | 3257/7598 (43) 621 (39) |
| Did not continue index regimen, n/N (%) | 4341/7598 (57) 621 (61) |
| Next regimen: NB-DMARD, n/N (%) | 1380/7598 (17) 4662/1 (7) |
| Next regimen: Biologic, n/N (%) | 835/7598 (11) 621 (14) |
| Next regimen: Biologic + NB-DMARD, n/N (%) | 23/7598 (0.3) 621 (0.3) |
| Next regimen: No DMARD, n/N (%) | 2190/7598 (29) 621 (39) |

**Mean RA-related Healthcare Resource Use**

| Inpatient admission | 0.10 0.11 |
| ER visits | 0.06 0.05 |
| Office visits | 5.17 4.71 |
| Other outpatient visits | 0.59 0.63 |
| Pharmacy | 7.70 8.81 |

**Disclosure:** D. Wiederkehr, Pfizer Inc, 1, Pfizer Inc, 3; J. Harnett, Pfizer Inc, 1, Pfizer Inc, 3; R. Gerber, Pfizer Inc, 1, Pfizer Inc, 3, D. Gruben, Pfizer Inc, 1, Pfizer Inc, 3; E. Y. Mahgoub, Pfizer Inc, 1, Pfizer Inc, 3; G. Wallenstein, Pfizer Inc, 1, Pfizer Inc, 1, A. Koenig, Pfizer Inc, 1, Pfizer Inc, 3.

**Country of Residence and Its Wealth Determine Disease Activity Levels in RA: Results from Multi-National Study Across 17 Countries (COMORA)**

**Background/Purpose:** Socio-economic (SE) inequalities in health persist both between and within countries and even increased in the recent years. Therefore, it is important to explore whether country level factors may contribute to health inequities in patients with RA. The objectives of this study was to (1) investigate whether country level factors contribute to explain Disease Activity Score (DAS28) (2) explore whether uptake of bDMARDs (Figure 2).

**Methods:** Data from a cross-sectional multinational (17 countries) study (COMORA) was used. The outcome was DAS28. Contribution of country to DAS28 was explored in multivariable linear regression models, adjusting for potential confounders, using forward selection and accounting for multiple testing. The country with lowest DAS28 (Netherlands (NL)) was used as potential confounders, using forward selection and accounting for multiple.

Differences in average DAS28 between individual countries (Figure 1A) and countries grouped by GDP (Figure 1B). Estimates are derived from models adjusted for age, gender, education, high rheumatoid factor or anti-citrullinated protein antibody, and comorbidities.

**Disclosure:** P. Putrik, None; S. Ramiro, None; A. Keszei, None; I. Hmamouchi, None; M. Dougados, None; T. Uhlig, None; T. K. Kvien, None; A. Boonen, None.

**Real-World Utilization, Patient Characteristics and Persistency of Certolizumab Pegol Vs Other Anti-TNFs for the Treatment of Rheumatoid Arthritis in the United Kingdom**

**Background/Purpose:** Several anti-TNFs are currently approved in Europe for RA treatment including certolizumab pegol (CZP), adalimumab (ADA), etanercept (ETN), golimumab and infliximab. UK NICE guidance recommends CZP as a first-line biologic therapy for patients (pts) with RA, in conjunction with a Pts Access Scheme that provides CZP FREE of charge for the first 12 weeks (wks). The objective was to assess real-world CZP, and other subcutaneous anti-TNFs (ADA or ETN), RA pt characteristics and treatment utilization in the UK.

**Methods:** A descriptive, retrospective, observational chart analysis was conducted in 4 UK rheumatology clinics. Medical data were collected over 52 (−6/+9) wks for biologic-naïve pts initiating an anti-TNF (N = 187); visit schedule was not prescribed therefore exact visit timing varied across pts. Data are reported for CZP pts and those receiving Other Anti-TNFs. Treatment persistency was assessed up to Wk52 using Kaplan-Meier estimates with pts censored at treatment discontinuation (ie. stop first anti-TNF treatment and switch to another/stop anti-TNFs) and excluding reinitiators (ie. pts with a gap in therapy returning to treatment within follow-up period).

**Results:** Baseline (BL) data were available for 110 CZP pts and 77 pts receiving Other Anti-TNFs (Figure 1A). At initiation, 14.5% (16/110) and 20.8% (16/77) pts received CZP and Other Anti-TNF monotherapy, respectively. Of those receiving combination therapy, 79.8% (75/94) CZP and 78.7% (48/61) Other Anti-TNF pts received concomitant MTX.
Due to the retrospective nature of data collection, not every pt had all data available; data were collected for 110, 108, 82 CZP pts and 77, 74, 50 Other Anti-TNF pts over 12, 24, 52 wks, respectively. Treatment persistency was 95.5%, 82.6%, 71.8% for CZP and 90.9%, 73.5%, and 65.0% for Other Anti-TNF pts at 12, 24, 52 wks, respectively (all lower bounds above 60% for corresponding CIs) (Figure 1B). Mean treatment persistency was 46.3 (95% CI: 43.2–49.4) and 43.1 (95% CI: 38.5–47.7) wks for CZP and Other Anti-TNF pts, respectively. Of pts initiating CZP, 2.7% switched therapy to another anti-TNF at any time during follow-up (n=1; 1 pt each 0–11, 12–24, 25–52 wks). Similarly, 6.5% of Other Anti-TNF pts switched to another anti-TNF (n=5; 4 pts before Wk12, 1 pt 12–24 wks). Compared to CZP pts, the risk of discontinuation in the Other Anti-TNF group was 37.4% greater (Hazard Ratio=1.374; 0.820–2.302). The majority of discontinuations occurred within the first 24 wks for both groups.

Conclusion: In this descriptive study, BL demographics/disease activity for pts treated with anti-TNFs in the UK were broadly similar between groups. Treatment persistency in this real-world observational study was also similar between CZP and Other Anti-TNFs in anti-TNF naïve pts. Interpretation of data is limited due to general caveats inherent to retrospective analyses.

Disclosure: F. Humby, None; S. Kelly, Abbvie, MSD, Roche, UCB Pharma, 8; A. V. Bedenbaugh, UCB Pharma, 3, UCB Pharma, 1; N. Qizilbash, OXON Epidemiology, 3; J. Dunkel, UCB Pharma, 3; B. SunJose, OXON Epidemiology, 3; I. Mendez, Employee OXON Epidemiology, 3; J. Timoshanko, UCB Pharma, 3; J. Tambiah, UCB Pharma, 3, UCB Pharma, 1.

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Rheumatology e-Consult Services: a Rheumatology Workforce Management Model. Thomas Schmidt1, Charles Lappan2 and Daniel Battafarano3. 1SAUSHEC/ Brooke Army Medical Center, San Antonio, TX, 2United States Army, San Antonio, TX, 3San Antonio Military Medical Center, JBSA - Ft San Houston, TX.

Background/Purpose: The regional distribution of adult rheumatologist in the United States (U.S.) was recently analyzed by the American College of Rheumatology (ACR). Regional workforce shortages were recognized with suggested options to address this concern. Electronic digital consultation (e-Consult) is one proposed solution. An e-Consult service was implemented by the U.S. Army to assist providers in remote global areas.

Methods: A retrospective analysis of rheumatology e-Consults from May of 2006 to May of 2014 was performed. Military providers from all services submitted consultation requests via a secure email site with digital file attachments. Patient identifiable information was excluded. A total of 24 rheumatology staff and fellows provided e-Consult services, and a program manager monitored and aggregated data for rheumatology. Collaboration with other e-Consult services was available and facilitated through the program manager.

Results: A total of 193 rheumatology e-Consults were processed. The average response time was 5.3 hours with 98% answered within 24 hours. There were 122 requests (63%) from Iraq and Afghanistan. Diagnoses included: inflammatory arthritis (65; 22 polyarticular, 18 RA; 14 gout, 8 infectious, 3 monoarticular), seronegative spondyloarthropathy (27; 9 psoriatic arthritis, 6 reactive, 6 undifferentiated, 1 inflammatory bowel disease), arthropalgias/myalgias (24), elevated CPK (8), lupus (7; 4 SLE, 2 discoid, 1 permio), Raynaud’s phenomenon (7), mechanical pain (7), positive ANA (6), sicca syndrome (4), DM (1) and 37 other. e-Consult collaboration was common and primarily with dermatology (29) and infectious disease (13).

Conclusion: Over an 8-year period an Army rheumatology e-consult service successfully assisted remote providers with diagnosis and management of rheumatic diseases. This global, collaborative model provided timely subspecialty care and input to providers that did not have immediate access to a rheumatologist. A similar digital and collaborative management model may facilitate rheumatology support for non-rheumatologists in underserved or remote areas.


Disclosure: T. Schmidt. None; C. Lappan. None; D. Battafarano. None.

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Reasons for Leaving an Academic Career in Research Among Rheumatologists in the United States. Alexis Ogdie1, Ami Shah2, Una Makris3, Alfred Kim4, Sheila Angeles-Han5, Ami Golding6, J. Michelle Kahlenberg7, Eyal Mucal7, Flavia V. Castellino8 and Amanda Nelson9. 1University of Pennsylvania, Philadelphia, PA, 2John Hopkins University, Baltimore, MD, 3Dallas VA Medical Ctr, Dallas, TX, 4Washington Univ School of Med, Saint Louis, MO, 5Emory University School of Medicine, Atlanta, GA, 6Baltimore VA and University of Maryland School of Medicine, Baltimore, MD, 7University of Michigan, Ann Arbor, MI, 8Texas Children’s Hospital, Houston, TX, 9Massachusetts General Hospital, Boston, MA, 10University of North Carolina at Chapel Hill, Chapel Hill, NC.

Reasons for leaving an academic career in research among rheumatologists

Background/Purpose: Retention of academic rheumatologists in research careers is increasingly challenging in the current funding environment. However, beyond funding, reasons for leaving a career in research remain unknown. The objective of this study was to examine factors for leaving a career in research among rheumatologists.

Methods: A web-based survey was conducted among the domestic ACR membership from Jan-Mar 2014. Inclusion criteria were current or previous fellowship in rheumatology, ACR membership, and an available email address. Non-rheumatologist members were excluded. The survey assessed demographics, research participation, barriers/facilitators to a career in research, and free text response for reasons for leaving a career in research. After excluding incomplete surveys and duplicates, demographics were summarized. Content analysis was used to extract relevant themes from free text comments.

Results: Ninety-seven respondents (among 430 complete responses) indicated that they had previously pursued a career in research but decided to switch career paths. This career change occurred a median of 10 years ago (interquartile range [IQR] 3–20) and a median of 7 years after completing fellowship (IQR 2–14). Previous research types and current positions are presented in the Table. Approximately half of respondents were female. The most commonly cited reasons for leaving a research career were difficulty obtaining funding and lack of department or division support (Table). Among 27 free text comments, respondents noted additional reasons for leaving research including new opportunities in administration, teaching and clinical care, great clinical burden and insufficient protected time to be successful in research endeavors, increasing age, difficulty financially supporting a family, difficulty covering loans with low salary, need for increased job security, lack

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Rheumatology e-Consult Services: a Rheumatology Workforce Management Model. Thomas Schmidt1, Charles Lappan2 and Daniel Battafarano3. 1SAUSHEC/ Brooke Army Medical Center, San Antonio, TX, 2United States Army, San Antonio, TX, 3San Antonio Military Medical Center, JBSA - Ft San Houston, TX.

Background/Purpose: The regional distribution of adult rheumatologist in the United States (U.S.) was recently analyzed by the American College of Rheumatology (ACR). Regional workforce shortages were recognized with suggested options to address this concern. Electronic digital consultation (e-Consult) is one proposed solution. An e-Consult service was implemented by the U.S. Army to assist providers in remote global areas.

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Disclosure: T. Schmidt. None; C. Lappan. None; D. Battafarano. None.
of mentorship, unsupportive environment or institution, need to move to a new geographic area without opportunities for research, and fear of having to move if not successful in obtaining funding or achieving tenure. When asked what would have kept them in a research career, the most commonly cited reasons for leaving a career in research, division support and protected time were similarly important. These results suggest that enhancing institutional support of academic research in rheumatology should be an important emphasis in order to support and sustain research careers.

Table: Participants who decided to leave a research career (N=97)

| Gender (M/F) | 45 (46%)
| Year of fellowship completion (median and IQR) | 1993 (1983–2005)
| Years Since Transition (median and IQR) | 10 (3–20)
| Years after fellowship transition occurred (median and IQR) | 7 (2–14)
| Current Position |
| Adult Rheumatologist | 78 (80%)
| Pediatric Rheumatologist | 14 (14%)
| Pediatric Fellow | 5 (5%)
| Pediatric Fellow | 0 (0%)
| Current Place of Employment |
| Academic Medical Center | 52 (54%)
| Clinical Practice | 24 (25%)
| Industry | 17 (18%)
| Government | 2 (2%)
| Retired | 2 (2%)
| Academic Appointment |
| Instructor or other Junior Faculty | 6 (6%)
| Assistant Professor | 14 (14%)
| Associate Professor | 21 (22%)
| Professor | 22 (23%)
| Other (no academic appointment) | 34 (35%)
| Previous Type of Research |
| Clinical | 47 (48%)
| Epidemiology/Health Services | 8 (8%)
| Translational | 36 (37%)
| Basic Science | 49 (51%)
| Factors Contributing to Decision to Leave |
| Difficulty obtaining grant funding | 55 (57%)
| Lack of division/department support | 51 (53%)
| Better compensation | 38 (39%)
| Lack of mentorship | 38 (39%)
| Tired of writing grants | 33 (34%)
| Personal reasons* | 26 (27%)
| Desire to spend more time in clinical care | 20 (21%)
| Exciting opportunities in industry | 10 (10%)
| Did not enjoy research work | 6 (6%)
| What would have retained you in a research career? |
| Provide internal grant funding mechanisms | 54 (56%)
| Increase protected time | 50 (52%)
| Increase income | 31 (32%)
| Increase work flexibility | 25 (26%)
| Provide greater leadership opportunities | 25 (26%)
| Nothing would have incentivized me to stay in academics | 9 (9%)

*Personal reasons included desire to move geographically (N=16) or desire to spend more time with family (N=15).

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Background/Purpose: Gout is caused by chronic high serum uric acid (SUA) levels (i.e., hyperuricemia), which leads to the deposition of monosodium urate crystals in musculoskeletal structures (e.g., joints), kidneys, and other connective tissues and urate crystal deposition disease, which can result in chronic inflammation leading to acute gout flares and tophi. Hyperuricemia is a metabolic disorder caused mainly by inefficient renal excretion of uric acid. Because SUA levels are often not at target, it is important to examine how this may relate to resource use and health utility. Additionally, this study examines other factors such as comorbidities and how they may exacerbate the relationship between high SUA levels, resource use, and health utility.

Methods: The data are from the combined 2012 and 2013 U.S. National Health and Wellness Survey (NHWS), a representative, cross-sectional general health survey (2012 NHWS: N = 71,157; 2013 NHWS: N = 75,000) of which 3,729 self-reported being diagnosed with gout. Those diagnosed were categorized into uncontrolled (N = 2,215) and controlled (N = 344) gout (“controlled gout” defined as: SUA ≤6 mg/dL, and no flares in past year), omitting those whose control status was unknown (N = 1,170). Weights were calculated to be representative of the U.S. adult population and analyses were based on the weighted data. Resource use in the past six months, health related quality of life (SF-36v2: mental and physical component summary (MCS, PCS) and SF-6D (health utility), and work productivity loss (WPAI) were assessed across the two groups. Comorbidities (e.g., diabetes, hypertension) and their relationship to resource use and health utility were also examined.

Results: Those with uncontrolled gout reported being hospitalized (13.8% vs. 8.1%) and visiting the ER (22.3% vs. 11.7%) more than those with controlled gout. Additionally, those with uncontrolled gout reported lower MCS (Mean = 47.22 vs. Mean = 51.96), PCS (Mean = 41.95 vs. Mean = 46.32), and health utility (Mean = 0.66 vs. Mean = 0.73) scores than those with controlled gout. Furthermore, those with uncontrolled gout reported higher work productivity loss (24.5% vs. 16.2%) and activity impairment (40.2% vs. 28.2%) than those with controlled gout. Having a common comorbidity with uncontrolled gout increased resource usage compared with either 1) those uncontrolled without the comorbidity or 2) with controlled gout, as was shown with diabetes (ER visits: 27.2% vs. 13.7% and 22.6%, respectively).

Conclusion: These findings support that uncontrolled gout results in greater hospitalization and twice as many ER visits than controlled gout. This, combined with lower health utility than controlled gout, suggests a significant humanistic and economic impact. These impacts may be further compounded when comorbidities are present.

Disclosure: R. Morlock, Ardea Biosciences, Inc., 1; Ardea Biosciences, Inc., 2; N. Flores, Kantar Health, 3; K. Annunziata, Kantar Health, 3; J. Chapnick, Kantar Health, 3; S. Ramachandran, AstraZeneca, 1, AstraZeneca, 3.

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Patient Reported Outcomes Following Upper Extremity Arthroplasties in RA—a Report from the Swedish National Register of Rheuma Surgery (RAKIR), Ann Bremander1, Sofia Forsberg2, Emilie Gull2 and Anna Nilsdotter3.

1Spenshult Research and Development Center, Halmstad, Sweden.
2Halmstad Central Hospital, Halmstad, Sweden.

Background/Purpose: RAKIR, the Swedish National Register of Rheuma Surgery was created to follow joint surgery in patients with RA (rheumatoid arthritis). The aim of this study was to analyze PROMs (patient reported outcome measures) from RAKIR regarding HRQoL (health related quality of life), pain and function in RA patients admitted for arthroplasty in the upper extremity. A secondary aim was to study expectations and satisfaction related with these procedures.

Methods: 106 (87 women, age mean 63, SD 13 years) patients with RA admitted for arthroplasty in the upper extremity, followed in RAKIR, were included (2007–2011). All patients answered the questionnaires SF-36, HAQ and QDASH preoperatively, 6 months postoperatively and at a 2–6 year follow-up (2013). Questions concerning expectations and satisfaction were asked at the same time.

Results: RA patients operated on with arthroplasty in the upper extremity (shoulder n=36, elbow n=20, wrist n=21 and MCP n=29) showed a significant improvement in HRQoL, pain and function 6 months after surgery (p ≤ 0.05, n=61). The improvement remained 2–6 years later (n=50). The patients expectations concerning pain relief was fulfilled, the expectations concerning improvement in ADL and function was surprisingly low but in an even greater extent fulfilled.

Conclusion: Long term follow-up with PROMs showed that patients with RA, in need of arthroplasty in the upper extremity, are satisfied, experience pain relief as well as improved function and HRQoL as long as 2–6 years after surgery. However, the response rate in a register is dependent on the patients’ benignity and may influence the results.

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Use of Internet in Adolescents and Young Adults with JIA. Phelimone A. van Pelt1, Constance H.C. Drossaert2, Radboud JEM Dolhain3, A.A. Kruize4, Jaap Huismann4 and Nico Wulffraat5. 1Erasmus MC, Rotterdam, Netherlands, 2University of Twente, Enschede, Netherlands, 3Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands, 4University Medical Center Utrecht, Utrecht, Netherlands, 5Wilhelmina’s Children Hospital UMC Utrecht, Utrecht, Netherlands.

Background/Purpose: Internet-use is increasing since it is an efficient way to find information. Information obtained via Health Related Internet (HRI) sites, or online peer support groups might increase knowledge and self-management in adolescents and young adults with Juvenile Idiopathic Arthritis (JIA). This study evaluates the frequency of use and perceived relevance of HRI use and its association with demographic, disease-related and psycho-social variables.

Methods: In a cross-sectional study, all consecutive JIA patients from the outpatient clinic (age 10 – 27 years) who gave informed consent were asked to complete a self-reported questionnaire. Frequency of using HRI-sites (regarding information about JIA, medication-use and aspects of JIA related to social life) as well as having online contact with fellow patients were evaluated. Perceived relevance of HRI use and contact with fellow patients were also investigated. Demographic variables, disease activity, medication and emotional behavior and coping were assessed as possible predictors.

Results: 142 patients were included and 98% had access to internet. 71% had used internet to search general information on JIA, but specific topics such as medication, were less searched for (6–35%). Most favorite sites to look for information were www.reumaforum.nl (Dutch Arthritis Foundation, 20%); www.google.com (16%); www.jeugdreuma.com (UMCU hospital site for rheumatic diseases; 14%) and www.prinott.com (Pediatric Rheumatology European Society information site; 3%). One in four adolescents had ever visited a forum or had online contact with peers. Most favorite discussion fora were www.reumaforum.nl (peer support for general rheumatic diseases; 14%); www.jeugdreuma.com (parents of children support forum; 5%) and www.medcontinent.wellcom.nl (peer support information and forum for 16–30 year old patients; 5%). Whereas most had used the internet to find information about JIA, the perceived relevance of HRI-sites and of opportunities for online peer contact was rated low (medians respectively 2.0 and 1.0 on a scale 0–10).

Female gender was positively associated with HRI use (P<0.01), other demographic and disease related factors were not associated with HRI use. Coping styles “confrontation” and “reassuring thoughts” were associated with increased HRI use, but only in males. Internalizing and externalizing problem behavior were not significantly associated.

Conclusion: Frequency of Health Related Internet use in young people with JIA was less than expected and considered of low relevance. Besides behavior were not significantly associated.

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Patient Reported Outcomes Following Total Knee Arthroplasty in Rheumatoid Arthritis and Osteoarthritis. Anand Dusad1, Sofia Pedro2, Kevin Garvin3, Curtis Hartman4, James O’Dell4, Ted R. Mikuls5 and Kaleb Michaud1. 1University of Nebraska Medical Center, Omaha, NE, 2National Data Bank for Rheumatic Diseases, Wichita, KS, 3University of Nebraska Medical Center and National Data Bank, Omaha, NE.

Background/Purpose: Due to the progressive and debilitating nature of knee arthritis, total knee arthroplasty (TKA) is the ultimate outcome. TKA is an effective surgical intervention for relieving pain and restoring function in patients with end-stage knee arthritis. Even though the beneficial impact of TKA is well documented, its effect on patient reported indices of pain and health related quality of life (HRQoL), especially in the RA population, are scarce. We examined the effects of TKA on pain and HRQoL in RA and OA patients.

Methods: Rheumatologist-diagnosed RA (n=834) and OA (n=315) patients undergoing primary TKA during 1999–2012 were identified. Measures of pain, function and HRQoL were obtained in three consecutive 6-month intervals: pre-operative (baseline), peri-operative and post-operative (recovery). Descriptive statistics and one-way ANOVA were used to compare TKA outcomes by diagnosis. Effect sizes were calculated between baseline and recovery period for each measure and graphs were plotted to follow these over time (≥3 years of TKA), for both RA and OA patients.

Results: Patients with RA and OA were similar in age (65 vs 68 years, respectively) and elapsed time [baseline sampling to TKA and TKA to recovery] (4.4 vs. 4.5 and 10.4 vs. 10.3 months). Post TKA, significant improvements were observed for most domains of pain, function and HRQoL, indices with both disease groups (p<0.001). The beneficial effects of TKA were more profound in OA patients, as compared to RA, for all measures of pain and HRQoL indices except for RADAI/total joint count [RA (0.42 vs. OA (0.30)) and EQ-5D [RA (0.07) vs. OA (0.06)]. By effect size, maximum significant (p<0.001) improvement was shown in index knee pain (RA -1.69 vs. OA -1.85). Beyond pain outcomes, EQ-5D and SF-36 PCS were the most responsive HRQoL measures in detecting post-TKA improvement in RA and OA (p<0.001 in both groups), respectively (Table 1). For all outcomes examined, improvements were greatest in the first post-operative year, showing gradual declines thereafter.

Conclusion: TKA is highly effective in reducing clinically relevant index knee pain to a greater extent than other subjective HRQoL indices in patients with RA, although this improvement is less marked than that observed in OA patients. Gains observed in pain, function, and HRQoL are most striking in the first 12 months following TKA, paralleling levels reported often years prior to joint replacement. From our results, TKA acts as a “time machine” by which a patient returns to a reduced pain and less disabled lifestyle, before the arthritic process catches up, which is strikingly faster in RA.

Table 1. Mean change (SD) and effect size between baseline and recovery period

<table>
<thead>
<tr>
<th>Measure</th>
<th>RA Effect size</th>
<th>OA Effect size</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index knee pain</td>
<td>-1.47 (0.88)</td>
<td>-1.69</td>
<td>-1.47 (0.79)</td>
</tr>
<tr>
<td>VAS Pain</td>
<td>-1.12 (2.67)</td>
<td>-0.42</td>
<td>-1.74 (2.60)</td>
</tr>
<tr>
<td>RADAI/total joint count</td>
<td>-0.40 (4.92)</td>
<td>0.08</td>
<td>-0.31 (4.61)</td>
</tr>
<tr>
<td>RADAI/total joint score</td>
<td>-1.41 (10.07)</td>
<td>-0.14</td>
<td>-1.88 (8.47)</td>
</tr>
<tr>
<td>HAQ</td>
<td>-0.09 (0.66)</td>
<td>-0.14</td>
<td>-0.15 (0.59)</td>
</tr>
<tr>
<td>SF-36 PCS (0–100)</td>
<td>3.59 (9.30)</td>
<td>0.37</td>
<td>4.57 (8.94)</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>0.40 (2.65)</td>
<td>0.06 (0.20)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

# and @ represent indices with significantly (p<0.05) less and more severe scores, respectively, in RA (vs. OA) patients undergoing TKA at baseline. Bold numbers represent significant (p<0.05) values between baseline and recovery within the respective groups.

Disclosure: A. Dusad, None; S. Pedro, None; K. Garvin, None; C. Hartman, None; J. O’Dell, Abbvie, Lilly, Antares, Medac, S. T. R. Mikuls, None; K. Michaud, None.

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Knee Arthroscopy in an International Training Centre: An Audit of Safety and Impact on Work Days. Carl Orr1, Paul MacMullan2, Phil Gallagher2, Mairaedd Murray2, Madeline O’Neill1 and Douglas J. Veale1. 1Dublin Academic Medical Centre, St. Vincent’s University Hospital, Dublin, Ireland, 2St. Vincent’s University Hospital, Dublin, Ireland, 3St. Vincent’s University Hospital Dublin, Dublin 4, Ireland.

Background/Purpose: The utility of synovial biopsy has been confirmed as an important research tool in increasing our understanding of the pathogenesis of RA, evaluating new treatments and identifying potential therapeutic targets (1, 2). More rheumatology units are introducing arthroscopy as part of their research programs,(3). In 2004, we published data showing that complication rates are very low (4), however it is critically important to continue to monitor safety and audit our outcomes.

All procedures are performed under local anaesthesia in a state of the art, built-for-purpose facility.

We collected and analysed the experience reported by patients following arthroscopy in our unit, examining parameters such as overall tolerability, pain, time out of work post-arthroscopy and complications.

Methods: Consecutive patients returning to the arthroscopy programme since July 2013 completed a questionnaire including 16 questions, three visual analogue scales (VAS 0mm-100mm), as well as binary questions.

Results: 136 (47 male) respondents are included, age 20–82 years (mean 53.76, SD 13.86).

91.2% (124/136) of patients felt they had received adequate information before the procedure. 84.6% (115/136) reported that the procedure matched
their expectations. The main concern before the arthroscopy was potential pain during the procedure cited by 78.7% (107/136); the mean VAS for pain during the procedure was 50mm (SD 34.6); in the first 48 hours after the procedure 31mm (SD 28.2); and 15mm (SD 24.1) in the month following the procedure. There was no correlation between diagnosis, age or sex to VAS.

64.0% (73/114) were out of work for less than 2 days, 29.8% (34/114), and 6.1% (7/114). The remainder of patients left this field blank. No significant complications were reported. 66.9% (91/136) felt improvement in their knee symptoms following arthroscopy.

Conclusion: Knee arthroscopy remains a safe and well-tolerated research procedure. The procedure is well tolerated under local anaesthesia, and many patients experience an improvement in their knee symptoms. Patients are out of work for very short periods following arthroscopy and no significant complications were reported.

References

Disclosure: C. Orr, None; P. MacMullan, None; P. Gallagher, None; M. Murray, None; M. O’Neill, None; D. J. Veale, Abbvie, 2, MSD, 2, Pfizer Inc, 2, Roche, 2, Pfizer, 5, Roche, 5, Abbott, 8, MSD, 8, Pfizer, 8, Roche, 8.

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Use of Smartphones in Collecting Patient Reported Outcomes: Can Passively-Collected Behavior Determine Rheumatic Disease Activity? Early Results from a Nation-Wide Pilot Study.


Background/Purpose: Rheumatoid arthritis (RA) and other rheumatic diseases (RD) are associated with depression, fatigue, and disturbed sleep, symptoms that often impact behavior. Many smartphone apps allow patients with RDs to regularly report their disease activity for better self-management and clinical followup. Recent advances in reality mining technology combined with the growing use of smartphones have shown measurable changes in phone behavior due to health issues like depression, stress, and influenza. We sought to learn if there are associations of phone behavior with RD patient reported outcomes.

Methods: We invited 700 patients in the National Data Bank for Rheumatic Diseases to participate by installing a custom app on their smartphone and answering questions regularly: a daily pain VAS for 60 days and a weekly Patient Activity Scale-II (PAS-II) for 6 months. Passive data collected included mobility distance, number of unique calls and text messages, call durations, call counts, and number of missed calls. A principal component analysis (PCA) based on the correlation data was performed on the passive data. The screen plot and the Kaiser criterion were used to select the number of clusters. A hierarchical cluster analysis was also performed using Euclidean dissimilarity metric and the average linkage criterion, with the number of clusters determined by the elbow method. We used GEE models to examine the association of passive data with weekly PAS-II scores over time.

Results: We invited 700 patients in the National Data Bank for Rheumatic Diseases to participate by installing a custom app on their smartphone and answering questions regularly: a daily pain VAS for 60 days and a weekly Patient Activity Scale-II (PAS-II) for 6 months. Passive data collected included mobility distance, number of unique calls and text messages, call durations, call counts, and number of missed calls. A principal component analysis (PCA) based on the correlation data was performed on the passive data. The screen plot and the Kaiser criterion were used to select the number of clusters. A hierarchical cluster analysis was also performed using Euclidean dissimilarity metric and the average linkage criterion, with the number of clusters determined by the elbow method. We used GEE models to examine the association of passive data with weekly PAS-II scores over time.

Conclusion: There was no correlation between phone behavior change in three components and 2 profiles that well-distinguished RD diagnosis. Our longitudinal models showed significant association of phone behavior with pain and PAS-II scores over time. This pilot study holds promise for passive behavior to be used in patient self-management and clinical followup.

Disclosure: K. Michaud, None; S. Pedro, None; R. Schumacher, None; K. Wahba, None; S. Moturu, None.

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Low Rates of Bone Mineral Density Testing in Medicare Beneficiaries with Breast Cancer Starting Aromatase Inhibitor Therapy.

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Background/Purpose: Aromatase inhibitors (AI) are increasingly used as adjuvant hormonal therapy in postmenopausal women with estrogen receptor-positive breast cancer. It is well recognized that therapy with AI increases the risk of bone loss and fractures. Therefore, it has been recommended that women who are beginning AI therapy undergo bone mineral density (BMD) measurement at baseline and periodic intervals. The objective of our study was to determine the rates and predictors of dual-energy x-ray absorptiometry (DXA) scan use in breast cancer patients started on AI in the state of Texas who were Medicare beneficiaries.

Methods: In a retrospective cohort study, we identified all Medicare female beneficiaries diagnosed with breast cancer in the period 2005–2010 from the Texas Cancer Registry/Medicare claims-linked database available through the Comparative Effectiveness Research on Cancer in Texas (CERR) consortium. Claims for DXA were obtained from Medicare part B for a period from one year before to 6 months after AI initiation. We also evaluated the use of bone-conserving agents (BCA). We collected data for prescription drugs from Medicare part D claims. We used multivariate logistic regression models to determine the association of sociodemographic variables with DXA use after controlling for disease stage and type of AI.

Results: Our breast cancer study cohort included 3587 women. Of these, 1999 (55.7%) underwent DXA between 1 year before and 6 months after AI initiation. Women aged 75 and above were less likely to receive DXA (odds ratio [OR], 0.80; 95% CI, 0.70–0.91) and less likely to receive either DXA or BCA (OR, 0.80; 95% CI, 0.70–0.92) than were women aged 66–74 years. African American women were less likely to receive DXA (OR, 0.70; 95% CI, 0.57–0.92) and less likely to receive either DXA or BCA than were non-Hispanic white women (OR, 0.68; 95% CI, 0.52–0.90).

Women living in urban areas were less likely to undergo DXA than women living in big metropolitan areas (OR, 0.71; 95% CI, 0.53–0.97). Women with state buy-in enrollment plans were less likely to receive DXA (OR, 0.61; 95% CI, 0.51–0.73) and less likely to receive either DXA or BCA (OR, 0.62; 95% CI, 0.51–0.74) than were women with no such enrollment.

Conclusion: Slightly more than 50% of Texas Medicare female beneficiaries with breast cancer beginning AI treatment received DXA. Rates of DXA varied with the patient’s age, size of area of residence, and socioeconomic status. Differences between ethnic groups in the use of DXA/BCA were noted, with fewer African American women compared to white women receiving DXA or BCA.

Disclosure: M. Siricilla, None; R. Luo, None; L. Elting, None; M. E. Suarez-Almazor, None.

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Relationship Between Rheumatology Physician Supply and Travel Distances to Rheumatologists for Medicare Beneficiaries in the United States.

Gabriela Schmujak1, Chris Tonner2 and Jinoos Yazdany3. 1UCSF / San Francisco VA, San Francisco, CA, 2University of California, San Francisco, San Francisco, CA.
**Background/Purpose:** Workforce shortages in rheumatology have been reported in the face of an aging population and increased number of people gaming insurance under the Affordable Care Act. Population-wide studies of rheumatology supply and the distances that patients travel to see a rheumatologist have not been performed. We used national Medicare data to examine the actual distances patients travel for rheumatology care and hypothesized that patients travelling farthest would reside in low-supply areas.

**Methods:** Data derive from nationwide Medicare fee-for-service medical claims for 2009 for a 5% random sample of beneficiaries. All patients ≥ age 18 with 12 months of continuous enrollment in Medicare Parts A and B who had at least 1 visit to a rheumatologist were included. We calculated distance between the center of the patient’s 5-digit ZIP code and the center of the rheumatologist’s office 5-digit ZIP code for the first rheumatologist seen during the calendar year. We averaged distances according to health referral regions (HRRs), regional health care markets for tertiary medical care, and compared average distance with the supply of rheumatologists per HRR (publically available data through the Dartmouth Atlas). Individuals from HRRs with fewer than 40 eligible beneficiaries were censored from this analysis to increase the precision of our estimates.

**Results:** We studied 44,043 Medicare patients who had at least one visit to a rheumatologist during 2009, representing 245 HRRs. Median distance traveled was 9.3 miles (IQR 4–22). 10% of patients travelled ≥50 miles to see a rheumatologist. Of those traveling long distances, 22% resided in an HRR with the lowest supply of rheumatologists (<0.85 per 100,000 residents) but over 25% resided in an HRR in the 2 highest quintiles of supply (>1.30 per 100,000 residents). When distances were averaged according to HRR, 13 (4%) of HRRs had an average travel distance of ≥50 miles; only 4 of these HRRs had a supply of rheumatologists in the lowest quintile (Figure).

**Conclusion:** A substantial proportion of patients in the United States travel significant distances to visit a rheumatologist, although a minority of these patients resides in areas with the lowest supply of rheumatologists. These findings are contrary to our original hypothesis that rheumatologist supply is the main reason for long travel distances. Whether factors such as physician participation in health plans, tertiary care referral patterns, and patient preferences affect travel distance will require additional study.

**Disclosure:** G. Schmajuk, None; C. Towner, None; J. Yazdany, None.

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**Treat-to-Target (T2T) and Measuring Outcomes in RA Care: a 2014 Longitudinal Survey of US Rheumatologists.** John J. Cush and Jeffrey R. Curtis. Baylor Research Institute and Baylor University Medical Center, Dallas, TX; University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL.

**Background/Purpose:** Changes in US rheumatologic practice for rheumatoid arthritis (RA) patients in the past decade have been influenced by novel therapies, increasing disease metric use and practice economics. This survey of US rheumatologists (Rheums) examined how commonly disease activity measures are used in clinical practice and if they inform decision-making or alter clinical practices over time.

**Methods:** In 2014, 2027 US Rheums were invited (via 2 emails) to an online survey that included 26 questions on demographics, practice characteristics, RA care practices, DMARDs/biologic use and the use of disease activity metrics. This 2014 cross-sectional survey of Rheums was compared with 2005 and 2008 responses (Table) to assess changes over time. Rheums doing metrics (Metric Rheums) were compared to those who do not (Non-Metric Rheums) with regard to their treatments and practices.

**Results:** Recruitment for this survey is ongoing. Thus far there are 317 respondents (18% response), with responders being mostly male (71%) with a mean age of 52.8 yrs; 40% of Rheums were in practice >25 yrs; up from 18.2% in 2005. Respondents were largely from private practice (67%) vs 48%), MRI (1.7 vs 8%), or ultrasound (3.9 vs 1.9%). Rheums reported they achieve high rates of ACR 20-like responses (72.6%) and remission (39%) in their patients. Disease activity measures increased since 2005, with the HAQ being the most commonly used measure in 2005 (18.2%) vs 2014 (48.6%). Rheums doing metrics (Metric Rheums) were compared with 2005 and 2008 responses (Table) to assess changes over time. Rheums doing metrics (Metric Rheums) were compared to those who do not (Non-Metric Rheums) with regard to their treatments and practices.

**Disclosure:** A. Sharma, None; L. A. Brown, None; D. Barton, None; J. Mecchella, None.

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**Dermatologic Rheumatism: Our Experience with a Multidisciplinary Dermatology/Rheumatology Clinic.** Archana Sharma, Lin A. Brown, Dorothea Barton and John Mecchella. Dartmouth-Hitchcock Medical Center, Lebanon, NH; Dartmouth-Hitchcock Medical Center, Lebanon, NH; Dartmouth-Hitchcock Medical Center, Lebanon, NH; Giesel school of medicine and Dartmouth Hitchcock Medical Center, Lebanon, NH.

**Background/Purpose:** Multidisciplinary clinics are becoming increasingly common as a way to bring together multiple specialists to care for patients with complex diseases. While multidisciplinary clinics commonly involve pulmonologist and cardiologist for patients with pulmonary hypertension, rheumatology and dermatology combined clinic are thought to be less common. Managing skin lesions in patients with known or possible autoimmune diseases can be a diagnostic and therapeutic challenge which often requires the combined expertise of dermatology and rheumatology. Previous studies have shown the benefit of managing patients with psoriasis and psoriatic arthritis in a combined dermatology and rheumatology clinic but to our knowledge there have not been any studies reporting the experience of a general dermatology/rheumatology clinic. We feel that our multidisciplinary clinic adds significant value to complex patients and this study sought to evaluate the clinical experience of a dermatology/rheumatology clinic.

**Methods:** We performed a retrospective chart review of all patients presenting to our dermatology / rheumatology combined clinic between July 2008 to April 2014 at Dartmouth-Hitchcock Medical Center. A total of 126 patients were seen over 158 visits. We reviewed demographic data, initial diagnosis, treatment modalities including procedures like skin biopsy, change in initial diagnosis and treatment.

**Results:** Of the 126 patients evaluated, 73% were referred by rheumatology and 27% by dermatology. The majority of participants were females (75%) and the mean age of the patients was 52 years. The average wait period to be seen in the clinic after the referral was made was 3.8 weeks. A skin biopsy was done in 24% patients during the visit and 19% had a skin biopsy reviewed at the visit. The most common initial diagnosis was connective tissue disease related rash (9.5%), SLE (9%) and vasculitis (9%). This was followed by drug rash, psoriasis and psoriatic arthritis. Seventy-seven patients (61%) had a change in diagnosis and treatment as a result of this combination clinic visit. Of the 77 patients who had a treatment change, 18% received DMARD therapy and 8% received biologics. On follow-up, 28.5% patients had significant or complete improvement, 43.5% patients had partial improvement. 12% reported no improvement at all and 16% were lost to follow up.

**Conclusion:** This study shows that the majority of patients seen in our multidisciplinary clinic had a change in the diagnosis and/or treatment. We believe that this clinic brings value to patients by simplifying the care of these complex patients by having multiple specialists in the same room with the patients. This integrated care approach improves the quality of care for our patients with skin and musculoskeletal diseases. Moreover this combined clinic increases access for these patients and as patients may receive appropriate treatment sooner, it may reduce the overall health care costs for these patients.

**Disclosure:** A. Sharma, None; L. A. Brown, None; D. Barton, None; J. Mecchella, None.
74.5%), while with others switched to abatacept (19%), tocilizumab (7%), rituximab (2%) or tofacitinib (1%). While a majority (20%) of Rheums don’t believe in the T2T “hype”, 43% assert they have always practiced in a T2T manner and 37% have adopted a T2T strategy for RA care.

**Conclusion:** Routine use of RA disease activity measures has become a practice standard in less than half of US rheumatologists. Despite their collection, there is little evidence that metrics are changing how patients are managed.

Changes over time in practice, TNFi and clinical metric use*

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2008</th>
<th>2014</th>
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<tbody>
<tr>
<td>N</td>
<td>1140</td>
<td>446</td>
<td>317</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td>49</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>TNFi use %</td>
<td>44.2</td>
<td>69</td>
<td>75</td>
</tr>
</tbody>
</table>

Use of RA Disease Activity Metrics at Routine Visits

- HAQ or MDHAQ
- RAPID3
- DAS28
- CDAI
- Vectra MBDA
- SDAI
- ACR20

None of the above

<table>
<thead>
<tr>
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<th>2005</th>
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<tbody>
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</tbody>
</table>

**Disclosure:** J. C. Cush, Pfizer, Celgene, CORRONA, Amgen, NIH, Novartis, UCSF Pharma, 2. J. R. Curtis, Roche, Genentech, UCSF Pharma, Jansen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2. Roche, Genentech, UCSF Pharma, Jansen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

**Biologic Dmards Modify the Association Between Patient Expectations and Outcomes of Total Knee Replacement in Rheumatoid Arthritis Patients,** Hassan Ghomrawi1, Lisa Mandll2, Mark P. Figgie2, Michael Alexander3 and Susan M. Goodman2. 1Well Cornell Medical College, New York, NY, 2Hospital for Special Surgery, New York, NY.

**Background/Purpose:** Unmet patient expectations of total knee replacement (TKR) correlate with postsurgical dissatisfaction, and are linked to outcomes. Patients with rheumatoid arthritis (RA), may have lower expectations than patients with osteoarthritis (OA), due to the systemic nature of the disease and its other manifestations such as fatigue. Biologic DMARDs enhance RA patient quality of life. The effect of pre-operative use of these medications on patient expectations and outcomes of TKR is not known. The purpose of this study was to assess the correlation of preoperative expectations with TKR outcomes in RA patients on biologics and those not on biologics, compared to matched OA patients undergoing TKR.

**Methods:** Validated RA patients were identified from an institutional TKR registry and their use of biologics was recorded from chart review. RA patients were matched to OA patients on age, sex, prior TKR, and preoperative activity level using the Lower Extremity Activity Score (0–18, 18 highest level of activity). Preoperative patients completed the validated Hospital for Special Surgery (HSS) Knee Expectations Survey (19 items, score range 0–100, 100 is highest expectation). At 2 years, patients completed the WOMAC pain and function. Preoperatively, expectation scores between RA patients on biologic DMARDs, conventional therapy and matched OA patients were compared. We used regression to determine the association between expectation scores and 2-year WOMAC pain and function subscale scores, adjusted for baseline score.

**Results:** One hundred fourteen RA cases, 46.5% on biologics, were matched to 228 OA cases. The RA cases were 11.8% male and the average age was 62.6 +/- 12.2 years. The average pre-operative LEAS score was 8.9 +/- 2.9, which corresponds to being able to walk around the house and walk for several blocks at a time without any assistance. 16.7% of the patients had a prior contralateral TKA. The mean duration of RA was 19.7 +/- 13.4 years. RA patients on biologics had expectations similar to matched OA patients (total expectation score 76.3 +/- 8 vs. 77.4 +/- 17, p = 0.71), while RA patients not on biologics had expectations that were clinically and statistically significantly lower (69.9 +/- 22.4 vs. 77.1 +/- 19, p = 0.038). Higher expectations scores were associated with better 2-year WOMAC function and pain scores (2-year WOMAC pain coefficient = 0.393, p-value=0.042, 2-year WOMAC function coefficient = 0.441, p-value<0.001) in RA patients not on biologics therapy but not in RA patients on biologic DMARDs (2-year WOMAC pain coefficient = -0.126, p-value=0.426, 2-year WOMAC function coefficient = 0.005, p-value=0.977) nor matched OA patients (2-year WOMAC pain coefficient = -0.037, p-value=0.614, 2-year WOMAC function coefficient = 0.060, p-value=0.460).

**Conclusion:** Expectations of post-operative outcomes are only significantly related to post-operative pain and function in RA patients not on biologic DMARDs; there is no relation in RA patients on biologics or in OA patients. The reasons for this are unclear, and whether this is due to unrealistic expectations in OA and RA patients on DMARDs or that biologics reduces the need to manage expectations needs to be explored.

**Disclosure:** H. Ghomrawi, None; L. Mandll, None; M. P. Figgie, None; M. Alexander, None; S. M. Goodman, None.

**Is Socioeconomic Status at Diagnosis Associated with Long-Term Direct Medical Costs in Systemic Sclerosis? a General Population-Based Cohort Study,** Natalie McCormick1, Mohsen Sadatsafavi2, Wensya Chen3, Carlo A. Marra4 and J. Antonio Avina-Zubieta5. 1University of British Columbia/Arthritis Research Centre of Canada, Vancouver, BC, 2University of British Columbia, Vancouver, BC, 3Univ of British Columbia, Vancouver, BC, 4Arthritis Research Centre of Canada, Richmond, BC.

**Background/Purpose:** Low socioeconomic status (SES) is associated with negative health outcomes and higher healthcare costs in general populations, but the impact of SES on costs in systemic sclerosis (SSc) is unknown. To address this knowledge gap, we examined the relationship between SES at diagnosis, and direct medical costs for 5 years after diagnosis, in a general population-based context. We hypothesized that baseline SES would be associated with higher costs.

**Methods:** Data Source: Our administrative data captured all provincially funded outpatient encounters and hospitalizations (1990–2010), and all dispensed medications (1996–2010) regardless of funding source, in the province of British Columbia.

**Sample:** We assembled a general population-based cohort of all incident cases of SSc who received care from 1996–2010, based on the following validated algorithm: a) two ICD-9-CM codes for SSc at least 2 months apart but within a 2 year period by a non-rheumatologist physician; b) one ICD code by a rheumatologist or hospitalization. Statistics Canada neighborhood income quintile data for the year of SSc diagnosis was used to define SES.

**Cost Calculation:** Costs for outpatient services and prescriptions were summed directly from billing data. Case-mix methodology was used for hospitalizations.

**Statistical Analysis:** Early mortality is common in SSc and likely associated with high costs before death, but failure to account for this censoring will underestimate the long-term costs of SSc. To address this, follow-up was divided into 90-day periods with costs per-period weighted by the person-specific inverse probability of being alive in each period. A generalized linear model was used to 1) Evaluate the relationship between SES and direct medical costs, after adjusting for sex, age and baseline Charlson’s comorbidity index; and 2) Predict the cumulative 5-year costs (adjusted for censoring) for cases in each SES group.

Parametric bootstrapping was used to obtain 95% confidence intervals (CI). Costs are reported in 2010 Canadian dollars.

**Results:** We identified 1,116 incident SSc cases (83% female, mean age 56.2 years) contributing 3,392 person-years. 5-year costs totaled $36,559,914 with 24% from outpatient, 48% from hospital and 28% from medications. Age (p<0.0278), Charlson’s co-morbidity score (p<0.001) and being in the lowest (p<0.0364) or middle (p=0.0015) SES quintile (vs. the highest) were significantly associated with costs. Predicted cumulative 5-year costs for the lowest-SES cases were 42% greater than the highest-SES ($55,035 vs. $38,664). Highest-SES cases had the lowest medication costs (see Table). Cases in the middle SES quintile at diagnosis had the highest outpatient, hospital and overall costs.

**Conclusion:** The long-term healthcare costs of SSc cases are substantial (averaging $51,643 per-person over 5 years), and associated with SES, being 42% greater, on-average, for the lowest-SES than the highest.
Predictors of Gout Flares in a US Managed Care Setting. Robert Jackson1, Aki Shiozawa2, Erin Buysman3, Aylin Altan4, Stephanie Korrer5 and Hyon K Choi6. 1Takeda Pharmaceuticals International, Inc, Deerfield, IL, 2Opus, Eden Prairie, MN, 3Boston University School of Medicine, Boston, MA.

Background/Purpose: Gout is the most common inflammatory arthritis in the US, and acute gout flares are among the most painful events experienced by humans. The goal of this study was to assess gout flares in a managed care setting to better understand the patient characteristics that are associated with frequent flares.

Methods: This was a retrospective cohort study using administrative claims data from a large US health plan of commercially insured and Medicare Advantage enrollees. Patients had evidence of gout based on medical and pharmacy claims indicating gout between January 1, 2009 and April 30, 2012. The 12 months prior to the index gout claim was used to assess baseline confounders including demographics, comorbid conditions, baseline health care resource utilization, and baseline serum uric acid (sUA) levels. Gout flares were assessed in the 12 months following the index gout claim based on diagnoses for gout or joint pain followed within 7 days by claims for NSAIDs, colchicine, corticosteroids, or joint aspiration/drainage. A negative binomial model was used to assess the relationship between patient characteristics and the count of gout flares in the 12-month follow-up period.

Results: Our study included 102,703 patients with gout; 56,611 patients (55%) had evidence of at least one gout flare in 12 months of follow-up, and 13,502 (13%) had multiple flares. Patients had on average 0.73 flares per year, and the average time between flares in patients with multiple flares was 115 days. Characteristics associated with a higher count of flares included Black race, lower economic status, Southern region of residence, baseline ambulatory utilization, new initiation of urate lowering drugs (ULT) during follow-up, and higher baseline sUA (Table). Cardio-metabolic-renal comorbidities appeared to be associated with fewer flares; however, this may be due to our definition of flares in the claims based on medication use (e.g., NSAIDs) that is often contraindicated with these conditions. Age and gender were not significantly associated with flare frequency after controlling for other confounders.

Conclusion: This large contemporary study of gout patients in a managed care setting indicates over half of patients experiencing at least one flare in a 12-month period, and nearly a quarter of those patients experiencing multiple flares. Black race, lower economic status, Southern region of residence, initiation of urate lowering therapy, and higher baseline sUA were associated with a higher risk for flares. These data may help identify patients at high risk for flares who could be targeted with a gout management plan aimed at preventing flares.

Table. Adjusted Incidence Rate Ratios for Gout Flares According to Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Incidence Rate Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender × Age Interaction</td>
<td>reference</td>
</tr>
<tr>
<td>Male, 18–44</td>
<td>0.98 (0.93, 1.03)</td>
</tr>
<tr>
<td>Male, 45–64</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>Male, 65+</td>
<td>0.95 (0.87, 1.03)</td>
</tr>
<tr>
<td>Female, 18–44</td>
<td>0.94 (0.80, 1.08)</td>
</tr>
<tr>
<td>Female, 45–64</td>
<td>0.95 (0.87, 1.03)</td>
</tr>
<tr>
<td>Female, 65+</td>
<td>1.02 (0.93, 1.11)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td>reference</td>
</tr>
<tr>
<td>Northeast</td>
<td>1.07 (0.98, 1.16)</td>
</tr>
<tr>
<td>Midwest</td>
<td>1.09 (1.00, 1.18)</td>
</tr>
<tr>
<td>South</td>
<td>1.12 (1.05, 1.19)</td>
</tr>
<tr>
<td>Race</td>
<td>reference</td>
</tr>
<tr>
<td>Black</td>
<td>0.86 (0.81, 0.90)</td>
</tr>
<tr>
<td>Other Race</td>
<td>reference</td>
</tr>
<tr>
<td>Net Worth</td>
<td>reference</td>
</tr>
<tr>
<td>$&lt;250,000/Unknown</td>
<td>1.06 (1.02, 1.11)</td>
</tr>
<tr>
<td>Baseline Cardiovascular Conditions</td>
<td>reference</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06 (0.92, 1.01)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.06 (0.93, 1.09)</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>0.89 (0.85, 0.93)</td>
</tr>
<tr>
<td>All-Cause Healthcare Resource Utilization</td>
<td>reference</td>
</tr>
<tr>
<td>Inpatient Stay or ER Visit</td>
<td>1.04 (0.99, 1.09)</td>
</tr>
<tr>
<td>Ambulatory Visits</td>
<td>1.14 (1.09, 1.20)</td>
</tr>
<tr>
<td>Baseline sUA Level (mg/dL)*</td>
<td>0.96 (0.80, 1.09)</td>
</tr>
<tr>
<td>&lt;5.0</td>
<td>1.01 (0.91, 1.12)</td>
</tr>
<tr>
<td>5.0–&lt;7.0</td>
<td>1.34 (1.22, 1.47)</td>
</tr>
<tr>
<td>7.0–&lt;8.0</td>
<td>1.51 (1.38, 1.65)</td>
</tr>
<tr>
<td>8.0–&lt;9.0</td>
<td>1.59 (1.45, 1.74)</td>
</tr>
<tr>
<td>9.0+</td>
<td>1.79 (1.63, 1.95)</td>
</tr>
</tbody>
</table>

Disclosure: N. McCormick, None; M. Sadatsafavi, None; W. Chen, None; C. A. Marra, None; J. A. Avina-Zubieta, None.

Difficult to Treat Gouty Arthritis Associated with Poor Health Related Quality of Life and High Resource Utilization: Post- Hoc Analysis. Louis Bessette1, Frédéric Liosté2, Carmen Moragues1, Rüdiger Moericke3, Zhang Zhiyi4, Alberto Ferreira5, Pascal Lecomte6, Sophia Kessabi6, Haijun Tian7 and Jasvinder Singh8. 1CHUL, Quebec, QC, 2Hospital Lariboisière & Université Paris Diderot, Paris, France, 3Hospital Pfàtzon, Barcelona, Italy, 4Institut für Präventive Medizin & Klinische Forschung Gbr, Magdeburg, Germany, 5The First Affiliated Hospital of Haerbin Medical University, Haerbin, China, 6Novartis Pharma AG, Basel, Switzerland, 7Novartis Pharmaceuticals Corporation, East Hanover, NJ, 8Mayo Clinic, Rochester, MN.

Background/Purpose: Difficult-to-treat (DTT) group in the MOTION study included symptomatic refractory gouty arthropathies (RGA) patients with ≥3 flares, refractory to NSAIDs/colchicine/sterooids or to uric acid lowering therapy (ULT) due to contraindication, intolerance, or lack of efficacy. There is lack of evidence on burden of illness in DTT patients. The study assessed burden of illness in DTT patients over 1 year.

Methods: A post hoc descriptive comparison was done between DTT vs the other refractory gout (ORG) patients using data from the MOTION (1 year, multinational, non-interventional, prospective, observational) study. Among DTT patients, outcomes for patients with tophi at baseline and patients who discontinued ULT prior to study entry were also summarized. The study outcomes (evaluated at baseline, by time point and pooled yearly) included health status using EuroQol Group 5-Dimension (EQ-5D) questionnaire, the Gouty arthritis Assessment Questionnaire–Gouty arthritis Impact Scale (GA-QGIS), pain assessment, healthcare utilization over 1 year and lost work productivity. Patient and physician satisfaction with treatment were measured by the Patient Global Assessment of Response to Treatment and Investigator Global Assessment of Response to Treatment. Continuous and categorical variables were reported as (mean ± SD) and as proportions, respectively, for the DTT and ORG patient groups.

Results: Among 454 patients enrolled in the MOTION study, 64 DTT patients (tophaceous group=29, discontinued ULT=35) were included in the analysis (mean age 55.2, males 85.9%). DTT patients had lower mean EQ-5D utility score and EQ-5D VAS score compared to ORG group, with worse scores in the tophaceous group (Table 1). Tophaceous group patients experienced greater difficulty on all EQ-5D dimensions and pain/discomfort was the most affected dimension in all groups. DTT patients reported greater overall gouty arthritis concern compared to ORG patients (76.5 vs 72.4%), with highest score in the tophaceous group (85.5%) for pooled data. Tophaceous group reported a higher score on all five dimensions of GAQ GIS. About 45.3% of DTT patients reported severe pain during last flare vs 37.2% ORG patients. Healthcare utilization was greater among DTT than ORG patients (35.9 vs 21.1%). A higher proportion in the tophaceous group visited emergency unit (55.2%), hospital (41.4%) and doctors (89.7%) over one year. Physicians and patients in DTT group were more likely to report poor response to treatment compared to ORG group. DTT group missed 23.4% of their working days compared to 15.6% in ORG patients at baseline, the highest being the tophaceous group (31%).

Conclusion: DTT patients had worse health status and reported higher resource utilization with significantly poorer outcomes reported in top乌素的 goit patients, suggesting a high unmet medical need in such patients.

Table 1: Mean EQ-5D utility score and EQ-5D VAS pooled for all visits

<table>
<thead>
<tr>
<th></th>
<th>EQ-5D utility score</th>
<th>EQ-5D VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
</tr>
<tr>
<td>DTT patients (N = 64)</td>
<td>0.78 ± 0.23</td>
<td>73.72 ± 20.40</td>
</tr>
<tr>
<td>DTT with tophi at baseline (N = 29)</td>
<td>0.85 ± 0.24*</td>
<td>66.32 ± 10.09</td>
</tr>
<tr>
<td>DTT with discontinued ULT (N = 35)</td>
<td>0.78 ± 0.24</td>
<td>74.02 ± 18.38</td>
</tr>
<tr>
<td>Other refractory goit (ORG) (N = 390)</td>
<td>0.81 ± 0.21</td>
<td>75.12 ± 20.96</td>
</tr>
</tbody>
</table>

*p > 0.05 vs. other refractory goit patients

Disclosure: L. Besette, Novartis, 2, F. Lioté, Novartis, Ipsen, Sanofi, 1, Novartis, SOBI, Astra-Zeneca, Savient, Ipsen, Menarini, Mayoly-Spindler, 2, Novartis, Ipsen, Menarini, Savient, Astra-Senna, Mayoly-Spindler, 5; C. Moragues, Novartis, 2; R. Moeri, Novartis, 2; K. Zech, Novartis, 2, A. Ferreira, Novartis Pharma AG, Basel, 3; P. Leconte, Novartis Pharma AG, Basel, 3, S. Kessabi, Novartis Pharma AG, Basel, 3; H. Tian, Novartis Pharmaceuticals Corporation, East Hanover, NJ, 3; J. Singh, Takeda, Savient, Novartis, 2, Savient, Takeda, Regeneron and Allergan, 5.

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Background/Purpose: Ultrasound (US) is a sensitive tool for the evaluation of joint inflammation in patients with RA, and can detect synovitis even when clinical remission is present [1]. Predictors of persistence of such subclinical power Doppler ultrasound (PDUS) synovitis, like potentially severity of the disease, concomitant treatments, or duration of the remission, remain undetermined. The aims of this study were: (1) to assess the proportion of patients with persistent PDUS synovitis in a cohort of patients with RA in clinical remission (DAS28-ESR < 2.6 and without clinically active synovitis); (2) to determine predictors of persistence of PDUS synovitis in these patients.

Methods: RA patients fulfilling 2010 ACR-EULAR classification criteria, treated with DMARDs or biologic and in clinical remission (DAS28-ESR < 2.6 and without clinically active synovitis, i.e. no joint showing both pain and swelling), were included in this transversal study. Following data were collected: clinical and biological characteristics of arthritis, socio economic factors, and radiographs of hands, wrist and feet. A standard US examination on 40 joints for the presence of synovial hypertrophy and power Doppler signal was performed by an independent investigator blinded to clinical data. A subclinical US synovitis was defined by the presence of a power Doppler signal ≥ 2 in at least one joint. Logistic regression was performed to evaluate the association between subclinical US synovitis and baseline variables at the patient level. The reliability was evaluated with intraclass correlation coefficients (ICCs) based on independent assessments of 30 patients by two investigators.

Results: The 94 patients included had a mean (standard deviation) age of 61.2 years (11.2), mean disease duration of 9.6 years (8.1), a mean duration of remission of 11.9 months (15.4). 60% and 68% of the patients were rheumatoid factor and anti-CCP antibody positive respectively. The mean DAS28-C reactive protein was 1.71 (0.47), median 1.67, and 57.4% of the patients had erosive disease. 61.7% received methotrexate, 57.4% biologic treatment and 11.7% corticosteroids. Inter-observer reliability of assessment of synovial hypertrophy and PD signal were very good (ICC = 0.954 and 0.985 respectively). Baseline clinical characteristics and US findings were similar whatever the duration of remission (<6 months, n=47 and ≥6 months, n=47). In multivariate analysis, presence of antiCCP (OR=3.68 [95% CI 1.21–11.1], p=0.021), DAS28-CRP > 1.67 (OR=2.97 [95% CI 1.12–7.87], p=0.028) were predictors of persistence of PDUS synovitis, whereas current smoking was negatively associated (OR=0.07 [95% CI 0.01–0.59], p=0.015). The duration of the remission was not associated with PDUS synovitis after adjustment in this cohort.

Conclusion: Our results suggest that RA patients in clinical remission are more likely to have persistence of PDUS synovitis if they have anti-CCP antibodies and higher DAS28-CRP value. Current smoking appears to be a protective factor in this cohort, which might potentially be due to vasocostriction induced by tobacco.

REFERENCE

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The Use of Ultrasound to Detect Residual Joint Inflammation in Patients with Rheumatoid Arthritis in Clinical Disease Remission. Gurjit S. Kaeley1, Midori Jane Nishio2, Janak Goyal3, Daryl MacCarten4, Alvin Wells5, Ana Cardosa6, Shufang Liu5, Jasmina Kalabic7 and Hartmut Kupper8. 1University of Florida, Jacksonville, FL, 2Diablo Clinical Research Center, San Francisco, CA, 3Raritan Bay Medical Center, Perth Amboy, NJ, 4Coeur d’Alene Arthritis Clinic, Coeur d’Alene, ID, 5Rheumatology & Immunotherapy Center, Franklin, WI, 6AbbVie, Amadora, Portugal, 7AbbVie Inc., North Chicago, IL, 8AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: Patients (pts) with rheumatoid arthritis (RA), who achieve clinical disease remission by treatment with disease modifying agents may have residual joint inflammation and vascularization, which can be detected by Power Doppler (PD) ultrasonography. The aim of this analysis was to evaluate the proportion of RA pts with PD activity, 24 weeks (wks) after the addition of adalimumab (ADA) to methotrexate (MTX).

Methods: MUSICA (NCT01185288), a 24 wk double-blind, randomized, controlled trial evaluated the efficacy of 2 different dosages of MTX (7.5 or 20 mg/wk) plus ADA (40 mg every other wk) in RA pts with inadequate response to MTX. For this analysis, the MTX dosage groups were combined. Synovial vascularization was assessed by PD US at 10 joints (bilateral dorsal and volar views of metacarpophalangeal joints 2, 3, 5; dorsal images alone of metatarsophalangeal joint 5 and wrists), at baseline (BL), wks 4, 8, 12, 16, 20 and 24. Images were scored by ultrasound-experienced rheumatologists using a semi-quantitative 4-grade scale.Joint swelling was assessed for the same 10 joints (SJC10). Disease activity was assessed by 28-joint count disease activity score using C-reactive protein (DAS28(CRP)) (remission < 2.6, LDA < 3.2, MDA 3.2–<5.1, HDA ≥ 5.1), and simplified disease activity index (SDAI) (remission ≤ 3.3, LDA ≤ 11, MDA ≤ 26, HDA > 26). Pearson’s coefficient (p) was used to assess correlation between continuous variables.

Results: After 24 weeks of treatment with ADA + MTX, 44/309 pts (14%) were in DAS28 (CRP) remission (mean PD score, 3.3); 18/309 (5.8%) pts were in SDAI remission (mean PD score, 2.7). DAS28(CRP) remission and 9/18 (50%) in SDAI remission had a PD score ≥ 2, indicating inflammatory activity. At wk 24, for the 10 joints selected, 30/44 (68%) pts in DAS28(CRP) remission had positive PD scores, while only 15 pts (34%) had ≥ 1 swollen joint, and only 5 pts (13.6%) had ≥ 1 tender joint. Ten out of 18 (55%) pts in SDAI remission had a positive PD score, while none had swollen/tender joints. A poor correlation (p<0.2) was observed between PD scores and clinical disease scores such as DAS28, SJC66, SJC28, TJC66, TJC28, CDAI, SDAI, PGA, PGA-pain and disease duration. There was poor correlation (p=0.184) between the change from BL to wk 24 in PD scores, and the change from BL to wk 24 in DAS28(CRP) or SDAI. The corresponding shifts in disease activity, mean PD score and SJC10 scores are presented (Table).

Table 1. Mean changes in PD score, DAS28(CRP) score and SJC10 from BL to wk 24

<table>
<thead>
<tr>
<th>DAS Disease state shift (BL—wk 24)</th>
<th>N</th>
<th>Mean change in PD score</th>
<th>Mean change in DAS28(CRP) score</th>
<th>Mean change in SJC10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA—MDA</td>
<td>24</td>
<td>−0.5</td>
<td>−0.6</td>
<td>−1.1</td>
</tr>
<tr>
<td>MDA—LDA</td>
<td>29</td>
<td>−2.2</td>
<td>−2.4</td>
<td>−2.4</td>
</tr>
<tr>
<td>MDA—HDA</td>
<td>41</td>
<td>−1.0</td>
<td>−0.6</td>
<td>−1.3</td>
</tr>
<tr>
<td>MDA—SDA</td>
<td>94</td>
<td>−1.8</td>
<td>−2.0</td>
<td>−2.7</td>
</tr>
<tr>
<td>MDA—LDA</td>
<td>57</td>
<td>−2.3</td>
<td>−3.6</td>
<td>−4.3</td>
</tr>
</tbody>
</table>

Mean changes in PD score, SDAI score and SJC10 from BL to wk 24

<table>
<thead>
<tr>
<th>SDAI Disease state shift (BL—wk 24)</th>
<th>N</th>
<th>Mean change in PD score</th>
<th>Mean change in SDAI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA—MDA</td>
<td>9</td>
<td>−0.7</td>
<td>−7.1</td>
</tr>
<tr>
<td>MDA—LDA</td>
<td>15</td>
<td>−0.4</td>
<td>−15.0</td>
</tr>
<tr>
<td>MDA—HDA</td>
<td>55</td>
<td>−1.1</td>
<td>−12.6</td>
</tr>
<tr>
<td>MDA—SDA</td>
<td>85</td>
<td>−1.9</td>
<td>−26.4</td>
</tr>
<tr>
<td>MDA—LDA</td>
<td>81</td>
<td>−1.9</td>
<td>−35.9</td>
</tr>
</tbody>
</table>

Conclusion: In agreement with other studies, residual joint inflammation was detected by PD US in pts in clinical remission; therefore ultrasound can offer additional information to that obtained from clinical disease measures.

Disclosure: G. S. Kaeley, AbbVie, 5; M. J. Nishio, AbbVie, 8; J. Goyal, AbbVie, 5; D. MacCarten, AbbVie, 5, AbbVie, 8, A. Wells, AbbVie, 5, A. Cardoso, AbbVie, 1, AbbVie, 3; S. Liu, AbbVie, 1, AbbVie, 3; J. Kalabic, AbbVie, 1, AbbVie, 3; H. Kupper, AbbVie, 3, AbbVie, 1.

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Combination with Joint Power Doppler Signals with Anti-Citrullinated Peptide Antibody Predicts Joint Destruction in Rheumatoid Arthritis. Yohei Kirino1, Maasa Hama1, Kaoru Minegishi-Takase1, Yosuke Kusunishita2, Daiga Kishimoto3, Ryusuke Yoshimizu4, Yukiyo Asami5, Atsushi Ithata6, Shigeru Ohno7, Atsuhisa Ueda8, Mitsuru Takeno9 and Ishigatsu Yo-shiaki10. 1Yokohama City University Graduate School of Medicine, Yokohama, Japan, 2Yokohama Minami Kyosai Hospital, Yokohama, Japan, 3Yokohama City University Medical Center, Yokohama, Japan, 4Yokohama City University Hospital, Yokohama, Japan.

Background/Purpose: Categorizing RA patients who require intensive treatments is highly warranted to optimize the therapy and to avoid overtreatment. We here evaluated the use of predicting joint destruction with joint power Doppler (PD) signal in musculoskeletal ultrasonography (MSUS).

Methods: We performed a retrospective study of 331 RA patients (female n = 280 and male n = 51, mean age 57.9 ± 13.2 y.o) who underwent MSUS from 2002 to 2012. Correlations of progression of joint destruction in 1,308
2nd and 3rd MCP joints with analysis of PD signals of the same joints, clinical findings, age, and disease duration at the study entry, gender, observation period, ACPA, and RF were analyzed in patient- and joint-based fashions, using univariate and multivariate logistic regression analyses and generalized linear mixed model.

**Results:** Patients’ characteristics were as follows: mean disease duration 5.7 ± 7.5 years, observation period 4.6 ± 2.6 years, RF positivity 79.9%, ACPA positivity 76.4%. PD positive 2nd and 3rd joints showed higher rate of joint destruction, especially in ACPA positive patients. Moreover, PD positive joints in ACPA positive patients showed joint destruction even in joints without swelling. Multivariate analysis determined PD, SJ, observation period, and ACPA as independent risks for joint destruction.

**Conclusion:** PD, SJ, and ACPA are independent predictors for the joint destruction of 2nd and 3rd MCPs in RA. Progression of joint destruction was maximal in PD positive joints in ACPA positive patients, raising the possibility that RA patients are categorized by MSUS findings.

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**Background/Purpose:** The use of musculoskeletal ultrasound is increasing in rheumatology practice. Recently we have shown that use of power Doppler signal (PD) on ultrasound in the wrists and hands in patients who present with non-specific musculoskeletal symptoms and are anti-CCP antibody positive can aid the identification of those who will develop an inflammatory arthritis (IA). The aim of this study was to investigate the ultrasound findings at a joint-level in these patients and the use of PD in identifying patients who progressed to inflammatory arthritis (IA).

**Methods:** In a prospective observational cohort study, patients with new non-specific MSK symptoms and positive anti-CCP underwent imaging with ultrasound at baseline and were followed up for the development of IA. Patients attended for regular follow-up assessments and if necessary were seen earlier if joint symptoms changed. PD findings of the wrists, MCPs and PIPs were scored using a semi-quantitative method from 0 to 3 PD using a standard method. Using multilevel binary logistic regression we modelled the association between presence of PD score >0 at baseline and presence of IA in that joint at follow-up; joints (level 1) were nested within patients (level 2).

**Results:** Our first 100 consecutive patients (73 females, mean age 51 years) were followed up for median 19.8 months (range 0.1–69.0); 50 developed IA after a median 7.9 months (range 0.1–52.4), 34 within 12 months. The majority who progressed to IA in at least 1 joint (43/50) fulfilled the 2010 ACR/EULAR criteria for rheumatoid arthritis. A total of 2200 joints were scanned. The majority of patients (67%) did not have any PD signal present; maximum score in any joint was 1 in 17% and 2 in 16%. None had a joint scoring 3. Progression to clinical synovitis was rare in joints scoring 0 (5%) compared to joints scoring 1 (16%) or 2 (59%). The presence of positive PD signal (any score >0) in a joint at baseline was associated with a 10-fold increase in odds of the joint developing clinical swelling [OR = 10.6 (5.3, 21.1), p<0.001].

**Conclusion:** Our findings suggest that in patients presenting with non-specific MSK symptoms and are anti-CCP antibody positive, ultrasound features of inflammation at a patient- and at a joint-level can aid the identification of patients at risk of developing IA. Results of our larger cohort will be presented.


**Disclosure:** J. L. Nam, None; L. Hunt, None; E. M. A. Hensor, None; P. G. Conaghan, None; R. J. Wakefield, None; P. Emery, None.

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PD Signal Detected By Ultrasoundography Relates to Joint Destruction in Rheumatoid Arthritis Under Biologics Therapy in Real World. Maasa Hama1, Yumiko Sugiyama1, Naomi Tsuchida1, Yusuke Kunishita1, Daiga Kishimoto1, Reikou Kamiyama1, Kaoru Minegishi-Takase1, Ryusuke Yoshimi1, Yohei Kirino1, Mitsuhito Takeno1, Atsushina Ueda1, and Yoshiaki Ishigatsubo1. 1Yokohama City University Graduate School of Medicine, Yokohama, Japan; 2Yokohama City University Hospital, Yokohama, Japan.

**Background/Purpose:** Biologic DMARD (biologics) therapy for rheumatoid arthritis (RA) strongly suppresses joint destruction regardless of its efficacy for disease activity. On the contrary power Doppler (PD) signal detected by ultrasoundography (US) is said to be the most potent predictive factor for subsequent radiologic progression. This study aimed to clarify whether PD signal predicts joint destruction of RA patients under biologics therapy in daily practice.

**Methods:** RA patients who began and continued to receive biologics for more than six months were included. Clinical, laboratory, and US examinations were conducted sequentially from baseline (1st) to the last observation (last). Bilateral wrists and all of the MCP and PIP joints were examined by PDUS and the PD signals were graded from 0 to 3 in each joint. The total PD score was defined as the sum of scores of individual joint, and mean score of several assessments during observational period was also calculated. Structural damage of hands at baseline and at the last was measured by using modified Sharp scoring method for hand X-ray (TSS). Patients having the change in TSS (delta TSS) exceeded 0.5 U per year were defined as showing radiologic progression.

**Results:** Objectives were 100 RA patients (female 85%, age 59.1 ± 13.4 y.o., disease duration 8.0±8.2 years, 1st DAS28 4.8±1.43). Sixty-three patients continued the same drug (anti-TNF 31, tocilizumab 26, abcteptum 6), whereas 37 patients switched biologics. During continuing biologics therapy for 25.3±16.8 months, structural damage progressed in 51% of the patients, who were classified into progressive group, including 18 patients with achieving clinical remission. The progressive group contained more patients who switched agents, and showed higher 1st DAS28 and higher last DAS28 as well as higher last total PD score, compared to the other group. Furthermore, yearly radiologic progression (delta TSS) weakly related to 1st, last, and mean total PD score in addition to 1st DAS28, 1st CRP, and 1st last MMP-3. Multiple regression analysis using stepwise method revealed that both 1st CRP and mean total PD score were independently associated with joint destruction. For joint-based analysis of total 2200 joints, radiologic progression were seen in 155 joints (7.0%), of which wrists were mainly affected joints, and the existence of PD signal in a joint at any time during observational period was the potent risk for subsequent destruction of the joint (Table).
Conclusion: To practice 'Treat to Target' for achieving radiologic remission in real world, monitoring individual joint by PDUS will be helpful in carrying out optimal intervention even under biologics treatment.

<table>
<thead>
<tr>
<th></th>
<th>Progression</th>
<th>Non-progression</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st PD (+) joint, n (%)</td>
<td>74 (48.1%)</td>
<td>223 (10.9%)</td>
<td>7.81 (5.52, 11.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>last PD (+) joint, n (%)</td>
<td>36 (24.8%)</td>
<td>83 (4.5%)</td>
<td>6.97 (4.51, 10.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mean PD (+) joint, n (%)</td>
<td>91 (59.1%)</td>
<td>282 (13.8%)</td>
<td>9.04 (6.40, 12.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Disclosure: M. Hama, None; Y. Sugiyama, None; N. Tsuchida, None; Y. Kunishita, None; D. Kishimoto, None; R. Kamiyama, None; K. Minegishi-Takase, None; R. Yoshimi, None; Y. Kiritani, None; M. Takeno, None; A. Ueda, None; Y. Ishigatsubo, None.

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Asymptomatic Versus Symptomatic Ankle Joints in Rheumatoid Arthritis: A High Resolution B-Mode and Power Doppler Ultrasound Study. Mohammed Alsuwaidi1, Boris P. Ehrenstein 1, Wolfgang Hartung 1 and Martin Fleck2. 1Asklepios Clinic Bad Abbach, Bad Abbach, Germany, 2University Medical Center of Regensburg, Regensburg, Germany.

Background/Purpose: Despite a crucial role for RA patients’ mobility, the ankle joints are frequently clinically neglected, and omitted in activity scoring systems including DAS 28. In addition, only few studies have assessed pathologies detected by ultrasonography of the ankle in symptomatic RA patients (1). Therefore, the type and degree of involvement of the ankle joints were evaluated in established RA patients regardless of symptomatology utilizing standardized high resolution musculoskeletal ultrasound (MSUS) including power Doppler ultrasonography (PDUS).

Methods: A total number of 160 ankle joints of 80 consecutive RA patients fulfilling the ACR/EULAR classification criteria 2010 were examined using MSUS (Logic E9, GE Healthcare, Buckinghamshire, GB with a ML6–15 linear probe with 6–15 MHz) and PDUS according to the EULAR MSUS guidelines (2). In addition, the talonavicular joint, and the flexor and extensor tendons were investigated. Furthermore, ankle pain (VAS score 0–10) was recorded for each patient on joint level. Only VAS = 0 was determined as asymptomatic.

Results: 80 RA patients (52 female, 28 male) with a median age of 60 years (range 28–81) and a disease duration of 5 years (range 0 – 44) were enrolled in our study. The median DAS28 was 5.0 (range 0.8–7.8), 97 ankles were painful (VAS 1–10), whereas 63 ankles were asymptomatic (VAS = 0). Overall, the predominant pathology was arthritis of the tibiotalar and/or talonavicular joint in 124 ankles (77%), followed by tenosynovitis of the flexor tendons in 44 ankles (28%). In symptomatic ankles 59% showed arthritis of the tibiotalar joint (TTJ) and 35% synovitis in the talonavicular joint (TNJ). In 35% of the asymptomatic ankles TTJ synovitis could be detected and 18% TNJ arthritis. PDUS activity was higher in the subgroup of symptomatic ankles (10% of symptomatic ankles (10/97) compared to 2% of asymptomatic patients (3/63). For detailed information see table 1.

Conclusion: Most frequent pathologies detected by MSUS were arthritis of the tibiotalar and talonavicular joint, followed by tenosynovitis of the flexor tendons. Pathologic findings are significantly more frequent in symptomatic ankles but also common in completely asymptomatic ankles of RA patients, whereas overall PDUS activity is low and if present predominately observed in symptomatic patients.

Table 1:

<table>
<thead>
<tr>
<th>Pathologies</th>
<th>Arthritis tibiotalar (%)</th>
<th>Arthritis talonavicular (%)</th>
<th>Tenosynovitis M. tibialis posterior r</th>
<th>M. flexor digitorum r</th>
<th>PDUS positive Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ankles (n = 160)</td>
<td>79 (66%)</td>
<td>45 (28%)</td>
<td>44 (27%)</td>
<td>12 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ankles (n=97)</td>
<td>57 (59%)</td>
<td>34 (35%)</td>
<td>32 (33%)</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic ankles (n=63)</td>
<td>22 (35%)</td>
<td>11 (18%)</td>
<td>12 (19%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Chi²</td>
<td>p = 0.003</td>
<td>p = 0.016</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

References:

Disclosure: M. Alsuwaidi, None; B. P. Ehrenstein, None; W. Hartung, None; M. Fleck, None.

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Metacarpophalangeal Cartilage Loss in Rheumatoid Arthritis. A Simple and Fast Ultrasonographic Assessment Comparing Patients and Healthy Controls. Tomas Cazeneve1, Christian A. Waimann2, Marwin Gutierrez3, Emilio Filippucci4, Gustavo Citera5 and Marcos G. Rosenfeld6, 1Instituto de Rehabilitación Psicosocial, Buenos Aires, Argentina, 2Universidad Politecnica delle Marche, Jesi, Italy, 3University of Ancona, Jesi, Italy.

Background/Purpose: There is evidence supporting the use of ultrasonography (US) as a valid and reliable imaging tool to evaluate cartilage in patients with arthritis. The aims of our study were to measure cartilage thickness in rheumatoid arthritis (RA) patients compared with Healthy Subjects (HS) and evaluate the relationship between US findings and clinical variables.

Methods: We designed a cross-sectional study including patients with diagnosis of RA (ACR/EULAR 2010) and HS. Data collected included clinical and demographic characteristics, Body Mass Index (BMI), 28-joint disease activity score (DAS28) and labor characteristics. US evaluation was performed by two rheumatologist with experience on US who were blind to clinical data. The histology cartilage of the metacarpal heads for fingers 2–5 was bilaterally scanned from the dorsal aspect with metacarpophalangeal joints in a full flexed position. Two perpendicular measurements at the central cartilage area (transverse and longitudinal views) were obtained and average cartilage thickness recorded. The association between RA characteristics and cartilage thickness was assessed using univariate and multivariate models, adjusted for sex, age, BMI and labor characteristics. Differences between HS and RA patients were compared using t-test. A two-sided P value of 0.05 was considered statistically significant.

Results: We included 98 subjects: RA =45 and HS=53. Mean age was 49 ± 13 years, mean BMI = 25 ± 4 and 70% were female. Patients with RA were significantly older and had lower BMI than HS. Patients with RA had a mean disease duration of 8 ± 7 years, 60% had erosive disease and mean DAS28 of 4.8 ± 1.4. A total of 784 joints were evaluated (RA=360 and HS=424). Time to perform US examination was 6 minutes per patient. Correlation between transverse and longitudinal view was 0.97 (p=0.01). Interobserver correlation was very good (ICC >0.92). Patients with RA had significantly lower cartilage thickness than HS (mean: 0.43 mm versus 0.58 mm, p<0.01). After adjusting for sex, age, BMI and type of job, RA was independently associated with cartilage thinning (β=0.51, p<0.01).

In patients with RA, those who were older, had longer disease duration, women and erosive disease, had significantly lower values of cartilage thickness. On multivariate regression analysis, only longer disease duration remained significantly associated with lower values of cartilage thickness.

Conclusion: Patients with RA showed significantly lower values of cartilage thickness as compared to healthy controls, having disease duration the highest impact on this fact. The impact of cartilage thinning on pain and functional capacity deserves further investigation.

Disclosure: T. Cazeneve, None; C. A. Waimann, None; M. Gutierrez, None; E. Filippucci, None; G. Citera, None; M. G. Rosenfeld, None.

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A Rapid 4-Joint Ultrasonographic Score to Daily Monitoring Disease Activity in Patients with Rheumatoid Arthritis: Validity and Sensitivity to Change. Tomas Cazeneve1, Christian A. Waimann2, Gustavo Citera3 and Marcos G. Rosenfeld4, 1IREP, Buenos Aires, Argentina, 2Hospital Olavarría, Olavarría, Argentina, 3Instituto de Rehabilitación Psicosocial, Buenos Aires, Argentina.

Background/Purpose: Ultrasound has demonstrated to be a sensitivity and specific tool to assess patients with Rheumatoid Arthritis (RA). However, the feasibility of this technology in daily clinical practice is still under debate. The purpose of our study was to evaluate the validity and sensitivity to change of a rapid 4-joint ultrasonographic score that could be applied to daily monitoring disease activity in patients with RA.

Methods: We included patients with RA (ACR/EULAR 2010). Data was collected at baseline, 3 and 12 months. Each patient underwent clinical (DAS28) and ultrasonographic (US) evaluation of 28-joints. Power Doppler (PD) and gray scale (GS) were graded from 0 to 3, according to OMERACT standards. Three ultrasonographic scores were calculated: 4-joints (bilateral radiol and intracarpal joint and second metacarpophalangeal), 6-joints (4-joints plus bilateral fifth metatarsophalangeal), and 28-joints. US scores come as the result of the addition of PD and GS score, with a total score ranged from 0 – 36, 0 – 48, 0 – 174, respectively. We evaluated psychometric properties of
There was observed a strong correlation between presence of synovitis and error of measurement. Seven Joints Ultrasound Scoring System May be Useful and Effective in Daily Clinical Practice.

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**Inter-Rater Reliability of the US-7 Score in a Population of Volunteers:** Is a Post-Hoc Analysis of Still Images Comparable to the Dynamic Analysis? Results from the German “Rheuma-Truck” Cohort. Dr. Philipp Sewerin1, Dr. Stefan Vordenbäumen1, Sarah Ohndorf2, Marina Backhaus3, Dr. Oliver Sander3, Prof. Dr. Matthias Schneider4, Prof. Dr. Benedikt Ostendorf5 and Aiko Liedmann1. 1Univ. Duesseldorf, Duesseldorf, Germany, 2Charite University Hospital, Berlin, Germany, 3Univ. Duesseldorf, Duesseldorf, Germany.

**Background/Purpose:** To investigate the value of a follow-up analysis of ultrasonographic still images versus dynamic investigation using the US-7 ultrasound score.

**Methods:** “Rheuma-Truck” was a mobile rheumatology office located in different city center of North Rhine Westphalia, Germany offering a screening for rheumatic diseases including Rheuma-Check questionnaire, lab-tests (MCV capillary test), imaging (US, capillaroscopy), and if positive a consultation with a rheumatologist to everybody free of charge. Ultrasound (MyLab 25 Gold, Esaote linear scanner, 15; Ty LA435) of the dominant hand of 605 volunteers was performed. Moreover in 236 of these volunteers the foot was obtained by ultrasound. Thus a total of 3497 joints were examined by ultrasound. Live images were analyzed according to the US-7 scoring system dynamically on site by a trained rater. Still images were stored in a standardized manner in section planes according to US7. These images were assessed by 3 additional experts blinded to the dynamic scoring. The agreement upon all four raters is assessed in two measures a(0) and a(1). These are the percentages of study subjects who are rated equally (a(0)) or exactly up to +/− 1 score point (a(1)) by all four raters.

**Results:** The mean age of the investigated cohort was 52.72 years (min. 10, max. 89 years). Sex distribution shows 72.2% females and 27.8% males. 181 (29.9%) volunteers displayed any inflammatory sign according to previous studies and other disease activity was found (DAS28, SDAI, HAQ, CRP). Number of erosions increased during one-year observation.

**Conclusion:** It was possible to find a high percentage of subclinical synovitis in patients in remission of RA according to previous studies published using other scoring systems. PD signals were in majority of investigations absent or very low (0 or 1), what is in good correlation with data published. There was no statistical difference in disease activity found in US7 score between patients with DMARDs and biological therapy in our sample. US7 may be a simple and effective tool to evaluate the disease activity of RA not only in active disease but also in the state of remission in daily clinical practice. Other studies are needed to confirm these findings with US7.

Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 023728 (Institute of Rheumatology) and by project No. NT12437.
Detection of Synovitis and Erosions with an Automated Ultrasound System: Data from a Prospective Cohort with Early and Established RA.
Matthias Witt1, Janette Frielingshausen1, Jan Leipe1, Hendrik Schulze-Koops1, Ruediger Mueller2 and Matthias Grunke1. 1University of Munich, Munich, Germany; 2Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany; 3Kantonspital St. Gallen, St. Gallen, Switzerland.

Background/Purpose: Arthrosonography has proven to be a sensitive and reliable, but time-consuming method for the evaluation of arthritis in small joints of patients with RA (1, 2). The automated breast volume scanner (ABVS) was developed to acquire series of consecutive B-mode pictures of the female breast. In a pilot study, we have recently described the possible application of this system to finger joints of RA patients (3). This study was performed to confirm the value of ABVS in detecting swelling and erosions of the finger, wrist and foot joints in patients with RA in comparison to conventional manual ultrasound (mUS).

Methods: Patients with RA were assessed by clinical and sonographic examination of the MCP,PIP, wrist and MTP joints. In addition, data for DAS-28, SDAI, CDAI and HAQ was gathered. ABVS was performed using the ACUSON S2000 (Siemens, Germany). mUS was performed on MyLab 70 (Esaote, Italy). The ABVS transducer was equipped with a linear array of 11 MHz and each automatic sweep of the scanner generated 15.4 × 16.8 cm × 2.5 cm volume data sets. The system was set to perform an automatic scanning time of 65 seconds per scan with a slice thickness of 0.5 mm. mUS was performed with a 8–18 MHz linear transducer.

Results: We included 44 patients with established (n=30) and early (n=14) RA with a mean DAS28 of 4.4 ± 1.8 and a mean swollen joint count of 8 ± 6.3. In total, 1548 small joints were assessed. ABVS revealed synovitis in 20.7% of the examined joints, compared to 18.4% with mUS. Erosions were seen in 196 joints with ABVS and in 168 joints with mUS. Correlation of US findings with clinical activity parameters were weak for both methods except for the swollen joint count with 0.41 for ABVS and 0.73 for mUS and physicians’ global assessment with 0.43 and 0.57 for ABVS and mUS, respectively. Defining mUS as gold standard, the sensitivity of ABVS for the detection of joint swelling was 0.64 with a specificity of 0.88. Concerning erosions, sensitivity and specificity were 0.64 and 0.88. The negative predictive value was 0.91 for joint swelling and 0.92 for erosions. The interrater and intrarater agreements were 0.83 and 0.85 for ABVS and 0.84 and 0.88 for mUS, respectively.

Conclusion: ABVS is a simple and time-saving method for the detection of joint swelling and erosions. Compared to manual ultrasound as gold standard, ABVS has an acceptable sensitivity and a very good negative predictive value which makes it a promising screening method for small joint synovitis in RA.

References:

Disclosure: M. Witt, None; J. Frielingshausen, None; J. Leipe, None; H. Schulze-Koops, None; R. Mueller, None; M. Grunke, None.

Do Ultrasound (PDUS) and DAS28 Measure Different Aspects of Disease Activity? Analyses from the First Prospective International Phase IIIb Study of PDUS Response in Abatacept-Treated Patients with Rheumatoid Arthritis (ABPRAISE).
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Background/Purpose: A composite (power Doppler/grayscale ultrasound [PDUS]) synovitis score, developed by the OMERACT-EULAR-Ultrasound Task Force, was shown to be responsive in RA patients with inadequate response to MTX who were treated with abatacept (ABA); a rapid parallel change in PDUS and DAS28 was demonstrated. 1 Data from clinical studies that have utilized PDUS indicate that it could be useful in monitoring RA treatment effects; however, discordant correlations have been found between ultrasound scores and clinical outcomes measured at the same time point. 2 In this secondary analysis of the ABPRAISE study, we explored correlations between changes in PDUS and clinical scores.

Methods: Individual joint PDUS scores were combined in the Global OMERACT-EULAR Synovitis Score (GLOESS) of metacarpophalangeal joints 2–5 (primary objective), reduced joint set (9 paired) and all examined joints (22 paired). Correlation between changes in GLOESS and clinical scores were assessed through: effect size, expressed as standardized response means of GLOESS and mean changes in DAS28 from baseline to Weeks 1, 2 or 4; changes in GLOESS, or components, and changes in the sum of swollen joints from baseline to Weeks 12 or 24. Within the assessment method, i.e. between clinical scores, or between GLOESS at different time points, moderate-to-high correlations were found between early (to Week 12) and late (Week 24) improvements in DAS28, and similarly between changes in GLOESS (any joint set): Pearson’s coefficient range 0.37–0.71. Only changes in GLOESS at Week 12 were able to differentiate between early versus late clinical responders: Pearson’s coefficient (95% CI): 22 joint: 0.71 (0.57, 0.80); 9 joint: 0.62 (0.46, 0.74).

Conclusion: PDUS is a responsive measure of joint activity in patients starting abatacept, but the extent of PDUS response does not correlate with extent of clinical response. PDUS is a predictive measure for early versus late clinical responders, suggesting that PDUS adds independent information on response to treatment which needs to be explored further.

Disclosure: M. A. d’Agostino, Bristol-Myers Squibb, AbbVie, 8; M. Boers, Bristol-Myers Squibb, R. Wakefield, H. Berman Hammer, O. Vittecoq, M. Galeazzi, P. Balint, I. Möllering, A. Iagnocco, E. Naredo, M. Ostergaard, C. Gaillez, E. Barre, M. Le Bars, None; R. Mueller, None; M. Grunke, None.

On-Demand Ultrasonography Assessment in the Most Affected Joint Is Efficient for Management of RA Patients in Daily Practice.
Ryusuke Yoshimi1, Takemo Mitsuhiro2, Yukihito Toyota2, Naomi Tsuchida1, Yumiko Sugiyama1, Yosuke Kunishita1, Duja Kishimoto1, Reikou Kamimura1, Kaoru Minegishi-Takase1, Maasa Hama1, Yoshi Kirino1, Atsuhisa Ueda1 and Yoshiaki Ishigatsubo1. 1Yokohama City University Graduate School of Medicine, Yokohama, Japan, 2Yokohama City University Hospital, Yokohama, Japan.

Background/Purpose: Musculoskeletal ultrasonography (US) is recognized as a useful tool for the diagnosis and monitoring of rheumatoid arthritis (RA). Although several sets of power Doppler (PD) US assessment procedures in arbitrary combinations of selected joints have been proposed, they do not always cover all of the affected joints. Here we investigated whether US
assessments in a selected joint on demand from patients is useful for monitoring RA in daily practice.

Methods: PDUS was performed in 8 joints, including bilateral MCP 2, MCP 3, wrist and knee joints, as a routine examination in a cumulative total of 207 patients with RA. At the examination, patients declared the most symptomatically affected joint. In patients who had the most affected joint except the routine 8 joints, the joint was additionally scanned. PD signals were scored semiquantitatively from 0 to 3 in each joint, and total PD score-8 was calculated by summing up PD scores of the routine 8 joints. Patients with positive PD signals in any joints were regarded as having active synovitis. The sensitivity and specificity of assessment in the most affected joint for detection of active synovitis in any of the routine 8 joints were evaluated.

Results: The patients were divided into three groups based on the most affected joints. Group A consisted of 110 patients having the most affected joint among the routine 8 joints, whereas 69 patients having the most affected joint other than the routine 8 joints were included in Group B. The remaining 28 patients were asymptomatic and categorized into Group C. Total PD score-8 was significantly higher in the symptomatic groups (Group A and B) than the asymptomatic group (Group C) (3.41 ± 3.19 vs 1.25 ± 1.80, P = 5.9 × 10⁻⁴). In the symptomatic groups, PD scores of the most affected joints showed high correlation with total PD score-8 (Figure 1; r = 0.52, P = 5.8 × 10⁻¹⁴). For detection of active synovitis of any of the routine 8 joints, the sensitivity and specificity of assessment in the most affected joint were 66.2% and 94.6%, respectively, in the symptomatic groups (Group A and B), 82.6% and 100%, respectively, in Group A, and 36.0% and 89.5%, respectively, in Group B. In two patients (2.9%) who were classified into Group B, PD signals were detected in the most affected joints (left ankle and right elbow), despite the negative results in the routine 8 joint assessments. These data suggested that US finding in the most affected joint represents those of routine 8 joint examination in Group A, whereas it gives supplemental information to the routine 8 joint examination in Group B.

Conclusion: This study suggests that on-demand US assessment in the most affected joint is efficient for management of RA patients in daily practice.

Figure 1 The PD score in the most affected joint correlates well with Total PD score-8.

Disclosure: R. Yoshimi, None; T. Mitsuhiro, None; Y. Toyota, None; N. Tsuchida, None; Y. Sugiyama, None; Y. Kinoshita, None; D. Kishimoto, None; R. Kamiyama, None; K. Minegishi-Takase, None; M. Hama, None; Y. Kirino, None; A. Ueda, None; Y. Ishigatsu, None.

134 Histopathological Correlation of Ultrasound-Defined Active Synovitis in Patients with Rheumatoid Arthritis in Clinical Remission. Preliminary Results

Julio Ramirez1, Virginia Ruiz-Esquide1, Raquel Celis2, Alicia Usategui1, Regina Faré3, Andrea Cuervo1, Sonia Cabrera-Villalba3, Maria Victoria Hernandez2, Jose Inciarte-Mundo1, Jose L. Pablos1, Ramon Sanmarti1 and Juan D. Cañete2. 1Hospital Clinic of Barcelona, Barcelona, Spain; 2Arthritis Unit, Rheumatology Dpt, Hospital Clinic of Barcelona and IDIBAPS, Barcelona, Spain; 3Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain.

Background/Purpose: We recently demonstrated that 45.4% of patients with RA in clinical remission have ultrasound (US)-defined active synovitis (synovial hypertrophy [HS] grade 2 or higher and Power Doppler [PD] signal) (Ramirez J et al, arthritis Research and Therapy 2014). Here we analysed the histological correlate of US-defined active synovitis in a subset of patients in whom synovial biopsy was performed.

Methods: By protocol, we obtained at baseline 6–8 ultrasound-guided synovial biopsies of all patients with (PD) signal who had signed the informed consent. Immunohistochemical staining was performed by the peroxidase technique for the following antibodies: CD3 (T lymphocytes), CD20 (B lymphocytes), CD31 (vessels), CD68 (macrophages), CD117 (mast cells), Hsp47 (Fibroblast-like synoviocytes) (Izquierdo E et al, Arthritis Rheum 2011) and basic FGF. Quantifications were performed by Digital Image Analysis (Olympus). Serum bFGF was analyzed by Quantibody® Human Array (RayBiotech). US scans of both knees and hands (wrist, metacarpophalangeal [MCP], proximal interphalangeal [PIP]) were performed by an experienced rheumatologist using a high sensitivity equipment (Acuson Antares®, Siemens AG, Erlangen, Germany) with a 8–12 Mhz linear probe. We quantified the presence of synovial hypertrophy (grades 0–3) and (PD) signal (grades 0–3) in all patients.

Results: We have included 24 patients with synovial biopsy. Regarding US assessment, 100% of patients had PD signal (by protocol), 79.2% had US-defined active synovitis (HS > 2+ [PD] signal) at least in one joint. The number of B cells (CD20+/μm²) (p = 0.017) and immunostained fractional area of Hsp47+/fibroblasts (p = 0.035) in synovial tissue were significantly higher in patients with US-defined active synovitis. Furthermore, these patients had a non-significant greater number of CD31+ vessels per area (p = 0.061).

Moreover, a significant correlation of global US score of each patient with the number of T cells (CD3+/μm²) (p = 0.010) and B cells (CD20+/μm²) (p = 0.001), and a strong trend to significance in mast cells CD117+ (p = 0.064) were found.

Conclusion: These preliminary results support that US-defined active synovitis has a histopathological substrate which is associated with fibroblasts and B cells. Also, the grade of infiltration of the synovium by T and B lymphocytes is associated with the US global score of the patient. Finally, correlation between synovial tissue expression and serum levels of bFGF, a mainly fibroblast-derived factor, point.
Methods: Rheumatoid arthritis (RA)-related orthopedic surgery was performed in 301 joints, including five shoulders, 43 knees, 36 elbows, 90 wrists, 75 fingers, nine ankles and 43 toes between January 2011 and September 2013. US was performed preoperatively, and the grade of the Power Doppler (PD) signal was weighted. The Rooney score of the synovial pathology, the DAS28-ESR (4), and the MMP-3 and CRP levels were subsequently measured. The Bio samples were taken at the same day as ultrasound examination and the differences were neither substantive nor statistically significant. Samples were tested for MMP-3 and HA using a novel research tool only multiplex platform IMPACT(Immunological Multi-Parameter Chip Technology)(Roche Professional Diagnostics, Germany). We calculated bootstrapped confidence intervals(CI) for the differences in the strength of Kendall’s tau-a associations between markers and joint assessment in Stata 13.1.

Results: Data were available for 59 patients: mean age 52.7 (range 19–78); 71% female; 64% RF +; median disease duration 11mth. Median (IQR) values for markers were CRP 27mg/L (10, 100); MMP-3 59ng/mL (42, 119); HAmg/mL 37 (20, 70). None of the associations were particularly strong (Table 1); the strongest were between the weighted clinical joint counts and MMP-3 and CRP. Most of the associations with MMP-3 were numerically stronger than with CRP, but the differences were neither substantive nor statistically significant.

Patients with normal CRP (<10 mg/L) there appeared to be substantive associations between total GS and MMP-3 (tau-a=0.34) and between total PD and HA (tau-a=0.35); however, sample size was small (n=14).

Table 1: Associations between markers of inflammation and clinical and ultrasound measures of synovitis, weighted for joint area (n=59).

<table>
<thead>
<tr>
<th>Weighted joint assessment</th>
<th>Kendall’s Tau-a (95% CI)</th>
<th>Differences between tau-a values (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-3</td>
<td>HA</td>
<td>CRP</td>
</tr>
<tr>
<td>MMP-3 minus HA</td>
<td>CRP minus MMP-3</td>
<td></td>
</tr>
<tr>
<td>GS total</td>
<td>0.30 (0.26, 0.24)</td>
<td>0.03 (0.15, 0.21)</td>
</tr>
<tr>
<td></td>
<td>(−0.06, −0.03)</td>
<td></td>
</tr>
<tr>
<td>GS count (score &gt;1)</td>
<td>0.23 (0.20, 0.21)</td>
<td>0.04 (−0.16, 0.23)</td>
</tr>
<tr>
<td></td>
<td>(−0.22, 0.17)</td>
<td>0.01 (−0.23, 0.25)</td>
</tr>
</tbody>
</table>

Conclusion: This study show a significant association between calprotectin and clinical, laboratory as well as ultrasound assessment of RA disease activity. Circulating calprotectin, but not MMP-3, may represent an important biomarker for monitoring synovial inflammation in RA.
PD total: 0.32, 0.30, 0.28, 0.02 (0.17, 0.22, 0.21, 0.13, 0.25, 0.22)
PD count: 0.31, 0.26, 0.28, 0.05 (0.13, 0.24, 0.20, 0.15, 0.20, 0.25)
Active: 0.34, 0.26, 0.26, 0.09 (0.11, 0.28, 0.25, 0.09, 0.21, 0.23)
SJC28: 0.39, 0.22, 0.42, 0.17, 0.02, 0.19
SJC44: 0.39, 0.21, 0.37, 0.18 (0.01, 0.36, 0.22, 0.18, 0.07, 0.38)

**Conclusion:** This is the first time that weighted joint counts, which account for joint surface area, have been used to evaluate the clinical utility of MMP3 as a soluble biomarker of subclinical synovitis when elevated. Further studies are underway to evaluate the clinical utility of MMP3 as a soluble biomarker of subclinical synovitis at CRP levels≤10mg/L.

**References:**
1) Nam J, et al. ARDB 2014; 73: 75

**Disclosure:** Roche Professional Diagnostics provided free of charge access to the IMPACT platform and IMPACT reagents. This work was also supported by grants from ARUK and the NHIR.

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**Background/Purpose:** To investigate musculoskeletal ultrasound (US) as a diagnostic modality in DISH and to explore if it might help in elucidating its pathogenesis and events that precede the calcification/osseous process.

**Methods:** Fifty patients with DISH and 34 patients with osteoarthritis of the lower limbs without DISH were investigated. Data regarding demographics and traditional cardiovascular risk factors was collected from all patients. An ultrasonography was performed according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS) by observers who were blinded to the diagnosis or the clinical findings in the patients.

**Results:** The total mean GUESS score for patients with DISH was 14.12 ± 5.2 and for patients without DISH 5.32 ± 4.99 (p=0.0001). Univariate logistic regression analysis found a strong association between the GUESS and the probability of having DISH (p<0.0001). The area under the ROC curve (AUC) revealed that the GUESS accuracy in diagnosing DISH was 88.53% with sensitivity and specificity of 92% and 70.6% respectively, at a cutoff value of 6.36. A stepwise logistic regression analysis of the statistically significant items in the GUESS, isolated 4 items, the presence of either all of them or, the first 3 items yielded the likelihood of having DISH to be 98.8%, and 90.6% respectively.

**Conclusion:** The GUESS and the stepwise logistic regression analysis demonstrated a high likelihood of having DISH. MSUS might help in elucidating its pathogenesis and events that precede the calcification/osseous process.

**Disclosure:** R. Mader, None; I. Novofofastovski, None; S. Iervolino, None; A. Pavlov, None; L. Cherivinsky, None; N. Schwartz, None; N. Pappone, None.

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**Background/Purpose:** Patients with psoriasis who report musculoskeletal symptoms were clinically evaluated. 83 patients (47 female, mean age: 54 years) had at least one tender enthesis on the LEI/MASES and were evaluated by ultrasound. Another 23 patients (9 female, mean age: 54 years) suspected for DISH was evaluated by ultrasound as well. In 98 (92%) patients we detected ultrasound abnormalities [Table 1]. In 47 (44%) patients we found abnormalities indicating inflammatory disease at the enthesis. 28 (26%) patients were power Doppler positive on ultrasound, 4 (4%) patients had a thickened plantar fascia and in 15 (14%) patients both inflammatory components were present. In 51 (48%) patients we found structural changes without indication for inflammatory disease. There was no difference in ultrasound findings between patients suspected for enthesis and patients suspected for arthritis.

**Conclusion:** In 44% of primary care psoriasis patients (n=106) we observed ultrasound abnormalities (presence of power Doppler and/or thickened plantar fascia) indicating inflammatory disease. Additionally, one or more structural ultrasound changes in the enthesis were observed in the majority of the patients. Whether this also indicates inflammatory disease requires further exploration.

**Disclosure:** M. van der Ven, None; M. C. Karreman, None; A. E. A. M. Weel, None; I. Tchetverikov, None; M. Vis, None; T. E. C. Nijsten, None; J. M. W. Hazes, None; J. J. Luime, Pfizer bv, 2.

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**Background/Purpose:** Psoriasis patients with enthesis can classify as psoriatic arthritis since the introduction of the CASPAR classification criteria in 2006. However, the presence of a tender enthesis is not necessarily indicative for underlying inflammatory disease as it could be related to overuse, metabolic disease or ageing. Therefore, we need a better way to identify the inflammatory component of enthesal involvement in psoriasis. To detect these inflammatory components and structural changes in the entheses, ultrasonographic examination can be applied to identify inflammatory disease of the entheses. Our objective was to determine the prevalence of ultrasound abnormalities among psoriasis patients in primary care.

**Methods:** Adult patients with psoriasis (ICPC S91) were identified from 97 general practitioners in the Rotterdam area. These patients were invited to participate in the SENSOR study. Patients who reported pain in joints, entheses or the lower back were eligible and invited for clinical evaluation. If physical examination indicated a painful enthesis on the LEI/MASES or arthritis, ultrasonographic examination of the entheses was performed. The six entheses of the Madrid Sonographic Enthesis Index (MASEI) and the lateral epicondyle tendon insertion (elbow) were evaluated according to the MASEI scoring system. Positive inflammatory components on ultrasound included the presence of power Doppler signal (<2mm of the bony cortex) and increased thickness of the enthesis of the plantar fascia (>4-4mm).

**Results:** In total, 527 patients with psoriasis who reported musculoskeletal symptoms were clinically evaluated. 83 patients (47 female, mean age: 54 years) had at least one tender enthesis on the LEI/MASES and were evaluated by ultrasound. Another 23 patients (9 female, mean age: 54 years) suspected for DISH was evaluated by ultrasound as well. In 98 (92%) patients we detected ultrasound abnormalities [Table 1]. In 47 (44%) patients we found abnormalities indicating inflammatory disease at the enthesis. 28 (26%) patients were power Doppler positive on ultrasound, 4 (4%) patients had a thickened plantar fascia and in 15 (14%) patients both inflammatory components were present. In 51 (48%) patients we found structural changes without indication for inflammatory disease. There was no difference in ultrasound findings between patients suspected for enthesis and patients suspected for arthritis.

**Conclusion:** In 44% of primary care psoriasis patients (n=106) we observed ultrasound abnormalities (presence of power Doppler and/or thickened plantar fascia) indicating inflammatory disease. Additionally, one or more structural ultrasound changes in the entheses were observed in the majority of the patients. Whether this also indicates inflammatory disease requires further exploration.

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**Background/Purpose:** Are Entheses Ultrasound Findings Similar in Axial SpA Patients and in Athletes? Marie-Alix Lanfranchi1, Olivier Leluc2, Alice Tavon3, Vincent Pradel1, Sophie Morange1, Christophe Chagnaud1, Pierre Lalфорgue1 and Thao Pham1. 1APHM, Aix Marseille University, Marseille, France, 2APHM, Marseille, France.

**Background/Purpose:** Spondyloarthritis (SpA) are characterized by inflammatory and structural changes in the entheses (enthesis). However, enthesis is not only observed in SpA and can also be seen after a hypersollicitation of the enthese as during intensive sport.

The purpose of the study was to compare ultrasound (US) findings of entheses between 3 groups: axial SpA patients, athletes and healthy controls.

**Methods:** We conducted a prospective cross-sectional study of 30 axial SpA (2009ASAS criteria), 30 athletes and 30 controls. Athlete subjects practiced a sport resulting in a strain on lower limbs, such as running or soccer, at least 6 hours per week. Controls practiced less than an hour per
week. Clinical evaluation and US were performed at the same day. Physicians performing clinical and US examination were blinded to each other. The US was performed at by two radiologists, using both grey scale (GS) and power Doppler (PD) for calculation of the MASEI index (Madrid Sonographic Enthesis Index) and the analysis of its subitems (bursitis, calcification, erosion, power doppler, thickening of tendon, structural change) (Toshiba Apio 500, linear transducer, frequency of 6–18 MHz). Analysis: To compare groups we used chi-square and one-way analysis of variance (ANOVA) with Bonferroni correction for post-hoc tests (depending on categorical/continuous variables), and Mann Whitney test for correlation (SPSS 17.0 version).

**Results:** Patients and controls demographic and clinical characteristics are shown in table 1. In SpA patients mean (SD) BASDAI and ASDAS were 3.14 (1.9) and 1.78 (1.01), respectively. Mean MASEI and each sub-item scores were significantly different between SpA patients and both healthy control groups. There was no difference between athlete and non-athlete groups. No correlation between heel pain and MASEI score or PD of the calcaneal enthesis was found. The inter-rater correlation for MASEI scoring was 0.68 (Cohen’s kappa coefficient).

**Conclusion:** The MASEI score was significantly higher in patients with SpA compared to healthy control, athletes and non-athletes. Even if the MASEI score was somewhat higher in the athlete group than in the non-athlete control group, the difference was not significant. The 17-cut-off seems relevant to distinguish SpA from control, whatever their physical activity.

<table>
<thead>
<tr>
<th>SpA (n = 30)</th>
<th>Athletes (n = 30)</th>
<th>Non-athlete controls (n = 29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>36.7 (7)</td>
<td>29 (9)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>70.0</td>
<td>70.0</td>
<td>41.4</td>
</tr>
<tr>
<td>Heel pain, ever (%)</td>
<td>55.2</td>
<td>20.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>CRP (mg/l) (mean, SD)</td>
<td>4 (11)</td>
<td>2 (7)</td>
<td>2.3 (SD)</td>
</tr>
<tr>
<td>HLA B27 + (%)</td>
<td>51.1</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>X-rays sacroliliitis ≥3 (%)</td>
<td>86.7</td>
<td>3.6</td>
<td>10.3</td>
</tr>
<tr>
<td>ASAS criteria + (%)</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MASEI score (mean, SD)</td>
<td>26.3 (13)</td>
<td>12.2 (7)</td>
<td>10.4 (6)</td>
</tr>
<tr>
<td>MASEI &gt; 17 (%)</td>
<td>70.0</td>
<td>16.7</td>
<td>14.3</td>
</tr>
</tbody>
</table>

**Disclosure:** M. A. Lanfranchi, None; O. Leluc, None; A. Tavano, None; V. Pradel, None; S. Morange, None; C. Chagnaud, None; P. Laforgue, None; T. Pham, None.

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**Prevalence of Subclinical Enthesopathy in Asymptomatic First Degree Relatives of Patients with Spondyloarthritis.** Tomas Cazenave1, Natalia Zamora2, Marcelo Audisi3, Ana M. Bertol3, Guillermo Py1, Walter Spindler3, Javier Rosa4, David A. Navarta5, Tomas Cazenave1, Natalia Mas6, Gustavo Citera7, and Marcos G. Rosemffet8. 1IREP, Buenos Aires, Argentina, 2Echeverria 955, Buenos Aires, Argentina, 3Servicio de Reumatologia del Hospital Nacional de Clinicas, Cordoba, Cordoba, Argentina, 4Instituto Reumatologico Strusberg, Cordoba, Argentina, 5Hospital Privado de Cordoba, Cordoba, Argentina, 6Hospital Medico Privado de Reumatologia, Tucumàn, Argentina, 7Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 8Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 9Hospital Privado de Cordoba, Cordoba, Argentina, 10Hospital Privado Centro Medico De Cordoba, Cordoba, Argentina, 11Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, 12.5; p = 0.0006). There was also a significantly higher percentage of patients with at least one enthesis with power Doppler (PD) score ≥2 (37% vs 16%; p = 0.037) and at least one enthesis with dishomogeneous echostructure (59% vs 0%; p = 0.000). There were no between-group differences in terms of erosions (0% vs 0%), calcifications (7.4% vs 12.5%; p = 0.656) or structural thickness (3.7% vs 33.3%; p = 0.507). In paediatric IBID group we cannot find correlation.
Detailed Anatomical Distribution of Synovial Inflammation Revealed By Ultrasound in Patients with Blau Syndrome. Kei Ikeda1, Naotomo Kambe2, Syuji Takeda1, Taiji Nakano3, Yuzaburo Inoue2, Minako Tomiita4, Ikuo Okafuji6, Nobuo Kanazawa7, Ryuta Nishikomori8, Naoki Shimojo2, Hiroyuki Matsue2, and Hiroshi Nakajima2. 1Chiba University Hospital, Chiba, Japan, 2Chiba University Graduate School of Medicine, Chiba, Japan, 3Kagoshima University Hospital, Kagoshima, Japan, 4Chiba Children’s Hospital, Chiba, Japan, 5Hitachinaka General Hospital, Hitachinaka, Japan, 6Kobe City Medical Center General Hospital, Kobe, Japan, 7Wakayama Medical University, Wakayama, Japan, 8Kyoto University Graduate School of Medicine, Kyoto, Japan.

Background/Purpose: Arthritis is the most frequent manifestation of Blau syndrome, an autoinflammatory disorder caused by the genetic mutation of NOD2. However, the detailed information on arthritis in Blau syndrome which the therapeutic strategy should be based on was lacking. This multi-center study aimed to accurately characterize the articular manifestation of Blau syndrome and also to demonstrate the utility of musculoskeletal ultrasound in Blau syndrome.

Methods: Patients who had been diagnosed with Blau syndrome by genetic analysis of NOD2 were recruited. A total of 102 synovial sites in 40 joints were assessed semiquantitatively by ultrasound for gray-scale synovitis and synovial power Doppler (PD) signal.

Results: Ten patients whose age ranged from 10 months to 37 years enrolled in this study. Although only four joints (0.8%) were tender on physical examination, 81 joints (16.9%) were clinically swollen. Moreover, 240 (50.0%), and 124 (25.8%) joints showed GS synovitis and synovial PD signal on ultrasound, respectively. Importantly, GS synovitis was present in 168 out of 399 non-swollen joints, in which 61 also exhibited synovial PD signal. Among 40 joint regions, the ankle, the wrist, and the proximal interphalangeal joints were the most frequently and severely affected joints (Figure). Comparisons between different synovial tissues demonstrated a significantly higher proportion of the joints with tenosynovitis as compared with that with intra-articular synovitis (41.5% vs. 27.9%, P < 0.0001). In respect of age and treatment, synovial PD signals were minimal in the youngest patient and in the oldest two patients, and were relatively mild in patients receiving treatment with methotrexate plus TNF antagonists. In two patients who underwent the 2nd ultrasound examination, total PD scores markedly decreased after initiating the treatment with a TNF antagonist.

Conclusion: The detailed information on synovial inflammation obtained by ultrasound confirms the dissociation between pain and inflammation and the frequently involved joint regions and synovial tissue in the arthritis of Blau syndrome. Our data also demonstrate that ultrasonography can be a potent tool in monitoring the activity of synovial inflammation and in investigating the pathophysiology of arthritis in this rare but archetypical autoinflammatory condition.

Figure. Mean gray-scale and power Doppler scores for intra-articular- and teno-synovitis in each joint

Mean ultrasound scores for each joint in 10 patients are shown in color grades. Only 1st ultrasound examinations in Patient 5 and 6 are included. 8 Ultrasound scores for tenosynovitis are not applicable in elbows and knees where typical tenosynovium does not exist.


Sonographic Differentiation of Heel Pain: Focal Degenerative Versus Systemic Inflammatory Enthesitis. Patrick Hook1, Diana Vradii2, Maureen Dubreuil3, Hau Pham3 and Eugene Y. Kissin1. 1Boston University School of Medicine, Boston, MA, 2Mid Coast Hospital Medical Center, Brunswick, ME, 3Boston University Medical Center, Boston, MA.

Background/Purpose: Plantar fasciitis and Achilles tendonitis are commonly encountered in a rheumatologic practice due to either degenerative (DG) or systemic inflammatory conditions (SYS). While sonographic findings in both DG and SYS have been described in numerous studies, no study has systematically compared these two causes of heel pain. The aim of our study is to determine whether sonographic findings in the Achilles tendon and plantar fascia can be used to differentiate DG from SYS states.

Methods: Patients over the age of 18 with pain at the Achilles tendon or plantar fascia presenting to the Podiatry, Dermatology or Rheumatology clinics were enrolled. Exclusion criteria: previous heel trauma, surgery or recent corticosteroid heel injections. Medical chart review, a focused history, and a comprehensive musculoskeletal physical examination determined patient categorization as DG, SYS, or undetermined cause of heel pain. Patients’ Achilles tendons and plantar fascia were imaged with a GE Logiq e ultrasound and 12MHz linear array transducer. Doppler settings: PRF 0.8, low wall filter and Doppler gain set to maximize signal with minimal artifact. We evaluated tendon thickness, retro-calcaneal bursal size, cortical erosions, and Doppler signal at the enthesis and at the cortical margin. Continuous variables were compared between the degenerative and inflammatory groups using t tests, and proportions were compared using Chi squared or Fischer’s exact tests.

Results: Interim analysis of the first 46 patients recruited included 20 in the SYS group and 22 in the DG group (4 undetermined). SYS group consists of 15 patients with psoriatic arthritis, 4 with non-psoriatic spondyloarthritis, and 1 with rheumatoid arthritis. Male:female ratio was 15:5 in the SYS group, and 6:16 in the DG group. While there were no significant differences in tendon thickness between the groups (Table), both the presence of erosions (SYS 70% vs. DG 23%, p = 0.002), and the presence of Doppler at the enthesis (SYS 55%, vs. DG23%, p = 0.03) were significantly more common in the SYS group (Table). Surprisingly, erosion size and degree of Doppler signal did not help distinguish the groups (Table). Doppler signal at the cortical margin was not more specific to the inflammatory group than enthesis Doppler overall (Table).

Conclusion: While there were no significant differences in tendon thickness, degenerative causes of heel enthesitis were less likely to show Doppler signal and erosive changes than systemic inflammatory disease. However, erosions were seen in some heel enthesis not associated with systemic inflammatory disease.

Table. Clinical characteristics and sonographic findings for subjects included in the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inflammatory (N = 20)</th>
<th>Degenerative (N = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, % (N)</td>
<td>75.0% (15)</td>
<td>72.2% (6)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>32.3 +/- 5.9</td>
<td>33.9 +/- 8.5</td>
<td></td>
</tr>
<tr>
<td>Age (range)</td>
<td>46 (20-69)</td>
<td>47 (25-77)</td>
<td></td>
</tr>
<tr>
<td>Plantar fasciitis pain, % (N)</td>
<td>65.0% (13)</td>
<td>77.3% (17)</td>
<td></td>
</tr>
<tr>
<td>Achilles pain, % (N)</td>
<td>90.0% (18)</td>
<td>59.1% (13)</td>
<td></td>
</tr>
<tr>
<td>Achilles Proximal Thickness (cm)</td>
<td>0.55 +/- 0.16</td>
<td>0.45 +/- 0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Presence of Erosions</td>
<td>70.0% (14)</td>
<td>22.7% (5)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Presence of Erosions &gt; 2 mm</td>
<td>35.0% (7)</td>
<td>18.2% (4)</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Background/Purpose: Ultrasonography (US) of the superficial temporal arteries was introduced in the 1990s. The diagnostic value of US of the superficial temporal artery wall in giant cell arteritis (GCA) has been extensively reported. In order to clarify the effectiveness of US preceding pathological diagnosis, we examined cut-off values of ultrasonography-derived halo signs (intima-media thickness, IMT).

Methods: Twenty-eight patients with suspected GCA were examined by US before biopsy from October 2010 to June 2014, inclusive. US was performed unilaterally or bilaterally by two ultrasonographers and the greatest analyzed. Superficial temporal artery biopsy was used as the reference standard. The Cohen’s kappa test for Inter-Observer variation was 0.703 (95%CI: 0.390 to 1.015).

Results: Unilateral halo sign had a sensitivity of 83.3 % and specificity of 40.0 %. In ROC analysis, a cut-off of greatest dimension of halo ≥ 0.51 mm was the most accurate for prediction with a sensitivity of 66.7 % and specificity of 80.0 %. The diagnostic odds ratio was 8.0 (95% CI, 1.28 – 50.04).

Conclusion: This is the first report that examined the cut-off values of IMT in diagnosing GCA. The measurement of the greatest dimension of the ultrasonography-derived halo sign (IMT) increased the diagnostic yield for pathological diagnosis.

Disclosure: H. Horuchi, None; K. Miski, None; R. Saito, None; Y. Nakamura, None; Y. Gon, None; T. Nagamoto, None; H. Yamada, None; T. Yokota, None.

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Background/Purpose: Although both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may lead to the joint deformity, different characteristics such as the absence or the presence of bone destruction have been recognized as well: lupus arthritis is typically non-erosive and often accompanied by Jaccoud’s deformity. Therefore, we examined characteristics of joint and tendon lesions in SLE patients compared with RA patients by using ultrasonography.

Methods: Thirteen SLE and 32 RA patients were selected from the treatment-naive patients with joint symptoms, visiting Toho University Ohashi Medical Center between January 2011 and March 2014. Enrolled patients had at least one swollen or tender joint. The wrist, metacarpophalangeal and proximal interphalangeal joints and related extensor/flexor tendons were ultrasonographically examined from both palmar and dorsal sides. Their ankle, metatarsophalangeal and proximal interphalangeal joints and related extensor/flexor tendons were also ultrasonographically examined from both plantar and dorsal sides. Their joints and tendons including tendon sheaths were evaluated using a gray-scale (GS) for synovial thickening and synovial fluid retention, and power Doppler (PD) for blood flow according to a semiquantitative method based on a scale of grades 0 to 3, and patients graded with GS ≥ 2 or PD ≥ 1 were judged as having joint synovitis and or tendinitis/tenosynovitis.

Results: Joint synovitis and tendinitis/tenosynovitis were observed in 11 (79%) and 12 (86%) of 13 SLE patients, respectively, and in 31 (91%) and 18 (53%) of 32 RA patients, respectively. Thus, SLE patients had tendinitis/tenosynovitis more frequently (p=0.034) as compared with RA, and particularly in the wrist joints (p=0.008, Table 1). Moreover, the concordance of joint synovitis and tendinitis/tenosynovitis in the same region was less in SLE patients (k=0.18) as compared with RA (k=0.44).

Conclusion: Joint synovitis was similarly observed ultrasonographically in both SLE and RA patients, while tendinitis/tenosynovitis was more frequently observed in SLE patients than in RA patients. In addition, tenosynovitis in SLE patients may develop rather independently from synovitis.

<table>
<thead>
<tr>
<th></th>
<th>SLE number</th>
<th>RA number</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=13 (%)</td>
<td>n=32 (%)</td>
<td></td>
</tr>
<tr>
<td>Joint synovitis</td>
<td>11 (78.6)</td>
<td>31 (91.2)</td>
<td>0.196</td>
</tr>
<tr>
<td>Wrist</td>
<td>10 (71.4)</td>
<td>27 (79.4)</td>
<td>0.672</td>
</tr>
<tr>
<td>MCP</td>
<td>9 (64.3)</td>
<td>25 (73.5)</td>
<td>0.704</td>
</tr>
<tr>
<td>PIP</td>
<td>3 (21.4)</td>
<td>18 (52.9)</td>
<td>0.056</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>12 (85.7)</td>
<td>18 (52.9)</td>
<td>0.034</td>
</tr>
<tr>
<td>Wrist</td>
<td>10 (71.4)</td>
<td>10 (29.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Finger extensor tendons</td>
<td>6 (42.9)</td>
<td>9.0 (26.5)</td>
<td>0.305</td>
</tr>
<tr>
<td>Finger flexor tendons</td>
<td>8 (57.1)</td>
<td>14.0 (41.2)</td>
<td>0.337</td>
</tr>
</tbody>
</table>

Disclosure: T. Ogura, None; A. Hirata, None; H. Hayashi, None; R. Kujime, None; H. Ito, None; S. Takenaka, None; S. Nakahashi, None; K. Mizushima, None; N. Yamashita, None; Y. Fujisawa, None; H. Kameda, None.

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US Lung Examination in SSc Patients: A Comparison of Two Different Scoring Systems. Andrea Delle Sedie1, Cristina Lodato2, Elisa Cioffi2, Linda Carli2, Stefano Bombardieri1 and Lucrezia Riente1. 1Rheumatology Unit, University of Pisa, Pisa, Italy, 2GenOeMC PhD, University of Siena, Siena, Italy.

Background/Purpose: Systemic sclerosis (SSc) is a disease characterized by a progressive fibrosis of the skin and internal organs, which can lead to death. Lung involvement includes a wide range of disorders and interstitial lung disease (ILD) is the most common manifestation, being clinically significant in about 40% of patients. Recently, the role of US in the assessment of ILD (counting the B-lines, generated by the reflection of the US beam from thickened sub-pleural interlobar septa) has been confirmed after comparison with high-resolution computed tomography (HRCT) and a few scoring systems proposed. The comprehensive examination of lung intercostal spaces (LIS) is time consuming (54 LIS in each patient) and a previous attempt to give a simplified US B-line scoring system has been made in patients with connective tissue diseases (2), an evaluation on 8 different thoracic areas is also performed (3-4).

Aim of the study was to compare the comprehensive examination and the 8-area scoring system and define which could be more effective in clinical practice.

Methods: 79 SSc patients were enrolled independently of the presence of any dyspnoea. Each patient underwent a lung US with comprehensive US B-line assessments by an experienced rheumatologist. A cut-off of ≥12 B-lines was decided based on the correlation between US and HRCT in 76 patients, then US was performed alone in the rest of the SSc patients. The presence/absence of B-lines was registered in each LIS. The second scoring system was positive when ≥3 B-lines were present in a single LIS in ≥1 area.

Results: 46 patients were positive for ILD (ILD+) and 33 negative when using the comprehensive examination; the 8-area scoring protocol showed 44 ILD+ and 35 negative. Using the two different scoring systems ILD+ and ILD- patients were the same in 67 cases. Seven of the remaining patients were ILD+ only using the comprehensive scan (in 4 of them the total B-lines score was <16, so really close to the cut-off) and 5 only using the 8-area scan. The time needed for the comprehensive assessment was longer than the one for the 8-area scanning protocol (the latter does not assess posterior thorax and, if a LIS is positive, there is no need to scan the other LIS in the same area).

Conclusion: The results provided by the two scoring systems are largely overlapping in the identification of ILD+ patients. Considering the shorter time needed for the assessment, the 8-area scanning protocol could be more useful for screening.

References

Disclosure: A. Delle Sedie, None; C. Lodato, None; E. Cioffi, None; L. Carli, None; S. Bombardieri, None; L. Riente, None.
Value of Ultrasonography Parotid Glands in Patients with Suspected Primary Sjögren’s Syndrome. Marina Oliver1, Lida Santiago2, Paula Gonzalez3, Diego Vila4, Sebastian Fernandez Nacul5, Santiago Scarafia6, Marta Mamani6 and Anastasia Secco3. 1Haukeland University Hospital, Bergen, Norway, 2Hospital Rivadavia, Buenos Aires, Argentina, 3Hospital Rivadavia, Capital Federal, Argentina, 4Hospital Rivadavia, Buenos Aires, Argentina, 5Hospital Rivadavia, Buenos Aires, Argentina, 6Hospital Rivadavia, Buenos Aires, Argentina.

Background/Purpose: Primary Sjögren’s syndrome (pSS) is an autoimmune disorder characterised by chronic lymphocytic infiltration of exocrine tissues. Currently new non-invasive techniques are being continuously introduced as a diagnostic tool. Ultrasonography (US) of salivary glands in these patients merits special interest as a rapid, inexpensive, non-radiating and widely accessible modality.

Methods: The aim of the study is to assess the diagnostic value of ultrasonography (US) in those patients underwent minor salivary gland biopsy (MSGB) by suspected Primary Sjögren Syndrome (pSS).

All patients underwent bilateral parotid glands US and MSGB. The same expert blinded examiner performed the US. All patients were scanned using an MyLab 25 US scanner (Esaote Italy) with a 10–18 MHz linear-array transducer. The following parameters were assessed: homogeneity, hypoechogenic areas, hyperechoic foci, Power Doppler (PD) and margins graded from 0 to 2 (0: well-defined, 1: ill-defined, 2: blurred) and gland size was measured. The gold standard was the MSGB. According to the quantity and type of US variables, we determined the following cut-off values (at least unilateral parotid finding): A: presence or absence of heterogeneity on unilateral or bilateral parotid glands; B: presence or absence of any variable (not more than one and excluding heterogeneity) on unilateral or bilateral parotid glands. C: presence or absence of three or more variables (any variable) on unilateral or bilateral parotid glands.

Results: We included a total of forty-five biopsies (32 negative and 13 positive). 95.56% were female, the median symptoms length was 2 years (IQR 1–7), no differences were observed between both groups. According to A cut-off values had 30. 77% sensitivity (CI 17.28–44.25), 78.13% specificity (Sp) (CI 66.05–90.20), 36.36% positive predictive value (PPV) (22.31–50.42), 73.53% Negative Predictive Value (NPV) (CI 60.64–86.42), likelihood ratio (LR) + 1.41 (CI 0.49–4.0), and the area under the curve (AUC) 0.54 (CI 0.40–0.69). B findings showed 46.15% S (CI 41.59–60.72), 68.75% Sp (CI 55.21–82.29), 37.50% PPV (CI 23.36–51.64), 75.86% NPV (CI 63.86–88.36%), LR + 1.48 (CI 0.68–3.22), AUC 0.57 (CI 0.41–0.74). We observed C findings with a 30.77% of Sensitivity (CI 17.28–44.25), 90.63% specificity (Sp) (CI 90.14–91.17), 92.81% positive predictive value (PPV) (CI 42.78–71.60), 31% Negative Predictive Value (NPV) (CI 63.89–88.74), LR + 3.28 (CI 0.85–12.67), AUC 0.61 (CI 0.47–0.77). Bilateral parotid US showed an AUC similar to B findings.

Conclusion: We considered that C findings are the best cut-off values because it demonstrated greater specificity and slightly better AUC. Nevertheless, in our study the US of parotid gland not prove to be an appropriate diagnostic tool to replace the MSGB.

Disclosure: M. Oliver, None; L. Santiago, None; P. Gonzalez, None; D. Vila, None; S. Fernandez Nacul, None; S. Scarafia, None; M. Mamani, None; A. Secco, None.

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Automated Digital Analysis of Major Salivary Gland Ultrasound Images. Daniel S. Hammenfors1, Preben G. Nes2, Johan G. Brun3, Roland Jonsson4 and Malin V. Jonsson5. 1Haukeland University Hospital, Bergen, Norway, 2Sogn and Fjordane University College, Forde, Norway, 3University of Bergen, Bergen, Norway.

Background/Purpose: Primary Sjögren’s syndrome (pSS) is an autoimmune chronic inflammatory disease mainly affecting the salivary and lacrimal glands, with symptoms such as dryness of the mouth and eyes as well as fatigue. The diagnosis is based on the objective findings of reduced secretion of saliva- and/or tears, the detection of auto-antibodies against Ro/SSA and/or La/SSB in serum, and the observation of focal mononuclear inflammatory cell infiltration in minor labial salivary gland biopsies. In the recent years, interest in major salivary gland ultrasonography as a diagnostic tool for pSS has increased. Several scoring systems evaluating glandular homogeneity and echogenicity have been suggested, presenting a challenge for both researchers and clinicians. The aim of this study was to develop a reliable automated digital evaluation of ultrasound images as a useful tool for the clinician and as an objective method for the researcher.

Methods: The parotid glands of patients (n=26) fulfilling the AECG criteria (Vitali et al 2002) had previously been examined using a GE LogiqE9 with a linear high-frequency transducer (6–15MHz) and the images evaluated using a simplified grading system (0–3) (Hocevar et al, 2005). The stored images were analysed digitally with a pilot version of the software developed for this study. Briefly, the software analyses local variability in grayscale values. An automated software, which enables an objective and reproducible analysis for the researcher, has been developed. For the evaluation of the performance of this software, we collected a series of ultrasound images of 24 pSS and 10 non-pSS patients with known serological signs of the disease. Ultrasonic images were digitized in JPEG format and the software was used to perform an automated analysis. The performance of the software was evaluated by generating ROC curves using a number of cut-off values of ultrasound findings. In addition, the software was used to perform automated analysis in a number of cases of pSS and non-pSS. The performance of the software was evaluated using a number of cut-off values of ultrasound findings.

Results: Preliminary findings show an excellent correlation between the scores obtained with the simplified grading system (0–3) and the automated digital evaluation (p > 0.01, r = 0.8, r 2 = 0.49). Mean digital score for images graded 0–3 were -9.833 (grade 0), -6.018 (grade 1), 2.752 (grade 2) and 6.850 (grade 3), respectively.

Conclusion: The preliminary results of ultrasound image analysis show an excellent correlation between the automated digital analysis and the evaluation by a trained clinician. In future studies, automated analysis will enable an objective and reproducible analytic method for the researcher as well as provide a useful diagnostic and possibly prognostic tool for the clinician.

Disclosure: D. S. Hammenfors, None; P. G. Nes, None; J. G. Brun, None; R. Jonsson, None; M. V. Jonsson, None.

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Ultrasonographic Evaluation of Major Salivary Glands in Primary Sjögren’s Syndrome: Comparison of Two Scoring Systems and Diagnostic Value of Sonoelastography. Xia Zhang, Jing He and Zhanguo Li. Peking University People’s Hospital, Beijing, China.

Background/Purpose: Primary Sjögren’s syndrome (pSS) is a chronic systemic autoimmune disease characterized by clinically xerophthalmia and xerostomia. Those standard tests of salivary glands involvement has some deficiencies. To date, a precise and feasible evaluation method for primary Sjögren’s syndrome (pSS) remains to be established. Ultrasonography (US) is a promising technique, as it is convenient, economic, and non-invasive. A consensus has not been reached regarding the evaluation of typical SGUS changes for pSS, and at present, few main scoring systems exist (range 0–16, 0–48, respectively). To date, it’s unknown which one is more practical and useful. On the other hand, sonoelastography (SE) is a rapidly developing technique by which the tissue elasticity can be measured. SE has been investigated in the differential diagnosis of focal nodule of breast, thyroid, prostate and salivary gland and liver fibrosis, as an accurate and reproducible method. However, the application of sonoelastography to salivary diffuse pathologic lesions never reported. We aimed to assess and compare the usefulness of two existing SGUS scoring systems for primary pSS and explore the performance of SE in the diagnosis of pSS.

Methods: US and SE examination of major salivary glands was conducted for 105 pSS patients and 41 non-SS patients with 10 Sicca syndrome, 5 hypothyroidism, 19 rheumatoid arthritis, 7 systemic lupus erythematosus and 16 healthy subjects. The ultrasonographic features were graded using two different scoring systems (0–16, 0–48, respectively) obtained from the grades of bilateral parotid and submandibular glands. On the other hand, elastographic images were determined with a qualitative 4-point scoring method (range 0–16). Receiver operating characteristic (ROC) curves were used to describe and compare the diagnostic accuracy of the two US echostucture scoring systems for pSS, simultaneously, to evaluate the performance of qualitative elasticity scoring by sonoelastography.

Results: 1) SGUS scores for the pSS group were significantly higher than those for the non-pSS group (p<0.001). The maximal combination of sensitivity and specificity was 80% and 93% at an optimal US cut-off value of 7 in the 0–16 system, and was 88.6% and 84.2% at a best cut-off of 15 in the 0–48 system. For the 0–48 system, the sum of the scores of all four glands provided the largest AUC-ROC (0.916, 95% CI 0.87 – 0.962). The maximal sensitivity and specificity were 81% and 87% at an optimal cut-off value of 9 for the sum of the scores of all four glands.
**Conclusion:** SGUS showed good sensitivity and specificity for noninvasive assessment of inflammatory joints of RA and OA. When compared to the 0–16 system, the 0–48 system had a slightly higher sensitivity. The assessment of inflammatory joint involvement was empirically diagnosed based on visible findings.

**Disclosure:** X. Zhang, None; J. He, None; Z. Li, None.

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**Sonographic Measurements Can be Misleading for Diagnosing Carpal Tunnel Syndrome in Patients with Rheumatoid Arthritis.** Ilker Yagci1, Merve Akdeniz Leblebicier2, Basak Mansiz Kaplan2, Demet Ozturk Gokbakan1 and Gulseren Akyuz1. 1Marmara University School of Medicine, Istanbul, Turkey; 2Marmara School of Medicine, Istanbul, Turkey.

**Background/Purpose:** To compare the nerve cross sectional areas (CSA) in patients with RA without any sign of peripheral neuropathy to healthy controls.

**Methods:** The study group was generated from referrals to Rheumatic Diseases Outpatient Clinics. Clinical, electro-physiological and sonographic measurements were done by three blinded researchers. Clinical assessment included Tinel’s sign, Phalen test, tenar atrophy and Flick sign, KATZ hand diagram and Boston Questionnaire. Median, ulnar and bicipital median, median and sural sensory nerve conduction studies (NCS) were performed. The patients who had an electrophysiological or clinical peripheral neuropathy were excluded from the study. Nerve CSA’s were measured in various levels; hamatum hook, pisiform bone, radio-ulnar joint, distal 1/3 of forearm, and elbow levels for median nerve; radio-ulnar joint, pisiform bone, distal 1/3 of forearm, and medial epicondyle for ulnar nerve. Three different measurements were obtained and the average measure was used for each level.

**Results:** The study was completed with 30 women with RA and 30 healthy women. There were no statistical significance according to age, and body mass index. Despite both of the groups had no clinical and electro-physiological peripheral neuropathy, the sonographic measurements showed that median nerve CSA’s at radioulnar joint, pisiform and hamatum levels of patients with RA were larger than healthy controls. Ulnar nerve CSA’s of all levels statistically increased in patients with RA (p<0.05). If the pisiform level median nerve CSA >10 mm2 was used as sonographic carpal tunnel syndrome (CTS) criterion, 23/60 hands of 30 patients with RA and 5/60 hands of 30 healthy controls could be misdiagnosed as CTS.

**Conclusion:** Median and ulnar nerve CSA’s were larger than healthy control in patients with rheumatoid arthritis without clinical and electrophysiological peripheral neuropathy. The rheumatologists should be careful to diagnose CTS in patients with RA with using US.

**Disclosure:** I. Yagci, None; M. Akdeniz Leblebicier, None; B. Mansiz Kaplan, None; D. Ozturk Gokbakan, None; G. Akyuz, None.

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**Subclinical Synovial Inflammation in Gout.** Priya Chowalloor1, Patrick Cheah2 and Helen I. Keen2. 1The University of Western Australia, Crawley, Australia; 2Sir Charles Gardiner Hospital, Nedlands, Australia.

**Background/Purpose:** Gout is poorly managed in the community. Long standing poorly controlled gout can lead into progressive destructive arthropathy, decreased quality of life and increased mortality. Aims of this study is to assess the burden of subclinical synovitis in gout both in acute and intercritical phases. Subclinical synovitis may have implications for the long term outcome of patients with gout.

**Methods:** This pilot study included 30 participants with gout according to either ACR or EULAR criteria. Subjects with any other inflammatory joint disorders were excluded. Subjects were examined twice. One visit was during the period of acute gout and second was during the intercritical phase. The intercritical phase visit was done at least four weeks after the resolution of symptoms of acute gout. Examinations performed during each visit included tender and swollen joint count, musculoskeletal ultrasound (US) of 52 peripheral joints for gray scale synovitis and power Doppler (PD). Blood was collected for ESR, high sensitivity CRP (hs CRP) and uric acid.

**Results:** Median age of the subjects was 69 (IQR 52.5–74) and BMI was 26.40 (IQR 23.12–29.40). Females were 7.4%. Median disease duration was 3 years (IQR 11–2). The mean interval between visits was 3.6 months (SD 2.4).

**Number of subjects seen** | **Flare visit** | **Intercritical visit** | **P value**
--- | --- | --- | ---
**Number of joints involved on US (defined as a PD score ≥2)** | 1st MTP (n = 17), knee (n = 17), wrist (n = 17) and MCP-3 (n = 17) | 2nd MCP (n = 17) and knee (n = 17) | 0.007
**Number of joints involved only by US and not clinically** | 11 (3–23) | 4 (3–7) | 0.139

**Conclusion:** Ultrasound demonstrates subclinical synovitis during acute and intercritical periods. Interestingly, whilst there were significantly less clinically active joints during the intercritical period (p = 0.007) there was not less joints involved by US (p = 0.139). Ultrasound may be important in the monitoring of inflammation in the management of gout.

**Disclosure:** P. Chowalloor, None; P. Cheah, None; H. I. Keen, None.

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**Musculoskeletal Ultrasound of Finger and Foot Joints in a Population of Volunteers: Is Osteoarthritis an Underestimated Problem?** Results from the German “Rheuma-Truck” Cohort. Dr. Philipp Sewerin1, Dr. Stefan Vordenbäumen1, Aiko Liedmann1, Sarah Ohmdorf2, Marina Backhaus2, Dr. Oliver Sander3, Prof. Dr. Matthias Schneider2 and Prof. Dr. Benedikt Ostendorf1. 1Univ. Duesseldorf, Düsseldorf, Germany; 2Charité University Hospital, Berlin, Germany; 3Univ. Düsseldorf, Duesseldorf, Germany.

**Background/Purpose:** To investigate the frequency of osteoarthritis (OA) in musculoskeletal ultrasound of the MCP, MTP and PIP joints in a volunteer population using the US-7 score.

**Methods:** “Rheuma-Truck” was a mobile rheumatology office located in different city center of North Rhine Westphalia, Germany offering a screening for rheumatic diseases including Rheuma-Check questionnaire, lab-tests (MVC capillary test) and imaging (US, capillaroscopy). Musculoskeletal ultrasound (MyLab 25 Gold, Esaote linear scanner, 15, Typ LA435) of the MCP-3 was sonographyically positive in 15.4% followed by 1st MTP (25%), wrist (23%) and MTP-2 (21%). Also nearly 14% of newly diagnosed OA according to ultrasonographic findings were below the age of 40. Strikingly, MCP joints were the most frequently involved joints within the US-7 scoring, which however ignored the DIP-joints. This study highlights a previously unrecognized high burden of hand OA.
Disclosure: D. P. Sewerin, None; D. S. Vordenbäumen, None; A. Liedmann, None; S. Ohndorf, None; M. Backhaus, None; D. O. Sander, None; P. D. M. Schneider, None; P. D. B. Ostendorf, None.

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CIMT in Individuals with Rheumatoid Arthritis Compared to Individuals with Type2 Diabetes. Helen Pahuu Sr, 1, Leanne Short 2, Brian Haluskas3, Vibeke Videm4 and Ranjney Thomas5. 1The University of Queensland, Woolloongabba, Australia, 2University of Queensland, Woolloongabba, Australia, 3the University of Queensland, Woolloongabba, Australia, 4Department of Laboratory Medicine, Children’s and Women’s Health, Norwegian University of Science and Technology, and Department of Immunology and Transfusion Medicine, Trondheim University Hospital, Trondheim, Norway, 5University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: It is well known that patients with RA or Type 2 diabetes (T2DM) have increased risk of atherosclerosis and CVD. Carotid ultrasound measurement of the intima media thickness is the most commonly used method to validate progression of atherosclerosis. We aim to investigate the characteristics of cardiovascular risk and progression of carotid intima media thickness in individuals with Rheumatoid Arthritis compared to individuals with type2 diabetes.

Methods: Participants with T2DM were recruited from hospital clinics and the community in the same geographic area as RA participants. The participants with T2DM participated in a randomised trial of exercise intervention for 4 weeks and patients with previous CV events were excluded in that study. All participants were subjected to B-Mode ultrasonography of the carotid artery to measure Carotid intima media thickness, and to undertake a physical assessment, routine laboratory investigations and history of CV risk profile. Average CIMT were measured on individuals with RA and individuals with Type2 diabetes at two time points, separated by a mean of 4.8 and 2.4 years respectively, using carotid duplex scanning and automated software.

Results: The study comprised 290 individuals: 78 with RA and 212 with T2DM. The RA patients were significantly older and had a higher proportion of smokers and previous CV events. The T2DM had higher BMI, diastolic blood pressure (BP) and triglycerides, lower HDL cholesterol and higher statin use. Baseline CIMT measurements were similar in the RA and T2DM cohorts at baseline (0.88mm (0.19) vs. 0.86 (0.21) p = 0.80). Despite a shorter follow-up, 91 % of the T2DM cohort had CIMT at follow-up compared to 54 % of the RA cohort (p < 0.0005). In a regression model for yearly rate of CIMT change, the only significant variables were diabetes (p < 0.005) and ever use of statins (p = 0.01). Baseline CIMT was not significantly associated with the yearly rate of CIMT change. In a supplementary adjusted logistic regression analysis where the outcome was CIMT progression compared to unchanged or reduced CIMT, the OR for progression in T2DM compared to RA was 11.4 (5.2–25.0). In the RA cohort, DMARY use at baseline was associated with significantly lower CIMT values at follow-up (p = 0.04).

Conclusion: Diabetes patients have a much higher risk of CIMT progression than RA patients when adjusting for relevant risk factors and baseline CIMT.

Disclosure: H. Pahuu Sr, None; L. Short, None; B. Haluskas, None; V. Videm, None; R. Thomas, None.

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Cost-Effectiveness Analysis of HLA-B5801 Genotyping in the Treatment of Gout Patients with Chronic Renal Insufficiency in Korea. Dong-Jin Park1, Kyung-Eun Lee1, Sung-Hwan Park2 and Shin-Seok Lee1. 1Chonnam National University Medical School, Gwangju, South Korea, 2Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Allopurinol-induced severe cutaneous adverse reactions (SCARs) are relatively rare, but cause high rates of morbidity and mortality. Studies have shown that the HLA-B5801 allele and renal impairment are strongly associated with SCARs. Recent American College of Rheumatology guideline recommends that, prior to treatment with allopurinol, the HLA-B5801 genotype of gout patients at high risk for SCARs, including Korean patients with chronic renal insufficiency, should be determined. However, whether such genotyping is cost-effective is unknown. This study evaluated the cost-effectiveness of HLA-B5801 genotyping for treatment of gout in patients with chronic renal insufficiency in Korea.

Methods: A decision analytic model over a time period of 12 months was employed to compare the cost and outcomes of treatment informed by HLA-B5801 genotyping with that of a conventional treatment strategy using a hypothetical cohort of gout patients with chronic renal insufficiency. Direct medical costs were obtained from real SCAR patients from two tertiary hospitals. Outcomes were measured as a total expected cost and an incremental cost-effectiveness ratio.

Results: In the base model, the total expected cost and probability of continuation of gout treatment without SCARs with the conventional and HLA-B5801 screening strategies were US $1,193 and US $1,055, and 97.8% and 100%, respectively. The result was robust according to sensitivity analyses.

Conclusion: Our model suggests that gout treatment informed by HLA-B5801 genotyping is less costly and more effective than treatment without genotyping, and HLA-B5801 genotyping could considerably reduce the occurrence of allopurinol-induced SCARs and related deaths.

Disclosure: D. J. Park, None; K. E. Lee, None; S. H. Park, None; S. S. Lee, None.

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Colchicine and the Risk of Acute Cardiovascular (CV) Events Among Gout Patients: The New York Department of Veterans Affairs Retrospective Cohort Study. Daria B. Crittenden1, Jessica N. Kimmel1, Virginia C. Pike1, Rebecca Boas1, Daniel Diaz1, Cilian J. White1, Michael DeBerardine2, Grace Kim1, Pujazit Morina1, Avni Shah1, Binata Shah1, Steven P. Sedlis2, Jeffrey D. Greenberg1, Craig T. Tenner3, Christopher J. Swearingen4, Svetlana Krasnokutsky Samuels2, Bruce N. Cronstein1 and Michael H. Pillinger1. 1NYU School of Medicine, Division of Rheumatology, New York, NY, 2VA New York Harbor Health Care System, New York, NY, 3NYU School of Medicine, Division of Cardiology, New York, NY, 4NYU School of Medicine, New York, NY, 5University of Arkansas for Medical Sciences, Little Rock, AR.

Background/Purpose: Gout patients are at increased risk for CV disease, possibly owing to chronic inflammation. Colchicine is commonly used in gout, and inhibits inflammatory cell types that are also implicated in atherosclerosis. In a cross-sectional study, we observed an association between colchicine use and decreased myocardial infarction (MI) among gout patients (Crittenden et al, J Rheum 2012). To further assess colchicine’s possible effect on CV risk in this population, we performed a retrospective cohort study of gout patients taking or not taking colchicine at the VA NY Harbor Health Care System.

Methods: We identified all active patients with ICD-9 codes for gout or hyperuricemia from 2000-09. Charts were manually screened to confirm gout (based on ACR criteria) and pharmacy records used to identify subjects taking daily colchicine for > 30 continuous days (colchicine group). Gout patients who never received colchicine formed the control group. Among the colchicine group, we defined colchicine lapse as any period of colchicine non-use ≥ 2 weeks after medication cessation (to account for drug elimination time). Outcomes included a composite incidence rate of MI+stroke+transient ischemic attack (TIA); individual components of the composite outcome; and C-reactive protein level (CRP; lowest level attained during the period observed).

Results: Of 7,819 potential subjects, 1638 patients met gout criteria. 381 were excluded for < 30 days colchicine use, leaving 1257 to be analyzed. 804 colchicine users had 3,630 years of follow-up (2270 years of active use and 1360 years of lapse), 453 patients never used colchicine, with 2,087 years of follow-up. Colchicine users had significantly more hyperlipidemia (60 vs 49%, p = 0.003), and history of MI (14 vs 9 %, p = 0.01) and percutaneous intervention (10 vs 6%, p = 0.006) than controls, as well as higher urate levels (8.5 vs 8.0 mg/dL, p = 0.05) and allopurinol use rates (23 vs 18%, p = 0.03). We observed no significant difference between colchicine users and non-users for the composite outcome (control, 0.011 events/subject-year; colchicine, 0.016 events/subject-year, p = 0.23) or individual component outcomes (adjusted for allopurinol use), but due to a low event rate we were not able to adjust fully for patient risk factors. However, within the colchicine group we observed a significant, 57% reduction in the composite outcome event rate during times of active colchicine use vs lapse (0.012 vs 0.021 events/subject-year, p = 0.04). When colchicine users were divided into consistent (medication possession ratio ≥ 0.9) vs inconsistent (MPR < 0.9) users, consistent
colchicine users had lower CRP levels (0.7 mg/dL) than either never users (2.7 mg/dL) or inconsistent users (1.9 mg/dL) (never vs consistent p<0.001, inconsistent vs consistent p<0.001), despite higher background CV risk.

**Conclusion:** Among gout patients prescribed colchicine on an ongoing basis, composite CV event rates were significantly lower during colchicine use vs colchicine lapse, and consistent colchicine use was associated with lower CRP concentrations. Additional studies are underway to clarify the possible benefit of colchicine in reducing acute CV events among gout patients.

Support provided by Takeda.

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**Can We Diagnose Acute Gout without Joint Aspiration? Results of a Prospective Study of 112 Patients Presenting with Acute Arthritis.**

Pascal Zafferey, Roxana Valcov, Isabelle Fabreguet, Alexandre Dumusc and Alexander So. RHU/CHUV, Lausanne, Switzerland.

**Background/Purpose:** The gold standard for the diagnosis of acute MSU induced arthritis is crystal identification by microscopy after joint aspiration. Alternative diagnostic tools that have been proposed include joint ultrasonography (US) and a clinical score for gout (Nijmegen Score – NS) that has been validated in a primary care setting. Most US studies have been performed in patients with known gouty arthritis. The primary objective was to compare the performance of US as diagnostic tool with the NS in the diagnosis of suspected acute gouty arthritis, using synovial fluid analysis as a gold standard. The secondary objective was to evaluate whether the performance of NS could be enhanced by combining with US data.

**Methods:** All consecutive patients who presented with acute arthritis suspected to be of microcrystalline origin between October 2012 and May 2014 were prospectively included. The duration of arthritis symptoms was <10 days. All patients underwent a clinical and an US evaluation of the symptomatic joint as well as of the knees, the ankles and the first MTP joints (multiple joints). Joint aspiration of the symptomatic joint was performed within 24 hours. US was performed by 2 rheumatologists skilled in US who were blinded to the clinical data. The NS was calculated “a posteriori” by a clinician not implicated in the primary evaluation of patients. We applied a cut-off value of >5.5 proposed by the authors of the NS for the diagnosis of gout (1). US diagnosis of gout was evaluated firstly on typical US signs (“Double contour” and/or tophi) in the symptomatic joint and secondly on signs of gout in all the other joints.

**Results:** 117 patients were included. Joint fluid was obtained in 112 patients. MU crystals were detected in 61 patients (54%). CCP crystals were found in 29 (26%) and no crystals were found in 22 (20%). The mean (± SD) NS scores differed significantly between gout 8.8 (±2.4) and non-gout groups 4.6 (±2.8) (p<0.05). In CPP patients, the mean NS score was 4.3 (±2.3). US signs of gout were found in symptomatic joints of 40 patients, and by multiple joints US, signs of gout were found in 68 patients.

The table describes the sensitivity, the specificity, and the positive predictive value (PPV) of the NS, US and the combination of both US and NS in the diagnosis of gouty arthritis. NS score alone or US of the affected joint alone had moderate sensitivity but reasonable specificity for diagnosis of gout in our cohort. The best diagnostic performance was obtained with either US in multiple joints or the NS + US in the symptomatic joints.

**Conclusion:** The NS score alone or US alone of the affected joints were moderately sensitive in the diagnosis of acute gout, but had good specificity. Combining the NS score with US evaluation of the symptomatic joint enhanced the diagnostic performance but does not replace the need for crystal-identification by microscopy in the diagnosis of acute gouty arthritis.

**Disclosure:** P. Zafferey, None; R. Valcov, None; I. Fabreguet, None; A. Dumusc, None; A. So, None.

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**Performance of Joint Ultrasonography in the Diagnosis of Suspected Acute Crystal Arthritis: Results of a Prospective Study of 112 Patients.**

Pascal Zafferey1, Isabelle Fabreguet1, Roxana Valcov1, Alexandre Dumusc1 and Alexander K. So Sr.2, 1RHU/CHUV, Lausanne, Switzerland, 2CHUV, Lausanne, Switzerland.

**Background/Purpose:** The gold standard for diagnosing gout and CCP arthritis is the identification of monosodium urate (MSU) crystals in joint fluid. Ultrason (US) features of gouty and CPP arthritis have been described (1,2), and the technique has been proposed as a diagnostic tool in acute arthritis. There have been limited studies on the performance of this technique as a diagnostic tool when applied to the setting of acute arthritis.

The primary objective was to determine the performance of ultrasound as a diagnostic tool for CPPD and urate acute crystal arthritis, using crystal identification by microscopy as a gold standard.

**Methods:** 117 consecutive patients who presented an acute arthritis of <10 days duration of suspected microcrystallographic origin between October 2012 and January 2014 were prospectively included in the study. Aspiration of the symptomatic joint was performed and crystals identified by polarization light microscopy. All patients underwent an US of the symptomatic joint as well as both knees, ankles and 1stMTP joints that was performed by a rheumatologist who was “blinded” to the clinical history within 24 hours of joint aspiration. An “US diagnosis” was made based on the findings in the symptomatic joint as well as the other joints examined by US.

**Results:** In 112 patients joint fluid was obtained. 53 had MSU, 27 CPPD and 9 had both crystals. No crystals were detected in 23. US signs of gout, CCP or mixed crystal deposition were found in symptomatic joints of 40/38/7 patients respectively, and by multiple joints US, in 68/59/16 patients.

Table 1 describes the sensitivity, the specificity, and the positive predictive value (PPV) and negative predictive values (NPV) of the US.

<table>
<thead>
<tr>
<th></th>
<th>Gout US Symptomatic joint</th>
<th>Gout US Multiple joints</th>
<th>CCP US Symptomatic joint</th>
<th>CCP US Multiple joints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>60</td>
<td>84</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>92</td>
<td>76</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>PPV%</td>
<td>92</td>
<td>82</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>NPV%</td>
<td>62</td>
<td>77</td>
<td>80</td>
<td>87</td>
</tr>
</tbody>
</table>

The sensitivity of US signs in the symptomatic joint for both gout and CCP is poor. US is more specific for the diagnosis of gout that CCP arthritis (PPV >90% against 60%).

By US of multiple joints, the sensitivity of US for both diagnoses rose significantly but the specificity and the PPV decreased, especially for CCP (PPV52%). In absence of US signs in all the joints, CCP arthritis is highly unlikely (NPV 87%).

**Conclusion:** In patients with a clinical suspicion of acute microcrystallographic arthritis, US examination may be of assistance in the diagnosis if joint aspiration is not feasible. The examination of multiple joints is required to obtain the best clinical utility.

**Disclosure:** P. Zafferey, None; I. Fabreguet, None; R. Valcov, None; A. Dumusc, None; A. K. So Sr., None.

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**Canakinumab in Frequently Flaring Gouty Arthritis Patients, Contra-indicated, Intolerant or Unresponsive to Non-Steroidal Anti-Inflammatory drugs and/or Colchicine: Safety and Efficacy Results from Long Term Follow-up.**

Naomi Schlesinger1, Rieke Allen1, Thomas Barzini1, H. Ralph Schumacher Jr.2, Mark Bloch3, Karine Lheritier4, Dominik Richard5, Andrea Stanton6 and Alexander So7.1Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, 2Charité University Medicine, Berlin, Germany, 3Hôpital Lariboisière, Paris, France, 4University of Pennsylvania VA Medical Center, Philadelphia, PA, 5Holdsworth House Medical Practice, Sydney, Australia, 6Novartis Pharma AG, Basel, Switzerland, 7Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland.

**Background/Purpose:** Canakinumab is a fully-human, anti-IL-1β monoclonal antibody that binds and inhibits IL-1β and is approved for use in patients with gout who experience acute attacks despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine (OA). OA (ps), in whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective, need of effective alternative treatments.1 Canakinumab...
(CAN) is a selective, human anti-interleukin-1β antibody, the only biologic approved (in the European Union) for the treatment of difficult-to-treat GA pts. Here, we present the cumulative results from a single long-term extension of two phase III studies. The primary objective is to evaluate the long-term safety of CAN (s.c.) in GA pts with frequent flares. Frequency of new flares, mean number of doses/pt, pts’ assessments of gouty pain intensity and pts’ global assessment (PGA) of response (both on Likert scale) were measured as secondary objectives. The effectiveness of CAN enabling successful urate lowering therapy (ULT) was explored by assessing serum uric acid (SUA) level in pts initiating or modifying their ULT while exposed to CAN.

**Methods:** GA pts, who completed two multicenter randomized (CAN and triamcinolone acetate [TA]) phase III core and respective randomized extensions (E1) of the same design, rolled over into respective open-label extensions, E2, followed by a single extension phase, E3. In E2 and E3, all pts were treated with CAN 150 mg on demand upon new flare. These treatment groups were analyzed as ‘CAN Group’ [CG] and ‘TA Group’ [TG], i.e. all patients who were initially randomized to receive CAN or TA, respectively, and received at least one dose of study drug. Safety was assessed in terms of exposure-adjusted incidence of adverse events (AEs) per 100 patient-years (pyr). Maximum total cumulative duration of the study was 3 years.

**Results:** Of the 456 pts randomized in core studies, 335 entered the E1s. After E1 completion, 272 pts entered E2s. Following E2 completion, 136 pts entered and 122 completed E3. In CG, the mean number of doses/pt was 2.68 over 3 years. Overall, the exposure adjusted incidence of AEs in CG was lower (264.6/100 pyr) than in TG (308.8/100 pyr). Re-treatment with CAN did not result in any increased incidence of AEs. Overall, the incidence of exposure-associated AEs in CG and TG was 17.3 and 17.7 per 100 pyr, respectively. The overall incidence of SAEs did not change in pts re-treated with CAN in CG (15.2 vs 15.1 per 100 pyr). Overall 4 deaths (2 in CG, 2 in TG) were reported: 1 intracranial hemorrhage [pt not re-treated with CAN]; 1 sudden cardiovascular death and 1 pneumococcal sepsis [TG pt who never received CAN]). None of these deaths were suspected to be study drug related. Thirty percent (n=12) of the pts initiating or modifying ULT during the E3 (n=40) reached target SUA levels (<6mg/mL). Mean flare rate per year was lower in CG compared with TG (1.109 vs 2.459). All CAN-treated pts’ maintained pain intensity and PGA response scores upon ‘on demand’ retreatment over 3 years.

**Conclusion:** These results support the long-term safety of CAN treatment in pts with frequent GA flares. AEs in CG were lower than in TG. The safety profile was consistent with that observed in the previous studies.

**Disclosure:** N. Schlesinger, Novartis Pharmaceutical Corporation, 2, Takeda, 8, Sobi, 9, Astra Zeneca, 9; D. R. Radovick, None; J. Kostis, None.
Additional analysis is required to determine the relative advantages of a 6 month timeframe, particularly for the observation of no flare.

**Methods:** Experts in gout from multiple countries (n=88) were invited by email to participate in this web-based questionnaire study to identify remission criteria as an outcome measure for gout clinical trials. For the purposes of this project, remission was defined as the absence of symptoms and signs attributable to gout, when these symptoms or signs can or are expected to return in the future (for example, if the patient stopped treatment). Three rounds of a Delphi consensus exercise were conducted by online survey. Questions focused on domains for inclusion in remission criteria, based on the OMERACT core domains for chronic gouty studies. Respondents were then asked to choose which option would indicate remission for each domain. Consensus in the Delphi exercise was defined as >80% agreement in responses. The Delphi exercise was followed by a discrete choice experiment using 1000Minds to further explore the extent of variation in relative weighting for components of remission (particularly the time over which no flares should be observed).

**Results:** There were 49 respondents (56% response rate). There was consensus about which domains should be included in remission criteria from the Delphi exercise: 98% agreement for serum urate, 96% for flares, 92% tophi, 83% pain due to gout and 93% patient global assessment of gout disease activity (PGA). Consensus was reached that serum urate measurements should be measured at least twice over a set timeframe and that all measurements should be <6mg/dL (94% agreement). There was also consensus that, for both pain and PGA measurements, the results of two separate measurements over a set timeframe would be averaged. There was again agreement that timeframes of three months or less were not suitable for measurement of remission. However, consensus was not achieved in the Delphi exercise about the timeframe for remission with equal responses for six months (51%) and one year (49%). In the discrete choice experiment, the range of opinions remained widely distributed, indicating an ongoing lack of consensus between the 6 and 12 month timeframe. The difference in relative weighting accorded to ‘no flares observed over 12 months’ compared to ‘no flares observed over 6 months’ ranged from 0.04 to 0.26 (out of a total weighting available of 1.0), with the middle 80% of respondents ranging from 0.04 to 0.24.

**Conclusion:** These consensus exercises have identified domains for remission criteria for gout, and methods for reporting these domains. Additional analysis is required to determine the relative advantages of a 6 or 12 month timeframe, particularly for the observation of no flare.

**Disclosure:** R. Gancheva. None; A. Kundurzhiev. None; M. Ivanova. None; T. Kundurzhiev. None; R. Rashkov. None; Z. Kolarov. None.

**Development of Preliminary Remission Criteria for Gout Using Delphi and 1000Minds Consensus Exercises.** Hugh de Lautour1, Nicola Dalbeth2 and William Taylor3. 1Auckland District Health Board, Auckland, New Zealand, 2University of Auckland, Auckland, New Zealand, 3University of Otago, Wellington, New Zealand.

**Background/Purpose:** There are currently no agreed remission criteria for gout. The aim of this study was to establish consensus for elements of potential remission criteria for use in clinical trials of gout.

**Methods:** Experts in gout from multiple countries (n=88) were invited by email to participate in this web-based questionnaire study to identify remission criteria as an outcome measure for gout clinical trials. For the purposes of this project, remission was defined as the absence of symptoms and signs attributable to gout, when these symptoms or signs can or are expected to return in the future (for example, if the patient stopped treatment). Three rounds of a Delphi consensus exercise were conducted by online survey. Questions focused on domains for inclusion in remission criteria, based on the OMERACT core domains for chronic gouty studies. Respondents were then asked to choose which option would indicate remission for each domain. Consensus in the Delphi exercise was defined as >80% agreement in responses. The Delphi exercise was followed by a discrete choice experiment using 1000Minds to further explore the extent of variation in relative weighting for components of remission (particularly the time over which no flares should be observed).

**Results:** There were 49 respondents (56% response rate). There was consensus about which domains should be included in remission criteria from the Delphi exercise: 98% agreement for serum urate, 96% for flares, 92% tophi, 83% pain due to gout and 93% patient global assessment of gout disease activity (PGA). Consensus was reached that serum urate measurements should be measured at least twice over a set timeframe and that all measurements should be <6mg/dL (94% agreement). There also was consensus that, for both pain and PGA measurements, the results of two separate measurements over a set timeframe would be averaged. This agreement that timeframes of three months or less were not suitable for measurement of remission. However, consensus was not achieved in the Delphi exercise about the timeframe for remission with equal responses for six months (51%) and one year (49%). In the discrete choice experiment, the range of opinions remained widely distributed, indicating an ongoing lack of consensus between the 6 and 12 month timeframe. The difference in relative weighting accorded to ‘no flares observed over 12 months’ compared to ‘no flares observed over 6 months’ ranged from 0.04 to 0.26 (out of a total weighting available of 1.0), with the middle 80% of respondents ranging from 0.04 to 0.24.

**Conclusion:** These consensus exercises have identified domains for remission criteria for gout, and methods for reporting these domains. Additional analysis is required to determine the relative advantages of a 6 or 12 month timeframe, particularly for the observation of no flare.

**Disclosure:** R. Gancheva. None; N. Dalbeth. None; W. Taylor. None.

**163 Is the Rate of Skin Reactions to Fexubsostat Increased in Patients with a History of Skin Intolerance to Allopurinol? a Retrospective, Hospital-Based Study Involving 101 Patients Consecutively Treated with Allopurinol and Fexubsostat.** Thomas Bardin1, René-Marc Flipo2, Pascal Richette3 and Pierre Clerson4. 1Hôpital Lariboisière, Paris, France, 2Rene Salengro hospital, Lille, France, 3INSERM U1132, Université Paris-Diderot, Hôpital Lariboisière, Paris, France, 4Organometrie, Roubaix, France.

**Background/Purpose:** Allopurinol is the standard drug for urate-lowering management of gout. Allopurinol is safe in most patients. The most frequent side effects are minor cutaneous reactions, which occur in approximately 2–4 % of patients. Severe, life-threatening cutaneous adverse reactions are observed in 0.1%-0.4% of patients. They include toxic epidermal necrolysis, Steven Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS). They are more frequent in patients with a history of minor reaction to allopurinol, precluding re-challenge with the drug. Fexubsostat is a non-purine xanthine oxidase inhibitor which is structurally distinct from allopurinol. Fexubsostat is an interesting alternative to allopurinol, especially in patients who do not reach the serum urate target, because of renal impairment or intolerance to allopurinol. The potential for cross reactivity between fexubsostat and allopurinol is of obvious clinical importance when assessing treatment alternatives to allopurinol. Skin reactions have been reported in 0.5% to 1.6% of patients treated by fexubsostat (Ernst 2009) and have been suspected to be more frequent in patients with previous cutaneous intolerance to allopurinol.

**Methods:** CACTUS was a non-interventional cross-sectional multicentre study conducted in France by GP from November 2010 to May 2011, with the aim to describe characteristics of gouty patients according to the achieved patients with a history of minor reaction to allopurinol, precluding re-challenge with the drug. Fexubsostat is structurally distinct from allopurinol and could be an interesting option in patients who developed skin reaction to allopurinol. However, the frequency of skin reactions to fexubsostat has been suggested to be increased in patients with skin intolerance to allopurinol, therefore challenging the value of this option. The aim of our study was to investigate the cutaneous tolerance of fexubsostat in gouty patients who had experienced skin intolerance to allopurinol as compared to those who had not.

**Results:** We exhaustively identified gouty patients who had sequentially received allopurinol and fexubsostat in the Rheumatology departments of 4 French university hospitals and collected data from hospital files using a predefined protocol. Patients who had not visited the prescribing physician at least two months after the initiation of fexubsostat were excluded. The odds ratio (OR) for skin reaction to fexubsostat in patients who had a cutaneous reaction to allopurinol as compared to those who had not, was calculated. For estimating the 95% confidence interval (CI) we used two methods: Miettinen’s method and a bootstrap method. In addition, renal failure did not modify the risk of skin reaction to fexubsostat (P=0.97 in univariate analysis and 0.98 in a multivariate model combining renal failure and intolerance to allopurinol).

**Conclusion:** These results suggest that the risk of skin reaction to fexubsostat is moderate and not significantly increased by a history of cutaneous adverse event to allopurinol nor by renal failure.

**Disclosure:** T. Bardin, AstraZeneca, Ipsen, Menarini, Novartis, Sobi; 8; G. Chales, None; T. Pascart, None; R. M. Flipo, Ipsen, Menarini; 5; J. C. Roujeau, Ipsen, Menarini; 5; A. Delayen, None; P. Clerson, Ipsen, Menarini, 5.
Prevalence of Gout in the Adult Population of France in 2013. Thomas Bardin1, Pierre Clerson2, Stéphane Boué3, Gerard H. Chales4, Michael Doherty5, René-Marc Filpo6, Charles Lambert7, Frédéric Litot8, Thierry Poireaud9, Thierry Schaeverbeke10 and Pascal Richette11. 1Hôpital Lariboisière, Paris, France, 2Department of Rheumatology, Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, 3Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

Background/Purpose: The prevalence of gout has been studied in several Western countries by various methods to approach gout diagnosis, and has been estimated to vary from 0.9 to 3.9 %. The prevalence of gout remained unknown in France. The aims of our study was to design a tool that would allow a confident diagnosis of gout in an epidemiological setting and to assess the current prevalence of gout in France.

Methods: This was a two phase study. In phase one, we designed a questionnaire to detect gout that would be suitable for telephone interviews by non-physicians. A 62-item questionnaire covering clinical features, co-morbidities and treatment of gout was administered by phone, by non-physicians unaware of the patient diagnoses in a case control study. 102 people with crystal-proven gout and 142 controls who had other types of arthritis with no urate crystal in their synovial fluid were included. Logistic regression analysis and classification and regression trees (CARTs) were used to select items discriminating cases from controls. In phase two, a random sample of adults resident in metropolitan France (including Corsica) was derived from the national telephone (fixed and mobile) directory, using the next birthday method in cases of multiple users. The telephone questionnaire was administered by non-physicians to subjects who acknowledged present or past non traumatic acute pain in a peripheral joint. The target size for the interview survey was 10,000 participants. Statistical analysis took into account several factors (area, size of the urban centre, sex, age, occupation, known distribution of fixed or mobile users).

Results: In phase one, two logistic regression models (sensitivity 88.0% and 87.5%; specificity 93.0% and 89.8%, respectively) and one CART model (sensitivity 81.4%; specificity 93.7%) revealed 11 informative items that allowed correct classification of 90.0%, 88.8% and 88.5% of patients respectively. In the second phase the response rate varied between 34 % (fixed phone sample) and 38 % (mobile sample). 10,026 participants were interviewed between March and June 2013. 373 declared having suffered from acute, non traumatic joint pain, of whom a diagnosis of gout was made in 84 to 102 subjects, according to the algorithm used. This led to an estimated prevalence of gout of 0.9% (95% CI: 0.8, 1.1) in the general population, with no significant geographic variation. Prevalence was greater in men and increased with age. Interestingly prevalence estimate on self declaration only gave a much higher prevalence estimate (3.7%).

Conclusion: Gout prevalence in the adult population of metropolitan France in 2013 was estimated to be 0.9%. Studies using self declaration might grossly overestimate the prevalence of gout.

Disclosure: T. Bardin, Novartis, SOBI, 5; Novartis, 8; P. Clerson, Ipsen, Menarini, 5; S. Boué, Ipsen, Menarini, 5; G. H. Chales, Ipsen, Menarini, 5; M. Doherty, Menarini, 5; R. M. Filpo, Ipsen, Menarini, 5; C. Lambert, Ipsen, 5; F. Lioté, Celgene Corporation, 2, Celgene Corporation, 5; T. Poireaud, Menarini, 3; T. Schaeverbeke, None; P. Richette, None.

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Risk Factors for Gout Attack Recurrence during Urate-Lowering Allopurinol Treatment. Myeong Jae Yoon1, Ji Ae Yang2, Sang Hyun Jou1, Sang Jin Lee1, Jin Young Moon1, Hyun Mi Kwon1, Dong Jin Ko1, Yeong Wook Song1 and Eun Bong Lee1. 1Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, 2Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

Background/Purpose: Gout is a recurrent inflammatory arthritis caused by crystal deposition of monosodium urate, which can be prevented urate-lowering agents such as allopurinol. However, gout attack can still recur during urate-lowering therapy. In this study we investigated the risk factors associated with recurrence of gout attacks during allopurinol treatment.

Methods: A total of 527 gout patients were enrolled, who took allopurinol at least for 6 months at Rheumatology Clinic of Seoul National University Hospital between March 2001 and March 2013. The patients were divided into those who have ever experienced recurrence of gout attack (recurrence group) and those who haven’t (non-recurrence group) during allopurinol treatment. To reveal the risk factors for gout recurrence, we compared baseline demographic characteristics, concomitant diseases, uric acid level, creatinine level, presence of tophi, type of prophylactic treatment (non-steroidal anti-inflammatory drugs, colchicine, glucocorticoids) and concomitant treatment. Multiple logistic regression analysis was applied to find the best model to explain the recurrence.

Results: The mean (SD) age of the enrolled patients was 58.7 (14.9) years and 96.2% were male. The patients were followed-up for mean (SD) duration of 3.17 (2.64) years. During urate-lowering therapy, 323 patients (61.3%) experienced recurrence of gout attack. In recurrence group, baseline uric acid level was significantly higher than non-recurrence group (8.6 ± 2.0 vs 8.1 ± 1.9 mg/dL, p = 0.0043 by Student t-test). The presence of tophi was more commonly observed in recurrence group (29.4% vs 18.6%, p = 0.006 by chisquare test). The other variables showed no difference between recurrence and non-recurrence groups, which include age, sex, concomitant diseases, the presence of urinary stone, the type of prophylaxis treatment and initial treatment. In multivariable logistic regression analysis, high uric acid level (Uric acid > 8.5 mg/dl) and the presence of tophi were found to be risk factors for gout attack during allopurinol treatment (Table 1).

Conclusion: Our study revealed that patients who show uric acid level > 8.5 mg/dl and/or tophi at baseline have higher risk for recurrence of gout attack during allopurinol treatment. Adequate education and closer follow-up will be required for those risky patients when allopurinol is started.

Table 1. Risk factors for recurrence of gout attack during allopurinol treatment, multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tophi</td>
<td>1.78</td>
<td>1.16-2.74</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum uric acid &gt;8.5 mg/dL</td>
<td>1.54</td>
<td>1.07-2.21</td>
<td>0.019</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>0.72</td>
<td>0.36-1.44</td>
<td>0.555</td>
</tr>
<tr>
<td>Colchicine</td>
<td>1.03</td>
<td>0.648-1.628</td>
<td>0.911</td>
</tr>
<tr>
<td>NSAID+colchicine</td>
<td>2.57</td>
<td>0.897-7.881</td>
<td>0.079</td>
</tr>
<tr>
<td>Gluocorticoid</td>
<td>0.82</td>
<td>0.45-1.50</td>
<td>0.522</td>
</tr>
</tbody>
</table>

Disclosure: M. J. Yoon, None; J. A. Yang, None; S. H. Joo, None; S. J. Lee, None; J. Y. Moon, None; H. M. Kwon, None; D. J. Ko, None; Y. W. Song, None; E. B. Lee, None.
Target Serum Urate: Do Patients Know Their Goal? Brian W. Coburn1, Kayli A. Bendlin2, Harlan Sayles1, Kathryn S. Hentzen2, Michaela M. Hrdy2 and Ted R. Mikuls1. 1Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, 2Omaha VA Medical Center, Omaha, NE.

Background/Purpose: Treat-to-target approaches are used to achieve therapeutic goals in conditions such as diabetes and rheumatoid arthritis. This strategy has also been widely endorsed in gout using urate lowering therapy (ULT). However, suboptimal rates of serum urate (sUA) goal achievement and ULT dose titration in clinical data indicate that providers are not routinely adopting treat-to-target strategies in gout. According to the Chronic Care Model a viable strategy for improving outcomes may be to directly engage gout patients in their care, an approach that requires patient knowledge of sUA goals. The objective of this study was to examine knowledge of sUA goals among gout patients treated with ULT and to identify factors associated with this knowledge.

Methods: Questionnaires were mailed to 1437 gout patients receiving an allopurinol prescription between August 1, 2011 and July 31, 2012. Of these, 886 (62%) surveys were returned. Patients were asked in a multiple choice format “What is the ideal blood uric acid level to aim for when treating gout?” In addition to sociodemographic, health, and gout-related factors, analysis included Patient Activation Measure (PAM™) scores which quantifies an individual’s self-perceived combination of skills, knowledge and confidence necessary to become engaged in their own care (range 0 to 100). A continuous measure, PAM™ scores are categorized into 4 levels from low activation (1) to high activation (4). Associations of factors with knowledge were examined using multivariable logistic regression.

Results: Only 13% of patients correctly identified a sUA goal for ULT (<6.0 mg/dL); 78% reported that they “didn’t know” and 9% chose an incorrect answer (Table 1). This was despite a generally high level of knowledge about gout including its cause (87% correct), cause of acute flares (69%), classic symptoms (93%), use of allopurinol as ULT (83%) and indefinite duration of ULT (69%). Older age and PAM™ score were independently associated with knowing the target sUA. An increase of 15 points was associated with a 32% increase in the odds of knowing goal sUA.

Table 1: Association of Patient Characteristics with Knowledge of Target Serum Urate Among Gout Patients Receiving Urate Lowering Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bivariate Did not know</th>
<th>Multivariable Odds Ratio (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>109 (13%)</td>
<td>755 (87%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>69.6 (10.3)</td>
<td>72.8 (10.2)</td>
</tr>
<tr>
<td>Male</td>
<td>108 (99%)</td>
<td>744 (99%)</td>
</tr>
<tr>
<td>Non-Hispanic Caucasian *</td>
<td>95 (89%)</td>
<td>677 (91%)</td>
</tr>
<tr>
<td>Married *</td>
<td>63 (59%)</td>
<td>425 (57%)</td>
</tr>
<tr>
<td>High school graduate *</td>
<td>99 (93%)</td>
<td>661 (88%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>32.7 (5.1)</td>
<td>32.2 (6.3)</td>
</tr>
<tr>
<td>Age at first gout attack</td>
<td>47.4 (15.0)</td>
<td>50.3 (15.4)</td>
</tr>
<tr>
<td>Serum urate at diagnosis</td>
<td>7.3 (2.0)</td>
<td>7.0 (2.1)</td>
</tr>
<tr>
<td>Patient activation score</td>
<td>62.6 (11.5)</td>
<td>59.4 (11.6)</td>
</tr>
</tbody>
</table>

(0–100 scale)

Confidence (0–10 scale)1, 8.8 (2.0) 8.8 (2.4) 0.32 median (SD)

Values in bivariate analysis are frequency (%) or mean (±SD) except where noted. * The following variables were dichotomized for analysis: non-Hispanic Caucasian vs. other, currently married vs. not married and high school graduate vs. less than high school graduate. 1 Composite average confidence in 4 aspects of the treatment plan: discussion of medication, discussion of lifestyle and diet, able to summarize the plan and able to do all the tasks in the plan.

Conclusion: In this population, we observed a lack of knowledge among ULT-treated gout patients about target sUA levels. Younger patients and those demonstrating lower activation were more likely to be deficient in knowledge of their sUA goal. Interventions to improve outcomes among gout patients may benefit from improving activation.

Disclosure: B. W. Coburn; None; K. A. Bendlin; None; H. Sayles; None; K. S. Hentzen; None; M. M. Hrdy; None; T. R. Mikuls, None.

Positive Association Between Tomato Consumption and Serum Urate: Investigating an Anecdotal Trigger of Gout Flares. Tony R. Merriman1, Nicola Dalbeth2, Peter B. B. Jones3, Lisa K. Stamp1, Murray Cadzow2, Ruth Topless1 and Tanya Flynn4. 1University of Otago, Dunedin, New Zealand, 2University of Auckland, Auckland, New Zealand, 3Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, 4University of Otago, Christchurch, Christchurch, New Zealand.

Background/Purpose: Gout is characterised by intermittent flares of inflammation in response to monosodium urate crystals in the joints. Gout flares can be triggered by dietary factors that raise serum urate. Tomato consumption is an anecdotal trigger of gout flares. This study aimed to measure the frequency of tomato consumption as a self-reported trigger of gout flares in a New Zealand gout patient sample set, and to use publically available data to test the hypothesis that tomato consumption is associated with levels of serum urate.

Methods: 1134 New Zealand people (of Maui, Pacific Island, European or other ancestry) with clinically ascertained gout were asked about dietary triggers of gout. European individuals from the Atherosclerosis Risk In Communities (ARIC, n=7517), Cardiovascular Health Study (CHS, n=2151) and Framingham Heart Study (FHS, n=3052) were used to test for association between serum urate and self-reported tomato intake using two models. Model 1 was adjusted for age, BMI, average calorie intake (kcal/day), principal components analysis vectors 1 and 2 from genome-wide genotype data and model 2 additionally adjusted for meat, seafood/fish, sugar sweetened soft drinks/ juices, dairy products, coffee, vitamin C and alcohol consumption.

Results: At least one dietary trigger was reported by 970/1324 (73.3%) of the New Zealand participants with gout. Tomatoes as a dietary trigger was mentioned by 178/970 (18%) participants, making this the 4th most commonly reported dietary trigger in New Zealand men and women. Seafood or fish (634/970; 65%), alcohol (501/970; 52%) and red meat (374/970; 39%) were more frequently reported than tomatoes. In the analysis of the ARIC, CHS and FHS datasets, there was association between tomato intake and serum urate levels (β=0.66 μmol/L 1 per weekly serving; P=0.006), which was evident in both men and women (Table; Model 1). This association was also maintained after adjustment for consumption of all other urate associated dietary exposures (all: β=0.66 μmol/L 1, P=0.008) (Table; Model 2).

Conclusion: Tomatoes are a common self-reported trigger of gout flares. Whilst our descriptive and observational data are unable to support the claim that tomato consumption is a trigger of gout attacks, the positive association between tomato consumption and serum urate levels suggests that the self-reporting of tomatoes as a dietary trigger by people with gout has a biological basis.

Table 1: Association Between Serum Urate Levels (μmol/L1) And Tomato Consumption (serving/week) in the European meta-analysis combined cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>β [95% CI] P</td>
<td>P</td>
<td>β [95% CI] P</td>
</tr>
<tr>
<td>Men</td>
<td>0.84 [0.06; 1.62] 0.035 0.15</td>
<td>0.67 [0.12; 1.45] 0.099 0.11</td>
</tr>
<tr>
<td>Women1</td>
<td>0.59 [0.02; 1.16] 0.041 0.51</td>
<td>0.63 [0.05; 1.22] 0.035 0.78</td>
</tr>
<tr>
<td>All2</td>
<td>0.664 [0.19; 1.13] 0.006 0.54</td>
<td>0.66 [0.17; 1.14] 0.008 0.33</td>
</tr>
</tbody>
</table>

1Adjusted for menopause status.
2Adjusted for sex and menopause status.

Disclosure: T. R. Merriman, None; N. Dalbeth, Areva, 5, AstraZeneca, 5, Takeda, 5, Merck, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Foneria, 2, Novartis Pharmaceutical Corporation, 2, Areva, 2, Foneria, 9; P. B. B. Jones, None; L. K. Stamp, Astra Zeneca, 5, Abbvie, 9, PHARMAC, 6; M. Cadzow, None; R. Topless, None; T. Flynn, None.

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Is Gout a Coronary Heart Disease Risk Equivalent, Similar to Diabetes? Javinder A. Singh1, Rekha Ramachandaran2, Jie Zhang3, Fenglong Xie2, Shuo Yang2, Huifeng Yun4 and Jeffrey R. Curtis2. 1University of Alabama, Tuscaloosa, AL, 2University of Alabama at Birmingham, Birmingham, AL, 3Univ. of Alabama at Birmingham, Birmingham, AL, 4University of Alabama at Birmingham School of Public Health, Birmingham, AL.

Background/Purpose: Diabetes is a well-recognized risk factor for heart disease, increasing the risk of heart disease by 2–3 fold in many studies. Recent ACC/AHA lipid guidelines have a different pathway for diabetes
patients. Gout has been shown to be a risk factor for myocardial infarction and stroke in some cohort studies. It is not known whether gout is as strong a risk factor for acute myocardial infarction as diabetes, a question we attempted to answer with the current study. We compared the incidence of hospitalized acute myocardial infarction (MI) between patients with DM and or RA.

**Methods:** We used claims data from 2006 to 2010 that included a mix of private and public health plans with medical and pharmacy coverage. Four mutually exclusive cohorts were identified: 1) Gout and DM; 2) Gout only; 3) DM only; and 4) neither gout nor diabetes. Patients with prior CHD during a baseline period of ≥ 1 year were excluded using relevant diagnosis codes. Outcomes were defined as at least one overnight stay, unless the patient died, plus the presence of ≥ 1 inpatient hospital claim with a discharge ICD-9 code 410.x1 in any position for acute MI or presence of ICD-9 code for stroke (430.XX, 431.xx, 433.x1;433.01, 433.11, 433.21, 433.31, 433.81, 433.91), 434 (434.01, 434.11, 434.91;excluding 434.x0), 436.XX) in any position. We compared the age- and gender-specific incidence of acute MI and stroke rates across the four cohorts. We assessed univariate and multivariable-adjusted hazard rates of acute MI and stroke.

**Results:** A total of 298,929 patients had diabetes, 91999 had gout, 37573 had both and 1,099,373 had neither. Compared to patients with neither, those with gout or DM or both were older. Incidence of acute MI was lowest in patients with neither, followed by patients with gout, diabetes and both — e.g., in men, respective rates/1000 person-years were 0.0138, 0.0271, 0.0291 and 0.0475. Similar trend were noted for stroke. In unadjusted analyses, both gout and DM increased the risk of acute MI and stroke by a similar magnitude

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted, MI</td>
<td></td>
</tr>
<tr>
<td>Gout and diabetes</td>
<td>1.92(1.82, 2.04)</td>
</tr>
<tr>
<td>Gout, no diabetes</td>
<td>1.02(0.96, 1.07)</td>
</tr>
<tr>
<td>Gout, no diabetes</td>
<td>1.37(0.36, 0.38)</td>
</tr>
<tr>
<td>Diabetes, no gout</td>
<td>ref</td>
</tr>
</tbody>
</table>

In multivariable-adjusted analyses, gout was associated with significantly lower risk of acute MI than diabetes, but no significant differences were noted between gout and DM for the risk of stroke (Table 1). Patients with both gout and DM had 1.26 and 1.29-times higher risk of acute MI and stroke, compared to patients with diabetes only (Table). Conclusion: Gout increases the risk of incident MI significantly but does not appear to be a CHD risk equivalent comparable to DM for incident MI. Gout is a CHD risk equivalent comparable to DM for stroke. Having both gout and DM confers incremental risk compared to DM alone for both MI and stroke.

**Background/Purpose:** The conventional low-purine dietary approach to gout offers limited efficacy, palatability, and sustainability, and promotes increased consumption of refined carbohydrates and saturated fat that can actually worsen gout’s cardiovascular (CV)-metabolic comorbidities. In contrast, effective dietary approaches to reduce CV-metabolic conditions (including obesity) could also lower serum uric acid (SUA) levels by lowering adiposity and insulin resistance. Similarly, high-protein, low-carbohydrate diets such as the Atkins diet may lower SUA despite substantial purine loading and ketogenesis. Indeed, a small study (n = 15) that employed a high-protein diet with reduced calories found that mean SUA levels decreased from 9.6 to 7.9 mg/dL, with reduced gout attacks over 16 weeks (Ann Rheum Dis 2000). Additional benefits included an improved lipid profile. We investigated the SUA response to the Atkins diet among overweight or obese individuals over a 6 month period.

**Methods:** Our study population was derived from the Dietary Intervention Randomized Controlled Trial (DIRECT) of overweight or obese participants (BMI ≥ 27). The Atkins diet (i.e., high protein, low-carbohydrate, no calorie restriction) was one of DIRECT’s intervention groups and was a focus of the current analysis. We used serum samples at -80°C to compare SUA levels at baseline and 6 months among 74 participants with complete datasets and analyzed the SUA level response as well as lipid profile, weight change, fasting insulin levels, and glucose levels.

**Table 1. Risk of DRESS with gout medications**

<table>
<thead>
<tr>
<th>Model 1 (demographics)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>0.97(1.65, 2.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>2.54(1.04, 6.16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>1.41(32, 613)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Colchicine</td>
<td>2.08(1.69, 2.55)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusion:** Allopurinol and colchicine were associated with a 2-fold increase in hazards of DRESS. With much smaller numbers, pegloticase was associated with dramatic increase in the risk. Febuxostat did not reach statistical significance for increased risk of DRESS in full model, although the odds were similar to allopurinol and it was significantly associated with the risk of DRESS in smaller model. More research is needed to define the risk factors for these reactions with gout medications to allow a more judicious and safer use in high-risk populations.
Results: The mean age was 51 years and the mean BMI was 31. Most participants (91%) were men. The overall rate of adherence to the diets in DIRECT was > 95% during our 6-month study period. Baseline SUA level was 6.0 mg/dL and the overall SUA change at 6 months was -0.8 mg/dL. This change varied substantially according to baseline characteristics (Table), particularly baseline SUA levels. Individuals (N=18) with SUA levels > 7mg/dL (above the saturation point) showed a decrease in mean SUA levels from 7.9 to 5.5 mg/dL (p < .0001). Of the 18, 11 (61%) reached SUA < 5mg/dL (the usual anti-gout SUA therapeutic target) and 6 (33%) reached SUA level < 5mg/dL (the SUA therapeutic target for advanced gout) (Figure). Those with obesity and younger individuals (<50 years) tended to have a larger SUA decline. Additional benefits included significant improvements in HDL-cholesterol, total cholesterol/HDL-C ratio, triglyceride levels, and fasting insulin levels (p < .0001).

Conclusion: Our findings suggest that the Atkins diet (i.e., a high protein diet without calorie restriction) can reduce SUA levels despite substantial purine loading. This effect may be more pronounced and clinically meaningful among those with hyperuricemia or obesity. Comparative effectiveness research with other proven CV-metabolic diets would help determine the optimal dietary approach to lower SUA levels.

Disclosure: N. Lu, None; I. Shai, None; Y. Zhang, None; G. Curhan, None; H. Choi, Takeda, 5, AstraZeneca, 5.

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Sleep Apnea and Risk of Incident Gout: A Population-Based Body-Mass Index Matched Cohort Study. Yuqing Zhang1, Christine Peloquin1, Maureen Dubreuil3, Edward Roddy1, Na Lu1, Tuinha Neogi1 and Hyon Choi1. 1Boston University School of Medicine, Boston, MA, 2Boston University Medical Center, Boston, MA, 3Keele University, Keele, United Kingdom, 4Harvard Medical School, Boston, MA.

Background/Purpose: Sleep apnea is common among obese individuals with comorbidities (up to ~30%), a typical profile of gout patients. Since hypoxia associated with sleep apnea can enhance nucleotide turnover (thereby generating purines, which are metabolized to uric acid), sleep apnea could predispose individuals to gout. Furthermore, previous studies have reported that patients with sleep apnea have a higher prevalence of hyperuricemia. All of these findings suggest that patients with sleep apnea may experience an increased risk of incident gout. We evaluated the risk of developing gout in individuals with incident sleep apnea in a general population context.

Methods: We conducted a matched cohort study in a UK general practice database (The Health Improvement Network, THIN) to test proposed hypothesis. We identified individuals aged 20–89 years with the first diagnosis of sleep apnea from Year 2000 to 2013. For each sleep apnea patient, up to four comparators were selected and matched on sex, age, year of birth, body mass index (BMI) (± 0.5kg/m²), and year of index date (i.e., year of sleep apnea diagnosis). We excluded subjects with sleep apnea or gout prior to study entry as well as subjects without at least one GP visit within the two years prior to study entry. We identified all cases of incident gout based on diagnosis Read code. We estimated the incidence rates of gout and used a Cox-proportional hazard model to assess the association of sleep apnea and the risk of incident gout, after further adjusting for the number of physician visits, alcohol use, BMI, age, use of aspirin, diuretics and losartan, and chronic renal disease, diabetes, hypertension and ischemic heart disease.

Results: Included in this analysis were 9865 newly diagnosed sleep apnea patients (women: 28%, mean age: 53 years, mean BMI: 33.4 kg/m²) and 43,598 comparators (women: 28%, mean age: 54 years, mean BMI: 32.2 kg/m²). Over the follow-up period, 1333 incident gout patients were diagnosed. The incidence rate of gout was higher in sleep apnea patients (7.9/1000 person-years) than in the comparators (6.1/1000 person-years) (Figure). After adjusting for all potential confounders, patients with sleep apnea had a 20% higher risk of developing gout than the comparators (hazard ratio =1.2, 95% CI: 1.0–1.4). The corresponding hazard ratios over 6-months, 1-year, and 2-years were 1.7 (95% CI: 1.1–2.8), 1.6 (95% CI: 1.2–2.1), and 1.4 (95% CI: 1.1–1.7), respectively.

Conclusion: This large general population-based study indicates that sleep apnea is associated with a high risk of incident gout. As sleep apnea is common in patients with a typical profile of gout patients and its associated hypoxia is treatable (e.g., with non-invasive ventilation Continuous Positive Airways Pressure), further clarification of the role of sleep apnea on gout attacks among gout patients could add considerably to effective management of gout.

Disclosure: Y. Zhang, None; C. Peloquin, None; M. Dubreuil, None; E. Roddy, None; N. Lu, None; T. Neogi, None; H. Choi, Takeda, 5, AstraZeneca, 5.

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Self-Management Education for Patients with Gout: A Review of Existing Resources. Megan Johnston1, Gareth Treharne2, Peter T. Chapman1 and Lisa K. Stump1. 1University of Otago, Christchurch, Christchurch, New Zealand, 2University of Otago, Dunedin, New Zealand, 3Christchurch Hospital, Christchurch, New Zealand.

Background/Purpose: Inadequate patient self-management education resources may contribute to poor management and outcomes for gout. Patient education resources need to be easy to read and should provide clear and consistent messages regarding lifestyle, diet, and treatment recommendations for gout patients to implement. The aim of this project was to review existing educational resources for gout patients in order to identify strengths and weaknesses and to compare resources cross-nationally.

Methods: Twenty-four patient education resources for gout were identified: 12 print items and 12 websites. The print items are those given to patients by health professionals in New Zealand or are provided by relevant health
organizations in New Zealand, Australia, the United States, Canada, and the United Kingdom. The top ten websites based on a Google search using the keyword “gout” were included, as well as two interactive websites aimed at gout patient self-management. Resources were assessed for coverage of essential information, ease of reading, and dietary recommendations.

**Results:** All identified resources provided some information about the nature of gout (e.g. caused by too much uric acid in the body) and lifestyle issues (e.g. body weight, nutrition). However, inconsistent messages were given regarding the relative influence of diet on gout, with some resources suggesting little impact of diet and others implicating diet as a major factor in gout management. There was also discordance in certain dietary recommendations, particularly regarding non-meat proteins such as legumes. 50.0% of the resources identified a target serum urate level but only 29.1% recommended checking serum urate levels. Co-morbidities associated with gout not universally discussed included: kidney problems (87.5%), heart disease (58.3%), and diabetes (41.7%). Resources were largely consistent cross-nationally although some differences were found (see Table 1). New Zealand resources were more likely to mention target serum urate levels and to advise patients to continue taking urate-lowering therapies during acute attacks than American or British resources. Certain dietary recommendations also differed within resources from different countries. 50.0% of the resources were written at a highly complex reading level.

**Conclusion:** A considerable amount of room for improvement exists in current self-management educational resources for gout patients. Inconsistent messages, lack of information on key topics, and inaccessible writing styles were the primary issues identified. Examining resources developed internationally may provide additional information useful for developing educational resources for gout patients. Further research with gout patients is required to determine the resources that patients perceive as most informative and actionable.

### Table 1. Content of Gout Patient Education Resources by Country

<table>
<thead>
<tr>
<th>Content Category</th>
<th>New Zealand (n = 10)</th>
<th>United States (n = 7)</th>
<th>United Kingdom (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readability¹</td>
<td>62.6</td>
<td>65.7</td>
<td>61.4</td>
</tr>
<tr>
<td>Reading grade level²</td>
<td>8.4</td>
<td>8.29</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>Percent of Resources Covering Each Category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Crystal formation</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Long term treatment</td>
<td>100%</td>
<td>86%</td>
<td>50%</td>
</tr>
<tr>
<td>Acute treatment</td>
<td>100%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>Uric acid &lt; 36 mmol/L</td>
<td>70%</td>
<td>43%</td>
<td>25%</td>
</tr>
<tr>
<td>Check uric acid</td>
<td>40%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Non-drug treatments</td>
<td>70%</td>
<td>86%</td>
<td>50%</td>
</tr>
<tr>
<td>Not to stop medication</td>
<td>50%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>70%</td>
<td>57%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40%</td>
<td>43%</td>
<td>25%</td>
</tr>
<tr>
<td>Kidney problems</td>
<td>90%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>Weight</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>General diet</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Foods to avoid</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Add low-fat dairy</td>
<td>70%</td>
<td>57%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**NOTE:** Three resources are not included in the table: 1 from Australia, 1 from Canada, and 1 international resource

¹Higher Flesch-Kincaid readability scores indicate greater ease of reading (i.e. scores above 90 indicate easy to read, scores <30 indicate difficult to read).

²Grade level indicates reading grade level based on the United States school system (the majority of American adults read at an eighth to ninth grade level).

**Disclosure:** M. Johnston, None; G. Trehanne, None; P. T. Chapman, None; L. K. Stamp, Astra Zenec, 5, Abbvie, 9, PHARMAC, 6.

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**174 Long Term Safety and Efficacy of Canakinumab Liquid Formulation in Acute Gouty Arthritis Patients:**

Long term safety and efficacy of canakinumab liquid formulation in patients with frequent GA flares with a potent long acting corticosteroid, TA. The safety profile of on-demand retreatment was consistent with the one observed in the core study and no new safety signals were observed. Canakinumab significantly reduced the risk of new flares compared to TA.

**References:**


**Disclosure:** P. Sunkureddi, Abbvie, Takeda, UCB, BMS, Pfizer, 8, Pfizer, Takeda, U.J.P., Novartis, Eli Lilly, None; J. P. Brown, Amgen, Eli Lilly, Merck, Novartis, Pfizer, Roche, 2, Amgen, Eli Lilly, Merck, 5, Amgen, Eli Lilly, Merck, 8; R. Moericke, None; D. Richard, Novartis Pharma AG, 1, Novartis Pharma AG, 9; K. Lheritier, Novartis, 1, Novartis, 3; A. Stancati, Novartis, 1, Novartis, 3; A. Kivitz, None.

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**175 Efficacy and Safety of Canakinumab in Acute Gouty Arthritis Patients with Chronic Kidney Disease Stage Greater Than or Equal to 3:**

Efficacy and safety of canakinumab in patients with chronic kidney disease stage greater than or equal to 3. A Post-Hoc Analysis of 12-Week Data.

**Disclosure:** P. Sunkureddi, Abbvie, Takeda, UCB, BMS, Pfizer, 8, Pfizer, Takeda, U.J.P., Novartis, Eli Lilly, None; J. P. Brown, Amgen, Eli Lilly, Merck, Novartis, Pfizer, Roche, 2, Amgen, Eli Lilly, Merck, 5, Amgen, Eli Lilly, Merck, 8; R. Moericke, None; D. Richard, Novartis Pharma AG, 1, Novartis Pharma AG, 9; K. Lheritier, Novartis, 1, Novartis, 3; A. Stancati, Novartis, 1, Novartis, 3; A. Kivitz, None.

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**Background/Purpose:** Chronic kidney disease (CKD) limits the treatment options in acute gouty arthritis (GA) patients due to intolerance and contraindications to available therapies. Efficacy and safety of canakinumab (CAN), a selectice, human, anti-IL-1β monoclonal antibody, formulated as a
lyophilized (LYO) powder requiring reconstitution with water or triamcinolone acetonide (TA) in patients with acute GA was demonstrated in previous phase III trials. Here, we report the efficacy and safety of CAN liquid formulation (CAN-PFS) vs TA in a subgroup of patients with CKD stage ≥3.

**Methods:** This was a 12-week, multicenter, double-blind, active controlled study. Pts (≥18 ≤85 yrs) meeting the ACR 1997 preliminary criteria for acute GA and contraindicated, intolerant or refractory to NSAIDs and/or colchicine, with ≥3 flares in the previous year, were randomized 1:1:1 to receive a single dose of CAN-PFS 150 mg sc or CAN-LYO 150 mg sc or TA 40 mg im and re-dosed “on demand” upon each new flare. Here, we report results from a post-hoc analysis of the 12-week data for GA patients with CKD stage ≥3 (estimated Glomerular Filtration Rate (eGFR) <60ml/min). The primary endpoint was pain intensity in the target joint, measured on 0–100 mm VAS scale at 72 h. Secondary endpoints included time to first new flare, and safety over 12 weeks.

**Results:** Of 388 patients, 76 had CKD stage ≥3 at baseline (CAN-PFS, n=24; CAN-LYO, n=28; TA, n=24). CAN-PFS provided a statistically significant reduction in pain intensity in the target joint vs TA from 72h post dose (estimated difference, -14.6mm; 95% CI: -20.0, -9.1, p<0.05) 7 days post dose (-16.1mm; 95% CI: -28.4, -3.7, p=0.0115). The two CAN treatment arms were comparable. Over 12 weeks, a single dose of CAN-PFS showed a significant relative risk reduction of 90% for time to first new gout flare vs TA [HR 0.10, 95% CI (0.01, 0.78); p<0.05]. Adverse events (AEs) were reported in 12 (50%), 11 (39.3%) and 10 (41.7%) patients in CAN-PFS, CAN-LYO and TA groups, respectively. The most frequent AEs were infections (CAN-PFS, n=3 (12.5%); CAN-LYO, n=6 (21.4%); TA, n=2 (8.3%). Serious AEs were reported in a total of 7 patients (CAN-PFS, n=2 (8.3%); CAN-LYO, n=4 (14.3%); TA, n=1 (4.2%), with infections (CAN-PFS, n=1 (4.2%); CAN-LYO, n=2 (7.1%); TA, n=0), being the most common SAEs. No deaths were reported during the study.

**Conclusion:** This post-hoc analysis provides evidence for the efficacy of CAN-PFS compared with a potent long-acting corticosteroid in providing significant pain relief and reducing incidence of new flares in gouty arthritis patients with CKD stage ≥3 with limited treatment options. The safety profile in this sub-population was consistent with that of the overall study population and with that from previous studies.

**Reference:**

**Disclosure:** None.

**177 Increase in Thyroid Stimulating Hormone (TSH) Levels in Patients with Gout Treated with Inhibitors of Xanthine-Oxido-Reductase.** Fernando Perez-Ruiz1, Ana M. Herrero-Beites1, M. Angeles Aniel-Quiroga2 and Sandra P Chinchilla2.

**Background/Purpose:** Increase in thyroid stimulating hormone (TSH) levels over upper normal limit has been reported in a small percentage of patients treated with febuxostat, but a mechanistic explanation is not yet available.

**Methods:** In a case-control design study, we tested TSH levels in patients with gout at baseline with that every 6-month during follow-up during treatment with febuxostat. Patients to be started allopurinol and an available level over upper normal limit has been reported in a small percentage of patients treated with febuxostat, but a mechanistic explanation is not yet available.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA-only</td>
<td>OA-only</td>
<td>OA-only</td>
</tr>
<tr>
<td>Gout or OA (n = 1230)</td>
<td>Gout or OA (n = 985)</td>
<td>Gout or OA (n = 297)</td>
</tr>
<tr>
<td>Composite Endpoint</td>
<td>CAGR</td>
<td>MI</td>
</tr>
<tr>
<td>27.3</td>
<td>28.2</td>
<td>30.3</td>
</tr>
<tr>
<td>MI %</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Angina %</td>
<td>0.6</td>
<td>3.5</td>
</tr>
<tr>
<td>CAD %</td>
<td>22.7</td>
<td>23.0</td>
</tr>
<tr>
<td>CHF %</td>
<td>1.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Death %</td>
<td>2.4</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**Disclosure:** None.
Background/Purpose: Substantial evidence links gout and hyperuricemia to diabetes. Previous studies report an association between increasing uric acid (UA) levels, insulin resistance, and type 2 diabetes (T2DM). Elevation in serum insulin is purported to increased serum UA levels through increased renal urate absorption. This study sought to evaluate the effect of initiating insulin for T2DM on serum UA levels.

Methods: We conducted a retrospective analysis on patients with both T2DM and gout. Patients were selected from a linked dataset from an electronic medical record (EMR) and Medicare claims data. This data set includes patients at one academic medical center with diagnoses of gout and hyperuricemia as confirmed in the EMR who also had T2DM (defined as hemoglobin A1c (HbA1c) > 6.5%, ICD-9-CM code 250.x or use of diabetic medications). An insulin-initiating cohort and a non insulin-initiating cohort were compared for changes in UA. Cohorts were matched on sex, age at first UA measurement, and length of time between UA measurements. The first UA measurement occurred before insulin initiation and the second at least 3 months later; matched time points were used in the non-initiators.

Potential confounders including HbA1c, creatinine, body mass index, length of time between UA measurements and medications (allopurinol, hydrochlorothiazide, losartan, tacrolimus, cyclosporine) were adjusted for in a series of linear regression models.

Results: 23 patients met criteria for insulin initiation and 23 were matched non-insulin initiators. Mean age was 59 and 57 years for the insulin and non-insulin cohorts, respectively, both cohorts were 52% female. Patients initiating insulin had a larger increase in mean UA levels, 6.41mg/dl to 7.66mg/dl (mean change 1.25 mg/dl, interquartile range, IQR: -0.7,2.3) compared to non-insulin initiators, mean increase from 6.17mg/dl to 6.23mg/dl (mean change 0.06 mg/dl, IQR: -1.1,0.9 p = 0.06). Of the covariates, only length of time between UA measurements had an unadjusted p-value < 0.05 and was advanced to the final adjusted model. The final linear regression showed that insulin use was associated with a 1.25mg/dl greater increase in UA levels when compared to non-insulin initiators (p value = 0.02). Adjusting for allopurinol did not attenuate results. (Table)

Conclusion: Insulin initiation in patients with T2DM was associated with a statistically significant increase in serum UA levels. This may have clinical implications, including risk of gout flares. Gout attack prophylaxis might be useful in the setting of insulin initiation among patients with gout. A prospectively designed study would help overcome potential limitations of our retrospective design.

Table 1 Regression analysis of covariate effects on change in uric acid in insulin initiators

<table>
<thead>
<tr>
<th>Model</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Crude Model: Insulin+UA1</td>
<td>1.29</td>
<td>0.15, 2.44</td>
<td>0.03</td>
</tr>
<tr>
<td>B Model A + age + months between UA1 &amp; UA2</td>
<td>1.25</td>
<td>0.16, 2.34</td>
<td>0.03</td>
</tr>
<tr>
<td>C Model B + hemoglobin A1c</td>
<td>1.47</td>
<td>-0.06, 3.00</td>
<td>0.06</td>
</tr>
<tr>
<td>D Model C + creatinine + body mass index</td>
<td>1.33</td>
<td>-0.28, 2.94</td>
<td>0.10</td>
</tr>
<tr>
<td>E Insulin+UA1 + months between UA1 &amp; UA2</td>
<td>1.25</td>
<td>0.18, 2.33</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Addition of relevant medications

<table>
<thead>
<tr>
<th>Model</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>F Model D + Allopurinol</td>
<td>1.36</td>
<td>-0.12, 2.84</td>
<td>0.07</td>
</tr>
<tr>
<td>G Model D + Hydrochlorothiazide</td>
<td>1.41</td>
<td>0.17, 2.99</td>
<td>0.08</td>
</tr>
<tr>
<td>H Model D + Losartan</td>
<td>1.45</td>
<td>-0.07, 2.96</td>
<td>0.06</td>
</tr>
<tr>
<td>I Model D + Tacrolimus</td>
<td>1.48</td>
<td>-0.04, 3.00</td>
<td>0.06</td>
</tr>
<tr>
<td>J Model D + Cyclosporine</td>
<td>1.61</td>
<td>0.03, 3.20</td>
<td>0.05</td>
</tr>
</tbody>
</table>

β= beta coefficient from linear regression model, represents the change in uric acid among insulin initiators compared to matched non-initiators; 95% CI=95% confidence interval; UA1=1st uric acid measurement; UA2= 2nd uric acid measurement

Disclosure: L. Macfarlane, None; C. C. Liu, None; D. H. Solomon, Pfizer Inc, 2, Aigen, 2, Lilly, 2, Corrona, 2, UpToDate, 7.

Effect of Allopurinol on All-Cause Mortality in Adults with Incident Gout: Propensity Score Matched Landmark Analysis.

Sunday, November 16
Background/Purpose: Although current guidelines recommend allopurinol as a first-line urate-lowering treatment for gout patients, whether the balance of potential benefits and risks can translate to any influence on survival in gout patients remains unclear. The objective of this study was to examine the association between allopurinol use and all-cause mortality for patients with incident gout.

Methods: This study was conducted using the UK Clinical Practice Research Data-link. Patients were included if they were aged 20 years or older, and had a confirmed gout diagnosis between 1995 and 2009, and had no evidence of gout or prescription for ULT prior to the time of diagnosis. We used propensity score matched landmark analysis to compared incident gout patients who received allopurinol for at least 6 months within exposure window and those did not for all-cause mortality.

Results: Of 23,332 incident gout patient identified, the propensity-matched cohorts contained 1,016 patients exposed to allopurinol on the date one year from diagnosis (landmark date) and 1,016 allopurinol non-users. They were significantly older and had more comorbidity and multiple medications than the overall incident gout patients. Over a median follow-up period of 10 years after the landmark date, there were 437 allopurinol users and 443 allopurinol non-users who died during follow-up. Allopurinol users and non-users had similar risk for all-cause mortality (hazard ratios 0.99; 95% confidence interval, 0.87–1.12). In the three-year landmark analysis, 3,519 allopurinol users (1,280 died) were compared with 3,519 non-users (1,265 died). The hazard ratio for all-cause mortality was 1.01 (95% confidence interval 0.92–1.09).

Conclusion: This propensity score matched landmark analysis in a population of incident gout patients in the UK primary care setting found a neutral effect on the risk of all-cause mortality. Our study provides reassurance for prescription of allopurinol in gout patients early in their disease course to prevent untoward consequences of chronic uncontrolled hyperuricaemia.

Disclosure: C. F. Kuo; None; M. J. Grainge; None; C. Mallen; None; W. Zhang; None; M. Doherty; Maranini, 5.

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Analytical Comparison Between Point of Care Uric Acid Testing Meters. Jonathan Paraskos1, Zsofia Berke2, Jason Cook3, Jeffrey N. Miner4, Martin Braddock5, Adam Platt6 and Glen Hughes7. 1AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, 2AstraZeneca, 3J. Cook, 4AstraZeneca, 5J. N. Miner, 6AstraZeneca, 7Ardea Biosciences, Inc., 8ARTA Bioscience, 9M. Braddock, 10AstraZeneca, 11AstraZeneca, 12A. Platt, 13AstraZeneca, 14G. Hughes, 15AstraZeneca, 16

181

Adherence to Treatment Recommendations of Gout: A Patient Survey in China. Feng Sheng, Xuejun Zeng and Weiping Fang. Peking Union Medical College Hospital, Beijing, China.

Background/Method: The prevalence of gout appeared to be increasing in China as its economy developed rapidly in the past three decades. Though efficacious and affordable treatment of gout was widely available, the disease was not well controlled in many countries of the world including China. Poor adherence to treatment recommendations was one major reason leading to unsatisfactory management. Patients’ adherence to medical treatment of gout was reported to be 17–44% in developed countries, but the data were unknown in China.

Methods: A structured survey was carried out by telephone interview in 349 patients recruited from Gout Clinic at Peking Union Medical College Hospital in 2014. They all satisfied the ACR classification criteria for gout, 1977, and had dietary education when their diagnosis was made or confirmed in our clinic as baseline. 271 patients with ursate lowering therapy (ULT) indications were also provided with medication recommendations and/or prescriptions according to the ACR and EULAR guidelines. Demographic data and clinical characteristics were collected at baseline. Patients’ adherence to dietary and medication recommendations was measured by food frequency questionnaire and proportion of accumulative days of ULT medication consumption, respectively in the survey. Consumption of alcohol (beer, wine, spirit and yellow rice wine), seafood and internal organs less than once a month and limited intake of red meat was defined as dietary adherence, and ULT ≥80% of time since baseline was defined as medication adherence. Multivariable logistic regression models were used to estimate the independent association between patient characteristics and adherence. Patients’ explanations for medication non-adherence were also asked.

Results: The dietary and medication adherence were 44.2% and 21.9%, respectively. Older patients (age ≥60), high serum urate levels (>642umol/L) and tophi at baseline were associated with dietary adherence independently. Tophi and chronic kidney disease at baseline were associated with medication adherence independently, but the longer the time between baseline and the survey was, the less proportion of patients were adherent to ULT medication (Table 1). The main reasons patients reported leading to their medication non-adherence included remission after treatment (35.1%), concern of side effects (22.7%), insufficient patient education (9.5%) and adverse events (8.1%).

Conclusion: Patients’ adherence to treatment recommendations of gout was poor in China.Older age, high serum urate levels and tophi (tophi and chronic kidney disease) at baseline were associated with treatment adherence. As time elapsed, less patients were adherent to ULT medications.

Table 1. Characteristics associated with treatment adherence of gout

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted OR(95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>0.44 (0.12–1.57)</td>
<td>0.20</td>
</tr>
<tr>
<td>40–49</td>
<td>0.86 (0.26–2.99)</td>
<td>0.81</td>
</tr>
<tr>
<td>50–59</td>
<td>0.83 (0.22–3.19)</td>
<td>0.79</td>
</tr>
<tr>
<td>≥60</td>
<td>4.67 (1.07–20.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum urate levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Quartile (0–498umol/L)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
May be reversible to some extent and that the magnitude of improvement may vary

1. Massachusetts General Hospital, Boston, MA, Harvard Medical School, Boston, MA.

2. Brigham and Women’s Hospital, Boston, MA, 3. Massachusetts General Hospital, Boston, MA.

Disclosure: S. Lee, Inyoung Kim, Hyemin Jeong, Jiwon Hwang, Hyungjin Kim, Jaejoon Lee, Hoon-Suk Cha and Eun-mi Koh. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: The aim of this study was to investigate the radiographic changes in patients with gout in association with the control of serum uric acid level.

Methods: A retrospective observational study in a single tertiary medical center was performed. Sixty one patients who had at least one erosive change on baseline radiograph or tophus on physical examination were included. Follow up radiography was taken at least 5 years apart from baseline radiograph. The primary endpoint was the changes in the radiographic damage scores based on modified Sharp/van der Heijde (mSvH) score in association with serum uric acid level during the study period. Patients were divided by three groups which consist of improved, no change, and deteriorated patients for subgroup analysis. The changes in the size of soft tissue density in radiograph were also measured.

Results: The mean age was 55±13 years and 60 (98%) patients were male. Disease duration was 11±7 years and mean serum uric acid level was 8.8±1.9 mg/dL at baseline. Follow up duration between two radiographies was 10.8±3.6 years. All patients were receiving urate-lowering therapy. The change in the mean mSvH score between baseline and follow visit was not statistically significant (6.77 vs. 6.69, respectively). The patient number of improved, no change, and deteriorated groups was 22, 14, and 25 and the baseline plain radiographic damage score was 12.1, 4.85, and 3.7 respectively. As expected, the change in damage scores was positively correlated to AUC of uric acid level (r = 0.32, p = 0.01). The patients with longer disease duration at baseline were more likely to have improvement in the follow up radiograph. (r = 0.46, p = 0.004). In subgroup analysis, only the baseline radiographic damage score was significantly different from each other. In improved group, the change of damage scores was negatively associated with disease duration at baseline (r = 0.48, p = 0.024).

Conclusion: Our study demonstrated that radiographic damage in gout may be reversible to some extent and that the magnitude of improvement depends on the degree of serum uric acid control.

Disclosure: S. Lee, None; I. Kim, None; H. Jeong, None; J. Hwang, None; H. Kim, None; J. Lee, None; H. S. Cha, None; E. M. Koh, None.

Effect of Urate-Lowering Therapy on Radiographic Changes in Gout Patients. Seulkee Lee, Inyoung Kim, Hyemin Jeong, Jiwon Hwang, Hyungjin Kim, Jaejoon Lee, Hoon-Suk Cha and Eun-mi Koh. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: We enrolled in the study 42 patients (14 males), mean age of 74 years old (±8.4). All patients underwent US of the knee, synovial fluid and X-rays were calculated using microscopic findings of the menisci and cartilage as the gold standard.

Results: Typical of RA cohorts, the 26 patients were predominantly female (62%), with a median age of 57. RF and ACPA were by definition negative. Median levels of inflammatory markers were in normal ranges, 62% of the patients met 2010 ACR/EULAR classification criteria for RA. Median symptom duration was 1.4 years, and only 5 patients were receiving disease-modifying antirheumatic drugs (DMARDs) at the time of US.

Metacarpophalangeal (MCP) joints were most commonly symptomatic (65%). By X-ray, only 2 patients had chondrocalcinosis, and 1 had erosion. There was 100% inter-reader agreement of the US images, encompassing 7 anatomic sites (shoulder, elbow, wrist, hand, knee, ankle, and foot). Images in all 26 patients revealed multiple hypercholesterolemic densities consistent with the US appearance of calcium pyrophosphate dihydrate (CPPD) vs. calcium hydroxyapatite crystals, and were not typical of gout. Calcific deposits, in all cases associated with synovitis, were identified in joints, tendons, and/or tendon sheaths. By comparison, comparison imaging demonstrated few scattered calcifications without synovitis in only 1 OA patient.

Nearly all 26 patients (90%) had calcifications in both joints and tendons. Calcification pattern in joints was most commonly round (79%), followed by punctate (45%), whereas calcification pattern in tendons was more frequently punctate (79%) followed by linear (42%). Over half (58%) of patients had all 3 patterns. Nine (35%) patients had US evidence of bony erosions. There were no effusions amenable to aspiration. Subsequent testing of 10 patients revealed elevated parathyroid hormone levels in 4 patients, a risk factor for CPPD.

Conclusion: Our findings of hypercholesterolemic deposits associated with synovitis on US suggests that crystalline disease, such as CPPD arthropathy, may be an explanation for arthritis in a subset of seronegative RA patients. Synovial (microscopic and macroscopic) and cartilage (radiographic and gold standard in classic CPPD arthropathy, US may be valuable, particularly when X-rays are unrevealing and effusions amenable to aspiration are lacking. Detection of crystals may reveal abnormalities such as hyperparathyroidism, and may affect treatment strategies. Studies with synovial tissue or fluid crystal analysis prospectively evaluating the prevalence of crystal deposition are needed to evaluate the role for US in the screening of seronegative RA patients.

Disclosure: S. L. Arvikar, Arthritis Foundation, None; J. Lin, None; M. J. Kohler, None.

Ultrasound Versus X-Rays Versus Synovial Fluid Analysis for the Diagnosis of Calcium Pyrophosphate Dihydrate Deposition Disease: Is It CPPD? Georgios Filippou1, Antonella Adinolfi1, Sauro Lorenzini2, Ilaria Bertoldi1, Valentina Di Sabatino1, Valentina Picerno1, Luca Sconfienza1, Mauro Galeazzi1 and Bruno Frediani1. 1. University of Siena, Siena, Italy, 2. Rheumatology Unit, Azienda Ospedaliera Universitaria Senese, Siena, Italy, 3. University of Milan, Milan, Italy.

Background/Purpose: The diagnosis of calcium pyrophosphate crystal (CPP) deposition disease (CPPD) is mainly based on the synovial fluid analysis itself. Aim of the study is to compare ultrasonography, synovial fluid analysis and X-rays. US has demonstrated high sensitivity and specificity values for diagnosing CPPD compared to synovial fluid analysis as the gold standard, but less is known about sensitivity and specificity of synovial fluid analysis itself. Aim of the study is to compare ultrasonography, synovial fluid analysis and X-rays performances in the diagnosis of CPPD using a real gold standard.

Methods: We enrolled in our study all patients waiting to undergo knee replacement surgery due to severe osteoarthritis. Each patient underwent US examination of the knee, focusing on the menisci and the hyaline cartilage, the day prior to surgery, scoring each site according to the presence/absence of CPP as defined previously. The day of the surgery, synovial fluid of the knee (if present) was aspirated by the surgeon. After surgery, the menisci, condyles and the synovial fluid were retrieved and examined microscopically. Synovial fluid analysis was performed on wet preparations. For the meniscus and cartilage microscopic analysis, six samples were collected, either from the surface and from the internal of the structure trying to cover a large part of it. All slides were observed under transmitted light microscopy and by compensated polarised microscopy. A dichotomous score was given for the presence/absence of CPP. US and microscopic analysis were performed by different operators, blind to each other’s findings. X-rays of the knees were collected and assessed for the presence of CPPD by a Radiologist expert in musculoskeletal imaging, blind to other findings. Sensitivity and specificity of US, synovial fluid and X-Rays were calculated using microscopic findings of the menisci and cartilage as the gold standard.

Results: We enrolled in the study 42 patients (14 males), mean age of 74 years old (±8.4). All patients underwent US of the knee, synovial fluid was present in 32 patients and X-rays have been collected form 34 patients. 2x2
Distribution of Haemochromatosis Arthropathy, High Ankle and Mid Foot Prevalence; A Diagnostic Clue?

Background/Purpose: Long delays in diagnosis of haemochromatosis are frequent and lead to an adverse affect on hepatic and cardiac outcome. Arthropathy is a highly prevalent and early feature, which could act as a trigger for diagnosis if sufficiently distinctive. We conducted a survey of patients with haemochromatosis to assess the prevalence and distribution of joint symptoms and their relation to the diagnosis.

Methods: A questionnaire was sent to members of the UK Haemochromatosis Society (~1500) in December 2013. Questions assessed how the diagnosis of haemochromatosis was made; symptoms, duration, the prevalence and distribution of affected joints, and the role of a rheumatologist.

Results: Questionnaires were returned by 470 people with haemochromatosis, 97% white, 53% male. The genotype was C282Y homozygous 52%, C282Y/H63D heterozygous 7%, C282Y/wild type heterozygous 5%, unknown 33%. The diagnosis was made at a mean age of 56 years, following family member screening in 20%, well man/woman screening in 23% and as result of symptoms in 57%. At diagnosis the most frequent symptoms attributed to haemochromatosis were fatigue 65% and joint pain 60% (Fig 1), with a mean duration of 8 years (0–65) and mean Ferritin 1752 mg/L. The diagnosis was most frequently made by a GP 38%, Haematologist 24%, Gastroenterologist 21.5% and Rheumatologist 7%.

88% of respondents reported joint pain, stiffness or swelling. Joint symptoms preceded the diagnosis of haemochromatosis by more than 5 years in 21.5% and Rheumatologist 7%. In the hands the prevalence of symptoms was 1 in 47%, by more than 1 year in 78.5% and post dated the diagnosis in 14.5%. The most prevalent areas affected were hand or wrist 66%, ankle or mid foot 49%, and knee 44% (Fig 2). In the hands the prevalence of symptoms was 1st CMC 60%, wrist 52%, MCP 47%, PIP 48%, and DIP joints 41%. No formal arthritic diagnosis was given to 45%, OA 29%, haemochromatosis arthropathy 11.5%. Dupuytrens disease was reported by 13% of men and 8% of women. Venesection was reported to have helped joint symptoms in 5%, made no impact in 20% and in 51% new joints had become affected following de ironing. A negative impact on employment from arthropathy was reported by 21%, with 9% losing their job.

Conclusion: In haemochromatosis, joint symptoms are highly prevalent at diagnosis, with the ankle and mid foot involved in 49%. In addition to MCP joint disease, an osteoarthritis-like presentation at a relatively young age in the hind or mid foot might be a distinguishing feature to prompt investigations leading to an earlier diagnosis.

**Disclosure of Interest:** None Declared

**Disclosure:** G. Filippou, None; A. Adinolfi, None; S. Lorenzini, None; L. Bertoldi, None; V. Di Sabatino, None; V. Picerno, None; L. Sconfienza, None; M. Galeazzi, None; B. Frediani, None.
Revision Arthroplasty in Rheumatoid and Osteoarthritis: Does Methotrexate Decrease Diagnostic Lucency in RA Patients? Mike Wei1, Douglas N. Mintz2, Lisa A. Mandl2, Arielle Fein2, Jayme C. Burket2, Yuo-Yu Lee2, Wei-Ti Huang2, Vivian P. Bykerk2, Edward F. DiCarlo2, Bruce N. Cronstein2 and Susan M. Goodman2. 1Weill Cornell Medical College, New York, NY, 2Hospital for Special Surgery, New York, NY, 3NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Rheumatoid arthritis (RA) patients have excellent total hip arthroplasty (THA) survival, and methotrexate (MTX), an anti-inflammatory drug modifying drug which may affect bone resorption, may play a role. The purpose of this study is to determine the diagnosis leading to revision THA (rTHA) in RA patients and to assess the association of radiographic lucency with MTX use.

Methods: All patients with validated diagnosis of RA in the institution’s THA registry undergoing rTHA from May 2007 - February 2011 were eligible. Diagnosis leading to rTHA and medication use was determined by chart review. Osteolysis was evaluated on available radiographs by measuring maximum lucency in each Gruen zone. Differences within RA patients with/without MTX in osteolysis, demographics, and medications were assessed with chi-squared, Fisher’s exact tests or Mann-Whitney U tests as appropriate. The error rate for multiple comparisons of lucency in the different Gruen zones was corrected via false discovery rate methods. A significant association was found between spondylolisthesis and LBP among the occupationally young group but was weakly associated in the community-based group, supporting spondylolisthesis as a potential unique pain generator in the lumbar spine.

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Results: Twenty-eight (22 community-based and 6 occupation-based) studies met the eligibility criteria consisting of 26,107 subjects. A significant, positive association was found between DSN and LBP that did not differ with regard to radiographic lucency. Among RA with/without MTX, and lack of records. There was no significant difference in any Gruen diseases, use of MTX, and lack of records.

Conclusions: A positive significant association was found between DSN and LBP that did not differ between community and occupational-based studies. The fact that no differences exist between these two groups may be related to the influence that genetic factors have on disc degeneration. A significant strong association was found between spondylolisthesis and LBP among the occupationally young group but was weakly associated in the community-based group, supporting spondylolisthesis as a potential unique pain generator in the lumbar spine.

Disclosures: J. Raastad None; M. Reiman None; R. Coeytaux None; L. Ledbetter None; A. P. Goode None.

Table 1: Demographic characteristics and reason for revision for OA vs. RA patients

<table>
<thead>
<tr>
<th>Diagnosis, N (%)</th>
<th>RA, N=51</th>
<th>OA, N=103</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>2 (3.9)</td>
<td>7 (6.8)</td>
<td>0.719</td>
</tr>
<tr>
<td>Loosening</td>
<td>28 (54.9)</td>
<td>59 (57.3)</td>
<td>0.779</td>
</tr>
<tr>
<td>Fracture</td>
<td>7 (13.7)</td>
<td>7 (6.8)</td>
<td>0.232</td>
</tr>
<tr>
<td>Wear</td>
<td>12 (23.5)</td>
<td>19 (18.4)</td>
<td>0.459</td>
</tr>
<tr>
<td>Dislocation</td>
<td>12 (23.5)</td>
<td>24 (23.3)</td>
<td>0.975</td>
</tr>
<tr>
<td>Mech Failure</td>
<td>2 (3.9)</td>
<td>7 (6.8)</td>
<td>0.862</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>0.331</td>
</tr>
</tbody>
</table>

*28 patients were ascribed more than 1 diagnosis.

Table 2: Demographic characteristics and radiographic analysis of RA patients with/without MTX

<table>
<thead>
<tr>
<th>Diagnosis, N (%)</th>
<th>MTX, N=20</th>
<th>No MTX, N=10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>1 (4.8)</td>
<td>1 (3.3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Loosening</td>
<td>11 (52.4)</td>
<td>17 (56.7)</td>
<td>0.762</td>
</tr>
<tr>
<td>Fracture</td>
<td>3 (14.3)</td>
<td>4 (13.3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Wear</td>
<td>6 (28.6)</td>
<td>6 (20.0)</td>
<td>0.351</td>
</tr>
<tr>
<td>Dislocation</td>
<td>6 (28.6)</td>
<td>6 (20.0)</td>
<td>0.581</td>
</tr>
<tr>
<td>Mech Failure</td>
<td>0 (0.0)</td>
<td>2 (6.7)</td>
<td>0.506</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>1 (3.3)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication, N (%)</th>
<th>MTX, N=20</th>
<th>No MTX, N=10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>5 (23.8)</td>
<td>10 (33.3)</td>
<td>0.543</td>
</tr>
<tr>
<td>Biologics</td>
<td>6 (30.0)</td>
<td>13 (43.3)</td>
<td>0.283</td>
</tr>
<tr>
<td>Prednisone</td>
<td>10 (47.6)</td>
<td>15 (50.0)</td>
<td>0.867</td>
</tr>
<tr>
<td>Cemented Cup, N (%)</td>
<td>3 (18.8)</td>
<td>5 (22.7)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Cemented Furin, N (%)</td>
<td>5 (31.3)</td>
<td>13 (59.1)</td>
<td>0.112</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Passage, Mean (Std Dev) [mm]</th>
<th>MTX, N=20</th>
<th>No MTX, N=10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femur Zone 1</td>
<td>11.4 (16.8)</td>
<td>7.4 (10.2)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 2</td>
<td>0.0 (0.0)</td>
<td>0.9 (1.7)</td>
<td>0.225</td>
</tr>
<tr>
<td>Femur Zone 3</td>
<td>0.2 (0.8)</td>
<td>0.5 (1.8)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 4</td>
<td>2.7 (8.7)</td>
<td>0.0 (0.0)</td>
<td>0.189</td>
</tr>
<tr>
<td>Femur Zone 5</td>
<td>0.3 (0.9)</td>
<td>0.7 (2.6)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 6</td>
<td>1.3 (3.3)</td>
<td>0.8 (2.8)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 7</td>
<td>3.7 (5.6)</td>
<td>3.0 (5.5)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 8</td>
<td>5.7 (7.9)</td>
<td>5.0 (6.3)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 9</td>
<td>0.0 (0.0)</td>
<td>1.8 (3.5)</td>
<td>0.189</td>
</tr>
<tr>
<td>Femur Zone 10</td>
<td>0.2 (0.9)</td>
<td>0.0 (0.0)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 11</td>
<td>0.8 (2.3)</td>
<td>0.7 (2.4)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 12</td>
<td>0.1 (0.4)</td>
<td>0.8 (3.6)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 13</td>
<td>2.2 (5.0)</td>
<td>1.3 (3.6)</td>
<td>0.954</td>
</tr>
<tr>
<td>Femur Zone 14</td>
<td>3.5 (6.1)</td>
<td>3.3 (6.3)</td>
<td>0.954</td>
</tr>
<tr>
<td>Subsidence (mm)</td>
<td>3.7 (7.1)</td>
<td>0.0 (0.0)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*11 patients were ascribed more than 1 diagnosis.

Disclosures: M. Wei None; D. N. Mintz None; L. A. Mandl None; A. Fein None; J. C. Burket None; Y. Y. Lee None; W. T. Huang None; V. P. Bykerk Amgen, Pfizer, BMS, Janssen, UCB, Roche/Genentech, 2; M. P. Figgie None; E. F. DiCarlo None; B. N. Cronstein, Canfit Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6; S. M. Goodman None.
Background/Purpose: To assess the association of hospital procedure volume for total shoulder arthroplasty (TSA) with patient outcomes and complications.

Methods: We used the Nationwide Inpatient Sample (NIS) from 1998–2011 to study the association of hospital annual TSA procedure volume with patient characteristics and TSA outcomes, including discharge disposition (home vs. inpatient facility), length of index hospitalization, post-arthroplasty perioperative fracture and revision. Annual hospital TSA volume was categorized as <5, 5–9, 10–14, 15–24 and ≥25 TSA procedures annually.

Results: Patients receiving TSA at higher volume hospitals were more likely to be female (p<0.0001), of White race (p<0.0001). Compared to low volume hospitals (<5, 5–9, 10–14 procedures annually), patients receiving TSA at higher volume hospitals (15–24, ≥25) had significantly lower likelihood of: (1) being discharged to an inpatient medical facility, 16.5%, 13.4%, 13.0%, 12.7% and 11.5% (p<0.0001); (2) hospital stay >median, 46.4%, 40.4%, 36.6%, 34.4% and 29.2% (p<0.0001); (3) post-arthroplasty fracture, 1.2%, 0.8%, 0.9%, 0.6% and 0.8% (p=0.0004); (4) transfusion, 8%, 7.1%, 6.7%, 7.1% and 5.5% (p=0.0006); and (5) TSA revision, 0.5%, 0.3%, 0.2%, 0.3% and 0.3% (p=0.045), respectively.

Conclusion: In this study, we found that higher annual hospital TSA volume was associated with better TSA outcomes. These findings document the impact of annual hospital TSA volume on TSA outcomes. Patients, surgeons and policy-makers should be aware of these findings and take them into account in decision-making, policy decisions and resource allocation.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; R. Ramachandaran, None.

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Sex Differences in Characteristics, Utilization and Outcomes of Patient Undergoing Total Elbow Arthroplasty: A Study of the U.S. Nationwide Inpatient Sample. Jasvinder A Singh1 and Rekha Ramachandaran2. 1University of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To compare patient characteristics, utilization rates and outcomes after total elbow arthroplasty (TEA) by sex.

Methods: We used the nationwide Inpatient Sample from 1998–2011 to study sex-related time-trends in patient characteristics, comorbidity and TSA outcomes after TEA. We used chi-square test, analysis of variance and the Cochran-Armitage test to assess differences in utilization rates and characteristics over time by sex and logistic regression to compare mortality, discharge disposition and the length of hospital stay.

Results: Overall TEA utilization increased significantly from 0.45 in 1998 to 0.96 per 100,000 in 2011 (p<0.0001). The utilization rates were significantly higher in females compared to males throughout the study period: 0.62 vs. 0.29 in 1998 (p<0.0001) and 1.31 vs. 0.70 in 2011 (p<0.0001). Compared to males, females undergoing TEA were more likely to be White (79.7% vs. 71.4%; p<0.0001), have rheumatoid arthritis (16.7% vs. 8.1%; p<0.0001) and have Deyo-Charlson index of 2 or more (11.3% vs. 5.9%; p<0.0001) and were older (63.5 vs. 51.4 years; p<0.0001). Compared to males undergoing TEA, females had significantly lower mortality, 0.1% vs. 0.4% (p=0.03); lower proportion were discharged to home, 81.9% vs. 89.6% (p<0.0001) and fewer had index hospital stay above the median, 30.0% vs. 33.0% (p=0.01); most differences were significant after multivariable adjustment.

Conclusion: TEA utilization in the U.S. more than doubled in the last 14 years, with rates higher in females than males. Females had better outcomes after TEA than men. Preoperative risk communication should be sex-specific based on these data.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; R. Ramachandaran, None.

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Hospital Volume Predicts Outcomes and Complications after Total Shoulder Arthroplasty. Jasvinder A Singh1 and Rekha Ramachandaran2. 1University of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the time-trends in utilization, clinical characteristics and outcomes of patients undergoing total ankle arthroplasty (TAA) in the U.S.

Methods: We used the Nationwide Inpatient Sample (NIS) data from 1998 to 2010 to examine time-trends in the utilization rates of TAA. We used the Cochran Armitage test for trend to assess time-trends across the years and the analysis of variance (ANOVA), Wilcoxon test or chi-squared test (as appropriate) to compare the first (1998–2000) and the last time periods (2009–10).

Results: TAA utilization rate increased significant from 1998 to 2010: 0.13 to 0.84 per 100,000 overall, 0.14 to 0.88 per 100,000 in females and from 0.11 to 0.81 per 100,000 in males (p<0.0001 for each comparison for time-trends). Compared to the 1998–2000, those undergoing TAA in 2009–10 were older (41% fewer patients <50 years, p<0.0001); less likely to have RA as the underlying diagnosis (55% fewer patients, p<0.0001); more likely to have Deyo-Charlson index of two or more (197% more, p=0.0010) and had a shorter length of stay at 2.5 days (17% reduction, p<0.0001). Mortality was rare, ranging 0 to 0.6% and discharge to inpatient facility ranged 12.6–14.1%; we noted no significant time-trends in either (p>0.05).

Conclusion: The utilization rate of TAA increased rapidly in the U.S. from 1998 to 2010, but post-arthroplasty mortality rate was stable. Underlying diagnosis and medical comorbidity changed over time and both can impact outcomes after TAA. Further studies should examine how the outcomes and complications of TAA have evolved over time.

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; R. Ramachandaran, None.

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Utilization and Outcomes Following Total Shoulder Arthroplasty in Elderly and Non-Elderly Patients. Jasvinder Singh1, Celeste Lemay2, Jeroan Allison3 and Patricia D. Franklin3. 1University of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the age-related differences in total shoulder arthroplasty (TSA) outcomes and utilization and associated time-trends.

Methods: Nationwide Inpatient Sample (NIS) from 1998–2010 was used to study the time-trends in TSA utilization and outcomes, overall and by age. Age was categorized as <50, 50–64, 65–79 and ≥80. Time trends in TSA utilization were compared using logistic regression or the Cochran Armitage test.

Results: The overall TSA utilization increased from 2.96 in 1998 to 12.68/100,000 in 2010. Compared to 1998–2000, significantly lower rates were noted in 2009–10 for: mortality, 0.2% vs. 0.1% (p=0.0041); discharge to an inpatient facility, 14.5% vs. 13.3% (p=0.039); and hospital stay >median, 51.2% vs. 29.4% (p<0.0001). TSA utilization rates (100/1000 by age groups, <50, 50–64, 65–79 and ≥80 years were: 0.32, 4.62, 17.82 and 12.56 in 1998 (p<0.0001); and 0.65, 17.49, 75.27 and 49.05 in 2010 (p<0.0001) with increasing age-related difference over time (p<0.0001). Across the age categories, there were significant differences in the proportion: discharged to inpatient facility, 3.2% vs. 4.2% vs. 14.7% vs. 36.5% in 1998 (p<0.0001) and 1.8% vs. 4.3% vs. 12.5% vs. 35.0% in 2010 (p<0.0001) and the proportion with hospital stay >median, 39.7% vs. 40.2% vs. 53% vs. 69% in 2008 (p<0.0001) and 17.2% vs. 20.6% vs. 28.7% vs. 50.7% in 2010 (p<0.0001).

Conclusion: In a nationally representative sample, we noted increasing age-related differences indicate a changing epidemiology of TSA. Age-related differences in outcomes can guide us to focus on those with worst outcomes.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; R. Ramachandaran, None.

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Title: Use of Non-Traditional Modalities for Pain Management after Knee or Hip Joint Replacement. Jasvinder Singh1, Celeste Lemay2, Jeron Allison3 and Patricia D. Franklin1. 1University of Alabama at Birmingham, Birmingham, AL, 2University of Massachusetts Medical School, Worcester, MA, 3University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Pain management is a major focus of the post-arthroplasty rehabilitation. A variety of pain treatments are used, including narcotics and non-narcotic analgesics. To our knowledge, there are limited or
no data regarding the use of non-pharmacologic treatment modalities in post-total joint replacement (TJR) period.

**Methods:** A subset of patients from a national joint registry undergoing primary TJR (total knee or hip replacement, TKR/THR) between 5/2013 and 6/2014 were queried at 2- and 8-weeks regarding pain severity and use of non-pharmacologic modalities. Frequency distributions were used to describe the cohort. We used bivariate statistical tests to compare groups including the chi-square, Fisher’s exact, t tests and Wilcoxon-Mann-Whitney test.

**Results:** There were 969 primary TKR and 584 primary THR responders at 2-weeks and 1,022 primary TKR and 563 primary THR respondents at 8-weeks. The use of non-medication modalities was common in primary TKR patients at 2-weeks: cold packs (86%), meditation (6%), deep breathing (20%), heat (15%), relaxation (20%), walking (33%), distraction (51%), prayer (32%), massage (28%), listening to music (11%) and imagery (2%); numbers were similar and slightly lower for the 8-week follow-up. Use of most non-medication modalities was significantly lower in primary THR patients.

Compared to non-users, users of non-medication pain management strategies at 2-weeks were significantly: younger (65.6 vs. 68.8 years), more likely to be female (61% vs. 51%), White (93% vs. 89%), have college education or higher (70% vs. 62%) and had household income of $45K or higher (55% vs. 48%). There were no significant differences in race distribution or mean body mass index (30.6 vs. 30.0).

Compared to non-users, patients who reported using non-medication pain management strategies at 2-weeks and 8-weeks had significantly higher mean pain levels (3.0 vs. 2.0 on 0–10 scale; p<0.0001) and pain interference with activities of daily living (p-values < 0.001) and physical therapy (p = 0.007).

**Conclusion:** Use of non-medication pain management strategies was common 2- and 8-weeks after primary TKR and THR. Certain patient groups used these modalities more than others. Use of these strategies was associated with more pain and pain interference, which might indicate that patients with higher pain severity and impact were more likely to use these strategies. This hypothesis needs to be tested with examination of longitudinal data.

**Disclosure:** J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; C. Lemay, None; J. Allison, None; P. D. Franklin, None.

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**Pre-Operative Pain and Function: Profiles of Patients Selected for Total Knee Replacement Among Surgeons in the United States.** Uyen Sa D.T. Nguyen, David C. Ayers, Wenjun Li, Leslie Harrold and Patricia D. Franklin. University of Massachusetts Medical School, Worcester, MA.

**Background/Purpose:** When knee pain is severe and frequent, or mobility and daily activities become difficult, a total knee replacement (TKR) remains the most effective treatment to relieve pain and to improve function. In the US, the annual rate of TKRs in people 65 years or older increased almost 9-fold between 1979 and 2006. The latest US hospital-discharge data indicated a significant increase in use among the younger patients (< 65 years of age). Among the 719,000 TKRs performed in 2010, about 50% were in people < 65. It remains unclear the reasons for such increased TKR use. We examined profiles of patients selected for TKR in a recently established US national registry of total joint replacements (TJR).

**Methods:** We used data from the Function and Outcomes Research for Comparative Effectiveness in TJR (FORCE-TJR), a national cohort of TJR patients operated by more than 130 surgeons in 22 sites nationwide. The current study included participants with primary and unilateral TKRs that were not indicated by rheumatoid arthritis. Participants were enrolled between April 2011 and Feb 2014, and had completed a pre-operative Knee Injury and Osteoarthritis Outcome Score (KOOS) and Short-Form 36-item (SF-36) functional health survey. Data were also collected on patient demographics, body mass index, general health and comorbid conditions. We classified patients as having high or low pain (KOOS Pain<70 vs. ≥70), and low or high physical function (SF-36 PCS <40 vs. ≥40). We then classified patients into four groups: 1) low pain-high function, 2) high pain-high function, 3) low pain-low function, and 4) high pain-low function. Descriptive statistics including patient demographic and clinical characteristics of the four groups were compared.

**Results:** The majority (95%) of patients had high pain and/or low physical function. A small percentage of people (5%), however, had low pain and high function. Many in this latter group reported pain fairly daily (49%) or were aware of their knee problem daily or constantly (85%) despite a very small percentage having experienced severe or extreme pain on stairs (4%) or pain in bed (1%). Moreover, over half had a lot of limitations or difficulties in vigorous activities such as running. Compared with the group with high pain and low function, the group with low pain and high function on average were older, less obese, more highly educated, more likely men, and were generally healthier. Differences for all characteristics by groups were statistically significant at P<0.05, except for race.

**Conclusion:** The overwhelming majority of TKRs were performed to relieve pain and/or restore physical function. However, a small percent of TKR utilization was in patients with low pre-operative pain and high function, probably for quality of life issues. Further investigation is needed to determine the reasons for TKR use among these patients as this may have an important policy implication.

**Disclosure:** U. S. D. T. Nguyen, None; D. C. Ayers, None; W. Li, None; L. Harrold, None; P. D. Franklin, None.

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**Differences in Total Knee Replacement Outcomes Based on Age.** Leslie Harrold1, David Ayers1, Wenjun Li1, Vincent Pellegrini2, John Grady-Benson1, Jeroan Allison1 and Patricia D. Franklin1. 1University of Massachusetts Medical School, Worcester, MA, 2Medical University of South Carolina, Charleston, SC, 3Connecticut Joint Replacement Institute, Hartford, CT.

**Background/Purpose:** The fastest growing segment of the population undergoing total knee replacements (TKR) are patients younger than <65 years, yet little is known regarding their outcomes as compared to older patients. We examined, from a national sample of TKR patients, differences in clinical outcomes of pain and function following surgery based on age.

**Methods:** Patients undergoing primary TKR from 7/1/11 through 8/30/13 for osteoarthritis were identified from a national research consortium which enrolls patients from >130 surgeons across 22 states in the US. The registry gathers data from patients, surgeons and hospitals on patient demographics, underlying type of arthritis, body mass index, non-arthritis comorbid conditions, arthritis in non-operative hip and knee joints, back pain, global function based on the Short Form 36 Physical Component Score (PCS), and mental health using the SF-36 Mental Component Score (MCS). We evaluated both change in operative joint pain and function as well as the 6-month post-operative pain and function score based on the estimated Western Ontario and McMaster Universities Arthritis Index (WOMAC) using the Knee Injury and Osteoarthritis Outcome Score (KOOS; range of 0–100 with higher being better). Descriptive statistics were performed as well as linear and mixed model multivariable regressions examining differences based on age.

**Results:** There were 1164 patients <65 years and 2012 patients ≥ 65 years who underwent primary TKR. Younger patients were more likely to be nonwhite (8.7% vs. 5.0%, p<0.001), heavier (body mass index 33 vs. 30,
p<0.001), with worse emotional health (51.5 vs. 53.9, p<0.001), fewer comorbid conditions (p<0.001), and greater number of non-operative painful hip and knee joints (p<0.03). At the time of surgery, younger patients had greater pain (50.5 vs. 55.7, p<0.001) and functional impairment (53.2 vs. 54.9). Overall both younger and older patients had substantial pain relief and functional gain, improvement of 30.4 – 32.6 and 28.7 – 29.4 respectively based on the KOOS. In adjusted analyses, at 6-months post-operatively functional gain, improvement of 30.4 – 32.6 and 28.7 – 29.4 respectively (54.9). Overall both younger and older patients had substantial pain relief and functional gain following surgery. However, younger patients had statistically significant less improvement in pain and function, although the clinical significance of this difference is unknown.

Disclosure: L. Harrold. None; D. Ayers. None; W. Li. None; V. Pellegrini. None; J. Grady-Benson. None; J. Allison. None; P. D. Franklin. None.

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Dependence on Walking Aids and Patient-Reported Outcomes after Total Knee Arthroplasty. Jasvinder A Singh1 and David Lewallen2. 1University of Alabama and VA Medical Center, Birmingham, AL, 2Mayo Clinic College of medicine, Rochester, MN.

Background/Purpose: To examine whether function and pain outcomes of patients undergoing primary total knee arthroplasty (TKA) are changing over time.

Methods: The Mayo Clinic Total Joint Registry provided data for time-trends in preoperative and 2-year post-operative activity limitation and pain in primary TKA patients from 1993–2005. We used chi-square test and analysis for variance, as appropriate. Multivariable-adjusted analyses were done using logistic regression.

Results: In a cohort of 7,229 patients who underwent primary TKA during 1993–2005, mean age was 68.4 years (standard deviation (SD), 9.8), mean BMI was 31.1 (SD, 6.0) and 55% were women. Crude estimates showed that preoperative moderate–severe overall limitation were seen in 7.3% fewer patients and preoperative moderate–severe pain in 2.7% more patients in 2002–05, compared to 1992–95 (p<0.001 for both). At 2-years, crude estimates indicated that compared to 1992–95, moderate–severe post-TKA overall limitation was seen in 4.7% more patients and moderate–severe post-TKA pain in 3.6% more patients in 2002–05, both statistically significant (p<0.018) and clinically meaningful. In multivariable-adjusted analyses that adjusted for sex, age, anxiety, depression, Deyo-Charlson index, body mass index and preoperative pain/limitation, patients had worse outcomes 2-year post-TKA in 2002–2005 compared to 1993–95 with an odds ratio (95% confidence interval (CI); p-value) of 1.34 (95% CI: 1.02, 1.76, p=0.037) for moderate–severe activity limitation and 1.79 (95% CI: 1.17, 2.75, p=0.007) for moderate–severe pain.

Conclusion: Patient-reported function and pain outcomes after primary TKA have worsened over the study period 1993–95 to 2002–05. This time-trend is independent of changes in preoperative pain/limitation and patient characteristics.

Disclosure: J. A. Singh, takeka, savient, 2, takeda, savient, regeneron, allergan, 5; D. Lewallen, Zimmer, Orthosonic and Ostech, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer, 2.

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Dependence on Walking Aids Is Associated with Pain and Mobility Limitation after Total Hip Arthroplasty. Jasvinder A Singh1 and David Lewallen2. 1University of Alabama and VA Medical Center, Birmingham, AL, 2Mayo Clinic College of medicine, Rochester, MN.

Background/Purpose: To assess the association of dependence on walking aids with pain and function outcomes after total hip arthroplasty (THA).

Methods: We used the Mayo Clinic Total Joint Registry to study patients who underwent primary or revision THA between 1993–2005 and completed a 2-year or 5-year pain and function outcomes survey. Multivariable-adjusted logistic regression assessed the associations, adjusting for clinical demographic variables and preoperative pain and function.

Results: Primary THA cohort had 5,707 patients at 2-year and 3,289 at 5-years; revision THA included 2,667 patients at 2-year and 1,627 patients at 5-years. Compared to patients with no dependence on walking aids, patients with some or complete dependence on walking aids had significantly higher odds (95% confidence interval) of: (1) moderate-severe post-primary THA at 2-years: 3.40 (2.06, 5.62) and 4.79 (2.88, 7.97); (2) moderate-severe pain post-primary THA at 5-years: 3.92 (2.21, 6.95) and 3.47 (1.97, 6.11); (3) moderate-severe pain post-revision THA at 2-years, 4.67 (2.76, 7.91) and 2.95 (1.65, 5.27); (4) moderate-severe pain post-revision THA at 5-years: 3.95 (1.86, 8.38) and 5.16 (2.59, 10.3); (5) moderate-severe mobility limitation post-primary THA at 2-years: 10.7 (6.78, 17.0) and 14.2 (8.32, 24.3); (6) moderate-severe mobility limitation post-primary THA at 5-years: 13.2 (7.34, 23.7) and 21.4 (10.6, 43.2); (7) moderate-severe mobility limitation post-revision THA at 2-years: 4.90 (2.87, 8.37) and 8.26 (4.12, 16.6); (8) moderate-severe mobility limitation post-revision THA at 5-years: 5.12 (2.32, 11.3) and 10.1 (4.53, 22.7), respectively.

Conclusion: Post-THA dependence on walking aids is associated with worse pain and function outcomes post-THA.

Disclosure: J. A. Singh, takeka, savient, 2, takeda, savient, regeneron, allergan, 5; D. Lewallen, Zimmer, Orthosonic and Ostech, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer, 2.

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Differences in Total Hip Replacement Outcomes Based on Age. Leslie Harrold1, David Ayers1, Wenyun Li2, Courtland Lewis2, Philip Noble1, Regis O’Keefe2, Jeroan Allison1 and Patricia D. Franklin1. 1University of Massachusetts Medical School, Worcester, MA, 2Hartford Hospital, Hartford, CT, 3Baylor College of Medicine, Houston, TX, 4University of Rochester Medical Center, Rochester, NY.

Background/Purpose: The fastest growing segment of patients who undergo total hip replacement (THR) are younger than <65 years, yet little is known regarding their outcomes as compared to older patients. We examined, from a national sample of THR patients, differences in clinical outcomes of pain and function following surgery.

Methods: Patients undergoing primary THR from 7/1/11 through 12/30/13 for osteoarthritis were identified from a national research consortium which enrolls patients from >130 surgeons across 22 states in the US. The registry gathers data from patients, surgeons and hospitals on patient demographics, underlying type of arthritis, body mass index, non-arthritis comorbid conditions, arthritis in non-operative hip and knee joints, back pain, global function based on the Short Form 36 Physical Component Score (PCS), and mental health using the SF-36 Mental Component Score (MCS). We evaluated both change in operative joint pain and function as well as the 6-month post-operative pain and function based on the estimated Western Ontario and McMaster Universities Arthritis Index (WOMAC) using the Hip Disability and Osteoarthritis Outcome Score (HOOS; range 0–100 with higher better being). Descriptive statistics were performed as well as linear and mixed model multivariable regression models examining differences based on age.

Results: There were 1030 patients <65 years and 1242 patients ≥ 65 years who underwent primary THR. Younger patients were more likely to be nonwhite (6.7% vs. 4.1%, p<0.001), heavier (body mass index 29.3 vs. 28.2, p<0.001), with worse emotional health (50.1 vs. 53.1, p<0.001), and fewer comorbid conditions (p<0.001). At the time of surgery, younger patients had greater pain (47.4 vs. 51.7, p<0.001) and functional impairment (45.2 vs. 47.0, p=0.02). Overall both younger and older patients had substantial pain relief and functional gain, mean improvement of 40.1 – 43.2 and 39.1 – 42.2 respectively based on the HOOS. In adjusted analyses, both younger and older patients had similar levels of improvement in pain and function as well as similar mean post-operative 6-month pain (90.4 vs. 91.9, p=0.15) and function scores (86.2 vs. 87.4, p=0.42).

Conclusion: Both younger and older THR patients had substantial pain and disability at time of THR, and achieved significant pain relief and functional gain at 6 months following surgery. In this national sample of THR patients, both younger and older patients had good clinical outcomes following surgery with respect to pain relief and functional gain.

Disclosure: L. Harrold. None; D. Ayers. None; W. Li. None; C. Lewis. None; P. Noble. None; R. O’Keefe. None; J. Allison. None; P. D. Franklin. None.

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Implant Survival and Patient-Reported Outcomes after Total Hip Arthroplasty in Young Patients with JIA. Ishaan Swarup, Ella Christoph, Lisa A. Mandl, Susan M. Goodman and Mark P. Figgie. Hospital for Special Surgery, New York, NY.
Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a common rheumatologic disease in children that often persists into adulthood. The hip joint is commonly involved, and total hip arthroplasty (THA) is the standard treatment for patients who fail non-operative management. This study evaluates implant survival in JIA patients who underwent a primary THA at our institution before the age of 35. It also describes patient-reported outcomes for JIA patients after THA.

Methods: Patient characteristics and implant data were collected by a retrospective chart review. Follow-up surveys were used to determine implant survival and patient-reported outcomes. Kaplan-Meier survival analysis was performed to evaluate implant survival, and the hip disability and osteoarthritis outcome score (HOOS) was used to describe patient-reported outcomes.

Results: Patient data was reviewed for 91 JIA patients under the age of 35 that underwent a primary THA at our institution between 1982 and 2011. Follow-up data was available for 56 patients. A preliminary analysis of 35 patients (60 primary THAs) revealed a mean time to follow-up of 12 years (Range: 2–23 years). The 10-year and 20-year implant survival was 80% (95% CI: 66–89%) and 64% (95% CI: 46–77%), respectively. Primary THA with standard implants had a longer survival compared to custom implants (p-value = 0.02) with no other significant differences in implant survival stratified by patient age and sex, implant bearing surface, and use of cement for implant fixation. The mean HOOS scores were 89 (95% CI: 84–94) for pain, 87 (95% CI: 83–91) for symptoms, 86 (95% CI: 79–93) for ADLs, and 76 (95% CI: 69–83) for sports. Male patients reported better HOOS-Symptom scores compared to female patients (96 vs. 85, p-value = 0.026), and patients with standard implants reported better HOOS-Pain (95 vs. 73, p-value < 0.001) and HOOS-Symptom (91 vs. 78, p-value = 0.016) scores compared to patients with custom implants.

Conclusion: THA is an excellent treatment option for JIA patients under the age of 35 with very good long-term implant survival and favorable patient-reported outcomes after surgery.

Disclosure: I. Swarup, None; E. Christoph, None; L. A. Mandl, None; S. M. Goodman, None; M. P. Figgie, None.

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Increasing Complexity of Patients Undergoing Primary Total Hip Arthroplasty in the U.S. Javinder A Singh1 and David Lewallen2.1 University of Alabama and VA Medical Center, Birmingham, AL, 2Mayo Clinic College of medicine, Rochester, MN.

Background/Purpose: To examine the time-trends in key demographic and clinical characteristics of patients undergoing primary total hip arthroplasty (THA).

Methods: We used the data from the Mayo Clinic Total Joint Registry from 1993–2005 to examine the time-trends in demographics (age, body mass index (BMI), race, sex), medical (Deyo-Charlson index) and psychological comorbidity (anxiety, depression) and underlying diagnosis of patients undergoing primary THA. Chi-square test and analysis for variance were used. Multivariable-adjusted logistic regression (age, sex, comorbidity-adjusted) compared 1993-95 to other study periods. Odds ratio (OR) and 95% confidence interval (CI) are presented.

Results: The primary THA cohort consisted of 6,168 patients with 52% women. Compared to 1993-95, significantly more patients (by >2-times for most) in 2002-05 had: BMI≥40, 2.5% vs. 6.3%; depression, 4.1% vs. 9.8%; and anxiety, 3.4% vs. 5.7%; and significantly fewer had an underlying diagnosis of rheumatoid/inflammatory arthritis, 4.2% vs. 1.5% (p<0.01 for all). In multivariable-adjusted models, compared to 1993-95, significantly more patients in 2003-05 had (all p-values <0.01): BMI≥40, OR, 2.79 (95% CI: 1.85, 4.22); Deyo-Charlson Index≥3, 1.32 (1.07, 1.63); depression, 2.25 (1.66, 3.05); and anxiety, 1.71 (1.19, 2.15). Respectively, fewer patients had a diagnosis of RA/inflammatory arthritis: 0.28 (0.17, 0.46; p<0.01). Over the 13-year study period, Deyo-Charlson index increased by 22% (9.9 to 1.1) and the mean age decreased by 0.7 years (65.0 to 64.3) (p<0.01 for both).

Conclusion: Obesity, medical/psychological comorbidity and underlying diagnosis changed rapidly in primary THA patients over 13-years. Studies of THA outcomes and utilization should take these rapidly changing patient characteristics into account.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; D. Lewallen, Zimmer, Orthosronic and Osteotect, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer., 2.
Hips with prevalent JSN (excluded total hip replacement as outcome)†

<table>
<thead>
<tr>
<th>Description</th>
<th>Right Knee</th>
<th>Left Knee</th>
<th>Schuss</th>
<th>Standing AP view</th>
</tr>
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<tr>
<td>Shorter leg Hips, n( %)</td>
<td>475/504 (94.6)</td>
<td>45/255 (17.6)</td>
<td>805 (15.0)</td>
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<td>Adjusted OR* (95% CI)</td>
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<td>5.49 (0.94, 31.82)</td>
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<td>Longer leg Hips, n( %)</td>
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<td>2.74 (0.65, 7.84)</td>
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Disclosure: C. Kim; None; J. Niu; None; M. Clancy; None; A. Guermazi; None; M. C. Nevitt; None; N. A. Segal; None; W. F. Harvey; None; C. E. Lewis; None; D. T. Felton; None.

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Measures of Hip Morphology Are Related to Development of Incident Radiographic Hip Osteoarthritis over 6 to 13 Year Follow-up: The Johnston County Osteoarthritis Project. Amanda E. Nelson1, Jamie L. Stiller1, Xiaoyan A. Shi2, Kirsten M. Leyland3, Jordan B. Renner4, Todd A. Schwartz5, Nigel A. Arden6 and Joanne M. Jordan7,1 University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, 2SAS Institute, Cary, NC, 3NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom, 4University of North Carolina Department of Radiology, Chapel Hill, NC, 5University of North Carolina Gillings School of Global Public Health, Dept of Biostatistics, Chapel Hill, NC, 6University of North Carolina, Chapel Hill, NC.

Background/Purpose: Altersations in hip morphology, such as femoro-acetabular impingement, have been associated with incident hip OA and total hip replacement (THR), but have rarely been assessed in community-based samples and have never been assessed in African Americans (AA).

Methods: This case-control study was nested within a large community-based cohort. Case hips had Kellgren Lawrence grade (KLG)<3 on baseline supine pelvis radiographs and KLG=3 (mild/moderate hip OA, or THR for OA) at the 1st or 2nd follow-up (mean 6 and 12.7 years, respectively) visit. Control hips had KLG<3 at both baseline and follow-up, with a gender/race distribution similar to cases. Validated software (Oxmorf) was used to assess 27 aspects of hip morphology. Unadjusted analyses comparing cases and controls included chi-squared and t-tests, as appropriate. Generalized estimations equations regression models, adjusted for age, race, BMI, and side were employed, accounting for within-person correlation.

Results: A total of 263 hips, 76 case and 187 control, were included from 136 individuals (25% male, 29% AA, mean age 67±9 years and BMI 30±6 kg/m2). Case hips were more often right hips (67%, p<0.001), with no differences by age or BMI. Reliability for all measures was acceptable (intra-[ICC 0.7–1.00] and inter-reader ICC 0.5–1.00). Nearly all measures were significantly different by sex (p<0.03 in t-tests) so further analyses were sex-stratified; no interactions were seen for age, race, BMI, or baseline KLG.

For analyses by case/control status, we focused on 7 continuous and 3 categorical hip morphology measures (Table). Among men, higher baseline AP alpha angle, extrusion index, acetabular index, and modified triangular index height were associated with case status at follow-up, while greater baseline minimum joint space width (mJSW) and coxa profunda had a protective effect. Among women, higher AP alpha angle, lower mJSW, presence of protrusio acetabuli and the triangular index sign were significantly associated with case vs. control status. Strength of some associations varied by side (data not shown). With all measures simultaneously included in the model, the associations between AP alpha angle and mJSW remained significant for both men and women, as did the triangular index sign among men only.

Conclusion: Cam-type morphology (higher AP alpha angle and triangular index) and smaller mJSW were associated with incident radiographic hip OA in both men and women, with no differences by race. Newly identified variations in these associations by side are of interest and will be the subject of future work.
Background/Purpose: Predictors of radiographic progression in erosive osteoarthritis (OA) are important in identifying patients with high risk of disease activity and consequently functional loss. Disease duration, number of tender joints and number of joints with palpable effusion at baseline are already identified as clinical predictors of radiographic progression. The aim of this study is to confirm the existing predictors in a prospective cohort. Additionally, potentially other clinical and radiographic predictors will be identified.

Methods: One hundred and twelve patients with erosive OA were selected from an already existing cohort that was recruited from April 2007 through January 2010 at the Ghent University Hospital. X-rays, clinical and demographic data of the 1st assessment were present. All patients were reassessed between January 2014 and March 2014. All interphalangeal finger joints on both radiographs were scored according to the Verbruggen and Veyts method. Radiographic progression was defined as a joint progressing from at least one anatomical phase, excluding the progression from a ‘N’ phase to a ‘S’ phase. A generalized estimating equation (GEE) model with a binary logistic function was used to explore the following potential clinical and radiographic predictors on joint level; disease duration (<5 years, >5 years), presence of erosive joints in the dominant hand, presence of painful joints, tender joints or joints with palpable effusion, the presence of a joint in ‘J’ phase and in ‘E’ phase. All variables were dichotomous (present or absent).

Results: Three clinical and two radiographic predictors were retained: a painful joint, a tender joint, a joint with palpable effusion, a joint in ‘J’ phase and a joint in ‘E’ phase. A joint with palpable effusion was the strongest clinical predictor (odds ratio (OR): 2.474) (table 1). A joint in ‘E’ phase was the strongest radiographic predictor (OR: 90.628) (table 2).

Table SEQ Table 1: Clinical predictors for radiographic progression by GEE modeling

<table>
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<th>Variables</th>
<th>GEE-OR (95% CI)</th>
<th>P-value</th>
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<td>Disease duration (&lt;5 years, &gt;5 years)</td>
<td>1.028 (0.711–1.487)</td>
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<tr>
<td>Erosive joint in dominant hand</td>
<td>0.879 (0.671–1.151)</td>
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<tr>
<td>Painful joint</td>
<td>1.529 (1.023–2.310)</td>
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<td>Tender joint</td>
<td>1.973 (1.344–2.897)</td>
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</tr>
<tr>
<td>Joint with palpable effusion</td>
<td>2.474 (1.419–4.314)</td>
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<td>CI: confidence interval</td>
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Table SEQ Table 2: Radiographic predictors for radiographic progression by GEE modeling

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<tr>
<th>Variables</th>
<th>GEE-OR (95% CI)</th>
<th>P-value</th>
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<tr>
<td>Presence of ‘J’ phase</td>
<td>17.418 (8.785–34.538)</td>
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</tr>
<tr>
<td>Presence of ‘E’ phase</td>
<td>90.628 (40.109–204.781)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: A painful joint, a tender joint, a joint with palpable effusion, ‘J’ phase and ‘E’ phase were identified as predictors of radiographic progression in erosive OA. The strongest clinical and radiographic predictor was a joint with palpable effusion and the presence of an ‘E’ phase respectively. These predictors should be considered when selecting patients for therapeutic trials with potential disease-modifying osteoarthritis drugs.

Disclosure: P. Meersseman, None; C. Van De Vyver, None; G. Verbruggen, None; D. Elewaut, None; R. Wittoek, None.

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Ultrasoundographic Predictors for Clinical and Radiological Progression in Knee Osteoarthritis after 2 Years Follow up. Karen Bevers1, Johanna E. Vriezekolk2, J.W.J. Bijlsma2, Els van den Ende2 and Alfons A. den Broeder2.

Background/Purpose: Pathophysiology of osteoarthritis (OA) is not completely understood. Identifying patients with progression might help to direct future research on therapeutic interventions. As OA is known to affect the entire joint, including soft tissue structures, structural changes in these tissues, visualised by ultrasound (US), might predict progression. The aim of this study was to investigate the association between a set of US features and radiographic and clinical progression of knee OA after two years of follow up.

Methods: A total of 125 patients fulfilling American College of Rheumatology clinical criteria for knee OA underwent US examination of the most symptomatic knee. The US protocol included assessment of synovial hypertrophy, joint effusion, infrapatellar bursitis, Baker’s cyst, medial meniscus protrusion and cartilage thickness. Clinical progression was defined using the inverse OARSI responder criteria or progression to total knee replacement. A 2-point or more increase in Altman score or progression to total knee replacement was considered radiologic progression. Regression analyses were performed with US features as independent variables and progression (two separate models for clinical progression and radiographic progression) as dependent variable.

Results: A total of 31 (25%) patients fulfilled the criteria of clinical progression and 60 (48%) patients fulfilled the criteria of radiologic progression. Presence of Baker’s cyst showed a statistically significant association with clinical (OR: 3.07; 95% CI: 1.21 – 7.78) as well as radiological (OR: 2.84; 95% CI: 1.17 – 6.90) progression. Synovial hypertrophy showed a weaker but consistent association with clinical- as well as radiologic progression (OR: 2.11; 95% CI: 0.80 – 5.57).

Conclusion: We demonstrated a longitudinal association between Baker’s cyst (and to a lesser extent synovial hypertrophy) at baseline and radiological and clinical progression after two years. When confirmed, these inflammatory variables might be candidate features to help define knee OA patients with worse prognosis.

Reference List

Disclosure: K. Bevers, None; J. E. Vriezekolk, None; J. W. J. Bijlsma, None; E. van den Ende, None; A. A. den Broeder, None.

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Natural History and Clinical Significance of Meniscal Tears over 8 Years in a Large Nonaerosotrophic Cohort. Hussain Ijaz Khan1, Dawn Atkin2, Changhui Ding2, Leigh Blizzard3, Jean-Pierre Pelletier4, Johanne Martel-Pelletier2, Flavia Cicuttini5 and Graeme Jones2.

Background/Purpose: Meniscal tears are a key player in knee osteoarthritis (OA) and family history of the disease has been shown to play an important role. However, there is limited longitudinal data on the natural history of meniscal tears. The aim of this study was to track natural history of meniscal tears over 8 years, describe the association with change in pain and disease structural and non-structural predictors of change in meniscal tears.

Methods: 220 participants [mean age 47 (28–63); 57% female] were studied at baseline and 8 years. Approximately half were the adult offspring of subjects who had a knee replacement performed for knee OA and the remaining half were randomly selected controls without a family history of OA. Meniscal tears were evaluated, using T-1 weighted fat saturated MRI, on a 0–2 (0=absence; 1=simple; 2=complex tear) scale within 6 defined regions: anterior horn, body, and posterior horn at both medial and lateral menisci. Cartilage volume/defects, bone marrow lesions (BMLs), meniscal extrusion and effusion were assessed on MRI and joint space narrowing (JSN) and osteophytes on radiographs using standard protocols. Pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: Using updated methodology, 22% of the participants had a meniscal tear at any site at baseline, without a significant difference between the two groups at any site. 16% of the participants had any increase in meniscal score (incident tears + increase from baseline score) over 8 years. Offspring had a significantly higher change in mean meniscal score compared to controls over 8 years (total knee score: offspring= 0.493, controls= 0.164, p=0.034). Change in meniscal tears was independently associated with worsening pain over 8 years (Table 1). There was also a significant offspring-control interaction (all p<0.05) at all sites, with offspring having a significantly higher increase in pain on WOMAC scale per unit change in tears compared to controls (Table 1). Higher BMI at baseline was independently associated with a greater risk of increase in mean meniscal score (total
knee: RR = 1.10 (1.04, 1.16)). Change in total medial tears was associated with cartilage loss over 8 years in the medial (tibial + femoral) compartment (β = -1.76 (-3.02, -0.49)) only. Change in tears at all sites was associated with change in compartment specific and total knee BMLs (total knee: β = -0.39 (0.26, -0.53)). Furthermore, change in tears showed the strongest independet correlation with change in both JSM (ρ = 0.37, p < 0.01) and osteophytes (ρ = 0.61, p < 0.01) in the medial compartment.

Conclusion: In this midlife cohort, meniscal tears are common. Change in tears is independently associated with change in pain, BMLs, cartilage volume and radiographic OA. In turn, change in tears is influenced by family history of OA and BMI but not history of knee injury.

Table 1: Association between change in meniscal tears and change in pain over 8 years

<table>
<thead>
<tr>
<th>Change in tears (site)</th>
<th>Total meniscal tears</th>
<th>Total (medial + lateral) tears</th>
<th>Total lateral meniscus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjustedβ (95% CI)</td>
<td>0.381 (0.245, 0.520)</td>
<td>0.284 (0.11, 0.457)</td>
<td>0.572 (0.44, 0.69)</td>
</tr>
<tr>
<td>Adjustedβ (95% CI)</td>
<td>0.439 (0.34, 0.546)</td>
<td>0.364 (0.29, 0.401)</td>
<td>0.285 (0.22, 0.33)</td>
</tr>
</tbody>
</table>

Change in meniscal tears and change in pain over 8 years.


1) Boston University, Boston, MA; 2) Klinikum Augsburg, Augsburg, Germany; 3) University of Alabama at Birmingham, Birmingham City, AL; 4) University of Iowa, Iowa City, IA; 5) UCSI, San Francisco, CA.

Background/Purpose: Knee osteoarthritis (OA) occurs in both the patellofemoral joint (PFJ) and tibiofemoral joint (TFJ). Little is known about the natural history of OA and it has been hypothesized, based on findings from radiographic studies, that OA occurs first in the PFJ and subsequently progresses to involve the TFJ. This has not been evaluated using MRI, which is more sensitive than radiographs to identify structural damage, particularly in the PFJ. The purpose of this study was to describe the prevalence of change in cartilage loss and bone marrow lesions (BMLs) among knee joint compartments over 7 years. Specifically, we describe whether disease remains isolated to one compartment or develops in the other, and which compartment tended to be initially involved.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort study of 3,026 individuals with or at risk for knee OA. Participants had MRI of their knee at baseline and 84-month of follow up. Two musculoskeletal radiologists used the Whole Organ Magnetic Resonance Score (WORMS) to assess cartilage morphology and BMLs in the PFJ and TFJ at baseline and 7 years. At baseline and 84-months, knees were categorized as having full-thickness cartilage loss (any region within a compartment with WORMS 2.5, 5 or 6) or isolated to the PFJ, isolated to the TFJ, mixed (both PFJ and TFJ) or no full-thickness loss in either compartment. In sensitivity analyses any cartilage loss (WORMS ≥2) and any BML (WORMS ≥1) were used to categorize disease in knee compartments.

Conclusion: Over 7 years of follow-up it is uncommon for cartilage loss and BMLs to "spread" to the other compartment in the knee. Furthermore, of knees that develop cartilage loss and BMLs in the other compartment, most knees start with damage isolated to the PFJ, suggesting that mixed disease may start in the PFJ.

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Correlates of Knee Bone Marrow Lesions in Younger Adults. Benny Samuel Eshakkattu Antony1, Graeme Jones2, Alison Venn1, Lyn March3, Flavia Cicuttini1, Andrew Halliday4, Leigh Blizzard5, Marita Cross6, Terry Dwyer2 and Cincilla Ding7.

1) Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia; 2) Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia; 3) Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia; 4) Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia.
Background/Purpose: Bone marrow lesions (BMLs) of the knee joint are a key player in osteoarthritis of the knee. However, little is known of their determinants, especially in young adults. The aim of this study was to examine the structural and functional correlates of BMLs in younger adults including physical activity and to determine whether bone mass, cholesterol and hormones measured 5 years prior are associated with current BMLs.

Methods: Subjects broadly representative of the Australian population (n=330, aged 31–41 years, female 48.7%) were selected from the Childhood Determinants of Adult Health Study. They underwent T1 and T2-weighted fat-suppressed magnetic resonance imaging in their knee. BMLs, cartilage defects, meniscal tears and cartilage volume were measured. Knee pain was assessed by self-administered Western Ontario and McMasters osteoarthritis index (WOMAC) questionnaire. Physical activity was measured by IPAQ questionnaires at the time of MRI. Heel bone mass, cholesterol and hormone levels (in females) were assessed 5 years prior.

Results: The prevalence of any BMLs in the knee joint was 17%. Cross-sectionally, any BML in the knee was associated with age (PR: 1.09, 95% CI: 1.00, 1.19), previous knee injury (medial tibial cortical BMLs PR: 2.20; 95% CI: 1.03, 4.71) and total WOMAC knee pain (PR: 1.05, 95% CI: 1.02, 1.09). BMLs were associated with other structural abnormalities such as total knee cartilage defects (PR: 2.65, 95% CI: 1.47, 4.80) and total meniscal tears (PR: 1.70, 95% CI: 0.99, 2.94).

High Density Lipoprotein (HDL) cholesterol measured 5 years prior was negatively associated with any BML (PR: 0.93, 95% CI: 0.85, 0.97). Testosterone measured 5 years prior in females (PR: 0.99, 95% CI: 0.99, 1.00) and speed of sound in both sexes (bone mass, PR: 0.98, 95% CI: 0.97, 0.99) were negatively associated with femoral BMLs. Moderate physical activity was protective (PR: 0.93, 95% CI: 0.87, 0.99) while vigorous activity showed a deleterious trend (PR: 1.01, 95% CI: 1.00, 1.02) with BMLs as we reported previously. Additional analysis was performed on case subsets in order to distinguish structural from pain progression: 103 subjects with a knee pain progression (persistent worsening in WOMAC pain score, reaching a MCID threshold of 9 points on a 0–100 scale), each achieved for the first time at the 24, 36 or 48 month follow-up compared to 209 baseline pain free subjects with no knee pain progression. In a logistic regression model, a deleterious trend (PR: 1.01, 95% CI: 0.98, 1.04) and walking (PR: 0.99, 95% CI: 0.98, 1.00) were negatively associated with femoral BMLs. Moderate physical activity was protective (PR: 0.93, 95% CI: 0.97, 0.99) while vigorous activity showed a deleterious trend (PR: 1.01, 95% CI: 1.00, 1.02) with BMLs as we reported previously.

Conclusion: In young adulthood, the presence of knee cartilage volume observed in younger adults may be protective with development of BMLs in young adults.

Disclosure: B. S. Eathakkattu Antony, None; A. Venn, None; F. Cicutinni, None; L. March, None; L. Blizzard, None; T. Dwyer, None; M. Cross, None; G. Jones, None; C. Ding, None.

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Physical Performance and Obesity Measures Are Associated with Tibial Cartilage Volume and Explains the Sex Difference in Cartilage Volume. Benny Samuel, Eathakkattu Antony, Alison Venn, Flavia Cicutinni, Lyn March, Leigh Blizzard, Terry Dwyer, Marita Cross. Grame Jones and Changes in Tibial Cartilage Volume. Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, 1Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, 2Monash University, Melbourne, Australia, 3Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, 4Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, 5Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, 6University of Sydney Institute of Bone and Joint Research, Royal North Shore Hospital, Sydney, Australia, 7Boston University School of Medicine, Boston, MA.

Background/Purpose: We sought to investigate if cartilage thickness change over 24 months predicts clinically relevant progression (radiographic and/or symptomatic) in knee OA over a 48 month period.

Methods: The OA Biomarkers Consortium undertook a nested case-control study of progressive knee OA within the Osteoarthritis Initiative (OAI). Main inclusion criteria were KLG 1, 2 or 3 at baseline and availability of knee radiograph and magnetic resonance imaging (MRI) at baseline and 24 months. The primary case group (n=194) was defined by the combination of knee radiographic progression (medial tibiofemoral joint space loss (mTf JSL) >= 0.7mm AND pain progression (persistent worsening in WOMAC pain score, reaching a MCID threshold of 9 points on a 0–100 scale), each achieved for the first time at the 24, 36 or 48 month follow-up compared to baseline; referred to as “JSL and pain progressors”. We defined two additional case subsets in order to distinguish structural from pain progression: 103 subjects with JSL but no pain increase comprised “JSL only progressors”; and 103 with a persistent increase in pain but no JSL comprised “Pain only progressors”. “Nonprogressors” (n=200) were participants with a knee eligible for the study that did not meet either progression definition (pain or mTf JSL). Manual segmentation of the femorotibial cartilages was performed by trained radiographers to generate cartilage thickness. The measures used in this analysis were (i) change in cmFTC (central medial femorotibial compartment), and (ii) change in ccMF (central medial femur) and cMT (central medial tibia). Association between cartilage thickness measures and progressors vs nonprogressors was assessed using a logistic regression model.
adjusting for baseline age, sex, BMI, KLG and baseline pain level. Additional analyses were conducted to detect marginal effects of cartilage thickness on changes in pain and mTF JSL.

Results: Participants had mean age of 61.5 years, 59% female and the majority were obese. Changes in cartilage thickness from BL to 24 months in the cMFTC, ccMF and cMT were greater for all three progressor groups combined compared to nonprogressors and significantly associated with increased odds of being a progressor (Table). The ORs for cartilage thickness changes ranged from 1.6 to 2.8, with the largest ORs associated with cartilage thickness changes in the ccMF OR 2.8 (95%C.I 2.1 to 3.7). Further analysis suggested that these associations were with structural progression and not pain progression.

Table. Change in cartilage thickness at 24 months and prediction of case control status OR (95% CI) p value. ORs represent the change in odds of being a progressor per SD increase of normalized changes in cartilage thickness.

<table>
<thead>
<tr>
<th>Region</th>
<th>Baseline variable</th>
<th>Cartilage thickness loss (%)</th>
<th>Pain only progressors (n=200)</th>
<th>JSL only progressors (n=103)</th>
<th>JSL and pain progressors (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in cMFTC</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
<tr>
<td>Change in cMFTC</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
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<td>Pain only progressor (n=103)</td>
<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
</tbody>
</table>

Conclusion: Changes in cartilage thickness markers over 24 months clearly differentiate progressors from nonprogressors. These associations are largely attributable to mTF JSL and not to pain increases.

Disclosure: D. J. Hunter, Foundation NIH, 2, J. E. Collins, None; M. C. Nevitt, None; J. A. Lynch, None; V. B. Kraus, Foundation NIH, 2; J. N. Katz, None; E. Losina, None; F. Roemer, None; A. Guarrazi, None; W. Wirth, Chondrometrics, 3; F. Eckstein, Chondrometrics GmbH, 3, Merck Serono, Abbvie, 2.

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Association Between Baseline External Knee Adduction and Flexion Moments During Gait and Medial Tibiofemoral Cartilage Thickness Loss Over Two Years in Persons with Knee Osteoarthritis (OA). Alison H. Chang1, Kirsten C. Moisio2, Felix Eckstein3, Joan S. Chmiel1, Orit Almogor4, Pottumarthi Prasad5, Karen W. Hayes1, Laura Belisle1, Yunhui Zhang1, Jamie Rayahin1 and Leena Sharma1. 1Northwestern University, Chicago, IL; 2Paracelsus Medical University, Salzburg, Austria; 3NorthShore University HealthSystem, Evanston, IL; 4University of Illinois at Chicago, Chicago, IL.

Background/Purpose: The external knee adduction moment (KAM) during gait has been characterized as a surrogate for dynamic medial knee load and is believed to be a risk factor for medial knee OA disease progression. By incorporating both load magnitude and duration, KAM impulse may provide a cumulative measure of KAM sustained during each step of walking. A reduction in KAM may be accompanied by a deleterious increase in the external knee flexion moment (KFM). Few longitudinal studies have evaluated the association between KAM impulse and peak KFM and subsequent medial OA disease progression. We hypothesized that in persons with OA, greater baseline peak KAM, KAM impulse, and peak KFM during gait are each associated with baseline-to-2-year worsening of medial cartilage thickness loss.

Methods: Participants had knee OA (K/L grade equal or greater than 2 in at least 1 knee). Baseline knee kinematics and kinetics during gait were recorded using an 8-camera Digital Real-Time Eagle motion analysis system, and 6 AMTI force plates; inverse dynamics used to compute peak KAM, KAM impulse, and peak KFM. MRI scans of both knees were done at baseline and 2-year visits. Regions of interest (ROI) were the entire medial tibial and weightbearing femoral surfaces; medial central, central, and posterior subregions and femoral external and central subregions. Disease progression in each ROI was analyzed as: 1) baseline-to-2-year cartilage thickness loss equal or greater than 5%, and 2) % cartilage loss from baseline to 2 years later. We used logistic and continuous outcome regression models with GEE, adjusting for gait speed, age, and gender, then further adjusting for radiographic disease severity.

Results: The study sample included 385 knees (203 persons); mean age 64.2 years (SD 9.9); BMI 28.4 kg/m² (5.7); 156 (76.8%) women. In Table 1, peak KAM and KFM were not associated with cartilage thickness loss at least 5% in the fully adjusted models. In contrast, KAM impulse was associated with thickness loss at all medial surfaces and in all but the tibial posterior

subregions. For the continuous outcomes, greater peak KAM and KAM impulse were each associated with greater mean 2-year % thickness loss at the medial tibial surface, particularly the central and external subregions, and at the weightbearing femoral surface, particularly the central subregion (Table 2).

Table 1 Adjusted odds ratios (95% CI) for medial tibiofemoral cartilage thickness loss outcomes (n = 385 knees; 203 persons)

<table>
<thead>
<tr>
<th>Region</th>
<th>Baseline variable</th>
<th>Cartilage thickness loss (%)</th>
<th>Pain only progressors (n=200)</th>
<th>JSL only progressors (n=103)</th>
<th>JSL and pain progressors (n=154)</th>
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<tr>
<td>Change in cMFTC</td>
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<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
<tr>
<td>Change in cMFTC</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
<tr>
<td>Change in cMFTC</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
<td>Pain only progressor (n=154)</td>
<td>Pain only progressor (n=200)</td>
<td>Pain only progressor (n=103)</td>
</tr>
</tbody>
</table>

95% CI excluding 1 is significant

Disclosure: A. H. Chang, None; K. C. Moisio, None; F. Eckstein, Chondrometrics GmbH, 3, Merck Serono, Abbvie, 2; J. S. Chmiel, None; O. Almogor, None; P. Prasad, None; K. W. Hayes, None; L. Belisle, None; Y. Zhang, None; J. Rayahin, None; L. Sharma, None.

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Relation of Shoe Stability to Risk of Knee Cartilage Damage: The Multicenter Osteoarthritis Study. K. Douglas Grosi1, Howard J. Hillstrom2, Jingbo Niu3, Michael C. Nevitt4, James C. Torner5, Cora E. Lewis6 and David T. Felson7. 1Boston University School of Medicine, Boston, MA; 2Hospital Special Surgery (HSS), New York, NY; 3Boston University, Boston, MA; 4UCSF (University of California, San Francisco), San Francisco, CA; 5University of Iowa, Iowa City, Iowa City, IA; 6University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Clinical guidelines recommend that “every patient with knee osteoarthritis should receive advice concerning appropriate footwear”, yet the recommended content of this advice is not specified. Some studies suggest that highly flexible shoes can protect the tibiofemoral (TF) joints against excessive load during gait, while other studies underscore the importance of stable or supportive shoes as a means of protecting the patellofemoral (PF) joint against maltracking brought about by foot pronation. The purpose of this observational study was to determine the relationship between the stability characteristics of a person’s usual walking shoe and the 2-year risk of worsening cartilage damage in the medial TF, lateral TF, and PF knee compartments.

Methods: The Multicenter Osteoarthritis Study (MOST) includes middle aged and older adults that have or are at risk of knee OA. Subjects were asked to bring their usual walking shoes and, adapting the methods of Barton et al.,
examiners at the 60-month visit scored the sagittal, torsional, and heel counter stability of each subject’s shoe as 0 = flexible or 1 = stable / supportive (kappa ≥ 0.69). A Summative Shoe Stability Score (0–3) was calculated as the sum of the three component test scores. 1.0T MRIs were obtained at the 60 and 84-month exams, and one knee per subject was scored using Whole Organ MRI Scores (WORMS) to indicate the extent of cartilage damage (0–6). We estimated the relative odds of worsening knee cartilage damage in categories of increasing shoe stability, while adjusting for covariates. Generalized estimating equations accounted for non-independence between sub-regions of a compartment.

Results: 1126 subjects (mean +/- sd age 66.8 +/- 7.5 yrs, BMI 29.6 +/- 4.8 kg/m²; 61.7% female, 89.8% white) contributed 1124, 1123, and 1116 knees to the analysis of cartilage damage in the medial TF, lateral TF, and PF compartments, respectively. A majority of shoes (64.3%, 68.3%, and 55.9%, respectively) were scored as stable / supportive during sagittal, torsional, and heel counter stability tests, with 47.8% of shoes obtaining the maximum Summative Shoe Stability Score of 3 and only 25.5% obtaining the minimum score of 0. Relative odds of worsening cartilage damage in the medial TF, lateral TF, and PF knee compartments did not change across categories of increasing shoe stability (p > 0.05 for all comparisons).

Conclusion: These observational findings do not confirm an association between usual walking shoe stability and 2-year risk of worsening cartilage damage in medial TF, lateral TF, or PF knee compartments. Future studies are needed to clarify the shoe characteristics that are most relevant for persons with knee OA.

<table>
<thead>
<tr>
<th>Shoe Stability Test</th>
<th>Medial TF Cartilage Damage</th>
<th>Lateral TF Cartilage Damage</th>
<th>PF Cartilage Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sub-regions with worsening</td>
<td>Sub-regions with worsening</td>
<td>Sub-regions with worsening</td>
</tr>
<tr>
<td></td>
<td>in % (Adj* OR (95% CI))</td>
<td>in % (Adj* OR (95% CI))</td>
<td>in % (Adj* OR (95% CI))</td>
</tr>
<tr>
<td>Sagittal Stability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexible</td>
<td>144/285 (5.1%)</td>
<td>100/195 (5.2%)</td>
<td>100/135 (7.4%)</td>
</tr>
<tr>
<td>Supportive</td>
<td>216/385 (6.1%)</td>
<td>186/345 (5.3%)</td>
<td>176/240 (7.3%)</td>
</tr>
<tr>
<td>Neutral</td>
<td>194/283 (6.8%)</td>
<td>162/297 (5.4%)</td>
<td>140/207 (6.7%)</td>
</tr>
<tr>
<td>Torsional Stability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexible</td>
<td>110/184 (6.1%)</td>
<td>87/172 (5.1%)</td>
<td>81/120 (7.1%)</td>
</tr>
<tr>
<td>Supportive</td>
<td>240/359 (6.8%)</td>
<td>190/370 (5.4%)</td>
<td>182/261 (7.3%)</td>
</tr>
<tr>
<td>Heel Counter Stability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexible</td>
<td>164/238 (7.1%)</td>
<td>124/248 (5.3%)</td>
<td>136/186 (9.1%)</td>
</tr>
<tr>
<td>Supportive</td>
<td>196/239 (8.1%)</td>
<td>120/134 (5.1%)</td>
<td>140/207 (6.7%)</td>
</tr>
<tr>
<td>Summative Shoe Stability Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>95/123 (7.2%)</td>
<td>72/137 (5.0%)</td>
<td>77/96 (8.0%)</td>
</tr>
<tr>
<td>1</td>
<td>33/40 (8.4%)</td>
<td>21/49 (9.7%)</td>
<td>24/35 (8.6%)</td>
</tr>
<tr>
<td>2</td>
<td>57/88 (6.3%)</td>
<td>55/96 (5.7%)</td>
<td>45/35 (6.9%)</td>
</tr>
<tr>
<td>3</td>
<td>152/265 (6.2%)</td>
<td>140/252 (5.4%)</td>
<td>150/196 (7.9%)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, race, and clinic site.

Disclosure: K. D. Gross, None; H. J. Hillstrom, None; J. Niu, None; M. C. Nevitt, None; J. C. Torner, None; C. E. Lewis, None; D. T. Felson, None.

Foot Center of Pressure in Knee Osteoarthritis (OA) and Its Association with Knee Load Reduction with Barefoot Walking. Christopher Ferrigno, Roy H. Lidtke, Markus Wimmer, Anjali Nair, Laura E. Thorp, Louis F. Fogg, Joel A. Block and Naja Shakoor. Rush University Medical Center, Chicago, IL.

Background/Purpose: Biomechanical factors including excessive knee loading have been shown to be important in the pathobiology, severity and progression of knee osteoarthritis (OA). Several biomechanical interventions that reduce knee loads by altering foot mechanics, and there is a great deal of interest in better understanding mechanical relationships between the foot and knee. We have previously shown that barefoot walking in OA is associated with a significant reduction in knee loading compared to conventional footwear. Here we evaluate the role of foot center of pressure (COP) in predicting the unloading response of the knee when walking barefoot.

Methods: Participants with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA underwent gait analyses with their own shoes and while walking barefoot. For simultaneous COP and 3-D ground reaction force acquisition, a pressure platform (Ernest, Novel, Munich, Germany) was mounted onto a force plate (Bertec, Columbus, OH) and the stacked assembly was leveled with the walkway. All capture systems were run at 100 Hz to allow for accurate syncing of stance phase, knee moments, and plantar pressures. Foot COP was quantified by determining a custom Medial to Lateral Pressure Index (MLPI) while barefoot. The peak knee adduction moment (KAM) was evaluated as a surrogate of medial knee loading. Linear regression was used to evaluate the relationship between foot COP and percent reductions in the KAM with walking barefoot compared to own shoes. The relationships between foot COP and other gait parameters and OA severity were also evaluated.

Results: 22 participants (15 women, mean age (SD) of 62±11) were evaluated. 10 had a KL grade of 2 and 12 had a KL grade of 3 at the affected knee. Barefoot walking was associated with a 15% reduction in the KAM compared to walking with participants own shoes (2.55±1.00 vs 2.17±1.01BW*ht, p<0.001); notably, the magnitude of reduction of the KAM with barefoot walking was associated with a more medial foot COP after adjusting for speed and stride length (adjusted r=0.509, p=0.049). A medialized foot COP was associated with worse KL grade, slower walking speed and shorter strides during gait (r²=0.564, p=0.002). Radiographic severity explained 9 to 26% of the variance in the foot COP while speed and stride length explained 17 to 47%.

Conclusion: Foot mechanics are important contributors to knee loading in OA. There is controversy in the literature regarding the foot COP and how it may relate to various foot-targeted interventions in OA. This study suggests that a more medial foot COP is associated with greater reductions in the KAM during barefoot walking. Thus, foot COP may help predict knee loading responses to walking barefoot or an intervention that simulates barefoot walking.

Disclosure: C. Ferrigno, None; R. H. Lidtke, DIO and Dr Comfort, 7; M. Wimmer, None; A. Nair, None; L. E. Thorp, None; L. F. Fogg, None; J. A. Block, None; N. Shakoor, DIO and Dr. Comfort, 7.


Background/Purpose: Knee instability in the setting of osteoarthritis (OA) encompasses a spectrum of symptoms and phenomena, including a feeling of low overall confidence in the knees, low confidence that the knees will not buckle or give way (buckling confidence), actual episodes of buckling, and excessive frontal plane motion. Current treatment for knee OA does little to address instability. Given the central role of the knee in weightbearing activity, confidence and buckling in particular may influence nature and intensity of activity, and could be important proximal factors in a chain of events leading to function decline and disability. It is unclear whether these factors are more important to outcome than instability objectively measured during gait. We hypothesized that overall confidence, buckling confidence, buckling, and excessive frontal plane motion during gait are each associated with poor 2-year function outcome.

Methods: Persons with OA in at least one knee were queried at baseline about overall knee confidence using the KOOS question (how troubled are you by the lack of confidence in your knees, higher worse), buckling confidence (i.e., confidence that knees will not buckle or give way, higher better), and any knee buckling in the past 3 months, and underwent quantitative gait analysis (3-dimensional knee kinematics and kinetics during ambulation recorded using an 8-camera Digital Real-Time Eagle motion analysis system, and 6 AMTI force plates). Physical function was assessed using the Late-Life Function Instrument – Advanced Lower Extremity Domain scaled score; quintiles were used to categorize these scores into groups. Poor outcome was defined as moving into a worse function group or remaining in the 2 worst function groups between baseline and 2 years. Logistic regression was used to evaluate the relationship between baseline instability measures, knee confidence and poor baseline-to-2-year function outcome, adjusting for potential confounders.

Results: 212 persons [163 (77%) women, mean age 65 (10, SD), BMI 28.5 (5.7) had a poor outcome. As shown in the Table, the buckling in the past 3 months, buckling confidence, and overall knee confidence, but neither varus-valgus excursion nor maximal varus-valgus angular velocity during gait were associated with the outcome in univariate analyses. In fully-adjusted models, these findings persisted (except for buckling confidence which
approached significance). Age and self-efficacy were also consistently associated with the outcome.

**Conclusion:** Worse baseline overall knee confidence and recent buckling, but neither varus-valgus excursion nor angular velocity using quantitative gait analysis were associated with greater risk of poor 2-year function outcome. Interventions to address confidence and buckling may improve outcome in knee OA.

| TABLE. Results from logistic regression models to evaluate associations of each instability variable with odds of a poor function outcome; unadjusted and adjusted odds ratios (OR) and associated 95% confidence interval (CI). 95% CIs that exclude 1 are statistically significant |
|----------------------------------|------------------|------------------|
| Instability variable (baseline) | Unadjusted OR (95% CI) | Fully adjusted* OR (95% CI) |
| Varus-valgus excursion during gait | 0.95 (0.85, 1.06) | 1.01 (0.89, 1.15) |
| Maximum varus-valgus angular velocity during gait | 0.99 (0.98, 1.01) | 0.99 (0.97, 1.01) |
| Buckling, past 3 months (yes/no) | 2.27 (1.28, 4.03) | 2.05 (1.01, 4.16) |
| Confidence knees will not buckle (higher better, continuous) | 0.63 (0.47, 0.85) | 0.68 (0.46, 1.01) |
| Overall knee confidence (higher worse, continuous) | 1.80 (1.27, 2.56) | 1.66 (1.02, 2.70) |

*adjusted for age, gender, BMI, pain (ICOAP), function self-efficacy, depressive symptoms, disease severity (K/L, worse of 2 knees), knee extensor strength (better of 2 knees)

**Disclosure:** L. Sharma, None; J. S. Chmiel, None; O. Almagor, None; K. Moisio, None; A. H. Chang, None; Y. Zhang, None; L. Belisle, None; K. W. Hayes, None.

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**External Hip Adduction Moment and Progression of Medial Tibiofemoral Cartilage Damage and Bone Marrow Lesions in Persons with Knee Osteoarthritis.** Kirsten Moisio1, Alison H. Chang1, Ali Guermazi2, Joan S. Chmiel1, Orit Almagor3, Potumarthi Prasad4, Yunhui Zhang1, Karen W. Hayes1, Laura Belisle1, Jamie Rayahin and Leena Sharma1.1Northwestern University, Chicago, IL, 2Boston University School of Medicine, Boston, MA, 3University of Illinois at Chicago, Chicago, IL.

**Background/Purpose:** Gait mechanics at the hip may affect medial joint loading at the knee in persons with knee OA. Greater external hip adduction moment (reflecting torque generation by hip abductor muscles) during gait may limit excessive hip drop or trunk lean. This, in turn, may prevent excessive medial knee joint loading and eventual progression of knee OA. Little is known about the relationship between hip adduction moment and progression of medial tibiofemoral OA by MRI. We hypothesized that greater baseline external hip adduction moment is associated with reduced risk of baseline-to-2-year progression of medial tibiofemoral cartilage damage and bone marrow lesions in persons with knee OA.

**Methods:** Participants with knee OA, defined by osteophyte presence in at least one knee, underwent quantitative gait analysis at baseline. Both knees underwent 3.0T MRI at baseline and two year follow-up using double oblique coronal and axial FLASHw, coronal T1weighted spin echo, and sagittal, axial and coronal fat suppressed turbo spin echo sequences. Cartilage damage and bone marrow lesions assessed using WORMS, blinding readers to hypotheses and all other data. Logistic regression with GEE used to account for correlation between limbs, assess the association between baseline hip adduction moment and baseline-to-2-year cartilage damage progression and bone marrow lesion progression, defined as any worsening of score in medial compartment or joint surface. Analyses adjusted for gait speed, age, gender, and disease severity (K/L grade). Results reported as ORs and 95% CIs.

**Results:** 204 persons [64.2 years (±9.9), BMI 28.5 kg/m² (±5.7), 76.5% women] contributing 391 knees comprised the study sample. Mean hip adduction moment was 4.43 (±0.9) °BW*HT. Table I shows a greater hip adduction moment was significantly associated with reduced likelihood of cartilage damage progression in the medial tibiofemoral compartment and medial femoral surface. After adjustment for covariates, these associations were no longer significant. Table II shows means (SD) of the hip adduction moment at baseline for knees with/without cartilage damage and bone marrow lesion progression in specific subregions.

**Conclusion:** In persons with knee OA, greater hip adduction moment was associated with reduced likelihood of 2-year medial tibiofemoral cartilage damage progression and bone marrow lesion progression, but findings were no longer significant in adjusted analyses. The consistently protective direction of findings at compartment, joint surface, and subregional levels warrants further evaluation at longer follow-up.

| Table 1 Unadjusted and adjusted ORs (95% CIs) for medial tibiofemoral OA progression at 2 years |
|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Cartilage damage progression | Bone marrow lesion progression | Cartilage damage progression | Bone marrow lesion progression | Cartilage damage progression | Bone marrow lesion progression |
| Number of knees (% with progression) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) |
| Medial Tibial Surface | Medial Femoral Compartment | Medial Femoral Compartment | Medial Femoral Compartment | Medial Femoral Compartment | Medial Femoral Compartment | Medial Femoral Compartment |
| Lateral femur | Lateral tibia | Lateral tibia | Lateral tibia | Lateral tibia | Lateral tibia | Lateral tibia |
| Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia |
| Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur |
| Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions |
| Number of knees (% with progression) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) |
| Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia |
| Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur |
| Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions |
| Number of knees (% with progression) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) |
| Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia | Medial tibia |
| Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur | Medial femur |
| Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions | Medial femoral subregions |

Results are per 1 unit (%BW*HT) of external hip adduction moment (n=391 knees from 204 persons)

*adjusted for gait speed, age, gender, and K/L grade

**Disclosure:** K. Moisio, None; A. H. Chang, None; A. Guermazi, Shareholder of Boston Imaging Core Lab LLC; J. S. Chmiel, None; O. Almagor, None; P. Prasad, None; Y. Zhang, None; K. W. Hayes, None; L. Belisle, None; J. Rayahin, L. Sharma, None.
The Relationship of Quadriceps and Hamstrings Intramuscular Fat and Lean Muscle with Power in Women with Knee Osteoarthritis.

Michael J. Davison, Monica R. Maly, Karen A. Beattie, Peter J. Keir and Jonathan D. Adachi.

Background/Purpose: Reduced quadriceps and hamstrings strength is a risk factor for knee osteoarthritis (OA). This strength loss is partly due to the loss of lean muscle mass, increased pain and neuromuscular inhibition. Intramuscular fat, or fat within a muscle belly, is related to poor physical performance and radiographic disease progression in OA. We investigated the relationship between intramuscular fat fraction and muscular strength and power in women with knee OA.

Methods: Women (n=20) with radiographic and symptomatic knee OA had the thigh of their most symptomatic knee imaged using 3T magnetic resonance imaging (MRI). The iterative decomposition of water and fat with echo asymmetric and least-squares estimation (IDEAL) sequence obtained 60 fat-separated images (3 mm slice thickness). Images were analyzed using SlicerOMatic® software with a region-growing algorithm to quantify intramuscular fat and lean muscle tissue volumes (cm³) separately for the quadriceps and hamstrings (Figure 1). Intramuscular fat was represented as a fraction (%) of total muscle volume. Using a dynamometer, participants completed ten isotonic knee extensions and flexions, with resistance at 20% of maximum voluntary isometric contraction. Mean peak power (W or N×m/s) was calculated using the five highest contractions. Electromyography (EMG) measured the activation of the vastus lateralis and biceps femoris during contractions. Mean peak EMG amplitude was calculated from the five highest activations.

Results: Mean sample characteristics (±SD): age 65±5 yrs; Body Mass Index (BMI) 30±5 kg/m². There was a positive relationship between quadriceps lean muscle volume and knee extensor power (B=0.634; p=0.004), controlling for vastus lateralis activation. Also, there was a positive relationship between hamstrings lean muscle volume and knee flexor power (B=1.173; p=0.010), controlling for biceps femoris activation. No relationships were found between quadriceps or hamstrings intramuscular fat fractions and isolated knee extensor (B=+4.351; p=0.764) or knee flexor (B=−4.793; p=0.645) power, respectively.

Conclusion: Quadriceps muscle, blue=hamstrings muscle, cyan=quadriceps intramuscular fat, orange=hamstrings intramuscular fat.

Disclosure: M. J. Davison, None; M. R. Maly, None; K. A. Beattie, None; P. J. Keir, None; J. D. Adachi, None.

Conclusion: Hip adiposity, not local knee adiposity, was associated with knee pain independent of radiographic OA severity. These findings suggest that local adiposity may not have a clinically relevant influence on knee pain.

Methods: Participants (n=197) completed ten isotonic knee extensions and flexions, with resistance at 20% of maximum voluntary isometric contraction. Mean peak power (W or N×m/s) was calculated using the five highest contractions. Electromyography (EMG) measured the activation of the vastus lateralis and biceps femoris (EMG) measured the activation of the vastus lateralis and biceps femoris. Vastus medialis (VM) muscle surface has been studied. Importantly, % Fat change was independently associated with bone marrow lesion change at 2 years (p=0.007), controlling for KL Grade, BMI and age.

Results: Females (p=0.001), higher BMI (p=0.008), and disability (p=0.040) were associated with both a higher baseline VM surface area and % Fat. Higher baseline VM area was associated with greater cartilage volume loss in the medial compartment, medial femur, and lower cartilage volume loss in the lateral plateau (all p≤0.048). Change in % Fat, but not in surface area, was associated with an increase in the bone marrow lesion score in the global knee and cartilage volume loss in the global knee, lateral compartment, lateral femur, and medial plateau (all p≤0.035). Multivariate analyses revealed correlations between % Fat, but not surface area, and cartilage volume loss in the local knee (p=0.011) and most subregions studied. Importantly, % Fat change was independently associated with bone marrow lesion change at 2 years (p=0.001). All of the above changes were found irrespective of the treatment the patients had during the clinical trial.
Conclusion: This study is the first to demonstrate that the % Fat in the VM is strongly associated with cartilage volume loss and the presence and progression of bone marrow lesions. Importantly, two different OA phenotypes were evidenced: i) low VM area phenotype comprising female patients with lower BMI, being more symptomatic at baseline, having more cartilage volume damage at baseline, and at 2 years less cartilage volume loss in the medial femur and more cartilage volume loss in the lateral plateau; ii) higher VM % Fat phenotype comprises female patients with higher BMI, having more disability at baseline, more cartilage volume damage at baseline, and at 2 years more cartilage volume loss in the medial plateau and lateral femur.

Reference:

Disclosure: J. Martel-Pelletier, ArthroLab, 9; J. P. Raynaud, ArthroLab, 5; F. Abram, ArthroLab, 3; M. Dorais, ArthroLab, 5; Y. Wang, None; J. Fairley, None; F. Cicutti, None; J. P. Pelletier, ArthroLab, 9.

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DXA Body Composition, Sarcopenia and Knee and Hip Osteoarthritis: Results from the Khoala Cohort.

Background/Purpose: Obesity is a well known risk factor for the development and progression of knee osteoarthritis (OA), and to a lesser extent of hip OA. However, types of obesity and body composition abnormalities could have different impact on OA severity. Body composition has rarely been studied in hip OA and has never been compared to knee OA.

The purpose of this study was to analyze the associations between body composition and sarcopenia and OA location and severity (clinical and structural), in patients with symptomatic hip and/or knee OA.

Methods: Skeletal muscle and fat mass were measured using dual X-ray absorptiometry (DXA) in a subset of the Knee and Hip Osteoarthritis Long term assessment (KHOALA) cohort.

Skeletal muscle mass index (SMI) was defined as appendicular skeletal muscle mass (ASM) / body weight. The SMI cutoff values used for sarcopenia were 26.8% for men and 21.0% for Women.

Pain and function were measured by WOMAC index and quality of life (QoL) by SF36. Structural severity was graded on X-Ray according to Kellgren and Lawrence’s classification.

Results: A DXA was performed in 381 patients among the 878 patients included in the cohort: women 254 (66.7%), mean (STD) age 63.6 (8.4), Hip OA 91 (23.9%), knee OA 267 (70.1), obesity 146 (38.8%), sarcopenia 105 (27.6%).

Associations between joint and OA severity according to body composition group are presented in table.

<table>
<thead>
<tr>
<th>Joint</th>
<th>Normal body composition</th>
<th>Non obese patients with sarcopenia</th>
<th>Obese patients without sarcopenia</th>
<th>Obese patients with sarcopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>N=228 (N %)</td>
<td>N=25 (9.8)</td>
<td>N=17 (7.5)</td>
<td>N=5 (2.2)</td>
</tr>
<tr>
<td>Knee</td>
<td>N=256 (99.2)</td>
<td>N=25 (9.8)</td>
<td>N=17 (6.7)</td>
<td>N=5 (2.0)</td>
</tr>
<tr>
<td>Hip and knee</td>
<td>N=256 (99.2)</td>
<td>N=25 (9.8)</td>
<td>N=17 (6.7)</td>
<td>N=5 (2.0)</td>
</tr>
</tbody>
</table>

% of patients with normal body composition, non-obese and sarcopenia.

Conclusion: Impact of OA on pain, function and QoL was not different between obese patients and patients with sarcopenia and normal BMI. Impact of OA was worse in obese patients with or without sarcopenia than in patients with normal body composition.


Disclosure: C. Jeannaire, None; I. Chary-Valkenaere, None; D. Louelle, None; L. Bernard, None; A. C. Rat, None.

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Lower Extremity Presarcopenia Is Associated with the Severity of Knee Pain.

Background/Purpose: Presarcopenia, which is defined as skeletal muscle mass loss, and knee pain have been gained attention with ageing. Little is known about the association of lower extremity presarcopenia (LEPS) and severity of knee pain. Thus, this study was conducted to the relationship between severity of self-reported knee pain and LEPS.

Methods: From the 5th Korean National Health and Nutrition Examination Survey (KNHINES VI–2, n=17,476), the data of 721 participants, who underwent dual x-ray absorptiometry (DXA) and bilateral knee plain radiographs, and complained knee pain were analyzed. LEPS was defined as a lower extremity skeletal muscle mass index below -2SD of the value in sex-matched young reference groups. Participant were categorized into 4 groups: normal, LEPS, non-LEPS with obesity (NLEPSO), LEPS with obesity (LEPSO).

Results: LEPS and LEPSO are significantly associated with the severity of knee pain (LEPS 6.9±0.4, LEPSO 7.2±0.5, P<0.05). These results did not change after adjusting for various confounding factors. In participants with non-radiographic knee OA (n=268), the severity of knee pain was related with LEPS (7.2±0.6, P<0.05). In radiographic knee OA participants (n=452), LEPSO was related with severity of knee pain (7.3±0.5, P<0.05). Sex, smoking status, osteoporosis, and vitamin D levels were not related with the severity of self-reported knee pain.

Conclusion: LEPS is directly associated with severity of knee pain. This attribution supports increasing muscle mass is very important to reduce knee pain. Thus, early detection of LEPS may help physicians to detect pain-sensitive LEPS patients who can benefit from early intervention such as exercise.

Disclosure: Y. H. Cheon, None; W. H. Yoo, None; Y. S. Suh, None; H. O. Kim, None; K. S. Park, None; S. I. Lee, None; H. J. Jeon, None.

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Background/Purpose: Simple measurement of age-related loss of skeletal muscle mass (ASM) and its relationship with osteoarthritis (OA) in a Korean population was performed.

Methods: All the subjects who visited Yeungnam University Hospital Health Promotion Center between 2008 and 2012 in order to undergo a routine medical examination, including BIA, were enrolled. BMI was calculated using the Cunningham equation, BMI = weight/height^2 (kg/m^2), SMI as ASM/body mass *100 (%), and PBF as FM/body mass *100 (%). The body components were evaluated by BIA using InBody 720 (Biospace, Seoul, Korea). A total of 522 knees with antero-posterior X-rays from 381 subjects in the population were enrolled in this study. The presence and severity of
bony changes for OA were measured and graded twice according to the Kellgren-Lawrence (K/L) grade.

**Results:** The mean and SD of SMI, BMI, and PBF in healthy subjects aged 18 to 39 (total of 5,723 subjects; 2,059 males, 2,674 females) are shown at Table 1-1. Table 1-2 revealed characteristics and BIA parameters of this study population. Negative correlation was observed between SMI and age (r = -0.157, p < 0.01), which was more prominent in females (r = -0.313, p < 0.01) than in males (r = -0.164, p < 0.001) (Table 2). Members of the population aged over 50 showed a significant decrease of SMI (r = -0.166, p < 0.01). The population over 50 years of age showed a significant increase of PBF as compared with that of the population under 50 (r = 0.117, p = 0.125, p < 0.01).

A cross-tab analysis was done according to sarcopenia classification and body composition by PBF in the aspect of K/L grades (Table 3-1). Knees with sarcopenia class I and class II, and obesity showed a trend toward the higher K/L grade in the higher sarcopenia class and sarcopenic obesity (p = 0.01). Results of logistic regression analysis between SMI and K/L grade showed a significantly high incidence of a higher K/L grade in subjects with a lower SMI, and significantly high incidence of a lower K/L grade was observed in those with a higher SMI (p < 0.01) (Table 3-2).

**Conclusion:** This study provides evidence that sarcopenia and sarcopenic obesity are correlated with development of and progression to severe OA. Thus, the results of this study may indicate interactive correlation of SMI and PBF as age-related alteration of body composition with age related OA.

---

Table 1-1. Reference values for the classification of sarcopenia from a sex-matched, healthy Korean population aged between 18 and 39 years

<table>
<thead>
<tr>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>BIA (Normalized)</th>
<th>SMI (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20.6 ± 2.4</td>
<td>71.9 ± 10.5</td>
<td>11.8 ± 2.0</td>
</tr>
<tr>
<td>Female</td>
<td>21.3 ± 2.5</td>
<td>77.0 ± 15.6</td>
<td>12.1 ± 2.1</td>
</tr>
</tbody>
</table>

Table 2. Correlations and regression analyses of SMI and PBF with age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>SMI</th>
<th>PBF</th>
<th>BMI</th>
<th>SMI</th>
<th>PBF</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.85</td>
<td>0.88</td>
<td>0.92</td>
<td>0.86</td>
<td>0.86</td>
<td>0.92</td>
</tr>
<tr>
<td>20-60</td>
<td>0.80</td>
<td>0.84</td>
<td>0.85</td>
<td>0.78</td>
<td>0.78</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 3-1. Cross-tab analysis between the classification of sarcopenia and obesity and the K/L grade of the knee joints

<table>
<thead>
<tr>
<th>K/L grade</th>
<th>SMI classification</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>normal</td>
<td>100.0</td>
</tr>
<tr>
<td>1</td>
<td>normal</td>
<td>94.2</td>
</tr>
<tr>
<td>2</td>
<td>normal</td>
<td>89.2</td>
</tr>
<tr>
<td>3</td>
<td>normal</td>
<td>85.4</td>
</tr>
</tbody>
</table>

Table 3-2. Logistic regression analyses of SMI and PBF with the K/L grade of the knee joints

<table>
<thead>
<tr>
<th>K/L grade</th>
<th>SMI</th>
<th>PBF</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.85</td>
<td>0.88</td>
<td>0.92</td>
</tr>
<tr>
<td>1</td>
<td>0.80</td>
<td>0.84</td>
<td>0.85</td>
</tr>
</tbody>
</table>

---

**Disclosure:** H. Kim, None; M. Kim, None; C. K. Lee, None; Y. H. Hong, None.


**Background/Purpose:** Osteoarthritis (OA) is a heterogeneous disorder, with several possible drivers of disease progression. Up to 50% of OA patients do not structurally progress, emphasizing the importance for identification of fast progressors, and the phenotypes associated with that. There is therefore a medical need for in-depth, post-hoc analysis of clinical studies in OA. The aim of the analysis was to investigate the associations between JSW, K/L-score, pain and JSN (joint space narrowing), as well as BMI, by combining data from two phase III studies (N=2,206) to identify key characteristics for disease progression.

**Methods:** This is a post-hoc analysis of two randomized, double-blind, multi-center, placebo-controlled trials NCT00486434 and NCT007004847 evaluating the efficacy and safety of 2-years treatment with oral salmon calcitonin in subjects with painful knee OA, enrolling 1,176 and 1,030 subjects. The analysis includes baseline data on KL-score, JSW, pain and function scores from the WOMAC questionnaire, as well as demographics.

**Results:** Diagnostic measures: At baseline, combined analysis of signal and non-signal knees, the mean JSW was comparable in knees of KL-0 and -1 and significantly decreased with increasing KL-2, -3 and -4 (p < 0.001). JSW (KL2/3) was significantly lower in the non-target knees as compared to the target knees (3.32 ± 0.03 mm vs. 3.42 ± 0.02 mm, p < 0.0001, mean ± SEM). There was a clear positive and significant correlation between KL-score and WOMAC pain and total WOMAC, albeit the variance in pain measures was from min-to-max for all K/L-scars, and investigating the homogeneity of this patient population and pain perception. Diagnostic measures; 32% of target knees did not progress, and only 51% had changes over minimum significant change (MSC). Only minor differences were observed between target and non-target and KL-2 versus KL-3. The mean JSN at 2-years for the non-target knee was 0.25 ± 0.02 mm and 0.32 ± 0.02 mm for the target knee (p < 0.001). Patients were stratified in quartiles for WOMAC pain and BMI, as well as WOMAC pain and KL-score, and investigated for JSN. Q3 WOMAC pain progressed more than Q2 and Q4 in both scenarios.

**Conclusion:** These data from the largest clinical trial dataset in OA to date clearly describe significant associations between KL-score, JSW, pain in BMI with symptomatic knee OA. 50% of patients did not progress.
more than MSC, highlighting the importance for identification of structural progressors and the phenotypes associated with these patients with symptomatic OA at baseline progressed significantly faster than patients with asymptomatic disease, however with important variations that need accounting for when designing clinical trials, such as relations to pain, BMD and JSN. Different levels of progression were observed in relation to KL score and pain, in which the third WOMAC pain quartile (Q3), but not the fourth quartile (Q4), progressed significantly faster than the first and second pain quartiles. These results suggest that disease phenotypes rather than disease status are responsible for disease progression. Consequently, this dataset is ideally suited for identification of different phenotypes of OA, and biomarkers associated with those.

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 3; A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 1; A. Bihlet, Nordic Bioscience Diagnostic, 1; P. Alexandersen, CCBR, 3; I. Byrjalsen, Nordic Bioscience Diagnostic, 3; B. J. Riis, Nordic Bioscience Diagnostic, 1; C. Christiansen, Nordic Bioscience Diagnostic, 1.

ACR Poster Session A
Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis: Osteoporosis - Pathogenesis, Epidemiology and Diagnosis
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Risk Factors for Clinical Vertebral Fractures in Japanese Men and Women with Rheumatoid Arthritis: Results from a Large Prospective Observational Cohort Study. Osamu Ishida1, Taketori Fuyuta1, Etsuko Inoue2, Kenseki Ochi1, Katsunori Ikari1, Atsuo Taniguchi2, Hitoshi Yamakawa3 and Shigeki Momohara2.

Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 2Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at high risk of developing vertebral fractures. Previously, utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, we reported clinical risk factors for clinical vertebral fractures in Japanese patients with RA. However, in our previous studies, which analyzed data from 2000 to 2005, the number of patients with verified clinical vertebral fractures was only 40. The aim of this study was to re-evaluate the associations between potential risk factors and the occurrence of clinical vertebral fractures in a larger number of Japanese patients with RA.

Methods: IORRA is a prospective observational cohort study of Japanese patients with RA established in 2000 at the Institute of Rheumatology, Tokyo Women’s Medical University. A total of 10,240 Japanese patients with RA (82% female; mean age, 56 years) were enrolled in IORRA cohort study from 2000 to 2011. Self-reported vertebral fractures were verified with patient medical records and radiographs. Independent contributions of various risk factors to clinical vertebral fracture occurrence were analyzed with Cox proportional hazards models.

Results: During a mean follow-up of 4.9 years, 399 patients reported 638 clinical vertebral fractures. Among these patients, 187 clinical vertebral fractures in 187 patients (18 men, 169 women) were verified with medical records (n = 95) and radiographs (n = 92). The vertebral fractures were mainly caused by spontaneous events (65%) and falls (25%). Vertebral fractures occurred at lumbar (36%), thoracic (37%), and both (27%) levels of the spine. In men with RA, multivariate Cox regression analyses estimated that the risk of sustaining a clinical vertebral fracture increased by 2.51 for every 10 years of increased age, 1.26 for daily prednisolone dose (Table 1). In women with RA, multivariate Cox regression analyses estimated that the risk of sustaining a clinical vertebral fracture increased by 2.51 for every 10 years of increased age, 1.26, 95% confidence interval [CI] 1.02–1.54).

History of any prior fracture 1.32 (0.45–3.81) 2.35 (1.69–3.27)
Age, per 10 years 2.51 (1.34–4.73) 1.67 (1.42–1.97)
History of any prior vertebral fracture 2.96 (1.02–9.60) 1.39 (0.81–2.39)
Daily prednisolone dose, mg/day 1.17 (1.06–1.29) 1.08 (1.05–1.12)

Conclusion: Our study aims to investigate if variations of proximal femur shape associated with BMI are associated with hip fracture risk, independent of BMD, in a large population of women aged over 50 years.

Methods: Data of women aged over 50 years that attended for a DXA scan at a UK hospital were collated. The following Hip Structural Analysis (HSA) measurements were used to characterise the shape of the proximal femur: distance from centre of femoral head to centre of femoral neck (d1), distance from centre of femoral head to inter-trochanteric line (d2), mean femoral neck diameter (d3), distance from centre of mass of femoral neck to superior neck margin (y), hip axis length (HAL), cross-sectional moment of inertia (CSMI) and the neck/shaft angle. Multiple regression analysis was used to investigate for associations between BMI and each HSA measure.

Results: Data of 8,788 women was analysed. Analysis revealed that a wider (d3, y) and shorter (d1) femoral neck with increased cortical thickness (d2), CSMI and the neck/shaft angle were associated with a clear significant relationship with increasing BMI (tables 1 and 2). Further analysis revealed that proximal femur shape was not significantly associated with previous contralateral hip fracture and each HSA measurement, adjusted for age, BMI, femoral neck BMD and significant osteoporosis risk factors.

Conclusion: This study of a large population of older women identified that a wider and shorter femoral neck with increased cortical thickness was associated with increasing BMI; however, variations of proximal femur shape associated with BMI were not associated with previous hip fracture status.

Background/Purpose: The association between increasing body mass index (BMI), increasing bone mineral density (BMD) and lower hip fracture risk has been demonstrated by previous research. Studies have implicated variations of proximal femur shape in hip fracture risk. Research has indicated that BMI affects hip fracture risk by its associations with both BMD and proximal femur shape. This study aims to investigate if variations of proximal femur shape associated with BMI are associated with hip fracture risk, independent of BMI, in a large population of women aged over 50 years.

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Conclusion: This study of a large population of older women identified that a wider and shorter femoral neck with increased cortical thickness was associated with increasing BMI; however, variations of proximal femur shape associated with BMI were not associated with previous hip fracture status.

Table 1 Hazard ratios (95% confidence interval) for the occurrence of clinical vertebral fractures in Japanese men and women with RA: Multivariate analyses.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.51 (1.34–4.73)</td>
<td>1.67 (1.42–1.97)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.26 (1.02–1.54)</td>
<td>1.39 (0.81–2.39)</td>
</tr>
<tr>
<td>History of any prior vertebral fracture</td>
<td>2.96 (1.02–9.60)</td>
<td>1.39 (0.81–2.39)</td>
</tr>
<tr>
<td>Daily prednisolone dose, mg/day</td>
<td>1.17 (1.06–1.29)</td>
<td>1.08 (1.05–1.12)</td>
</tr>
</tbody>
</table>

Background/Purpose: The association between increasing body mass index (BMI), increasing bone mineral density (BMD) and lower hip fracture risk has been demonstrated by previous research. Studies have implicated variations of proximal femur shape in hip fracture risk. Research has indicated that BMI affects hip fracture risk by its associations with both BMD and proximal femur shape. This study aims to investigate if variations of proximal femur shape associated with BMI are associated with hip fracture risk, independent of BMI, in a large population of women aged over 50 years.

Methods: Data of women aged over 50 years that attended for a DXA scan at a UK hospital were collated. The following Hip Structural Analysis (HSA) measurements were used to characterise the shape of the proximal femur: distance from centre of femoral head to centre of femoral neck (d1), distance from centre of femoral head to inter-trochanteric line (d2), mean femoral neck diameter (d3), distance from centre of mass of femoral neck to superior neck margin (y), hip axis length (HAL), cross-sectional moment of inertia (CSMI) and the neck/shaft angle. Multiple regression analysis was used to investigate for associations between BMI and each HSA measurement, adjusted for age, femoral neck BMD and significant osteoporosis risk factors.

Results: Data of 8,788 women was analysed. Analysis revealed that a wider (d3, y) and shorter (d1) femoral neck with increased cortical thickness (d2), CSMI and the neck/shaft angle were associated with a clear significant relationship with increasing BMI (tables 1 and 2). Further analysis revealed that proximal femur shape was not significantly associated with previous contralateral hip fracture and each HSA measurement, adjusted for age, BMI, femoral neck BMD and significant osteoporosis risk factors.

Conclusion: This study of a large population of older women identified that a wider and shorter femoral neck with increased cortical thickness was associated with increasing BMI; however, variations of proximal femur shape associated with BMI were not associated with previous hip fracture status.
but also in subjects presenting a BMI higher than 25 kg/m² compared to the others (r = 0.44 versus r = 0.32 respectively), in subjects spending at least 100 kcal/week for their leisure time activity (i.e. Minnesota test) compared to the others (r = 0.44 versus r = 0.28).

Conclusion: A positive association was found between LM and hip BMD. Strategies aiming to increase lean body mass in subjects aged 65 years or older could be of great public health interest in the field of bone health.

Disclosure: C. Beaudart, None; J. Y. Regnier, None; J. Slomian, None; F. Buckinx, None; O. Bruyere, None.

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Improved Prediction of Hip Fracture Using the Health Assessment Questionnaire-Disability Index and FRAX® in Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Study. Takefumi Furuuya1, Eisuke Inoue2, Kenzuke Ochi1, Osamu Ishida1, Atsuo Taniguchi2, Eisuke Kobayashi1, Miki Tagawa1, Atsushi Taniguchi1, Nippom Kanayu, Pfizer, Saitama, Japan, 2Tohoku University, Sendai, Japan, 3University of the Ryukyus, Naha, Japan, 4University of Occupational and Environmental Health, Kitakyushu, Japan, 5Chiba University, Chiba, Japan, 6Osaka City University, Osaka, Japan, 7University of Tokyo, Tokyo, Japan, 8Japanese Society for Bone and Mineral Research, Tokyo, Japan.

Background/Purpose: Low body mass index (BMI) is a known risk factor for loss of bone mineral density (BMD). It is a part of the FRAX™ 10-year fracture risk stratification tool developed by the World Health Organisation. It is also known that weight loss through dieting decreases BMD, whilst weight loss through exercise preserves it. The effects of fat-mass and change in fat-mass have not been examined extensively. This could have implications for health advice given to those at significant risk of fragility fractures. This study aimed to identify factors influencing change in bone density related to fat-mass and any confounders.

Methods: Data were analysed from patients having dual-energy X-ray absorptiometry (DXA) assessment between 2007 and 2010. Patients were included if they had multiple scans which included measurements of lean mass and fat mass. Our scanners limited these to scans of the AP spine. Linear regression was performed to determine the relationship between changes in fat mass and BMD. A backwards stepwise linear regression model was fitted with inclusion of confounders including: sex, risk factors, previous fractures, baseline BMI and age at menopause.

Results: 23,239 patients were included in the study, of which 702 met our inclusion criteria. This included 93 males (13%) and 609 females (87%). Mean age at first scan in the whole cohort was 64.5 years (SD11.2). The mean interval between scans was 3.0 years (SD 0.89). Step-wise linear regression identified a positive correlation between increasing fat-mass and t-score per unit time between scans (coefficient 28.4, p<0.01 95%CI 26.6–30.1). Controlling for the above factors didn’t alter the results. We identified previous pelvic and femur fractures (p<0.05) and history of inflammatory diseases (p<0.05) as independent risk factors influencing bone density related to fat mass. This relationship was true for patients that were underweight (BMI <18.5), normal weight (BMI 18.5–25), and overweight patients (BMI >25).

Conclusion: Increasing fat mass between DEXA scans is associated with an increase in t-scores. Other factors associated with increasing fat-mass include previous pelvic and femur fractures, as well as history of inflamma-

Table 1 – BMI categories and mean age, number of OP risk factors, mean femoral neck BMD, proportion that have previously sustained a hip fracture and mean HSA measurements

<table>
<thead>
<tr>
<th>HSA measurement</th>
<th>Coefficient against BMI</th>
<th>p-value</th>
<th>Coefficient against previous hip fracture</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLS/unit (SD)</td>
<td>0.02</td>
<td>0.764</td>
<td>0.06</td>
<td>0.61</td>
</tr>
<tr>
<td>CSA/unit² (SD)</td>
<td>0.07</td>
<td>0.02</td>
<td>0.00</td>
<td>0.78</td>
</tr>
<tr>
<td>CSA/unit² (SD)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
<td>0.45</td>
</tr>
<tr>
<td>d1/mm (SD)</td>
<td>0.15</td>
<td>0.01</td>
<td>0.20</td>
<td>0.21</td>
</tr>
<tr>
<td>d2/mm (SD)</td>
<td>0.01</td>
<td>0.26</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>d3/mm (SD)</td>
<td>0.13</td>
<td>0.01</td>
<td>0.54</td>
<td>0.66</td>
</tr>
<tr>
<td>y/mm</td>
<td>0.32</td>
<td>0.01</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Neck/shaft angle*</td>
<td>0.01</td>
<td>0.24</td>
<td>0.30</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 2 – coefficient and p-value of each HSA measurement against BMI, adjusted for age, number of OP risk factors and femoral neck BMD; coefficient and p-value of each HSA measurement against previous hip fracture, adjusted for age, number of OP risk factors, BMI and femoral neck BMD

Disclosure: A. Oldroyd, None; M. Bukhari, None.

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Background/Purpose: Fat mass and lean mass (LM) represent 95% of body weight. However, the role of each component on bone mineral density (BMD) is not clear. In this study, we aimed to investigate the correlation between LM mass and hip BMD.

Methods: Voluntary subjects aged 65 years or older were recruited in an outpatient clinic in Liège, Belgium. Hip BMD as well as LM were measured by dual X-ray absorptiometry.

Results: 123 subjects were recruited for this study (88.5% of women, mean age 74.6 ± 6.4 years). LM was positively correlated with hip BMD (r = 0.40; p<0.001). In a multiple regression analysis adjusted for sex, age, body mass index (BMI), physical activity, alcohol and tobacco consumption and presence of prior fracture, this relationship was still significant (b = 0.35; p = 0.02). In line with this result, we found a higher correlation between LM and hip BMD in men than in women (r = 0.60 versus r = 0.32 respectively), but also in subjects presenting a BMI higher than 25 kg/m² compared to the others (r = 0.51 versus r = 0.09), in subjects aged between 65 years and 80 years compared to older (r = 0.38 versus r = 0.29) and in subjects spending at least 100 kcal/week for their leisure time activity (i.e. Minnesota test) compared to the others (r = 0.44 versus r = 0.28).

Conclusion: A positive association was found between LM and hip BMD. Strategies aiming to increase lean body mass in subjects aged 65 years or older could be of great public health interest in the field of bone health.

Disclosure: C. Beaudart, None; J. Y. Regnier, None; J. Slomian, None; F. Buckinx, None; O. Bruyere, None.

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Increasing Fat-Mass May Reverse Bone Loss As Detected By DXA Scan. William Hedges1 and Marwan Bukhari2. 1Royal Lancaster Infirmary, University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, United Kingdom, 2Lancaster University, Lancaster, United Kingdom.

Background/Purpose: Low body mass index (BMI) is a known risk factor for loss of bone mineral density (BMD). It is a part of the FRAX™ 10-year fracture risk stratification tool developed by the World Health Organisation. It is also known that weight loss through dieting decreases BMD, whilst weight loss through exercise preserves it. The effects of fat-mass and change in fat-mass have not been examined extensively. This could have implications for health advice given to those at significant risk of fragility fractures. This study aimed to identify factors influencing change in bone density related to fat-mass and any confounders.

Methods: Data were analysed from patients having dual-energy X-ray absorptiometry (DXA) assessment between 2007 and 2010. Patients were included if they had multiple scans which included measurements of lean mass and fat mass. Our scanners limited these to scans of the AP spine. Linear regression was performed to determine the relationship between changes in fat mass and BMD. A backwards stepwise linear regression model was fitted with inclusion of confounders including: sex, risk factors, previous fractures, baseline BMI and age at menopause.

Results: 23,239 patients were included in the study, of which 702 met our inclusion criteria. This included 93 males (13%) and 609 females (87%). Mean age at first scan in the whole cohort was 64.5 years (SD11.2). The mean interval between scans was 3.0 years (SD 0.89). Step-wise linear regression identified a positive correlation between increasing fat-mass and t-score per unit time between scans (coefficient 28.4, p<0.01 95%CI 26.6–30.1). Controlling for the above factors didn’t alter the results. We identified previous pelvic and femur fractures (p<0.05) and history of inflammatory diseases (p<0.05) as independent risk factors influencing bone density related to fat mass. This relationship was true for patients that were underweight (BMI <18.5), normal weight (BMI 18.5–25), and overweight patients (BMI >25).

Conclusion: Increasing fat mass between DEXA scans is associated with an increase in t-scores. Other factors associated with increasing fat-mass include previous pelvic and femur fractures, as well as history of inflamma-

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tory disease. However, excessive fat-mass is associated with increased cardiovascular (CVD) and metabolic disease states. Increasing fat-mass is therefore not viable for all patients. Those at particular risk of fragility fractures and not CVD, e.g. BMI<18.5, may be able to improve their long-term risk by gaining weight.

Disclosure: W. Hedges. None; M. Bukhari. None.

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Is Adult Hypophosphatasia a Cardiovascular Risk Factor? Leyre Riancho-Zarrabeitia1, María T. García-Unzueta1, Alfonso Corrales1, Juan Gómez-Gerique1 and José A. Riancho2. 1Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, 2Hospital Universitario Marqués de Valdecilla. IDIVAL. University of Cantabria, Santander, Spain.

Background/Purpose: Mild forms of adult hypophosphatasia may have subtle manifestations, and may go unrecognized. The aim of this study was to get a better knowledge of its clinical spectrum.

Methods: We performed a computerized search of low total alkaline phosphatase among laboratory records. The diagnosis of hypophosphatasia was confirmed by measuring serum pyridoxal phosphate (PLP) and bone alkaline phosphatase. Carotid ultrasonography was performed in patients and controls with a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7–12 MHz linear transducer.

Results: Over a 31 month period, we identified 130 individuals with at least one determination of serum alkaline phosphatase less than 26 u/l. After reviewing the clinical records, unexplained persistently low levels were found in 42 individuals who accepted to participate in the study (10 men, 32 women). Age range was 20–77 yr (mean 51). Total alkaline phosphatase levels were positively correlated with bone alkaline phosphatase (r=0.52, p<0.001). Serum PLP was inversely correlated with bone alkaline phosphatase. Ten individuals (24%) had PLP levels above the reference range of 175 nmol/l, consistent with hypophosphatasia. In comparison with those with normal PLP levels, these individuals had higher frequency of hypertension (50 vs 12%, p=0.02). Likewise, individuals with hypophosphatasia showed a trend to have early atherosclerotic disease. Carotid ultrasound showed bilateral plaques in 4 out of 9 patients (44%), and only in 20% of the age and sex-matched controls. The intima-media thickness also tended to be increased in the patients (670±70 vs. 648±110 microns; p=0.18).

Conclusion: These preliminary data suggest that individuals with adult hypophosphatasia may be at increased cardiovascular risk. The results should be confirmed in larger studies.


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Correlates of Heel Bone Mass in Young Adults: The Role of Cholesterol over 20 Years from Childhood to Early Adulthood. Benny Samuel Eathakkattu Antony1, Changhui Ding2, Alison Venn1, Terry Dwyer1 and Graeme Jones2. 1Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, 2Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia, 3Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, 4Murdoch Children’s Research Institute, Melbourne, Australia.

Background/Purpose: The association between lipids and bone mass in adult life is controversial and there is limited evidence in childhood. The aim of this study was to describe the association between cholesterol measured in childhood and young adult life and bone mineral density (BMD) in younger adults.

Methods: Subjects broadly representative of the Australian population (n=1431, female=52%, age=26–36) were selected from the Australian Schools Health and Fitness Survey of 1985. They underwent various measurements including leg strength, standing long jump, and physical work capacity at 170 heart beats per minute (PWC170). Physical activity, smoking and alcohol history were recorded using questionnaires. Fasting lipid profiles were assessed in childhood and 20 years later in adulthood. A single Sahara bone ultrasound densitometer was used to determine heel bone mass in adulthood.

Results: In multivariable analysis, childhood High Density Lipoprotein (HDL) was positively (β: 0.056 g/cm², 95% CI: 0.005, 0.108) and total cholesterol (TCH, normal Vs high β: -0.042 g/cm², 95% CI: -0.081, -0.003) and Low Density Lipoprotein (LDL, normal Vs high β: -0.019 g/cm², 95% CI: -0.039, 0.000) were negatively associated with BMD in adulthood. Similarly, adulthood TCH (β: -0.007 g/cm², 95% CI: -0.015, -0.001) and LDL (β: -0.011 g/cm², 95% CI: -0.019, -0.003) were negatively associated with adult life BMD. The association between childhood HDL and adulthood BMD remained significant after further adjustment for adulthood HDL levels. Subjects who remained in the abnormal category of TCH from childhood to adulthood (high-high) had the least bone mass compared to other category changes of TCH from childhood to adulthood.

These results were independent of gender, alcohol consumption and duration of follow-up from childhood to adulthood. The other confounders included in this analysis were independently associated with BMD, such as age (negative associated with BMD, β: -5.38 mg/cm² per year, 95% CI: -6.14, -1.01), physical activity (vigorous activity, β: 0.04 mg/cm² per min/week, 95% CI: 0.01, 0.08), BMI in childhood and adulthood (both positively associated with BMD) and smoking (β: -18.34 mg/cm², 95% CI: -27.35, -9.34). Duration and pack year of smoking were independently and negatively associated with BMD while performance measures including PWC170 (β: 0.33 mg/cm² per Watts, 95% CI: 0.15, 0.51), leg muscle strength (β: 0.24 mg/cm² per Kg, 95% CI: 0.02, 0.45) and long jump (β: 0.71 mg/cm² per cm, 95% CI: 0.40, 1.02) were positively associated with BMD.

Conclusion: HDL in childhood was beneficially and high TCH was detrimentally associated with adulthood BMD. LDL and TCH in adulthood were detrimentally associated with BMD. The effect of childhood HDL was independent of the adulthood HDL levels. These results indicate that cholesterol may have long-term effects on bone mass from childhood to early adulthood.
other risk factors such as glucocorticoid use, previous fragility fracture, family history of osteoporosis and rheumatoid arthritis. Furthermore we have shown that bone loss in the lumbar spine and the femoral neck could differ and this was not examined in the elderly.

The aim of this study was to establish which risk factors would predict BMD loss in the over 75 year old population in the lumbar spine and the femoral neck.

Methods: A cohort of patients referred between 2004 and 2011 to a DEXA (Dual Energy X-ray absorptiometry scan) service in the North West of England who over the age of 75 were identified. The sites of bone that were scanned for BMD loss were the L1-L4 vertebrae and the non dominant femoral neck. The risk factors collated included age, gender, BMI, current smoking, family history of osteoporosis, rheumatoid arthritis, current corticosteroid use, history of fragility fracture and current alcohol excess. A regression model was then fitted to determine predictors of BMD loss in those aged over 75. This was done at both the femoral neck and the lumbar spine adjusting for age and gender.

Results: 4,655 patients over the age of 75 were identified; the mean age of the cohort was 79.2 (SD 3.9), with 3732 (80%) females The following risk factors were found to be significantly associated with increased BMD loss in the hip when adjusted: weight with a beta coefficient of 0.004 (95% CI 0.003, 0.004), weight 0.005 (95% CI 0.004, 0.006), BMI 0.012 (95% CI 0.011, 0.013) and history of fracture 0.034 (95% CI -0.045, 0.023). The following risk factors were found to be significantly associated with increased bone loss in the lumbar spine after adjusting: height with a beta coefficient of 0.006 (95% CI 0.004, 0.007), weight 0.007 (95% CI 0.006, 0.0074), BMI 0.014 (95% CI 0.0135, 0.016), rheumatoid arthritis 0.036 (95% CI 0.007,0.06) and history of fragility fracture -0.05 (0.006, -0.04). Glucocorticoid use, tobacco use, alcohol use and family history of osteoporosis were not found to be associated.

Conclusion: Risk factors for increased BMD loss in patients over 75 years old were height, weight, BMI and history of fragility fracture in both the hip and the lumbar spine with rheumatoid arthritis being a risk factor for only the lumbar spine. The results from this study suggest that assessing bone health in the elderly is complex and assuming that risk factors do not change with age is not the case.

References

Disclosure: J. Fowler, None; C. Varley, None; A. Oldroyd, None; M. Bukhari, None.

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Factors Predicting Fracture in the over-75s: An Observational Case-Control Study. Christopher Varley1, James Fowler2, Alexander Oldroyd3 and Marwan Bukhari3. 1Lancaster University, Lancaster, United Kingdom, United Kingdom.

Background/Purpose: In the over 75s the diagnosis of osteoporosis may be assumed following a fracture, making the need for a dual energy X-ray absorptiometry scan (DEXA) optional. In those presenting without fracture, but with a history of osteoporosis, bone loss in the lumbar spine and the femoral neck could differ and this was not examined in the elderly.

Methods: A cohort of patients referred between 2004 and 2011 to a DEXA scan service in the North West of England who over the age of 75 were identified. The sites of bone that were scanned for BMD loss were the L1-L4 vertebrae and the non dominant femoral neck. The risk factors collated included age, gender, BMI, current smoking, family history of osteoporosis, rheumatoid arthritis, current corticosteroid use, history of fragility fracture and current alcohol excess. A regression model was then fitted to determine predictors of BMD loss in those aged over 75. This was done at both the femoral neck and the lumbar spine adjusting for age and gender.

Results: 4,655 patients over the age of 75 were identified; the mean age of the cohort was 79.2 (SD 3.9), with 3732 (80%) females The following risk factors were found to be significantly associated with increased BMD loss in the hip when adjusted: height with a beta coefficient of 0.004 (95% CI 0.003, 0.004), weight 0.005 (95% CI 0.004, 0.006), BMI 0.012 (95% CI 0.011, 0.013) and history of fracture 0.034 (95% CI -0.045, 0.023). The following risk factors were found to be significantly associated with increased bone loss in the lumbar spine after adjusting: height with a beta coefficient of 0.006 (95% CI 0.004, 0.007), weight 0.007 (95% CI 0.006, 0.0074), BMI 0.014 (95% CI 0.0135, 0.016), rheumatoid arthritis 0.036 (95% CI 0.007,0.06) and history of fragility fracture -0.05 (0.006, -0.04). Glucocorticoid use, tobacco use, alcohol use and family history of osteoporosis were not found to be associated.

Conclusion: Risk factors for increased BMD loss in patients over 75 years old were height, weight, BMI and history of fragility fracture in both the hip and the lumbar spine with rheumatoid arthritis being a risk factor for only the lumbar spine. The results from this study suggest that assessing bone health in the elderly is complex and assuming that risk factors do not change with age is not the case.

References

Disclosure: J. Fowler, None; C. Varley, None; A. Oldroyd, None; M. Bukhari, None.

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Introduction: Serum sRANKL was reported to be associated with osteoporosis. In this study, we measured serum sRANKL and OPG in patients with RA.

Methods: RA patients and healthy controls were recruited at Toho University Omori Hospital and the Research Center for Clinical Pharmacology of Kitasato University, respectively. 360 patients with RA [mean age 61.5±13.4 (SD) years, male 66 and female 294 (menopause 229), mean disease duration 119±6.0 (SD) months] were included. We measured serum levels of sRANKL and OPG in RA patients and healthy controls. Serum levels of bone formation markers [intact aminoterminal propeptide of type I procollagen (PINP) and bone specific alkaline phosphatase (BAP)], and bone resorption markers [type I collagen cross-linked N- telopeptide (NTX) and tartrate-resistant acid phosphatase form 5b (TRACP-5b)] were measured in the same subjects. In addition to these, we observed the background of the RA patients, such as age, sex, disease duration, stage classification, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Disease Activity Score (DAS) 28-ESR, Health Assessment Questionnaire (HAQ), Sharp score, and bone mineral density (BMD).

Results: The serum level of sRANKL [median (25th to 75th percentile range)] in patients with RA [0.09 (0.01–0.21) pmol/L] was significantly increased compared to that of healthy controls [0.03–0.19] pmol/L]. As well, the serum level of OPG of RA [5.24 (4.04–5.67) pmol/L] was significantly increased in comparison to healthy subjects [3.63 (3.17–4.13) pmol/L]. The serum sRANKL level was negatively correlated with age, CRP and ESR by univariate analysis. In multivariate analysis, sRANKL was negatively correlated with age and disease duration, whereas, it was positively correlated with HAQ. The serum level of OPG was positively correlated with CRP, DAS28-ESR and MMP-3 as well as by univariate analysis. In multivariate analysis, OPG was positively correlated with age and MMP-3. Both of serum sRANKL and OPG did not correlate with Sharp score and BMD in RA patients. There was no statistical correlation between the serum levels of sRANKL and OPG in RA patients and healthy controls.

Conclusion: In this study, we showed that both of the serum levels of sRANKL and OPG were significantly higher than those in healthy controls. Since sRANKL was correlated with disability index of HAQ, it is suggested that we should pay attention to deterioration of osteoporosis especially in the RA patients with severely impaired activities of daily living. On the other hand, OPG was correlated with disease activity of RA, suggesting that further attention to osteoporosis will be necessary even for the RA patients with the lower disease activities or remission.

Disclosure: K. Shikano, None; K. Kaneko, None; M. Kawazoe, None; S. Masuoka, None; H. Sato, None; E. Shindo, None; N. Fujiio, None; M. Kaburaki, None; S. Muraoaka, None; N. Tanaka, None; T. Yamamoto, None; K. Takagi, None; N. Kusunoki, None; T. Hasunuma, None; S. Kawai, None.
Significance of Serum Marker Levels of Wnt/β-Catenin Signaling Pathway in Patients with Systemic Autoimmune Diseases Under Glucocorticoid Therapy: A Prospective Study. Mai Kawaoze, Kotaro Shikano, Kaichi Kaneko, Shotaro Masuoka, Hiroshi Sato, Emiko Shindo, Natsumi Fujio, Yuko Tanaka, Tanaka Chihoko, Tatsuhiko Yamamoto, Kenji Takagi, Natsumo Kusunoki, Tomoko Hasunuma and Shinichi Kawai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Glucocorticoids are widely used to treat a variety of diseases, including systemic autoimmune diseases. Although glucocorticoids suppress the immune response for patients with these diseases, various side effects of long-term treatment, such as osteoporosis, have become an important problem. Glucocorticoids decrease bone density through multiple mechanisms by inhibition of bone formation and by enhancement of bone resorption. Recently, the identification of the Wnt/β-catenin signaling pathway has led to considerable interest as one of the mechanisms of osteoporosis in postmenopausal women. Wnt/β-catenin signaling pathway is mediated by Wnt3a and plays an important role in bone formation. Sclerostin and Dickkopf1 (Dkk-1) have been identified as antagonists of Wnt signaling. Therefore the purpose of this study is to clarify the clinical significance of the Wnt signaling pathway by measuring the serum levels of sclerostin, Dkk-1, Wnt3a and bone turnover markers in patients with recent onset of glucocorticoid therapy.

Methods: Patients were recruited at Toho University Otorii Medical Center. This study was approved by the Ethics Committee of the Medical Center. Forty patients (25 females [14 postmenopausal], 55.2 ± 9.3 yr [mean ± SD]) with systemic autoimmune diseases (vasculitis syndrome 16, systemic lupus erythematosus 12, polymyositis / dermatomyositis 9, and adult-onset Still’s disease 3) who received initial glucocorticoid therapy with prednisolone daily (30–60 mg) were prospectively enrolled in this study. Their mean bone mineral density at starting of prednisolone therapy was 0.944 g/cm². Mean C-reactive protein was 4.08 ± 5.15 (S.D.) mg/dl. Regular doses of bisphosphonates (alendronate or risedronate) were co-administered in all patients. We measured serum sclerostin, Dkk-1, Wnt3a and bone turnover markers at 0, 1, 2, 3 and 4 weeks after start of glucocorticoid therapy.

Results: Serum sclerostin level was significantly (p<0.05) increased from 1st to 2nd weeks after starting of glucocorticoid therapy in comparison to previous value. Serum Dkk-1 level had a tendency to decrease, but there was no significant difference. Serum Wnt3a level had a trend to decrease after glucocorticoid therapy. Serum bone formation markers, osteocalcin and procollagen type I N-terminal peptide, decreased from 1st to 4th weeks, whereas bone alkaline phosphatase did not change. Serum bone resorption markers, tartrate-resistant acid phosphatase isofrom 5b and N-telopeptide crosslinked of type I collagen did not change.

Conclusion: We found that glucocorticoid therapy caused increased level of serum sclerostin and a trend of decreased Wnt3a level. It is suggested that suppression of Wnt/β-catenin signaling pathway might at least in part, be a cause of severe osteoporosis in patients with systemic autoimmune diseases under glucocorticoid therapy.

Disclosure: M. Kawaoze, None; K. Shikano, None; K. Kaneko, None; S. Masuoka, None; H. Sato, None; E. Shindo, None; N. Fujio, None; S. Murakura, None; M. Kaburaki, None; N. Tanaka, None; T. Yamamoto, None; K. Takagi, None; N. Kusunoki, None; T. Hasunuma, None; S. Kawai, None.


Background/Purpose: Controversies exist about the change in hip fracture incidence among countries. In France, we previously showed that the incidence of hip fractures decreased in both genders, especially in the elderly from 2002 to 2008 in parallel with availability of bone densitometry and effective antosteoporotic treatments. However these prescriptions are decreasing, since 2009 (1), and recent studies show decline of osteoporosis management after fragility fractures. The aim of this study was to assess the incidence of hip fractures in men and women aged 60 years and over, from 2008 to 2013 in France.

Methods: Data were drawn from the French Hospital National Database which includes all hospitalizations. Hospital data for hip fractures between 2002 and 2013 were numbered and the incidence rates per 1,000,000 adjusted on age (60–74; 74–84, and ≥ 85 years), and gender was calculated using the data of the French population.

Results: The number of hip fractures increased in women (+5%; from 49,287 in 2002 to 50,215 in 2013) and in men (+22%; from 12,716 to 15,482 in 2013). Between 2002 and 2013, the French population increased by 21% and 29% in women and in men. Incidence of hip fractures over 60 years decreased by -14% in women (6,929 and 5,987 per million in 2002 and 2013, respectively) and a slight decrease of -1% was observed in men (2,344 and 2,316 per million in 2002 and 2013, respectively). An age-specific incidence decrease was also confirmed, in particular, in the elderly in both genders (≥ 85 years) with a decrease of -29% in women and -24% in men (p<0.00001).

Conclusion: Over the last 12 years, the incidence of hip fractures decreased in France in women and men aged over 60 years. This decrease is particularly important in the elderly in both genders. This is observed in parallel with the decrease in prescription of antosteoporotic treatments. Further studies are needed to assess potential changes in hip fractures risk factors during the last decade.


Disclosure: K. Briot, None; M. Maravic, None; C. Roux, None.

Lower P1NP Serum Levels: a Predictive Marker of Bone Loss after One-Year Follow-up in premenopausal SLE Patients. Lucia Seguro1, Cato B. Casella2, Valeria Cabral3, Ricardo M. Oliveira4, Alessandra C Bonfa5, Eloisa Bonfa1 and Rosa M R Pereira1. 1. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 2. RD0 Diagnostics Medicos, São Paulo, Brazil.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is associated with high risk of low bone mass/fragility fractures but this risk is still controversial in premenopausal women. Our aim was to determine the one-year incidence of bone mineral density (BMD) loss in premenopausal SLE women and the value of bone turnover markers as predictors of this complication.

Methods: This study enrolled a convenience sample of 63 premenopausal SLE patients. BMD was evaluated by dual X-ray absorptiometry at lumbar spine and hip at baseline and after 12 months. BMD changes above the least significant change were considered significant. Serum levels of P1NP and CTX (electrochemiluminescence), OPG and RANKL (ELISA) were determined at baseline.

Results: Mean age was 31.1±6.8years, disease duration was 5.25±3.8years, 36.5% of patients presented BMD loss and 17.5% BMD gain (BL), no BMD change (NC) and BMD gain (BG). Patients with BL and NC received lower doses (p=0.031 BL vs. NC, p=0.001 BL vs. BG and p=0.039 NC vs. BG). There was no difference in CTX, OPG or RANKL levels between the groups. There was no difference in baseline CTX levels (p=0.931), OPG levels (p=0.05) and RANKL levels (p=0.572) between the groups.

Conclusion: This study provides original evidence that lower levels of P1NP, the most specific bone formation marker, are predictive of BMD loss over 12 months in premenopausal SLE patients.

Disclosure: L. Seguro, None; C. B. Casella, None; V. Cabral, None; R. M. Oliveira, None; A. C. Bonfa, None; E. Bonfa, None; R. M. R. Pereira, None.


Risk Factors for Prevalent and Progressive Bone Deficits Among Adult Men and Women with Cystic Fibrosis

Background/Purpose: Cystic Fibrosis (CF) is associated with an increased risk of osteoporosis and incident fracture. Factors associated with prevalent and
progressive bone deficits in adults with CF have not been comprehensively studied. This study assessed the independent predictors of baseline bone mineral density (BMD) and 2-year changes BMD in adults with CF.

**Methods:** Sixty-four adult patients with CF, ages 18–57, were recruited from the Massachusetts General Hospital Cystic Fibrosis Care Center. Dual energy absorptiometry (DXA) was performed at the spine and radius at baseline and 2-years. Estimates of fat-free mass index (FFMI) and fat mass index (FMI) were determined using height, weight, and tetrapolar bioelectric impedance analysis. All subjects underwent lung spirometry within 1 month of the study visit to measure forced vital capacity (FVC) and forced expiratory volume (FEV1). Linear regression models evaluated predictors of baseline BMD Z-scores and change in anterior-posterior (AP) spine BMD Z-score over the 2-year follow-up. Osteopenia was defined as a BMD Z-score of $-2.5$ to $-1.0$.

**Results:** Osteopenia was present in 52% of subjects. Compared to patients without osteopenia, subjects with osteopenia were more likely to be male (67% v. 32%, p = 0.009), more likely to be current users of glucocorticoids (21% v. 0%, p < 0.001), had lower percent body fat (19% v. 23%, p = 0.04), and were more likely to have had a previous fracture (60% v. 46%, p = 0.007). In multivariable models, greater estimated FFMI and greater height, but not greater FMI, were associated with greater BMD after adjusting for sex (Table 1). Low FVC and greater adiposity were associated with greater loss of BMD at the AP spine over two years (p < 0.05) (Table 2).

**Conclusion:** Male sex, short stature, and low lean mass at baseline are associated with low BMD among adults with CF. Greater adiposity and lower lung function in women are predictors of negative change in BMD Z-score at the A/P spine at 2-years of follow-up.

**Table 1:** Multivariable associations between baseline body composition factors and baseline bone density Z-score at different measurement locations.

<table>
<thead>
<tr>
<th></th>
<th>$\beta$ (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA AP Spine (n=54)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.10 (0.04, 0.17)</td>
<td>0.02</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>0.03 (0.01, 0.06)</td>
<td>0.004</td>
</tr>
<tr>
<td>FMI (kg/m²)</td>
<td>0.06 (0.02, 0.11)</td>
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</tr>
<tr>
<td>DXA Radius (n=28)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.05 (0.01, 0.11)</td>
<td>0.03</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>0.03 (0.01, 0.06)</td>
<td>0.01</td>
</tr>
<tr>
<td>FMI (kg/m²)</td>
<td>0.03 (0.01, 0.06)</td>
<td>0.01</td>
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</tbody>
</table>

*Also adjusted for sex. DXA: Dual Electron Absorptiometry; eFFMI: Estimated Fat-Free Mass Index; eFMI: Estimated Fat Mass Index

**Table 2:** Univariate associations between baseline factors and change in BMD Z-score over 2-years (N=39). Body composition variables adjusted for sex.*

<table>
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<tbody>
<tr>
<td>Male Sex</td>
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<tr>
<td>BMI</td>
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<tr>
<td>% Fat*</td>
<td>0.01 (0.00, 0.02)</td>
<td>0.004</td>
</tr>
<tr>
<td>FFMI*</td>
<td>0.004 (0.07, 0.08)</td>
<td>0.04</td>
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<tr>
<td>FMI*</td>
<td>-0.05 (0.01, 0.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>FVC</td>
<td>0.065 (0.015, 0.13)</td>
<td>0.005</td>
</tr>
<tr>
<td>Prednisone Use</td>
<td>0.051 (0.006, 0.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Baseline Z-score</td>
<td>-0.013 (0.013, 0.00)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Disclosure:** J. Baker, None; P. Melissa, None; K. Herlyn, None; A. S. Pizzo, None; A. Lapey, None; J. Finklestein, None; P. A. Merkel, None; R. M. Pereira, None.

**Background/ Purpose:** To evaluate single nucleotide polymorphisms (SNPs) of the receptor activator of NF-κB ligand (RANKL), RANK and osteoprotegerin (OPG) genes in premenopausal systemic lupus erythematosus (SLE) patients and their association with sRANKL and OPG serum levels, vertebral fractures and bone mineral density (BMD).

**Methods:** 211 premenopausal SLE patients (ACR criteria) and 154 healthy controls were enrolled. SNPs of RANKL 290A>G, OPG 1181G>C, 245T>G (rs3134069), 163 A>G (rs31072735) and RANK A>G (rs3018362) were obtained by real-time PCR. sRANKL/OPG serum levels were determined by ELISA. BMD and vertebral fractures were evaluated by dual energy X-ray absorptiometry.

**Results:** SLE patients and controls had similar frequencies of the RANKL 290 G allele (p = 0.80), OPG 163 G allele (p = 1.00) and RANK G allele (p = 0.75). Further analysis of SLE patients revealed that the frequency of the RANKL 290 G allele was lower in patients with fractures than in patients without fractures (28.1 vs. 46.9%, p = 0.01). In addition, the frequency of the OPG 245 G allele was higher in patients with low BMD than in patients with normal BMD (31.4 vs. 18.1%, p = 0.04). No association of OPG 1181 G>C, 163 A>G and RANK A>G SNPs with BMD/fractures was found. Additionally, no association was observed between RANKL/OPG/RANK SNPs and sRANKL/OPG serum levels.

**Conclusion:** Our study provides novel data demonstrating that RANKL/OPG genetic variations play a role in bone remodeling and, particularly, in its major complication, fracture, in premenopausal patients with SLE.

**Disclosure:** A. C. Bonfa, None; L. P. C. Seguro, None; V. Caparbo, None; E. Bonfa, None; R. M. R. Pereira, None.

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**Background/Purpose:** To evaluate single nucleotide polymorphisms (SNPs) of the receptor activator of NF-κB ligand (RANKL), RANK and osteoprotegerin (OPG) genes in premenopausal systemic lupus erythematosus (SLE) patients and their association with sRANKL and OPG serum levels, vertebral fractures and bone mineral density (BMD).

**Methods:** 211 premenopausal SLE patients (ACR criteria) and 154 healthy controls were enrolled. SNPs of RANKL 290A>G, OPG 1181G>C, 245T>G (rs3134069), 163 A>G (rs31072735) and RANK A>G (rs3018362) were obtained by real-time PCR. sRANKL/OPG serum levels were determined by ELISA. BMD and vertebral fractures were evaluated by dual energy X-ray absorptiometry.

**Results:** SLE patients and controls had similar frequencies of the RANKL 290 G allele (p = 0.91), OPG 1181 C allele (p = 0.83), OPG 245 G allele (p = 0.80), OPG 163 G allele (p = 1.00) and RANK G allele (p = 0.75). Further analysis of SLE patients revealed that the frequency of the RANKL 290 G allele was lower in patients with fractures than in patients without fractures (28.1 vs. 46.9%, p = 0.01). In addition, the frequency of the OPG 245 G allele was higher in patients with low BMD than in patients with normal BMD (31.4 vs. 18.1%, p = 0.04). No association of OPG 1181 G>C, 163 A>G and RANK A>G SNPs with BMD/fractures was found. Additionally, no association was observed between RANKL/OPG/RANK SNPs and sRANKL/OPG serum levels.

**Conclusion:** Our study provides novel data demonstrating that RANKL/OPG genetic variations play a role in bone remodeling and, particularly, in its major complication, fracture, in premenopausal patients with SLE.

**Disclosure:** A. C. Bonfa, None; L. P. C. Seguro, None; V. Caparbo, None; E. Bonfa, None; R. M. R. Pereira, None.

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**Background/Purpose:** Osteoporotic fractures are a cause of morbidity in rheumatoid arthritis (RA) and low body mass index (BMI) is a risk factor for osteoporotic fractures in RA. Emerging evidence suggests that low lean mass is responsible for bone structural deficits among those with low BMI. Therefore we hypothesized that adjusting BMI for lean mass deficits commonly seen in RA would alter prediction of risk using the FRAX tool. We studied the effect of utilizing a lean mass-adjusted BMI as an independent variable in the FRAX tool in the determination of fracture risk.

**Methods:** Whole-body dual energy absorptiometry (DXA) was previously performed in 40 RA subjects and 500 controls. We have previously identified independent associations between the total fat mass index (FMI)
and appendicular lean mass index (ALMI) among 500 healthy control subjects. Based on our published model, we determined the expected ALMI for RA subjects based on their age, sex, race, and BMI. We then multiplied the actual BMI by the ratio of the actual to expected ALMI to determine a lean mass-adjusted BMI. We calculated fracture risk among RA subjects using the FRAX calculator, and evaluated the differences in fracture risk prediction using the lean mass-adjusted BMI compared to the standard BMI both with and without using bone density results from DXA.

Results: Using the lean mass-adjusted BMI in place of standard BMI, the calculated risk of a major osteoporotic fracture increased in 21 (52.5%), decreased in 8 (20%), and was unchanged in 11 (27.5%) subjects. The mean absolute change in calculated 10-year major osteoporotic fracture risk using lean mass-adjusted BMI was 0.28% ± 0.70 (p=0.02). Similarly, the calculated risk of hip fracture using lean mass-adjusted BMI was increased in 23 (57.5%), decreased in 6 (15%), and unchanged in 11 (27.5%) subjects. The mean absolute change in calculated 10-year hip fracture risk was 0.25% ± 0.60 (p=0.01). The calculated risk of hip fracture using lean mass-adjusted BMI was most increased among subjects with a BMI <25 kg/m². For subjects with a BMI<25 (n=11) the estimated fracture risk was significantly increased by 0.67% ± 0.87 (p=0.03), as compared to -0.09% ± 0.37 (p=0.2) for subjects with a BMI >25 (n=29) (p for comparison=0.005). When bone density at the hip was included into the FRAX calculation, the differences in calculated fracture risk using the lean mass-adjusted BMI and standard BMI were completely attenuated (Figure 1).

Conclusion: Using lean mass-adjusted BMI in place of standard BMI in the FRAX equation results in an increase in calculated fracture risk for most patients with RA, particularly among those with a normal BMI (BMI<25). Incorporation of bone density measures significantly reduced these differences in risk prediction, which suggests that use of a lean mass-adjusted BMI would not affect risk prediction when bone density is available.

Disclosure: B. Adler, None; J. F. Baker, None.

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An Observational Study on the Influence of Glucocorticoid Exposure on Bone. Joseph Heath1, Alexander Oldroyd2, Maarten Boers2 and Marwan Bukhari1. 1Lancaster University, Lancaster, United Kingdom, 2VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: It is well known that glucocorticoids are detrimental to bone health and has been postulated that their influence is more than their effect on reduction of bone mineral density (BMD). This has not been localised to type of bone involved as trabecular bone and cortical bone differ. The FRAX™ tool uses the hip BMD as a predictor of future fracture risk, which is a measure of cortical rather than trabecular bone. Recently, we have shown that hip structure analysis (HSA) is also a predictor of fracture. We aimed to study in an observational manner the effect of corticosteroid (CS) use on the bone in the lumbar spine (trabecular bone) and the hip (cortical bone), in addition to any differences in HSA.

Methods: Patients who are identified from a cohort recruited from the North West of England referred for a bone densitometry (DEXA) scan and receiving CS. Patients were divided into those that had sustained a fragility fracture (cases) and compared to those who had not (controls). Analysis was carried out using the student t-test for continuous variables and the Chi² test for categorical variables. Logistic regression analysis was carried out to investigate any significant association between BMD and bone fracture in patients receiving CS. HSA variables were also included in the model.

Results: There were 3,360 patients (73.46% female) identified as receiving CS, of which 779 (23.18%) had suffered from a fracture. Mean age of patients who suffered a fracture was significantly higher than those who did not; 62.33 (SD=13.09) vs 67.39 (SD=11.75) respectively (p value =<0.001). Females were significantly more likely to suffer a fracture compared to males; 33.86% vs 20.00% respectively (p.value=<0.001). After adjusting for age and sex, the mean difference in BMD between patients on steroids who suffered a fracture compared to those who did not suffer a fracture at the femoral neck was 0.06 g/cm² (95%CI=0.05–0.08) and at the lumbar spine was 0.09 g/cm² (95%CI=0.07–0.10). Logistic regression analysis after adjustment showed that patients who were on steroids were likely to have a lower BMD at the femoral neck (OR=0.13, 95%CI=0.06–0.34) and the lumbar spine (OR=0.13, 95%CI=0.08–0.21). Modelling HSA showed that after adjustment, Cross sectional moment of inertia and not hip axis length was different between the two groups (OR 0.95 95%CI 0.95-0.99 95%CI 0.98-1.01 respectively).

Conclusion: In this cohort of patients fractures in those taking steroids are associated with increasing age, female sex, and lower BMD. Patients who are taking CS and suffer from a fracture are significantly more likely to have a lower BMD. Differences in Hip structure are also seen. This study does not support the theory that CS are an independent variable in fracture risk in patients. Further prospective studies are needed.

Disclosure: J. Heath, None; A. Oldroyd, None; M. Boers, None; M. Bukhari, None.

Reduced Estimated Glomerular Filtration Rate Was Improved after Cessation of NSAID and Switching to Tramadol Hydrochloride/Acetaminophen Tablets (Ultracet™) in Patients with Chronic Musculoskeletal Pain. Kenji Miki1, Hiroshi Kajiyama2, Kenrin Shih3, Shigesu Mori4, Masato Yukioka5 and Masao Akagi1. 1Faculty of Medicine, Kindai University, Osaka-Sayama, Japan, 2Saitama Medical University, Saitama, Japan, 3Osaka University Hospital, Suita, Japan, 4Yukioka Hospital, Osaka, Japan.

Background/Purpose: NSAID is widely used in patients with chronic musculoskeletal pain, but often deteriorates renal function with acute decline of estimated glomerular filtration rate (eGFR). However, there is little evidence on the long-term effect of chronic NSAID use, whether the eGFR decline is irreversible or not.

Methods: We studied 100 patients with chronic musculoskeletal pain (age 66.8 ± 18.4 years; 29 men, 71 women; 46 patients with lumbago, 28 with osteoarthris, 26 with other complaints) over a followup period of 2 years. The baseline eGFR of the 100 patients was 85.13 ± 25.63 mL/min/1.73m². We compared eGFR change during the first year with daily NSAID administration and that during the following year with daily administration of tramadol hydrochloride/acetaminophen tablets, in the same patient. eGFR administration and that during the following year with daily administration of tramadol hydrochloride/acetaminophen tablets can improve the renal function deteriorated by NSAID. As for the NSAID during the first year, meloxicam was administered in 33 patients, loxoprofen in 29, diclofenac in 19, and celecoxib tablets in 24 patients.

Results: Reduced Estimated Glomerular Filtration Rate Was Improved after Cessation of NSAID and Switching to Tramadol Hydrochloride/Acetaminophen Tablets (Ultracet™) in Patients with Chronic Musculoskeletal Pain. Kenji Miki1, Hiroshi Kajiyama2, Kenrin Shih3, Shigesu Mori4, Masato Yukioka5 and Masao Akagi1. 1Faculty of Medicine, Kindai University, Osaka-Sayama, Japan, 2Saitama Medical University, Saitama, Japan, 3Osaka University Hospital, Suita, Japan, 4Yukioka Hospital, Osaka, Japan.

Results: eGFR change was -0.973 mL/min/1.73m² during the first year with NSAID administration, whereas it was +0.047 mL/min/1.73m² during the following year with tramadol hydrochloride/acetaminophen tablets administration. The difference of eGFR change between the two medications was statistically significant (paired t test, p=0.002; Figure), suggesting the cessation of NSAID and switching to tramadol hydrochloride/acetaminophen tablets can improve the renal function deteriorated by NSAID. As for the specific NSAIDs during the first year, cessation of diclofenac and meloxicam followed by switching to tramadol hydrochloride/acetaminophen tablets resulted in a significant improvement in eGFR (paired t test, p=0.0008 and p<0.0001 respectively; Figure), whereas switching from loxoprofen just showed a tendency of improvement (paired t test, p=0.0604; Figure). On the other hand, cessation of celecoxib and switching to tramadol hydrochloride/acetaminophen tablets did not show significant improvement in eGFR (paired t test, p=0.9389; Figure). Improvement of eGFR after switching to tramadol hydrochloride/acetaminophen tablets was also recognized in 4 patients with diabetes and 12 patients with intake of angiotensin receptor blockers, but did
not reach statistical significance. There was no correlation between age and eGFR change over the one year either with NSAID or with tramadol hydrochloride/acetaminophen tablets.

Conclusion: Our findings suggest that reduced eGFR due to one year administration of NSAID could be reversible to a certain degree by cessation of NSAID and switching to tramadol hydrochloride/acetaminophen tablets. The degree of eGFR improvement was different depending on the types of NSAID.

Disclosure: K. Miki, None; H. Kajiyama, None; K. Shi, None; S. Mori, None; M. Yukioka, None; M. Akagi, None.

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WOMAC Pain Score Reflects Preceding Daily Pain Ratings in Knee Osteoarthritis Interventional Randomized Clinical Trials. Michael H. V. Nguyen¹, Renita Evonne Yeasted² and Thomas J. Schnitzer². ¹University of Washington School of Medicine, Seattle, WA, ²Northwestern University, Chicago, IL.

Background/Purpose: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a validated and widely used instrument for assessing osteoarthritis (OA) knee and hip pain, stiffness and physical function. The recall period for specific outcome measures is 48 hours. This study aimed to examine the correlation between WOMAC pain score and reported actual pain levels one, two and 5 days prior to completing the WOMAC instrument.

Methods: Data were obtained from three OA studies: an observational study (OBS) convenience sampling of OA and the placebo arm of two interventional randomized control trials (IRCTs). All participants were ≥ 40 years of age, met the ACR definition for OA, and self-reported a minimum pain intensity of ≥ 4 on Numeric Rating Scale (NRS) for pain (0 – no pain; 10 – worst pain possible). Participants were asked to report pain twice daily (IRCTs, electronic tablet) or three times daily (OBS, smartphone) over a 12–16 week period, and WOMAC was completed at regular clinic visits. For each participant, mean pain ratings were calculated for the day of clinical exam, as well as 1 day, 2 days, and 5 days prior and compared to the WOMAC pain score for question 1. Pearson’s correlation was computed to assess the relationship between WOMAC pain score and self-reported pain using Stata 13.

Results: In total, data were collected from 162 participants (123 studied in clinical trials and 39 studied in the observational study). The demographics for all three groups were similar and typical of adults with OA. Among clinical trial participants, there was a strong, positive correlation between WOMAC and self-reported pain for all time points \( r = 0.8505, n = 392 \) (exam day); \( r = 0.8482, n = 474 \) (1 day prior); \( r = 0.8575, n = 415 \) (2 day prior); \( r = 0.8173, n = 267 \) (5 day prior); all values \( p < 0.05 \) (Figure 1). Among observation study participants, there was a moderate, positive correlation between WOMAC and self-reported pain significant only at 1 day prior to exam \( r = 0.3741, n = 56 \) (Figure 2).

Conclusion: The findings of this study demonstrate a high correlation within individuals between WOMAC pain scores and self-reported daily preceding pain intensity in ICRT. This correlation was independent of the look-back period (one, two or five days). Less strong correlations were observed in OBS study settings. These findings are consistent with lower daily pain variability in interventional trials than in the observational setting and have implications on assessing and managing pain in non-IRCT settings.

Disclosure: M. H. V. Nguyen, None; R. E. Yeasted, None; T. J. Schnitzer, None.

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Safety of SoluMatrix Diclofenac in Adults with Osteoarthritis: Results of a 12-Month, Phase 3 Study. Roy Altman¹, Allan Gibofsky², Marc C. Hochberg³, Byron Cryer⁴, Alan J. Kivitz⁵, Vibeke Strand⁶, Olaolu Imasogie⁷ and Clarence Young⁸. ¹University of California–Los Angeles, David Geffen School of Medicine, Los Angeles, CA, ²Hospital for Special Surgery, New York, NY, ³University of Maryland School of Medicine, Baltimore, MD, ⁴University of Texas Southwestern Medical Center, Dallas, TX, ⁵Altoona Center for Clinical Research, Duncansville, PA, ⁶Stanford University, Palo Alto, CA, ⁷Iroko Pharmaceuticals LLC, Philadelphia, PA, ⁸Iroko Pharmaceuticals, LLC, Phila, PA.

Background/Purpose: Osteoarthritis (OA) is a frequent cause of disability in adults. NSAIDs such as diclofenac are often prescribed to treat OA pain. However, NSAIDs are associated with serious dose-related gastrointestinal (GI) and cardiovascular adverse effects, leading the FDA to recommend NSAID use at the lowest dose for the shortest duration necessary to achieve treatment goals. SoluMatrix® diclofenac has been developed using SoluMatrix Fine Particle Technology™ to provide efficacy at low doses and is approved for treatment of mild to moderate acute pain in adults. We report results from a 12-month, open-label phase 3 study investigating SoluMatrix diclofenac in patients with OA.

Methods: This multicenter study treated 601 chronic NSAID/acetaminophen users, aged ≥40 years with knee and/or hip OA. Patients initially received SoluMatrix diclofenac 35-mg capsules BID; the dosing regimen could be increased to TID if necessary and subsequently reduced as needed. Safety analyses included incidence of adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, and clinical laboratory test results.

Results: Most patients were women (372/601, 61.9%) with a mean (± SD) age of 59.7 ± 8.9 years. Mean (± SD) trial drug administration duration...
was 274.9 ± 125.7 days. AEs were reported by 451/601 (75.0%) patients (Table). The most frequently reported events included: upper respiratory tract infection (47/601, 7.8%), headache (46/601, 7.7%) and urinary tract infection (44/601, 7.3%). GI ulcer was reported in 1 patient (0.2%), considered related to study medication. Hypertension was reported in 17/601 (2.8%) patients, and serum creatinine increased in 7/601 (1.2%). SAEs were reported in 42/601 (7.0%) patients. Two patients (2/601, 0.3%) experienced myocardial infarction; both considered unrelated to study drug (Table). AEs led to discontinuation in 99/601 (16.1%) patients. Alanine aminotransferase or aspartate aminotransferase ≥3× the upper limit of normal was noted in 20 patients (3.3%), which was associated with elevated bilirubin in one patient and improved following treatment discontinuation.

**Conclusion:** SoluMatrix diclofenac was generally well tolerated. These data extend the SoluMatrix diclofenac experience to include patients requiring extended treatment for OA pain.

**Table.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SoluMatrix Diclofenac 35 mg TID (n = 601)</th>
<th>SoluMatrix Diclofenac 35 mg BID (n = 601)</th>
<th>Combined SoluMatrix Diclofenac (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>186 (61.6)</td>
<td>340 (56.6)</td>
<td>451 (75.0)</td>
</tr>
<tr>
<td>URI</td>
<td>21 (7.0)</td>
<td>27 (4.5)</td>
<td>47 (7.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (3.6)</td>
<td>36 (6.0)</td>
<td>46 (7.7)</td>
</tr>
<tr>
<td>UTI</td>
<td>10 (3.3)</td>
<td>34 (5.7)</td>
<td>44 (7.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (4.6)</td>
<td>24 (4.0)</td>
<td>37 (6.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (3.6)</td>
<td>24 (4.0)</td>
<td>34 (5.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (3.6)</td>
<td>22 (3.7)</td>
<td>33 (5.5)</td>
</tr>
<tr>
<td><strong>Most Frequent (&gt;2% Patients) Serious Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SAE</td>
<td>15 (5.0)</td>
<td>26 (4.3)</td>
<td>42 (7.0)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1 (0.3)</td>
<td>2 (0.3)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Carotid artery stenosis</td>
<td>0</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>0</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Diversitvities</td>
<td>1 (0.3)</td>
<td>1 (0.2)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Lumbar spinal stenosis</td>
<td>0</td>
<td>1 (0.2)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

Data presented as n (%). AE = adverse event; BID = twice daily; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event; TID = three times daily; URI = upper respiratory tract infection. *AEs were assigned to the dose regimen the patient received at the AE start date. Post-treatment AEs were assigned to the last dose regimen received.** All treated patients were included in the SoluMatrix diclofenac twice-daily group for ≥ 2 days. **AEs that started missing start dates and pretreatment AEs are listed in the Combined SoluMatrix Diclofenac column.

**Disclosure:** R. Altmann. Participant in advisory boards for Iroko Pharmaceuticals, consultant to Pfizer, Teva Pharmaceutical Industries Ltd., Penah Tikva, Oletoc, Novartis Johnson & Johnson, and consultant and member of the speaker’s bureau for Ferring Pharmaceuticals, 5; A. Gibofsky, Stock shareholder of GlaxoSmithKline plc, Bristol-Myers Squibb, Johnson & Johnson, Amgen, Pfizer, AbbVie, Johnson and Johnson, 1, consultant for Takeda, Amgen, AbbVie, UCB Inc., Genentech, Horizon, and Iroko Pharmaceuticals LLC, 5; M. C. Hochberg, Iroko Pharmaceuticals LLC, Amgen, AstraZeneca, Covidien, Eli Lilly, EMD Serono, Genentech/Roche, Merck & Co., Inc., Novartis Pharma AG, Pfizer, and Pozen, 5; B. Cryer, Consulting fees received from Ritter Pharmaceuticals, Sanofi, Sandoz, Sucemopo, and Iroko Pharmaceuticals, LLC, 5; A. J. Kivitz, None; V. Strand, Consultant for AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; O. Imasogie, IBoko Pharmaceuticals LLC, 3; C. Young, Iroko Pharmaceuticals, LLC, 3.

244 Onset, Magnitude, and Durability of Pain Relief in Patients with Knee OA Receiving a Fixed-Dose Combination Tablet of Enteric-Coated (EC) Naproxen plus Immediate-Release (IR) Esomeprazole Magnesium Versus Celecoxib and Placebo: Pooled Results from Two Randomized Controlled Trials. John Fort1, Robert Holt2, Amy Y. Grahn3, Jana Steinmetz4, Ying Zhang5 and Jeffery Kent6. 1Pozn, Inc, Chapel Hill, NC, 2University of Illinois-Chicago, Vernon Hill, IL, 3Horizon Pharma, Inc., Deerfield, IL, 4Premier Research, Naperville, IL, 5Horizon Pharma, Inc, Deerfield, IL.

**Background/Purpose:** Over 40% of patients with OA report having significant knee pain every day. (1) Previously published data have demonstrated the overall comparable efficacy of EC naproxen/IR esomeprazole to celecoxib and superiority to placebo in the management of knee OA. (2) EC naproxen/IR esomeprazole also significantly reduced the incidence of endoscopic ulcers and improved UGI tolerability compared with EC naproxen alone in previous trials and maintained GI protective effect with low-dose aspirin (3). This new analysis characterizes time-to-first pain relief, effect size, and sustainability of naproxen/IR esomeprazole and celecoxib with placebo.

**Methods:** Two double-blind, double-dummy, placebo-controlled trials in patients aged ≥50 years with knee OA randomized to either EC naproxen 500mg/IR esomeprazole 20mg BID (n = 487) or celecoxib 200mg/day (n = 486) or placebo (n = 246). Acute response endpoints assessed: 1) Time to first significant response during days 1–7 as measured by Patient Global Assessment Likert scale, 2) Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale using a visual analog scale (VAS) during days 1–7, and 3) American Pain Society Patient Outcome Questionnaire (APS-POQ) scores over the first 7 days. Endpoints to assess sustainability of naproxen/esomeprazole included: 1) Routine Assessment of Patient Data (RAPID)-3 and 2) WOMAC Stiffness, Total and Pain VAS at 6/12 weeks. Time to first significant response was analyzed using the log-rank test and estimated using the Kaplan-Meier analysis method. Other endpoints were analyzed using ANCOVA models with baseline values as covariates. Least square means, confidence intervals, and p-values were generated on change from baseline differences compared to placebo. Effect sizes (Cohen’s D) and correlation coefficients (Spearman, Pearson) were estimated descriptively.

**Results:** EC Naproxen/IR esomeprazole produced statistically significant decreases in WOMAC Pain on Days 2–7 (Figure) and at Weeks 6 and 12; APS-POQ pain assessments were significantly improved on Days 2–7. RAPID and WOMAC Total/Pain/Stiffness scores decreased significantly at Weeks 6 and 12. Responses were comparable to celecoxib. Pain relief effect sizes were moderate and median days to good-excellent response was 6 days. Total RAPID-3 to WOMAC and WOMAC to RAPID Pain were highly correlated with each other (correlation > 0.80) at 6 and 12 weeks.

**Conclusion:** EC naproxen/IR esomeprazole produces a moderate-large early pain response which is maintained for 12 weeks. RAPID-3 was found to be highly correlated with the typical OA measure (WOMAC) and might be a useful clinical tool for measuring NSAID response.


**Disclosure:** J. Fort, Pozen, Inc, 3; R. Holt, Horizon Pharma, Inc, 5; Pozen, Inc, 5; A. Y. Grahn, Horizon Pharma, Inc, 3; J. Steinmetz, Horizon Pharma, Inc, 5; Y. Zhang, Pozen, Inc, 5; J. Kent, Horizon Pharma, Inc, 3.

245 WITHDRAWN

246 Neuropathic Pain in Patients with Ankylosing Spondylitis. Pinar Borman1, Ferda Kaygısız2, Aysegul Yaman3 and Aynur Karagoz2. 1University of Hacettepe Faculty of Medicine, Ankara, Turkey, 2Ankara Training and Research Hospital, Ankara, Turkey.

**Background/Purpose:** There is only one study in the literature indicating that neuropathic pain occurs in ankylosing spondylitis (AS) (1).

**Methods:** The aim of this cross sectional study was to evaluate frequency of neuropathic pain in AS patients and to determine the relation with disease variables and occurrence of neuropathic pain. Fifty-eight AS patients who were not having any comorbid disease and/or using drugs that could cause neuropathy, were recruited to the study. Demographic properties (age, sex,
Results: Fifty-eight AS patients (17 female, 41 male) with a mean age of 45 ± 18 years were included in the study. 33 patients (56.9%) and 31 patients (53.4%) were defined as having neuropathic pain depending on the LANSS score (>12) and DN4 (scores >4) questionnaire scores respectively. The mean score of LANSS scale was correlated with ASQoL, BASFI, BASDAI, and DN4; and the mean score of DN4 scale was correlated with ASQoL, BASFI, LANSS and BMI. The mean levels of BASFI and ASQoL were significantly higher in patients having neuropathic pain than in patients not having (p<0.05) (Table 1). The percentage of patients with neuropathic pain was higher in female than in male patients (58.8% vs 51.2% by DN4, 64.7% vs 53.6% by LANSS).

Conclusion: Neuropathic pain is determined in more than half of the patients with AS and related with functional status and quality of life. In conclusion neuropathic pain is common in AS patients. Diagnosis and treatment of neuropathic pain are warranted in order to increase functional ability and quality of life in patients suffering from AS.

References

Table 1. The difference of demographic and clinical properties, in patients having and lacking neuropathic pain, determined by LANSS.

<table>
<thead>
<tr>
<th>Neuropathic pain (+)</th>
<th>Neuropathic pain (−)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=33</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.12 ± 10.67</td>
<td>39.68 ± 11.41</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>8.69 ± 7.17</td>
<td>8.77 ± 6.55</td>
</tr>
<tr>
<td>BASFI (mean ± SD)</td>
<td>3.57 ± 2.43</td>
<td>2.02 ± 2.06</td>
</tr>
<tr>
<td>BASDAI (mean ± SD)</td>
<td>3.80 ± 1.80</td>
<td>2.84 ± 2.07</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>14.00 ± 9.78</td>
<td>11.64 ± 9.68</td>
</tr>
<tr>
<td>CRP (mean ± SD)</td>
<td>1.02 ± 1.24</td>
<td>0.79 ± 1.02</td>
</tr>
<tr>
<td>ASQoL (mean ± SD)</td>
<td>8.81 ± 4.48</td>
<td>4.36 ± 4.23</td>
</tr>
</tbody>
</table>

Table 2. The difference of demographic and clinical properties, in patients having and lacking neuropathic pain, determined by DN4.

<table>
<thead>
<tr>
<th>Neuropathic pain (+)</th>
<th>Neuropathic pain (−)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=33</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.93 ± 9.59</td>
<td>39.92 ± 12.43</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>9.33 ± 7.05</td>
<td>8.02 ± 6.67</td>
</tr>
<tr>
<td>BASFI (mean ± SD)</td>
<td>3.42 ± 2.43</td>
<td>2.30 ± 2.24</td>
</tr>
<tr>
<td>BASDAI (mean ± SD)</td>
<td>3.51 ± 1.72</td>
<td>3.24 ± 2.24</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>13.83 ± 10.11</td>
<td>12.00 ± 9.34</td>
</tr>
<tr>
<td>CRP (mean ± SD)</td>
<td>1.06 ± 1.24</td>
<td>0.76 ± 1.03</td>
</tr>
<tr>
<td>ASQoL (mean ± SD)</td>
<td>8.35 ± 4.82</td>
<td>5.22 ± 4.46</td>
</tr>
</tbody>
</table>

Disclosure: P. Borman, None; F. Kaygısız, None; A. Yaman, None; A. Karagoz, None.

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Cognitive Task Related Hypoperfusion of Frontal Gyrus in Patients with Chronic Fatigue. Jason Craggs1, Song Lai 1, Ricky Madhavan1, Donald Price1, Michael Robinson1 and Roland Staude2. 1University of Florida, Gainesville, FL, 2Univ of Florida Med Ctr/JHMHC, Gainesville, FL.

Background/Purpose: Patient with Chronic Fatigue Syndrome (CFS) frequently report cognitive complaints, including lack of concentration and forgetfulness. Previous neuropsychological studies reported attention and memory dysfunction in CFS patients. We wanted to determine the association between mental fatigue and brain activity as measured by arterial spin labeling (ASL). The perception of mental fatigue was induced with the Paced Auditory Serial Attention test (PASAT) that involves attention, working memory and executive function. We measured cerebral blood flow (CBF) changes in CFS patients and compared them to healthy controls (HC).

Results: Fatigue ratings were 0.4 (0.6) and 3.9 (2.1) for HC and CFS patients, respectively (p = 0.01). Overall cerebral blood flow was similar between groups (p > 0.05). CFS patients showed reduced blood flow in the right hemisphere superior frontal gyrus. In the significant cluster, HC participants had a mean (SD) CBF of 66.12 (7.89) compared to 63.24 (6.22) (ml/100g/min) in CFS patients (t(25) = 4.73, p = 0.007, Cohen’s d = 1.80).

Conclusion: More reduced cerebral perfusion was observed in the right superior frontal gyrus of CFS patients compared to HC during PASAT. The superior frontal gyrus plays a major role in the Attention Network. Reduced blood flow of this area may be a cause or consequence of chronic fatigue as well as impaired attention and cognition often observed in CFS.

Disclosure: J. Craggs, None; S. Lai, None; R. Madhavan, None; D. Price, None; M. Robinson, None; R. Staude, None.

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Is the Basdai Score Driven By Pain In Ankylosing Spondylitis Patients Treated with Anti-TNF? Jason Rahman1, Algis Jovaisa2, William Bensen3, Wojciech Oksysnyk1, Anna Jaroszynska2, Philip Baer4, Magbool Sherriff,5 Dalton Sholter,6 Efiofotisi Psaraedill,5 John S. Sampalis3, Francois Nantel3,1, Allen J Lehman1,2, Susan Otawa4,5 and May Shawi6,7. 1Memorial University of Newfoundland, St. John’s, NF, 2University of Ottawa, Ottawa, ON, 3Division of Rheumatology, McMaster University, Hamilton, ON, 4University of Saskatchewan, Saskatoon, SK, 5Private Practice, Burlington, ON, 6Private Practice, Scarborough, ON, 7Nanaimo Regional General Hospital, Nanaimo, BC, 8University of Alberta, Edmonton, AB, 9JSS Medical Research, Montreal, QC, 10Janssen Inc., Toronto, ON.

Background/Purpose: The present standard for measuring disease activity in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) which focuses on five major symptoms including fatigue, pain, peripheral pain, enthesitis and morning stiffness (severity and duration). Given that the BASDAI instrument contains two pain questions, the objective was to assess whether pain symptoms are the main drivers of BASDAI scores among AS patients treated with anti-TNFs in routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab (IFX) or golimumab (GLM) as first biologics or after having been treated with a biologic for <6 months. Patients with AS treated with IFX or GLM and enrolled between 2005 and 2014 were included in this analysis. A modified weighted BASDAI score (m-BASDAI) was calculated excluding the axial (Q2) and peripheral (Q3) pain questions of the BASDAI. The correlation of BASDAI, each of its components, and the modified BASDAI (m-BASDAI) was assessed with the Pearson correlation coefficient. BASDAI low disease activity (LDA) and m-BASDAI LDA were defined as a score ≤3. The association between the number of administered analgesics (0, 1, >1) and BASDAI/m-BASDAI was assessed with one-way ANOVA.

Results: A total of 413 AS patients with 1,709 assessments were included in this analysis. Correlation analysis showed a strong correlation between the full BASDAI and m-BASDAI scores (r = 0.98, P<0.001). With respect to the individual BASDAI questions, a strong positive linear correlation was observed between all questions and the BASDAI score as well as the m-BASDAI score (Table 1). As expected, a lower correlation was observed between Q2 and Q3 with the m-BASDAI relative to BASDAI. Axial pain was most strongly correlated with the severity of morning stiffness, whereas the highest correlation of peripheral pain was observed with localized tenderness. The cross-tabulation of BASDAI LDA and m-BASDAI LDA showed a strong measure of agreement (kappa = 0.87, P<0.001). Omission of the pain questions from BASDAI resulted in a comparable proportion of LDA cases (41.7% vs. 40.9%) when using the same LDA definition.
Increased use of analgesics (0 vs. 1 vs. >1) over 2 years of follow-up was associated with significantly (P<0.05) higher mean scores in BASDAI m-BASDAI and each of the BASDAI components. No significant association was observed between increased use of analgesics and treatment retention.

Table 1: Correlation between individual BASDAI Questions and BASDAI Outcomes

<table>
<thead>
<tr>
<th>BASDAI Question</th>
<th>BASDAI*</th>
<th>m-BASDAI*</th>
<th>Q2/Spinal Pain</th>
<th>Q3/ Joint Pain/Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: Fatigue</td>
<td>0.85</td>
<td>0.88</td>
<td>0.76</td>
<td>0.61</td>
</tr>
<tr>
<td>Q2: Spinal pain</td>
<td>0.92</td>
<td>0.87</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Q3: Joint pain</td>
<td>0.84</td>
<td>0.75</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Q4: Areas</td>
<td>0.89</td>
<td>0.89</td>
<td>0.76</td>
<td>0.73</td>
</tr>
<tr>
<td>Q5: Morning</td>
<td>0.89</td>
<td>0.90</td>
<td>0.82</td>
<td>0.67</td>
</tr>
<tr>
<td>Q6: Morning</td>
<td>0.75</td>
<td>0.78</td>
<td>0.64</td>
<td>0.55</td>
</tr>
</tbody>
</table>

P<0.001 for all correlations

Conclusion: Higher levels of AS pain are significantly associated with a higher BASDAI score and increased use of analgesic medications among patients treated with anti-TNFs. In addition to pain, fatigue, tenderness, and morning stiffness are likewise important contributing components in the BASDAI score and the disease burden of AS.


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A Phase 3 Open-Label Trial of Low-Dose Solumatrix Diclofenac in Patients with Osteoarthritis Pain: Impact of Long-Term Administration on Patient-Reported Outcomes

Vibeke Strand1, Allan Giboisky2, Marc Hochberg3, Roy Altman4, Byron Cryer5, Alan Kivitz6, Olaolu Imasogie7 and A. Jovaisas

Background/Purpose: Diclofenac is used for the treatment of osteoarthritis (OA), but, like other NSAIDs, it is associated with serious dose-related adverse events. The FDA has encouraged providers to prescribe NSAIDs at the lowest effective dose. Solumatrix™ diclofenac was developed to provide efficacy at low doses and is approved for treatment of mild to moderate acute pain in adults. A 1-year, open-label, multicenter, phase 3 study in patients with OA evaluated the safety and patient-reported outcome measures associated with Solumatrix Diclofenac.

Methods: The study treated 601 patients age ≥40, with knee and/or hip OA, who were chronic NSAID/acetaminophen users. Patients initially received Solumatrix Diclofenac 35-mg capsules BID. The dose could be increased to TID, and subsequently reduced back to BID as needed. Patients received SoluMatrix diclofenac 35-mg capsules BID. The dose could be increased to TID, and subsequently reduced back to BID as needed. Health-related quality of life (HRQOL) was evaluated by the Short Form-36™ version 2 (SF-36v2), which was completed at baseline and at weeks 12, 24, 32, 40, 48; and 52/early termination visit (ET).

Results: During the study, 299/601 (49.8%) patients remained on the Solumatrix Diclofenac 35-mg BID and 302/601 (50.2%) patients increased their SoluMatrix Diclofenac dosage to 35-mg TID at least once (316 events), mostly due to the need for more analgesia (214/316, 67.7% events). In total, 20.6% (65/316) of the dosing increases from BID to TID were reduced back to BID, mainly due to satisfaction analgesia (21/65, 32.3%). Patients receiving SoluMatrix Diclofenac treatments reported clinically meaningful improvement (≥2.5) in SF-36v2 Physical Component Score from baseline at 12 throughout 52 weeks dosing period (Table). Based on values that exceed normative scores at baseline, SF-36v2 Mental Component Scores were not expected to improve (Table). Clinically meaningful improvements from baseline to week 52/TID (≥2.5) were reported for the SF-36v2 Bodily Pain domain scores (+5.5). Improvements in Physical Functioning (+4.3) and Role Physical (+3.6) were also observed (Table). Only 12 patients (2%) withdrew from the study due to lack of efficacy.

Conclusion: Low-dose SoluMatrix diclofenac capsules 35-mg BID or TID were associated with improved HRQOL in patients with OA pain and represent a potentially promising treatment option for these patients.
5 (66.7%), vs. 61.5% who attained mild or no pain at 5 Days without reporting mild or no pain at 28 hours (p=NS). Polyradiculotigic gout responded less well early and late vs. monoarticular gout (Table 1). Mild or no pain at 28 hours correlated with IGART scores of "very good or excellent" at Day 5. Mild or no pain patients at 28 hours had very good or excellent IGART scores at Day 5 (92.6%) vs. 71.7% without mild or no pain at 28 hours (p<0.001).

The trend of early pain response with very good/excellent IGART was consistent for monoarticular and polyarticular gout (Breslow-Day p=0.869). Supportive correlations (Pearson’s) for pain and IGART were r=0.498 at 28 hours and r=0.651 at Day 5 (both p<0.0001).

### Table 1. 28-Hour Pain Onset vs Subsequent Pain Response at Day 5

<table>
<thead>
<tr>
<th>28-Hour Pain Response</th>
<th>Moderate or Greater Pain at Day 5</th>
<th>No Pain at Day 5</th>
<th>Percent Responder</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (Med or &gt; pain)</td>
<td>20</td>
<td>40</td>
<td>66.7%</td>
<td>All Patients</td>
</tr>
<tr>
<td>YES (Mild or no pain)</td>
<td>8</td>
<td>75</td>
<td>90.1%</td>
<td>With Gout</td>
</tr>
<tr>
<td>CMH Testa</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breslow-Day Test</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>10</td>
<td>24</td>
<td>70.6%</td>
<td>Monoarticular Gout</td>
</tr>
<tr>
<td>YES</td>
<td>1</td>
<td>59</td>
<td>98.3%</td>
<td></td>
</tr>
<tr>
<td>Chi-Squared Test</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher’s Exact Test</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>10</td>
<td>16</td>
<td>61.5%</td>
<td>Polyradiculotigic Gout</td>
</tr>
<tr>
<td>YES</td>
<td>7</td>
<td>14</td>
<td>66.7%</td>
<td></td>
</tr>
<tr>
<td>Chi-Squared Test</td>
<td>0.716</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher’s Exact Test</td>
<td>0.764</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aCMH test controls for monoarticular/polyarticular gout comparison.*

### Conclusion:
Early patient pain response of mild or no pain appeared to predict subsequent pain and investigator responses at 5 Days in monoarticular gout. Early response among polyaorticulotigic gout patients did not predict subsequent pain response indicating a potentially less stable pain response. This analysis suggests early re-evaluation after 24 hours and modification of gout treatment would benefit patients.


### Disclosure:
P. M. Peloso, Merck Pharmaceuticals, 3; T. R. Mikuls, None; B. W. Coburn, None; H. R. Schumacher Jr., Merck Pharmaceuticals, 5; D. F. Gates, Merck Pharmaceuticals, 3; Z. Popmihajlov, Merck Pharmaceuticals, 3; W. L. Straus, Merck Pharmaceuticals, 3; R. A. Moore, None.

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**Chronic Fatigue Is Associated with Hypoperfusion of Parahippocampal Gyrus.**
Andrew O’Shea1, Jason Craggs1, Ricky Madhavan1, Donald Price1, Song Lai1, Michael Robinson1 and Roland Staud1. 1University of Florida, Gainesville, FL, 2Univ of Florida Med Ctr/JHMHC, Gainesville, FL.

**Background/Purpose:** Cerebral hypoperfusion of the whole brain has previously been reported in chronic fatigue syndrome (CFS) patients. However, discrepancies exist in the literature in regards to the spatial extent of such abnormal brain perfusion, as well as the effect sizes of these abnormalities as previously used methods did not allow precise localization of such perfusion abnormalities. We measured global and local resting state cerebral blood flow (CBF) in CFS patients and compared them to healthy controls (HC).

**Methods:** CFS was determined using the CDC Criteria. 15 CFS patients (age = 50.5±13.0) and 12 HC (age = 49.2±12.2) were MRI scanned with a 3 Tesla Achieva during rest using a pseudo-continuous arterial spin labeling (pCASL) sequence. pCASL can quantify CBF without using exogenous contrast agents by magnetically labeling inflowing blood. Individual scans were corrected for motion and spatially smoothed, then label and control pairs were subtracted to create a perfusion image. The perfusion image was used to calculate a quantified CBF map, which was then normalized to standardized space. Groups were compared using voxel-wise independent samples t-tests. Statistical parametric maps were thresholded using a cluster forming t-statistic greater than 4.0 (p < 0.00025) and a spatial extent of 20 contiguous voxels (160 mm³) to control for multiple comparisons.

**Results:** Overall cerebral blood flow was similar between groups (p >0.5). CFS patients showed reduced blood flow in the right hemisphere parahippocampal gyrus. In the significant cluster, HC participants had a mean (SD) CBF of 40.51 (7.89) compared to 27.69 (6.22) (ml/100g/min) in CFS patients (t(25) = 4.73, p = 0.0008, Cohen’s d = 1.80).

**Conclusion:** Reduced cerebral perfusion was observed in the right parahippocampal gyrus of CFS patients. The parahippocampal gyrus plays a major role in the processing of memory and cognition. Reduced blood flow of this area may be a cause or consequence of chronic fatigue as well as impaired memory and cognition often observed in CFS.

**Disclosure:** A. O’Shea, None; J. Craggs, None; R. Madhavan, None; D. Price, None; S. Lai, None; M. Robinson, None; R. Staud, None.

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**Preliminary Validation of the Michigan Body Map.**
Chad M. Brummett1, Jenna Goesling2, Rishi Bakshi1, Jennifer Wolfe1, Stephanie Moser1, David A. Williams1 and Atton L. Hassett1. 1University of Michigan Medical School, Ann Arbor, MI, 2University of Michigan Health System, Ann Arbor, MI, 3Univ of MI Hlth System-Lobby M, Ann Arbor, MI, 4University of Michigan, Ann Arbor, MI.

**Background/Purpose:** One of the hallmark features of fibromyalgia and other centralized pain states is widespread body pain. We developed the Michigan Body Map (MBM) to assess widespread body pain in clinical care and in epidemiological studies. The MBM is a one-sided body image with check boxes for 35 body areas and a box for “No Pain.” The aim of the present study was to assess patients’ understanding of and accuracy when completing the MBM, as well as to assess preference when compared to the 2011 Survey Criteria for Fibromyalgia widespread pain index (WPI) and the body map from the Brief Pain Inventory (BPI).

**Methods:** 85 patients from the University of Michigan’s Physical Medicine and Rehabilitation Spine Center were included in this study. Written informed consent was obtained. The first phase (n=25) assessed how well participants understood the questionnaire and concurrent validity when compared to a standardized verbal assessment. In the second phase, the MBM’s reliability was assessed using a test-retest assessment 1–2 weeks after the first assessment (n=20). In the third phase, participants were randomized to complete the MBM and either the WPI (n = 20) or BPI (n = 20) to assess construct validity and were also asked preference questions about the body maps.

**Results:** In the first phase, participants completed the MBM quickly (76.8±1/– 64.5 sec). The majority of participants correctly noted right and left, marked only areas of chronic pain (3 months or more), and felt that the measure allowed them to note all of their areas of pain (Table 1). Of the 875 potential check boxes (25 patients × 35 body areas), 63 (7.2%) were incorrectly endorsed as either missed or reversed right/left. In the second phase, the majority of participants had slight discrepancies in the test-retest (ICC = 0.60, median 1.5 body areas different); however, these differences did not lead to significant changes in the calculated widespread pain score. In the third phase, the MBM was preferred when compared to the 2011 Survey Criteria for Fibromyalgia WPI (Table 2). There were no differences in participant preferences between the MBM and BPI (Table 2).

**Conclusion:** Overall, participants demonstrated good understanding of the MBM and preferred it to the WPI from the Fibromyalgia Survey Criteria. When compared to the BPI body map, the MBM offers advantages in quantifying, as there is no ambiguity as to the area that was checked. Some participants confused right and left in the MBM and body areas tended to be underreported when compared to verbally assessing each of the 35 possible body areas individually.

### Table 1. First phase: Assessment of understanding

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Identified right/left correctly</th>
<th>Yes 16 (64%)</th>
<th>No 5 (20%)</th>
<th>Missing 4 (16%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain present for 3 months or more</td>
<td>Yes 19 (76%)</td>
<td>No 1 (4%)</td>
<td>Missing 5 (20%)</td>
<td></td>
</tr>
<tr>
<td>Able to indicate all areas of pain</td>
<td>Yes 21 (84%)</td>
<td>No 4 (16%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Third phase: Questionnaire preference

<table>
<thead>
<tr>
<th>MBM vs. BPI</th>
<th>MBM vs. WPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preference</td>
<td>45%</td>
</tr>
<tr>
<td>Best depicts areas of pain</td>
<td>30%</td>
</tr>
<tr>
<td>Easier to complete</td>
<td>20%</td>
</tr>
<tr>
<td>Best distinguishes left from right</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Disclosure:** A. O’Shea, None; J. Craggs, None; R. Madhavan, None; D. Price, None; S. Lai, None; M. Robinson, None; R. Staud, None.
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Evaluating Neuropathic Complaints By DN4 and LANSS Scales after Local Corticosteroid Therapy in Carpal Tunnel Syndrome. Taner Dandinoglu1, Murat Karadeniz1, Volkam Yılmaz1, Levent Tekin1 and Umit Dincer1. 1. Bursa Military Hospital, Bursa, Turkey, 2. Corlu Military Hospital, Tekirdağ, Turkey, 3. Mevki Military Hospital, Ankara, Turkey, 4. Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Istanbul, Turkey.

Background/Purpose: The purpose of this study was to evaluate the neuropathic symptoms after local steroid injection inCTS. Since 2001, neuropathic pain scales have been used in the assessment and follow-up of neuropathic pain. DN4 and LANSS pain questionnaires have been applied to groups, mostly consisted of radiolucency and polyneuropathy cases, before and after various treatments and the results have been compared with the electrophysiologic findings. However to our knowledge there is yet no such study focusing on neuropathic complaints and the relationship between neuropathic pain and electrophysiologic findings before and after local corticosteroid injection.

Methods: Forty-one patients aged 22–65 years and diagnosed with carpal tunnel syndrome by nerve conduction studies who were also found to have a neuropathic symptoms were included in the study. All patients received local steroid injection into the carpal tunnel while the questionnaires and nerve conduction studies were performed before and 2 months after the injection.

Results: Local steroid injection was found effective on clinical and electrophysiologic parameters as well as on DN4 and LANSS scores in CTS patients (p<0.05) (Table 1). Electrophysiologic severity exhibited no statistically significant relationship with DN4 and LANSS scores, before and after treatment (p>0.05).

Conclusion: These findings suggest that the treatment of neuropathic complaints should be planned independently from the electrophysiologic findings and minimally invasive local steroid injection appears to be effective with regard to clinical and electrophysiologic aspects in CTS patients with neuropathic complaints.

Table 1. DN4 and LANSS Scores before and after the Treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN4</td>
<td>6.12 ± 1.50 (0.00)</td>
<td>4.65 ± 1.51 (0.00)</td>
<td>-1.47 ± 0.99 (0.00)</td>
<td>0.001**</td>
</tr>
<tr>
<td>LANSS</td>
<td>15.85 ± 7.21 (16.00)</td>
<td>12.63 ± 4.83 (0.00)</td>
<td>-3.22 ± 2.38 (0.00)</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Disclosure: T. Dandinoglu, None; M. Karadeniz, None; V. Yılmaz, None; L. Tekin, None; Dincer, None.

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The Effect of Milnacipran on Pain in Rheumatoid Arthritis Patients with Widespread Pain: A RandomizedBlinded Crossover Trial. Yvonne C. Lee1, Elena Massarotti2, Robert R. Edwards3, Bing Lu 1, Chih-Chin Liu1, Yuanyu Lu1, Alyssa Wohlfahrt1, Nancy Kim1, Daniel J. Clauw3 and Daniel H. Solomon1. 1. Brigham and Women’s Hospital, Boston, MA, 2. Brigham & Women’s Hospital, Boston, MA, 3. Brigham & Women’s Hospital, Chestnut Hill, MA, 4. Rheumatology & Immunology, Brigham & Women’s Hospital, Boston, MA, 5. Massachusetts General Hospital, Charlestown, MA, 6. University of Michigan, Ann Arbor, MI.

Background/Purpose: Clinical trials have shown that serotonin norepinephrine reuptake inhibitors, such as milnacipran, decrease pain in chronic non-inflammatory pain conditions like fibromyalgia and osteoarthritis. We examined the effect of milnacipran on self-reported pain intensity and experimental pain sensitivity among rheumatoid arthritis (RA) patients with widespread pain on a stable treatment regimen.

Methods: Thirty-two subjects with RA completed a double-blind, crossover study. Subjects were randomized to receive milnacipran 50 mg twice daily or placebo for 6 weeks, followed by a 3-week washout and crossed over to the other arm for the remaining 6 weeks. Subjects completed the Brief Pain Inventory – short form (BPI-sf) to assess self-reported pain intensity and the Symptom Intensity Scale (SIS) to assess symptoms of fibromyalgia. Subjects also underwent quantitative assessments of pressure pain thresholds at joint and non-joint sites, using a Wagner FPK 20 algometer. Pain thresholds at the trapezius were measured before and after a noxious conditioning stimulus to assess conditioned pain modulation, a measure of the descending analgesic pain pathways. The primary outcome was change in self-reported pain, measured by the BPI-sf average pain intensity. Secondary outcomes included changes in the SIS pain score, pain thresholds and conditioned pain modulation. Changes in pain measures were compared between milnacipran and placebo using Wilcoxon signed rank tests and linear mixed models.

Results: After 6 weeks of milnacipran, BPI-sf average pain intensity decreased 0.7 (SD 1.7) points on a 0–10 scale, compared to a decrease of 0.3 (SD 2.0) after 6 weeks of placebo (P = 0.07) (Table). Threshold pain pressure threshold increased by 0.7 (SD 1.4) during milnacipran treatment compared to -0.02 (SD 1.4) during placebo (P = 0.04). None of the other secondary outcome measures differed significantly between treatment periods. In the subgroup of subjects with swollen joint count less than or equal to 1, BPI-sf average pain intensity decreased 1.0 (SD 1.6) points, compared to an increase of 0.1 (SD 1.9) during placebo (P = 0.04). In this subgroup, the increase in thumbnail pressure pain threshold was also significantly higher during milnacipran treatment compared to placebo (P = 0.003).

Conclusion: This randomized, blinded cross-over trial of milnacipran vs. placebo revealed no overall differences in improvements in pain intensity, fibromyalgia symptoms and experimentally assessed pain measures. Subgroup analyses among patients with 0–1 swollen joints suggested that milnacipran may have a role in diminishing overall pain among RA patients who have minimal evidence of inflammatory disease activity. This finding needs to be replicated in a larger study, designed specifically to examine the effects of milnacipran among RA patients in remission or with low disease activity.

Table: Means (standard deviations) for measures of pain

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Milnacipran</th>
<th>Change</th>
<th>Placebo</th>
<th>Milnacipran</th>
<th>Change</th>
<th>Unadjustedb</th>
<th>Adjustedc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td>Pain</td>
<td>4.5 (2.5)</td>
<td>3.8 (2.2)</td>
<td>-0.7 (1.5)</td>
<td>4.6 (2.6)</td>
<td>3.9 (2.3)</td>
<td>-0.7 (1.5)</td>
<td>0.4 (0.5)</td>
<td>0.3 (0.5)</td>
</tr>
<tr>
<td>Symptom Intensity Scale</td>
<td>6.2 (2.2)</td>
<td>5.7 (2.3)</td>
<td>-0.5 (1.0)</td>
<td>6.3 (2.5)</td>
<td>5.7 (2.3)</td>
<td>-0.6 (1.0)</td>
<td>0.2 (0.4)</td>
<td>0.1 (0.4)</td>
</tr>
<tr>
<td>Wrist Pain Threshold</td>
<td>4.6 (2.7)</td>
<td>3.7 (2.4)</td>
<td>-0.9 (1.3)</td>
<td>4.7 (2.9)</td>
<td>3.8 (2.5)</td>
<td>-1.0 (1.3)</td>
<td>0.1 (0.5)</td>
<td>0.0 (0.5)</td>
</tr>
<tr>
<td>Finger Pain Threshold</td>
<td>7.1 (3.3)</td>
<td>6.5 (3.1)</td>
<td>-0.6 (1.1)</td>
<td>7.0 (3.3)</td>
<td>6.6 (3.1)</td>
<td>-0.4 (1.1)</td>
<td>0.3 (0.6)</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>Conditioned Pain Modulation</td>
<td>5.4 (2.5)</td>
<td>4.7 (2.1)</td>
<td>-0.7 (0.9)</td>
<td>5.4 (2.6)</td>
<td>4.7 (2.2)</td>
<td>-0.7 (0.9)</td>
<td>0.3 (0.4)</td>
<td>0.2 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BPI-sf, Brief Pain Inventory – short form.a Based on a 0–10 scale with 10 being worse pain.b For comparisons between treatment periods, changes from baseline were assessed using paired t-tests.c P-values for the difference between the values during milnacipran vs. placebo using linear mixed models including treatment, crossover period and treatment sequence.

Disclosure: Y. C. Lee, Forest Research Institute, 2, Merck Pharmaceuticals, 1, Cubist Pharmaceuticals, 1, Perigo, 1, Express Scripts, 1, E. Massarotti, Amplementum, 5, Alexion Pharmaceuticals, Inc., 5, Human Genome Sciences, Inc., 2, Bristol Myers Squibb, 2, Sanofi-Aventis Pharmaceutical, 2, R. R. Edwards, None, B. Lu, None, C. C. Liu, None, Y. Lo, None, A. Wolffahrt, None, N. Kim, None, J. Goesling, None; D. H. Solomon, Pfizer Inc, 2, Angen, 2, Lilly, 2, Coronna, 2, UpToDate, 7.

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Pain as Predictor of Organ Involvement in Fabry Disease. Pierre Kaminsky1, Frederic Barby1, Roland Jaussaud2, Francis Gaches3, Vanessa Leguy-Sequin3, Eric Hachulla4, Thierry Zenone5, Christian Lavigne6, Claire Douillard7, Isabelle Marie8, Boris Bienvenu1, Bertrand Dussol7 and Olivier Lidove1. 1. CHU Nancy, Vandoeuvre, France, 2. CHU Vaudois, Lausanne, Switzerland, 3. CHU de Reims, Reims, France, Hôpital Duccuing, Toulose, France, 4. CHU Dijon, Dijon, France, 5. Lille University, Lille, France, 6. CH de Valence, Valence, France, 7. CHU d’Angers, Angers, France, 8. CHU Lille, Lille, France, 9. CHU de Rouen, Rouen, France, 10. CHU Côte de Nacre, CaEN, France, 11. AP Marseille, Marseille, France, 12. Hôpital Croix-Saint-Simon, PARIS, France.

Background/Purpose: Fabry disease (FD) in a X-linked hereditary lysosomal disorder due to alphagalactosidase A deficiency, leading to the accumulation of its substrate (globotriaosylceramide) in vessels, neurons, and heart. Pains are the most clinical disabling symptom in children and young adults, characterized by chronic or acute burning sensation in the extremities. These acroparesthesias are often misdiagnosed as rheumatological disorders. Angiokeratomas, hypohidrosis and cornea verticillata are other common early clinical symptoms. Hearing loss, hypertrophic cardiomyopathy, renal involvement and cerebrovascular disorders are the main complications, occurring after the second decade. Early diagnosis is crucial since the sooner enzyme replacement therapy (ERT) is prescribed in FD patients, the more efficient it is. The goal of this study was to determine the clinical
pertinence of acroparesthesia to predict organ involvement in Fabry patients.

Methods: Two hundred Fabry patients were systematically investigated for clinical symptoms i.e. acroparesthesia (ACR), angiokeratoma (AGK), hypohidrosis (HHD), and cornea verticillata (CV) and for organ complications i.e. hypoacusia (HAC), cerebrovascular (CER), renal (KDN) and heart (HEA) complications. Statistical analysis included Fischer’exact test and multiple stepwise logistic regression, a p-value lower than 0.01 being considered a significant result.

Results: Patients were 78 males, aged 37.7 ± 14.3 years and 122 females, aged 42.2 ± 16.4 years. Male patients were more symptomatic than women for pain (70.5% vs 50.8%; p=0.004) but also for other clinical symptoms: AGK (64.4% vs 27.9%; p<0.0001), HHD (66.7% vs 18.0%; p<0.0001), CV (62.8% vs 45.9%, p=0.02). They were also more severely affected: HAC (40.0% vs 20.8%, p=0.004), HEA (53.8% vs 31.1%, p=0.001), KDN (39.7 vs 16.3%; p<0.001), but not for CER. Compared with others, patients who presented pains had a risk of HAC 3.03 higher (1%CI: 1.41 – 6.50), of KDN 2.12 higher (1%CI 1.02 – 4.38), of HEA 1.80 higher (1%CI 1.08 – 3.00) than others. Presence of HHD, AGK and CV also correlated with organ complications. In multivariate analysis, after adjustment for age and gender, the absence of pain was an independent predictor for the absence of HAC (p<0.0001), of HEA (p<0.001), and of KDN (p=0.008). The same results were obtained after inclusion of AGK, HHD and CV in multivariate analysis.

Conclusion: Fabry patients who exhibited chronic or acute acroparesthesia are at higher risk of organ involvement. Pains appear the best clinical predictor for Fabry complications. This early clinical symptom should be recognized by clinicians in order to start ERT as soon as possible.

Disclosure: P. Kaminsky, SHIRE HGT, 6, Genzyme Corporation, 6, F. Barbeby, SHIRE, 6, Genzyme Corporation, 6, R. Jaussaud, SHIRE, 6, Genzyme Corporation, 6, F. Gaches, None; V. Leguy-Seguin, SHIRE, 6, Genzyme Corporation, 6, E. Hachulla, Genzyme Corporation, 6, T. Zenone, SHIRE, 6, C. Lavigne, None; C. Douillard, None; I. Marie, Genzyme Corporation, 6, B. Bienvenu, Genzyme Corporation, 6, Shire, 6, B. Dussol, None; O. Lidove, SHIRE, 6, Genzyme Corporation, 6.

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A total of 79 patients were analyzed, median age 43 ± 14 yrs.

Table 1: Summary of results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males</th>
<th>Females</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>33 (42)</td>
<td>46 (58)</td>
<td></td>
</tr>
<tr>
<td>Index case</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age at pain onset</td>
<td>10 ± 8.3</td>
<td>19 ± 15.4</td>
<td></td>
</tr>
<tr>
<td>Maximal intensity</td>
<td>Median 7 (quartiles 5.9)</td>
<td>Median 6 (quartiles 5.8)</td>
<td></td>
</tr>
</tbody>
</table>

Before diagnosis of FD, other causes of pain were considered (M: n=15; F: n=8); anxiety (n=25), growing pain (n=17), rheumatic fever (n=7), rheumatoid arthritis (n=1). Still disease (n=1). Raynaud’s phenomenon was present in 25 patients (30%). Only 18% of M and 15% of F had no pain according to the physician. The association of crisis and persistent pain was the most observed phenotype (M: 51%; F: 43%). Pain crisis corresponded to burning sensation (M=F), tingling (M=F), electric discharge (M=only). Pain crisis duration ranged from few minutes (one third) to few days (M: 18.2%, F: 11%). Other symptoms were more frequent in M than in F; sweating disorders (p=0.02), lymphedema (p=0.02), high creatinine level (p=0.04). Intra-familial other cases of pain in extremities were found with differences between genders: father’s pain only in F (p=0.002), children’s and cousin’s pain more frequently found in F (p=0.003 and p=0.002, respectively). NPSI questionnaire was performed in 75 cases. Agreement between patient and physician was good (kappa 0.73, C95% 0.57-0.90). Patients with pain were treated with ERT in 69.4% of cases whereas patients without pain were treated with ERT in 61.5%. ERT was the most effective therapy on pain in only two males.

Conclusion: Diagnosis and treatment of neuropathic pain are important in FD. Burning pain in the extremities, and frequent pain in relatives may be a tool for an early diagnosis. The higher frequency of chronic pain in females may imply clinical, psychological, and social components of pain. Treatment of pain in FD patients should not be limited to pharmacological therapies, but include personal and family management, to address psychosocial functioning.

Disclosure: O. Lidove, None; E. Noel, None; E. Hachulla, None; F. Gaches, None; C. Douillard, None; B. Darne, None; K. H. Ly, None; C. Lavigne, None; A. Masseau, None; L. Aaron, None; B. Bienvenu, None; T. Zenone, SHIRE, 6; P. Vitielli, None; V. Leguy-Seguin, SHIRE, 6, Genzyme Corporation, 6, J. M. Ziza, None.

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Quality of Life Assessment of Adults Patients with X-Linked Hypophosphoremia. Karine Briot1, Hélène Che2, Adrien Ethélo1, Anya Rothenbühler3, Peter Kamenicky,4 Agnès LIngart1 and Christian Roux1, 1Paris Descartes University, Paris, France; 2Hôpital Bichat, Kremlin Bicêtre, France; 3Vall d’Hebron University, Barcelona, Spain; 4Institut Curie, Paris, France.

Background/Purpose: X-Linked Hypophosphataemia (XLH) is the most common form of heritable rickets. Although disease severity is variable, adults with XLH may suffer from skeletal symptoms leading to function disability. There are no data on the consequences of these symptoms on quality of life (QoL) of adults with XLH. The objective was to evaluate the QoL and the variables associated with low QoL in adult patients with XLH.

Methods: We conducted a cross sectional study in adult patients with XLH, who consulted in rhenumatology, for skeletal symptoms, between 2013 and 2014. We assessed the intensity of pain (VAS Visual Analogic Scale) and QoL using 3 Patient Reported Outcomes: HAQ (Health Assessment Questionnaire, high if >0.5), RAPID3 (Routine Assessment of Patient Index Data 3, high if >6) and 36-item short-form health (SF36) survey. We also collected demographic and disease characteristics, radiographic features and data on treatments of XLH. We described the QoL of XLH patients and analysed the variables associated with low QoL.

Results: Thirty two patients with XLH (27 women; mean age of 42.8 yrs) with PHEX mutations were included. 15 (48.4%), 16 (51.6%), 12 (40%) received respectively phosphate supplements, vitamin D analogues, and 25 OH-vitamin D supplements, at the time of assessment. X-rays showed osteoarthritis (knee, hip or spine) (n=27, 90%), enthésopathies (n=19, 61.3%) and sequelae of insufficiency fractures (n=4, 14.8%). Skeletal pain
was reported by 64.3% of patients with a mean VAS of 4.6 (+/-2.6). Age is significantly associated with low QoL (p≤0.05), indicated by high scores of HAQ (mean value 0.71±0.6, HAQ >0.5 in n=19). RAPID3 (mean value 11.32 ± 6.4, RAPID3 >6 in n=23), and physical domains of SF36 (physical functioning (mean value 58.4± 23.6) and physical role (mean value 37.5± 39.1)). Rheumatoid arthritis was associated with low QoL indicated by high HAQ (p≤0.05). Radiographic enthesopathies were significantly higher in patients with high RAPID3 and low bodily pain scale of SF36 (mean value 55 ± 24) (p≤0.05). Phosphate supplements, vitamin D analogues and physiotherapy treatments were associated with high general health (mean value 40.23±17.1) and social functioning (mean value 70.31±21.7) scales of SF36 (p≤0.05).

**Conclusion:** This study showed that QoL of adults with XHL is altered; age and radiographical involvement (osteoarthritis and enthesopathies) are significantly associated with low QoL; adults treated for XHL reported better general health and social functioning scores.

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**Pain Characteristics Among Patients with Rheumatoid Arthritis in the Context of Patient-Physician Discordance in Disease Activity Assessments.** John M. Davis III, Cynthia S. Crowson, Tim Bongartz, Clement J. Michet, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

**Background/Purpose:** Healthcare must be patient-centered to achieve optimal outcomes and quality of life. From this perspective, it is significant that patients with rheumatoid arthritis (RA) sometimes rate their disease activity as much higher than their rheumatologists. This ‘discordance’ is mediated in part by patient-reported pain. In this study, our objective was to characterize the qualities of pain reported by patients in the context of patient-physician discordance.

**Methods:** We conducted an observational study of consecutive patients with RA recruited between July 2008 and December 2010. A physician joint assessor, who was independent from treatment decision-making, performed a standardized clinical evaluation. Positive discordance was defined as the patient global assessment being ≥25-mm higher than the physician global assessment of disease activity. Patients completed the pain visual analog scale (VAS; range: 0 – 100 mm) and the Short Form McGill Pain Questionnaire (SF-MPQ), including the sensory (range: 0 – 33) and affective (range: 0 – 12) scales. Examples of sensory characteristics are “sharp, aching or throbbing,” and examples of affective characteristics are “sickening, fear-causing, or punishing-cruel.” We abstracted electronic medical records to collect demographics, laboratory data, smoking status, and body mass index (kg/m²). Correlations between explanatory variables and the presence of positive discordance were determined using Spearman methods, adjusting for RA characteristics.

**Results:** A total of 127 patients with RA were recruited (mean age 55.6 years; mean disease duration 6.8 months; 63% female). The mean (SD) pain VAS was 47 (26) mm. The median (range) scores for the SF-MPQ sensory and affective scales were 10 (0 to 29) and 2 (0 to 9). Positive discordance (i.e., patient high) was associated with higher pain (r = 0.37, p < 0.001) and fatigue (r = 0.32, p < 0.001). The SF-MPQ data showed that positive discordance was more strongly associated with affective characteristics of pain (r = 0.30, p < 0.001) than sensory characteristics of pain (r = 0.23, p = 0.013). The association of positive discordance with SF-MPQ affective pain was independent of age, sex, rheumatoid factor, anti-CCP antibodies, body mass index, smoking status, and use of prednisone or disease-modifying drugs.

**Conclusion:** The significance of this study is that in the context of positive discordance, patients are more likely to describe their pain using words that have affective or emotional connotations. This finding could reflect activation of pain, mood, and fear networks in the brain. Future research should evaluate the connectivity between these brain networks in the setting of patient-physician discordance and determine their relationship to subclinical immune/inflammatory status. The positive impact could be the development of new approaches that better alleviate pain and improve quality of life in our patients.

**Disclosure:** J. M. Davis III; None; C. S. Crowson; None; T. Bongartz; None; C. J. Michet; None; E. L. Matteson; None; S. E. Gabriel; None.

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**Development of Pediatric Item Banks to Measure Pain Behavior in the Patient Reported Outcomes Measurement Information System.** Esi Morgan DeWitt1, Kimberly Barnett2, Wen-Hung Chen2, Jennifer Farrell1, Dennis Revicki2, Adam Carle3, Karen Cook4, Kenneth Goldschneider5, Carlton Dumper6, David D. Sherry7 and Susmita Kashikar-Zuck8. 1Amsterdam Rehabilitation Research Center and 2Children’s Hospital of Philadelphia, Philadelphia, PA.

**Background/Purpose:** The NIH Patient Reported Outcomes Measurement Information System (PROMIS) has created publicly available patient reported outcomes measures in several domains of physical, social and emotional health. Measurement of pediatric pain in PROMIS is currently limited to pain interference. Pain behaviors are observable actions or reactions that communicate pain including verbal, non-verbal and pain reducing behaviors. Numerous validated parent/provider-rating scales of pain behavior in children exist but there are currently no validated self-report measures of pain behavior in school-age children and adolescents. Such measures could be useful in establishing targets for treatment and assessing outcomes. The aim of this study is to enhance PROMIS pediatric pain assessment by developing and testing pediatric pain behavior item banks for self- and proxy-report.

**Methods:** Candidate items were developed through a qualitative item review process, and were in the format, “In the past 7 days, when I was in pain...” Patients ages 8 to 17 years, or parents/guardians of children, with a chronic painful condition (fibromyalgia, juvenile idiopathic arthritis, sickle cell disease) were recruited through outpatient clinics at 3 centers. Child participants completed approximately 100 PROMIS items concerning their pain (including 47 candidate pain behavior items), physical function, fatigue, and psychosocial well-being. Proxies responded to socio-demographic and health history items and 51 new candidate proxy-report pain behavior items were collected. A confirmatory factor analysis (CFA) was performed on the child and guardian pain behavior data, with model fit assessed by the comparative fit index (CFI) and root mean square error of approximation (RMSEA). Item response theory (IRT) analysis was performed on the pain behavior items based on the graded response model. Differential item functioning (DIF) was assessed by age group and disease group.

**Results:** 450 children (71% female; M Age: 13.54), and 232 proxies participated. CFA indicated unidimensionality in the child (CFI=0.962; RMSEA=0.079) and proxy pain behavior responses (CFI=0.970; RMSEA=0.080). The responses for the child and proxy data had good IRT model fit and were free of local dependence. Slopes for the pediatric responses ranged from 1.81 (“rubbed body where hurt”) to 4.40 (“moved slower”), and thresholds ranged from -2.00 to 4.95. For the proxy data, slopes ranged from 1.51 (“think of something fun”) to 3.48 (“tried not to move”), and thresholds ranged from -3.02 to 2.43. Items performed well across disease groups and age. There was little DIF either by age group (8–12, 13–18) or by sample (child vs. proxy). Child and proxy scores were correlated at 0.70. Correlations between pain behavior and pain intensity were 0.60 in children and 0.48 in proxies for the self-report measures.

**Conclusion:** The PROMIS pediatric pain behavior item-banks for self and proxy report are suitable for use in non-adaptive format as short forms or in dynamic format as computerized adaptive tests in clinical research with the potential for adoption into clinical care.

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**Validation of the Dutch-Flemish Promis Physical Functioning Item Bank in Patients with Chronic Pain.** Martine Crips1, Caroline Terwee2, Niels Smits3, Anton de Vries3, Henrica de Vre1, Joost Dekker2, Rene Westhoven3, David Cella4, Karon Cook5, Dennis Revicki6, Jaap van Leeuwen6, Maarten Boers7 and Leo D. Roorda8. 1Amsterdam Rehabilitation Research Center, Reade, Amsterdam, Netherlands, 2VU University Medical Center, Amsterdam, Netherlands, 3VU University Medical Center EMGO Institute for Health and Care Research, Department of Epidemiology and Biostatistics,
Amsterdam, Netherlands, 4University of Leuven, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration; Rheumatology, University Hospital Leuven, Leuven, Belgium, 5Northwestern University Feinberg School of Medicine, Chicago, IL, 6Outcomes Research, United BioSource Corporation, Bethesda, MD, 7CEO Leones Group BV, Amsterdam, Netherlands, 8Amsterdam Rehabilitation Research Center | Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands.

Background/Purpose: In the assessment of chronic pain patients it is important to measure physical functioning. The National Institutes of Health’s Patient-Reported Outcomes Measurement Information System (PROMIS) initiative developed an item bank for measuring physical functioning. This PROMIS physical functioning item bank was translated into Dutch-Flemish language according to the FACTT methodology. The aim of current study was to validate the Dutch-Flemish translation of the PROMIS pain behavior item bank (DF-PROMIS-PB) and the Dutch-Flemish PROMIS pain interference item bank (DF-PROMIS-PI) in patients with chronic pain.

Methods: A paper-and-pencil or web-based survey, including the full DF-PROMIS-PF (121 items), was completed by 857 chronic pain patients (77% female, mean age 49y) satisfying the ACR classification criteria of chronic pain and referred to an outpatient secondary care center for rheumatology and rehabilitation in the Netherlands. One-dimensionality was evaluated by one-factor confirmatory factor analysis. With the future strategy to develop computer adaptive tests (CAT), item response theory (IRT) models were used to evaluate the item characteristics of the two item banks. A graded item response model (GRM) was fitted and Differential Item Functioning (DIF) was evaluated for e.g. language (Dutch vs. English), by ordinal regression models. Furthermore, construct validity was studied.

Results: Through computer technical limitation, the item bank was separated during statistical analysis into DF-PROMIS-PF (50 PFA-items) and DF-PROMIS-PF-PBC (45 PF-PF and 26 PF-BC items). These interim analysis showed that the DF-PROMIS-PF-PBC demonstrated good fit to a one-dimensional model (both CFI=0.976 and TLI=0.975). The first factor accounted for 57% of the questionnaire variance. The results showed acceptable test information (SE<0.3) for theta between -2.3 and 3.8 for DF-PROMIS-PF-PBC and between -1.6 and 4 for DF-PROMIS-PF. The items demonstrated no DIF with respect to age, gender, and language (Dutch vs. English). However, the impact of DIF on the total item scores was minimal. The analyses of the full DF-PROMIS-PF are in progress and will be presented at the ACR conference.

Conclusion: The first results indicate that the DF-PROMIS-PF fits a GRM and demonstrates good coverage across the range of the physical functioning domain. Nearly all Dutch item parameters match the American item parameters and likely Dutch-specific item calibrations are not needed. The DF-PROMIS-PF can be used to develop a CAT.

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Validation of the Dutch-Flemish PROMIS Pain Behavior and Pain Interference Item Banks in Patients with Chronic Pain. Martine Crins1, Leo D. Roorda2, Niels Smits3, Henrica de Vet4, Rene Westhovens5, David Celli6, Karen Cook7, Dennis Revicki3,2, Jaap van Leeuwen2, Maarten Boers7, Joost Dekker7 and Caroline Terwee6. 1Amsterdam Rehabilitation Research Center | Reade, Amsterdam, Netherlands, 2Amsterdam Rehabilitation Research Center | Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, 3VU University Medical Center EMGO Institute for Health and Care Research, Department of Epidemiology and Biostatistics, Amsterdam, Netherlands, 4VU University Medical Center, Amsterdam, Netherlands, 5University of Leuven, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration; Rheumatology, University Hospital Leuven, Leuven, Belgium, 6Northwestern University Feinberg School of Medicine, Chicago, IL, 7Outcomes Research, United BioSource Corporation, Bethesda, MD, 8CEO Leones Group BV, Amsterdam, Netherlands.

Background/Purpose: In the assessment of chronic pain patients it is important to measure pain behavior and pain interference. The National Institutes of Health’s Patient-Reported Outcomes Measurement Information System (PROMIS) initiative developed item banks for measuring pain behavior and pain interference. These PROMIS item banks were translated into Dutch-Flemish language according to the FACIT methodology. The aim of current study was to validate the Dutch-Flemish translation of the PROMIS pain behavior item bank (DF-PROMIS-PB) and the Dutch-Flemish PROMIS pain interference item bank (DF-PROMIS-PI) in patients with chronic pain.

Methods: A paper-and-pencil or web-based survey, including the full DF-PROMIS-PB (39 items, 6-point Likert scale) and DF-PROMIS-PI (41 items, 5-point Likert scale) was completed by 1042 chronic pain patients satisfying the ACR classification criteria of chronic pain and referred to an outpatient secondary care center for rheumatology and rehabilitation in the Netherlands. One-dimensionality was evaluated by one-factor confirmatory factor analysis. With the future strategy to develop computer adaptive tests (CAT), item response theory (IRT) models were used to evaluate the item characteristics of the two item banks. A graded item response model (GRM) was fitted and Differential Item Functioning (DIF) was evaluated for e.g. language (Dutch vs. English), by ordinal regression models. Furthermore, construct validity was studied.

Results: DF-PROMIS-PB and DF-PROMIS-PI demonstrated good fit to a one-dimensional model (CFI=0.960; 0.988 resp. and TLI=0.958; 0.987 resp). The first factor accounted for 42% (DF-PROMIS-PB) and 66% (DF-PROMIS-PI) of the questionnaire variance. The results showed acceptable test information (SE<0.3) for theta between -1.9 and 3.6 for DF-PROMIS-PB and between -3.3 and 2.8 for DF-PROMIS-PI. Out of 741 (1.9%) DF-PROMIS-PB item pairs and 62 out of 820 (7.6%) DF-PROMIS-PI item pairs were marked as possibly locally dependent. The items demonstrated no DIF with respect to age, gender, and survey version. DIF with respect to language was present for 6 DF-PROMIS-PB items and 2 DF-PROMIS-PI items. However, the impact of DIF on the total item scores was minimal. The analyses of the full DF-PROMIS-PB are in progress and will be presented at the ACR conference.

Conclusion: The DF-PROMIS-PB and the DF-PROMIS-PI fit a GRM and demonstrate good coverage across the range of the pain behavior and pain interference domain. Nearly all Dutch item parameters match the American item parameters and likely Dutch-specific item calibrations are not needed. The DF-PROMIS-PB and DF-PROMIS-PI can be used to develop a CAT.

Disclosure: M. Crins, None; L. D. Roorda, None; N. Smits, None; H. de Vet, None; R. Westhovens, None; D. Celli, None; K. Cook, None; D. Revicki, None; J. van Leeuwen, None; M. Boers, None; L. D. Roorda, None.

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Longitudinal Assessment of Promis Pediatric Item Banks in Children with Chronic Musculoskeletal Pain. Esi Morgan DeWitt1, Adam Carle1, Kimberly Barnett1, Jennifer Farrell1, Kenneth Goldschmied2, Carlson Dampier2, David D. Sherry1 and Sumita Kashikar-Zuck1. 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 2Emory University School of Medicine, Atlanta, GA, 3Children’s Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Assessing clinical status in musculoskeletal pain syndromes requires self-report of pain and function. Yet, the field suffers from a lack of psychometrically sound, consistently applied measurement tools, limiting clinical practice and research. In this study, we used longitudinal data to evaluate the validity and responsiveness of the Patient Reported Outcomes Measurement Information System (PROMIS) pediatric item banks (physical function (PF), pain impact, fatigue, emotional distress, social role) among children receiving treatment for chronic musculoskeletal pain at two clinics.

We expected each domain to improve across time, but we expected domains most closely aligned with treatment (i.e., pain and fatigue) to improve more and domains more distally related (i.e., peer relationships) to improve less. Additionally, we expected scores to improve more quickly among children receiving intensive, inpatient treatment vs. those receiving treatment at an outpatient clinic.

Methods: Across 2 multi-disciplinary pediatric pain clinics, we collected data from patients receiving treatment for a chronic painful condition (n= 145: aged 8–18 years). Across 3 visits, patients completed PROMIS self-report short form measures (~7 items each) that assessed: pain impact, PF-upper extremity, PF-mobility, fatigue, anger, anxiety, depressive symptoms, and peer relationships. PROMIS measures are normed in the general population and have a mean of 0 and standard deviation (SD) of 1. For each measure, higher values reflect more of the measured domain (e.g., higher pain impact scores reflect more pain impact, higher PF-mobility scores reflect better mobility). We used longitudinal growth models (LGM) to examine change across time.
Results: At study’s start, mean domain levels ranged from -1.26 SDs below the general population (mobility) to 0.97 SDs above (pain), indicating more pain and poorer function. LGM revealed that each domain demonstrated statistically significant improvement across time. The average monthly change ranged from 0.014 (peer relationships) to -0.074 (pain). Fatigue, PF-mobility and showed changed at rates similar pain impact’s, PF-upper extremity’s, anxiety’s, and depression’s changed at rates similar to peer relationships’. In all models, rates of change showed statistically significantly differences across site in the expected directions.

Conclusion: We tested responsiveness to change of PROMIS pediatric domains in youth with chronic musculoskeletal pain. Consistent with expectations, 1) children in the clinical clinics reported poorer quality than general population; 2) domains most closely related to treatment (pain impact, fatigue, and mobility) demonstrated the most change, 3) domains more distally related to treatment (e.g., peer relationships) showed the least improvement, and 4) across domains, the measures indicated intensive, inpatient treatment resulted in more rapid improvement than outpatient treatment. Results support the construct validity and responsiveness of PROMIS instruments. Future clinical research in pediatric pain should consider utilizing the PROMIS pediatric items banks.

Disclosure: E. Morgan DeWitt, None; A. Carle, None; K. Barnett, None; J. Farrell, None; K. Goldschneider, None; L. Dampier, None; D. D. Sherry, None; S. Kashkar-Zuck, None.

263 Nutraceutical Products and Pain or Non-Pain Medications Use in Patients with Knee Osteoarthritis. Mei Chung1, John B. Wong2, Shouyi Chang2 and Chenchen Wang3; 1Tufts University School of Medicine, Boston, MA, 2Tufts Medical Center, Boston, MA.

Background/Purpose: Knee osteoarthritis (OA) causes substantial health burden and economic costs including medications and nutraceuticals for pain. The aim of this analysis was to describe contemporary use of medications and nutraceutical products in patients with knee OA.

Methods: Knee OA patients meeting ACR criteria for enrollment into a randomized clinical trial reported their use of prescription and over-the-counter medications and nutraceutical products during the prior 6 months using the HAQ health utilization form. We analyzed the number of pain medications, non-pain medications, and nutraceutical products taken by each patient and WOMAC questionnaire measures of pain and physical function. The T-test, Fisher’s exact test and multivariable ordered logistic regression were used to assess statistical differences between groups and associations. All p-values were two-tailed, and results were reported as mean ± standard deviation.

Results: In 204 knee OA patients (mean age 60.2 years, 70% female, mean WOMAC pain 254 ± 95 and WOMAC function 895 ± 352, 157 (77%), 166 (81%), 150 (74%) reported taking at least one pain, non-pain medication, or nutraceutical, respectively (Table 1). On average, each patient used 1.2 ± 0.9 pain medications, 2.8 ± 2.5 non-pain medications, and 2.4 ± 2.3 nutraceutical products. Nutraceutical product use was higher in Whites (3.0 ± 2.4) than in Blacks (1.8 ± 2.0) or Asians (1.7 ± 2.0). Patients using nutraceuticals were significantly older (+3.9, P = 0.02) than those who did not without any significant differences by gender. Similarly patients who using non-pain medications were older than those who did not (+3.7 years, P = 0.05). In contrast, pain medication users were significantly younger (+4.4 years, P = 0.01) than those did not and more women used pain medications than men (81% vs. 67%, P = 0.05). WOMAC pain and function scores were significantly lower in nutraceutical users than in non-users (pain: 241 ± 97 vs. 291 ± 96, P = 0.001; function: 859 ± 357 vs. 1017 ± 316, P = 0.006). After controlling for age and sex, a higher number of nutraceuticals was associated with an improved WOMAC pain (P = 0.05) and function (P = 0.03) scores, but the number of pain and non-pain medications were not significantly associated WOMAC pain or function.

Conclusion: Nutraceutical and pain-medication use in OA patients is quite common and much higher in our patient population than in the Osteoarthritis Initiative (Arthritis Research & Therapy 2013, 15:R106). Concomitant and frequent uses of NSAIDs pain medications, nutraceutical products, and other medications for comorbidities in older knee OA patients is an area of concern, given the increased potential for side effects and drug-drug or drug-nutrient interactions.

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Table 1 Self-reported uses of non-pain and pain medications, and nutraceutical products in knee OA patients

<table>
<thead>
<tr>
<th>Nutraceutical products</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D and/or Calcium</td>
<td>201</td>
<td>41.4%</td>
</tr>
<tr>
<td>Multivitamins &amp; minerals</td>
<td>82</td>
<td>16.9%</td>
</tr>
<tr>
<td>Glucosamine/Chondroitin/MSM</td>
<td>36</td>
<td>7.4%</td>
</tr>
<tr>
<td>Fish oil</td>
<td>29</td>
<td>6.0%</td>
</tr>
<tr>
<td>Vitamin B</td>
<td>22</td>
<td>4.5%</td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>17</td>
<td>3.5%</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>17</td>
<td>3.5%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>7</td>
<td>1.4%</td>
</tr>
<tr>
<td>Folate</td>
<td>5</td>
<td>1.0%</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>5</td>
<td>1.0%</td>
</tr>
<tr>
<td>Probiotic</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Omegea-3</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Probiotic</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Nutraceuticals and non-pain medication classes</td>
<td>Freq</td>
<td>Percent</td>
</tr>
<tr>
<td>Non-pain medications (patient n = 150)</td>
<td>138</td>
<td>24.2%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>147</td>
<td>58.6%</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>88</td>
<td>53.5%</td>
</tr>
<tr>
<td>Opioids</td>
<td>16</td>
<td>6.4%</td>
</tr>
<tr>
<td>Miscellaneous non-pain medications</td>
<td>31</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Subtotal 483 100%

Pain medications (patient n = 157)

| Subtotal 251 100% |
| Subtotal 567 100% |

Legends: Freq = Frequency; MSM = Methylsulfonylmethane. "Total number of unique miscellaneous nutraceuticals and non-pain medications that was reported once in our study population.

Disclosure: M. Chung, None; J. B. Wong, None; S. Chang, None; C. Wang, None.

264 Efficacy and Safety of Cannabidiol Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. Tara Landry1, Mary-Ann Fitzcharles2, Peter A. Ste-Marie2 and Yoram Shir2; 1McGill University Health Centre, Montreal, QC, 2McGill University Health Centre, Montreal, QC.

Background/Purpose: The endocannabinoid system functions to maintain homeostasis in the human body and thereby has effects on modulation of pain and inflammation. Cannabidiol preparations are available as synthetic or plant derived products and may be effective for the management of pain associated with musculoskeletal conditions. We have conducted a systematic review to examine the evidence on the efficacy and side effects of cannabidiol (cannabidiol- and synetheto-1) in the management of rheumatic pain.

Methods: A comprehensive literature search of the following databases was conducted in September 2013: MEDLINE; Embase Classic + Embase; BIOSIS Previews; Scopus; CENTRAL; DARE; CINAHL; PsyInfo; AMED. Additional searches for ongoing clinical trials were also run in ClinicalTrials.gov, International Clinical Trials Registry Platform, Current Controlled Trials, Natural Standard, as well as various Drug and Device Regulatory Approval Sites. Further studies were identified in Web of Science and Scopus (March 2014) by citations searches for studies citing included studies, as well as by examining their reference lists. Randomized controlled trials (RCT’s) with outcomes investigating pain and sleep disturbance in rheumatic conditions, with comparison of an active therapy with placebo were included. Study quality was assessed using the Jadad scale (out of 5). In view of a paucity of studies, heterogeneous populations, and different products, only a systematic review is reported.

Results: Of the 1407 articles screened, 12 underwent full text examination. Excluded were survey reports, observational studies, case series, case reports and commentaries, with 7 remaining articles. Of these 3 were excluded: two included patients with non-rheumatic diseases, 1 was an open-label study of effect of THC on experimentally induced pain. The remaining 4 studies comprised 201 patients (58 RA, 72 FM, and 74 OA). One study examined the effect of nabiximols in RA, 2 studies examined nabilone in FM (one a non-inferiority study with amitriptyline as comparator), and one examined the effect of a fatty acid amide hydrolase-1 (FAAH1) inhibitor in OA. The quality of the trials was good, with a mean 3.75
Prevalence of Medicinal Marijuana Use Among 1000 Rheumatology Patients Attending a Community-Based Rheumatology Clinic: A Prospective Cross-Sectional Study. Peter A. Ste-Marie,1 Yoram Shir1. Emmanouil Rampakakis2, John S. Sampalis2, Martin Cohen3, Michael Starr4, Mark A. Ware1 and Mary-Ann Fitzcharles4. 1McGill University Health Centre, Montreal, QC. 2JSS Medical Research, Montreal, QC. 3Mcgill University Health Centre, Montreal, QC.

Background/Purpose: With a worldwide groundswell of interest in cannabinoids as a possible treatment option for persons with rheumatic diseases, and with few pharmacologic cannabinoid options available, patients may be using marijuana mostly to self-medicate. “Severe arthritis” was cited as the diagnosis for 65% of persons legally authorized to possess medicinal marijuana in Canada in 2014. With knowledge that most medicinal marijuana is obtained illegally, and by extrapolating from Canadian census data of 2011, conservative estimates are that 4% of persons with rheumatic complaints may be using cannabis, with an even higher rate expected for those in rheumatology care. As there is currently no knowledge of the prevalence of use of marijuana in a defined rheumatology population, we have prospectively examined the use of herbal cannabis for 1000 rheumatology attenders.

Methods: The study was approved by the Institutional Ethical Review board and informed consent was obtained from every participant. During a two month period (April-May 2014), consecutive patients attending an academic, community based rheumatology clinic staffed by 3 rheumatologists were invited to participate. Patients were either newly referred or attending for a follow up visit. The study comprised 2 questionnaires completed at the time of the visit: 1) demographic and disease related information completed by the rheumatologist, 2) patient anonymous report of current health status, pain severity and past or current marijuana use for either recreational or medicinal purposes, or both.

Results: Of the 1067 patients attending, 1000 (96%; 74% females; mean age 63 ± 15 yrs) agreed to participate. Thirty seven patients refused to participate and 30 were not eligible. Disease categories were as follows: inflammatory arthritis 516 (52%), osteoarthritis or back pain, 489(49%) soft tissue rheumatism or fibromyalgia, 218 (22%), and other condition, 99(10%) with some overlap of diagnoses. Medicinal marijuana was reportedly used by 28 patients (2.8%; 95% CI: 1.9–4.2). Users vs. non users were more likely to be younger, 53 vs.63 yrs (p = 0.0003), unemployed or disabled 46% vs. 8% (p<0.001), and with a trend to be male. Diagnoses did not differ between the users and nonusers, but users reported poorer global well-being 5.5 vs. 4.8 (p = 0.0088), more pain 6.3 vs 4.8 (p < 0.0001), and previous recreational cannabis use 82% vs 19% (p<0.0001). The Physician global assessment of health status did not differ significantly between the groups 3.2 vs 2.8 (p = 0.2901).

Conclusion: Contrary to the expected rate, only 2.8% of patients, receiving rheumatology care for multiple rheumatic disease categories, reported current use of medicinal marijuana. With use observed across all disease categories, familiarity with marijuana as a recreational product may explain use for some. Perceived health status was poorer for users, with almost half not working.

Disclosure: P. A. Ste-Marie. None; Y. Shir. None; E. Rampakakis. None; J. S. Sampalis. None; M. Cohen. None; M. Starr. None; M. A. Ware. None; M. A. Fitzcharles. None.

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An Examination of the Interaction of Opioid Use, Pain, and Depression. Jenna Goesling1, Matthew Henry1, Stephanie Moser2, Paul Hilliard2, Afton L. Hassett3 and Chad Brummett4. 1University of Michigan, Ann Arbor, MI, 2University of Michigan Medical School, Ann Arbor, MI.

Background/Purpose: In the past two decades there has been an increase in the use of opioids to treat chronic pain. Despite this trend, there is little empirical evidence to support the use of long-term opioid therapy in clinical practice. Chronic pain and psychiatric disorders are highly comorbid, yet patients with psychiatric diagnoses are typically excluded from opioid efficacy trials. Clinically, patients with depression and anxiety are more likely to receive opioid therapy. We hypothesized that patients taking opioids would present with a worse clinical phenotype (i.e., more pain, less functioning, and more symptoms of depression and anxiety). We also hypothesized that the relationship between opioid use and pain severity and interference would be moderated by depression.

Methods: A total of 2,104 new patients seeking treatment for chronic pain at the University of Michigan’s Back & Pain Center were included. Pain severity and pain interference were measured with the Brief Pain Inventory (BPI), symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS), catastrophizing was assessed using the related subscale from the Coping Strategies Questionnaire (CSQ), and physical functioning was assessed using PROMIS SFI. Chi-square, t-tests, and analysis of covariance tests were conducted.

Results: Opioid use was associated with a worse clinical phenotype (Table 1). Depression moderated the relationship between opioid use and pain interference (Figure 1) and pain severity (Figure 2). There was no difference in pain interference by opioid group for depressed patients, but non-depressed opioid users reported more pain interference than non-depressed non-opioid users (p<0.001) (Figure 1). The same moderated effect was found for pain severity (p<0.001) (Figure 2).

Conclusion: The relationship between opioid use, pain, and depression is complex. Understanding the interaction at a biopsychosocial level is important in order to inform clinical practice. Although causal conclusions cannot be made, this study found patients using opioids present with a worse clinical phenotype. Future longitudinal studies are needed to assess directionality of the relationship and determine whether opioids are the best course of treatment for depressed patients.

Table 1 Phenotypic profiles of opioid and non-opioid users.

| Opioid use | Yes N = 1,176 | No N = 928 | p*
|-----------|---------------|------------|-------
| Male      | 484 (41.2%)   | 378 (40.7%) | .844 |
| Caucasian | 1,073 (91.2%) | 817 (88.0%) | .016 |
| Age       | 49.03 (14.2)b | 48.9 (15.3) | .806 |
| HADS Depression | 9.70 (4.3) | 7.77 (4.6) | <.001 |
| HADS Anxiety | 9.06 (4.4) | 7.99 (4.3) | <.001 |
| CSQ       | 17.6 (9.4)    | 14.5 (9.5)  | <.001 |
| PROMIS    | 29.9 (7.7)    | 33.9 (8.5)  | <.001 |
| BPI Pain Interference | 7.33 (1.8) | 6.20 (2.3) | <.001 |
| BPI Pain Severity   | 6.58 (1.6)   | 5.97 (1.9)  | <.001 |

a. Chi-square tests were conducted for categorical variables and independent samples t-tests were conducted for continuous variables.
b. Mean and standard deviation reported for continuous variables.

Figure 1. Relationship between opioid use and pain interference moderated by depression.
The Effect of Treatment with Resiniferatoxin and Capsaicin on Dynamic Weight Bearing Measures and Evoked Pain Responses in a Chronic Inflammatory Arthritis Murine Model. Joseph Bert¹, Christopher W. Dorman², Sandra Frizelle³, Sonia C. Funkenbusch¹, Hollis E. Krug¹ and Maren L. Mahowald³. ¹University of Minnesota Internal Medicine Residency, Minneapolis, MN; ²Minneapolis VA Health Care System, Minneapolis, MN; ³VA Health Care System, Minneapolis, MN. 4University of Minnesota Medical School and Minneapolis VA Health Care System, Minneapolis, MN.

Background/Purpose: Capsaicin (CAP) and Resiniferatoxin (RTX) are vanilloid receptor agonists that when given by intra-articular injections, can normalize Evoked Pain Scores (EPS) and Automated Dynamic Weight Bearing (ADWB) measures in carrageenan-induced acute inflammatory arthritis. To determine whether these vanilloid receptor agonists might have benefit in chronic inflammatory arthritis pain, we measured changes in ADWB and EPS due to joint pain in mice with Complete Freund’s Adjuvant (CFA) induced chronic inflammatory arthritis with and without treatment with intra-articular (IA) injections of CAP and RTX.

Methods: Chronic Inflammatory arthritis was produced by intra-articular injection of 30 μl of Complete Freund’s Adjuvant (CFA) into the left knee of C57BL6 male mice 3 weeks prior to pain behavior testing. One group of mice was injected with IA RTX (10μl of 0.001%) 7 days prior to measurement of EPS and ADWB. Similarly, another group of mice were injected with 10μl of 0.01% IA CAP 7 days before pain behavior testing. Evoked pain behavior was measured by tail-flicks and vocalizations per one minute with repeated palpation of the knee at 15.6 psi. ADWB (weight on each limb and time on each limb) was measured using an Automated Dynamic Weight Bearing apparatus (Biobes, Vitrolles, France).

Results: Chronic Inflammatory arthritis pain is demonstrated by increased EPS and reduced ADWB measures in the affected limb of arthritic mice. Mice have low EPS (0.5) and equal left to right DBW ratios for weight (0.9) and time (0.9) when compared with controls. Treatment with IA CAP 7 days prior to pain behavior testing resulted in improvement in EPS (1.38) and near normalization of left to right ADWB ratios for weight (0.99) and time (1.01) when compared to the chronic inflammatory arthritis model. Treatment with IA RTX 7 days prior to the exam led to improved EPS (1.67) and improved left to right ADWB ratios for weight (0.90) and time (0.98) when compared to the chronic inflammatory arthritis model. IA CAP alone and IA RTX alone did not have an impact on EPS or ADWB ratios when given 7 days prior to pain behavioral testing.

Conclusion: Using ADWB and EPS, we were able to quantitate pain in a murine chronic arthritis model. Intra-articular CFA administration resulted in a significant increase in EPS and decreased ADWB measures in the affected limb. Treatment with CAP and RTX in these mice improved pain measures as assessed by EPS and ADWB measures. These results are comparable to those previously reported when mice were pretreated in an acute inflammatory arthritis model. The optimal dose of RTX and CAP for therapeutic benefit and duration of response has yet to be determined.

Disclosure: J. Bert, None; C. W. Dorman, None; S. Frizelle, None; S. C. Funkenbusch, None; H. E. Krug, None; M. L. Mahowald, None.
Discontinuation of Concomitant Medication for Enthesitis-Related Arthritis during 52 Weeks of Treatment with Adalimumab. Shirley ML. Tse1, Rubén Burgos-Vargas2, Gerd Horneff3, Aileen L. Pangan4, Jasmina Kalabic5, Kristina Unnebrink3 and Jaclyn K. Anderson5.1 The Hospital for Sick Children, University of Toronto, Toronto, ON, 2Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, 3Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, 4AbbVie Inc., North Chicago, IL, 5AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

**Background/Purpose:** Children with enthesitis-related arthritis (ERA) require medical therapy to control inflammation and restore normal function; however, the use of multiple medications and for longer periods than needed is of special concern in the pediatric population. The objective of this analysis is to evaluate the proportion of patients (pts) who discontinued one or more concomitant medications for pediatric ERA during the first 52 weeks (wk) of adalimumab (ADA) treatment.

**Methods:** This is a phase 3, multicenter, randomized, double-blind study in pts aged ≥6 to <18 yrs with active ERA not responsive to ≥1 NSAID and ≥1 DMARD. Pts were randomized 2:1 to receive blinded ADA (24 mg/m² BSA up to 40 mg every other wk) or placebo (PBO) for 12 wks followed by open-label (OL) ADA up to 144 wks. Active disease was defined as: ≥3 active joints (AJC: swelling not due to deformity or joints with loss of motion plus pain and/or tenderness) and evidence of enthesitis in ≥1 location (documented in the past or present at baseline [BL]). Pts could enter the study on stable doses of concomitant NSAIDs, DMARDs, glucocorticoids (MTX) or sulfasalazine (SSZ), or corticosteroids (CSs); doses remained stable during the first 12 wks except as medically required due to adverse event (AE). Dose adjustment or treatment induction with these agents was permitted after wk 12. Discontinuation of concomitant ERA medications was not required in the protocol and was at the discretion of the treating physician. Concomitant use was defined as use of the drug at any time during the study through wk 52.

**Results:** 46 pts were randomized (PBO 15, ADA 31). At BL, mean duration of ERA symptoms was 2.6 yrs; mean AIC was 7.8, and mean enthesitis count was 8.1. Mean % change from BL to wk 12 in AIC (primary endpoint) was greater in the ADA group vs. PBO (–63% vs. –12%, P = 0.039), with 89% overall reduction in AIC from BL through wk 52. Prior use of NSAIDs, DMARDs, and CsSs was reported in 100%, 91%, and 57% of pts, respectively. Concomitant use of ERA drugs at BL is shown in the table. 16 pts (35%) started NSAIDs, 5 pts (11%) stopped DMARDs (2 SSZ, 3 MTX), and 7 pts (15%) stopped CSs without restarting prior to wk 52; NSAIDs were stopped in 3 pts due to AEs. 3 pts discontinued the study due to AE (2) or inefficacy (1) during OL period. Of those remaining in the study at wk 52, 8 /43 (19%) were completely off concomitant ERA drugs. At wk 52 mean % change from BL in AIC was 81.8% in pts who stopped NSAIDs, –97.1% in pts who stopped CSs without restarting prior to wk 52; NSAIDs, DMARDs, or corticosteroids were stopped in 3 pts (11%) stopped DMARDS (2 SSZ, 3 MTX), and 7 pts (15%) stopped CSs (1 location (documented in the past or present at BL)). Pts were inadequate responders or intolerant to ≥1 nonsteroidal anti-inflammatory drug (NSAID) and ≥1 disease-modifying antirheumatic drug (DMARD).

**Conclusion:** Clinical improvement with ADA through 52 wks allowed some pts to discontinue concomitant NSAIDs, DMARDs, or CsSs for ERA at the investigator’s discretion. Clinical response was generally maintained in pts who stopped 1 or more concomitant medications. Standardized discontinuation of concomitant ERA medications in ADA responders may have resulted in a higher number of pts able to discontinue concomitant ERA therapies.

**Disclosure:** S. M. Tse, AbbVie, 2, AbbVie, Pfizer, 3, R. Burgos-Vargas, AbbVie, 2, AbbVie, BMS, Janssen, Pfizer, and Roche, 5, AbbVie, BMS, Janssen, Pfizer, and Roche, 8; G. Horneff, AbbVie, Pfizer, and Roche, 2, AbbVie, Novartis, Pfizer, and Roche; S. L. Pangan, AbbVie, 1, AbbVie, 3; J. Kalabic, AbbVie, 1, AbbVie, 3; K. Unnebrink, AbbVie, 1, AbbVie, 3, J. K. Anderson, AbbVie, 1, AbbVie, 3.

**Background/Purpose:** To compare baseline disease characteristics of pediatric patients (pts) with enthesitis-related arthritis (ERA) and polyarticular juvenile idiopathic arthritis (pJIA) from clinical trials with adalimumab (ADA).

**Methods:** Baseline (BL) data were derived from 1 study in ERA (M11–328) and 2 studies in pJIA (M10–444, DE038). M11–328 was a Phase 3, double-blind (DB), placebo-controlled, multicenter study in pediatric pts aged 6–17 yrs (yrs) at BL with ERA as defined by International League of Associations for Rheumatology (ILAR). Disease activity was defined by 1) ≥3 active joints (swelling not due to deformity or joints with limitation of motion (LMM) plus pain and/or tenderness) AND evidence of enthesitis in ≥1 location (either past or present at BL). Pts were inadequate responders or intolerant to ≥1 nonsteroidal anti-inflammatory drug (NSAID) and ≥1 disease-modifying antirheumatic drug (DMARD). M10–444 was a Phase 3b open-label multicenter study in pts aged 2 to <4 yrs and age ≥4 yrs weighing <15 kg with moderately to severely active pJIA (ILAR categories: polyarticular rheumatoid factor (RF) positive, polyarticular RF negative, extended oligoarthritis, undifferentiated, and systemic arthritis). Active disease was defined as arthritis affecting ≥5 joints at BL. EU pts must have previously failed, had insufficient response to, or intolerance to ≥1 DMARD. Study DE038 was a multicenter, Phase 3, randomized, DB study in pts aged 4–17 yrs with pJIA by American College of Rheumatology (ACR) criteria (onset may have been systemic, polyarticular, or oligoarticular/pauciarticular). Active disease was defined as ≥3 swollen joints (SJC) and ≥3 joints with LOM at screening. A trial of NSAIDs was required, and pts were stratified according to methotrexate use.

**Results:** 203 pJIA pts (M10–444, n=32, DE038, n=171) and 46 ERA pts were evaluated. Polyarticular JIA pts were predominantly female compared to ERA pts (pJIA, 79–88% vs ERA, 33%). (Table) C-reactive protein (CRP) was elevated at BL in 66% of pts in DE038 compared to about 39% of the 2–4 year-old pJIA pts and ERA pts. Mean active joint count (AJC) at BL was greater in ERA pts than in ERA pts (10 and 17.2 vs 7.8 joints). Mean BL tender joint count (TJC) was similar in pJIA study DE038 and M11–328 compared to a lower TJC in the younger age group enrolled in M10–444. pJIA pts at baseline (BL) were predominantly female compared to ERA pts (pJIA, 79–88% vs ERA, 33%). (Table) C-reactive protein (CRP) was elevated at BL in 66% of pts in DE038 compared to about 39% of the 2–4 year-old pJIA pts and ERA pts. Mean active joint count (AJC) at BL was greater in ERA pts than in ERA pts (10 and 17.2 vs 7.8 joints). Mean BL tender joint count (TJC) was similar in pJIA study DE038 and M11–328 compared to a lower TJC in the younger age group enrolled in M10–444. Mean physician’s global assessment of disease activity, parent’s global assessment (PaGA) of pt’s overall well-being, PaGA of pt’s pain, and childhood health assessment questionnaire scores were similar across JIA subtypes.

**Table Concomitant Medications for Enthesitis-Related Arthritis**

<table>
<thead>
<tr>
<th>Placebo/Adalimumab</th>
<th>Adalimumab/Adalimumab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 15 n (%)</td>
<td>N = 31 n (%)</td>
<td>N = 46 n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>DMARDs</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>13 (87)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>At week 52*</td>
<td>8 (57)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>At baseline</td>
<td>11 (73)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>At week 52*</td>
<td>14 (82)</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

*Observed data; includes pts who started ERA concomitant medication after the double-blind period; includes 3 pts who discontinued the study after wk 12 and prior to week 52; N=14/29/43; PBO/ADA/total.

**Conclusion:** Clinical improvement with ADA through 52 wks allowed some pts to discontinue concomitant NSAIDs, DMARDs, or CsSs for ERA at the investigator’s discretion. Clinical response was generally maintained in pts who stopped 1 or more concomitant medications. Standardized discontinuation of concomitant ERA medications in ADA responders may have resulted in a higher number of pts able to discontinue concomitant ERA therapies.

**Disclosure:** S. M. Tse, AbbVie, 2, AbbVie, Pfizer, 3, R. Burgos-Vargas, AbbVie, 2, AbbVie, BMS, Janssen, Pfizer, and Roche, 5, AbbVie, BMS, Janssen, Pfizer, and Roche, 8; G. Horneff, AbbVie, Pfizer, and Roche, 2, AbbVie, Novartis, Pfizer, and Roche; S. L. Pangan, AbbVie, 1, AbbVie, 3; J. Kalabic, AbbVie, 1, AbbVie, 3; K. Unnebrink, AbbVie, 1, AbbVie, 3, J. K. Anderson, AbbVie, 1, AbbVie, 3.
etanercept (ETN), approved in the UK in 2002. Since that time, the use of biologic agents for PDA has increased, with a total of 358 patients enrolled in the UK, a further 104 patients in Europe, and ongoing recruitment in Canada. The use of biologic agents has been associated with improved disease outcomes, including a reduction in joint inflammation and improvement in physical function.

Methods: This study used data from the British Society for Paediatric and Adolescent Rheumatology (BSPAR) registry, which collects data on patients with JIA who are treated at participating hospitals in the UK. The study included 442 patients who received biologic therapy for JIA between 2002 and 2015. The main outcomes were sustained improvement in disease activity and patient-reported outcomes.

Results: The study found that biologic therapy was associated with sustained improvement in disease activity and patient-reported outcomes in 80% of patients. The most commonly used biologic agents were etanercept, adalimumab, and anakinra. The study also found that biologic therapy was associated with a decrease in the use of disease-modifying antirheumatic drugs (DMARDs) and corticosteroids.

Conclusion: Biologic therapy is an effective treatment for JIA, and its use has increased in recent years. Further research is needed to identify which patients are most likely to benefit from biologic therapy and to optimize treatment strategies.

Disclosure: This study was supported by the British Society for Paediatric and Adolescent Rheumatology (BSPAR) and the Arthritis Research UK (ARUK). The authors report no conflicts of interest.

Table: Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Multivariate JIA</th>
<th>ERA</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 101</td>
<td>N = 101</td>
<td>N = 202</td>
</tr>
<tr>
<td>Age, years</td>
<td>11.2 (6.9)</td>
<td>10.8 (6.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>62 (61.4)</td>
<td>57 (56.4)</td>
</tr>
<tr>
<td>Prior corticosteroids, n (%)</td>
<td>44 (43.6)</td>
<td>48 (47.6)</td>
</tr>
<tr>
<td>Prior DMARDs, n (%)</td>
<td>83 (82.7)</td>
<td>87 (86.1)</td>
</tr>
<tr>
<td>Prior NSAIDs, n (%)</td>
<td>78 (77.2)</td>
<td>82 (81.1)</td>
</tr>
</tbody>
</table>

References:
abatacept) as well as those licensed for rheumatoid arthritis (rituximab, infliximab (IFX) and anakinra (ANA). ETN is most often the first choice biologic in the treatment of JIA; however there may be occasions where ETN is not the preferred choice, for reasons of either efficacy or safety. Understanding how biologics are being selected will help inform future practice and research. Therefore, the aim of this analysis was to describe the choice of first-line biologics in UK CYP with JIA and explore possible reasons behind this choice.

Methods: Both the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN), established 2004, and the Biologics for Children with Rheumatic Diseases (BCRD) study, established 2010, are ongoing prospective observational cohorts, collecting detailed information on CYP starting either ETN (BSPAR-ETN) or any other biologic (BCRD) for JIA. At start of therapy, demographic and disease information is collected. Biologic-naïve patients registered on or after 01/01/2010 starting their first biologic were identified and baseline disease characteristics compared between therapies, using descriptive statistics. An additional cohort of children starting ETN <2010 were also included to analyse changes in ETN prescribing since initial approval.

Results: To 07/04/2014, 870 patients were recruited starting a first-line biologic (123 BCRD; 747 BSPAR-ETN (582<2010, 165>=2010) (Table). From 2010, children with systemic JIA (sJIA) were almost exclusively prescribed ADA or TCZ. Choice between anti-TNF therapies was largely driven by prevalence of uveitis (5% ETN versus 70% ADA and 72% INF). Children starting ETN were also more likely to have a polyarticular subtype. Only half of the patients starting ETN received concomitant methotrexate compared to the other biologics (69–90%). Compared to ETN patients pre-2010, CYP starting ETN from 2010 had shorter disease duration and were less likely to be receiving corticosteroids, have less prevalence of sJIA and lower rates of uveitis.

Conclusion: Although ETN remains the most common biologic prescribed for JIA, there has been a clear shift towards the use of alternative biologics, including unlicensed biologics, in certain patient situations, largely driven by disease subtype and the presence of uveitis. This channelling of certain children towards specific therapies will need to be considered both in terms of future comparative effectiveness studies and also as a guide to ongoing research priorities within rheumatology.

Table: Overview of Observational Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Disease state</th>
<th>MTX</th>
<th>ADA</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active joint count</td>
<td>3 (2.9)</td>
<td>26 (2.4)</td>
<td>1 (1.0)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Limited joint count</td>
<td>3 (2.6)</td>
<td>26 (2.0)</td>
<td>1 (1.0)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Physician Global Assessment (10cm VAS)</td>
<td>3 (2.5)</td>
<td>24 (1.7)</td>
<td>1 (1.0)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Paediatric Global Assessment (10cm VAS)</td>
<td>4 (1.6)</td>
<td>24 (2.3)</td>
<td>1 (1.0)</td>
<td>5 (4.5)</td>
</tr>
</tbody>
</table>

Long-Term Safety and Effectiveness of Adalimumab in Children with Moderately to Severely Active Polyarticular or Polyarticular-Course Juvenile Idiopathic Arthritis. Hermine Brunner1, Nicola Ruperto2, Carol A. Wallace2, Mary Toth3, Ivan Foeldvari4, John Bohnsack5, Diana Mijovic6, Carol A. Rubinovich7, Paula Vavrinova8, Daniel J. Kingsbury9,10, Katherine Marzan11, Pierre Quartier12, Kirsten Minden13, Elizabeth Chalom14, Gerd Horneff15, Rolf M. Kuester16, Jason Dare16, Mareike Bereswill17, Hartmut Kupper17, Jusmina Kalabie17, Daniel Lovell18 and Alberto Martin19.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases of childhood. Adalimumab (ADA) is one approved for moderate to severe polyarticular JIA (pJIA) in patients (pts) ≤17 yrs (yrs) (EULAR 2014) with moderate to severe polyarticular or polyarticular-course JIA. At start of therapy, demographic and disease information is collected. Biologic-naïve patients registered on or after 01/01/2010 starting their first biologic were identified and baseline disease characteristics compared between therapies, using descriptive statistics. An additional cohort of children starting ETN <2010 were also included to analyse changes in ETN prescribing since initial approval.

Results: To 07/04/2014, 870 patients were recruited starting a first-line biologic (123 BCRD; 747 BSPAR-ETN (582<2010, 165>=2010) (Table). From 2010, children with systemic JIA (sJIA) were almost exclusively prescribed ADA or TCZ. Choice between anti-TNF therapies was largely driven by prevalence of uveitis (5% ETN versus 70% ADA and 72% INF). Children starting ETN were also more likely to have a polyarticular subtype. Only half of the patients starting ETN received concomitant methotrexate compared to the other biologics (69–90%). Compared to ETN patients pre-2010, CYP starting ETN from 2010 had shorter disease duration and were less likely to be receiving corticosteroids, have less prevalence of sJIA and lower rates of uveitis.

Conclusion: Although ETN remains the most common biologic prescribed for JIA, there has been a clear shift towards the use of alternative biologics, including unlicensed biologics, in certain patient situations, largely driven by disease subtype and the presence of uveitis. This channelling of certain children towards specific therapies will need to be considered both in terms of future comparative effectiveness studies and also as a guide to ongoing research priorities within rheumatology.

*All values median/IQR or n(%)
**Conclusion:** Overall, ADA is well-tolerated in these pts with active pJIA. No new safety signals were observed, and based on this interim analysis, the known safety profile of ADA remains unchanged.

**Disclosure:** H. Brunner, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Regeneron, Hoffman-La Roche, Novartis, UCB, and Genentech, 5, Genentech Pharmaceuticals, 8, N. Ruperto, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTo from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilli and Co., “Francesco Angelini”, 3, Astellas, AstraZeneca, the network of Modena, and Novartis, Bristol-Myers Squibb, Italfarmaco, Janssen Biologics B.V., MedImmune, Roche, and Wyeth/Pfizer, 8, G. A. Wallace, Pfizer and Amsgen, 2, Amsgen and Novartis, 5, M. Toth, None; L. Foadvari, AbbVie and Novartis, 9, J. Bolmskov, Novartis Pharmaceuticals Corporation, 5, D. Miljeovic, Genentech and Novartis, 5, C. E. Rabinovich, UCB Pharma, Janssen Research & Development, LLC, Hoffmann-La Roche Inc., and AbbVie, 9, P. Varrinova, None, D. J. Kingsbury, AbbVie, 9, K. Marzan, AbbVie, 2, P. Quartier, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 2, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 9, K. Minden, Pfizer and Abbvie, 2, Pfizer, Abbvie, Roche/Chugai, Novartis, Medac and Pharma-Allergan, 5, E. Chalonier, E.R. Squibb, AbbVie, Pfizer, and Roche, 2, A. B. Buitrago, Pfizer and Roche, 8, R. M. Kuester, AbbVie Inc. and Wyeth/Pfizer; J. Dare, AbbVie, AstraZeneca, Horizon Pharma, and Medac GmbH, 9, M. Bereswill, AbbVie, 1, AbbVie, 3, H. Kupper, AbbVie, 1, AbbVie, 3, J. Kalabic, AbbVie, 1, AbbVie, 3, D. Lovell, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Pfizer, Regeneron, Hoffman-La Roche, Novartis, UBC, Xoma, and Genentech, 5, Wyeth Pharmaceuticals, 8, Amsgen and Forest Research, 9; A. Martini, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTo from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilli and Co., “Francesco Angelini”, 3, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, and Medimmune, 8.

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**Treatment Prescribing Patterns in a Cohort of Patients with Juvenile Idiopathic Arthritis (JIA).** Data from the Childhood Arthritis Prospective Study. Rebecca Davies1, Roberto Carrasco2, Helen Foster3, Eileen Baldam4, Alice Chiang5, Joyce Davidson5, Yiannis Ioannou5, Lucy R. Wedderburn6, Wendy Thompson7, Kimme L. Hyrich8, and on behalf Of Childhood Arthritis Prospective Study (CAPS)11. 1University of Manchester, Manchester, United Kingdom, 3The University of Manchester, Manchester, United Kingdom, 2Newcastle University, Newcastle, United Kingdom, 3Alder Hey Children’s Foundation NHS Trust, Liverpool, United Kingdom, 5Manchester Children’s Hospital, Hospital, Manchester, United Kingdom, 4Royal Hospital for Sick Children, Glasgow, United Kingdom, 7Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, 9Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, 10Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, 11University of Manchester, Manchester, United Kingdom.

**Background/Purpose:** Juvenile idiopathic arthritis (JIA) is a heterogeneous disease, classified according to the International League of Associations for Rheumatology (ILAR). Initial treatment is based largely on disease severity; intra-articular injections for oligoarthritis, methotrexate (MTX) for polyarthritis and systemic presentations. The recent licensing of biologic modifying anti-rheumatic drug (DMARD) including MTX and biologics has led to increased use of these treatments in children with JIA. This analysis uses data from the Childhood Arthritis Prospective Study (CAPS), a prospective observational inception study of inflammatory arthritis, which was included.

**Methods:** Children with at least 3 years of follow-up within the Childhood Arthritis Prospective Study (CAPS), a prospective observational inception study of inflammatory arthritis, were included.

For analysis, children were grouped into a disease pattern according to the physician-assigned ILAR category and number of active joints at first presentation (baseline); oligoarticular, polyarticular, systemic (sJIA) and enthesitis-related arthritis (ERA). Treatment exposures over the 3-year period were determined and categorised into NSAID, intra-articular steroids, disease-modifying anti-rheumatic drug (DMARD) including MTX and biologics including etanercept (ETN) and infliximab (INF).

**Results:** 790 children had 3 years of follow-up. Of these, 78 had missing ILAR subtype data and were excluded, leaving 712 in total (406 oligoarticular, 221 polyarticular, 42 sJIA and 43 ERA). Over a 3-year period, almost 100% of children with polyarticular and 50% with oligoarticular presentation received a DMARD. 46% with polyarticular and 17% with oligoarticular presentation also received a biological (Figure 1). The most recent ILAR category among children with oligoarticular onset who received a biological included 39% extended oligoarthritis, 19% polyarthritis, 4% ERA, 11% other; 27% had persistent oligoarthritis. All sJIA patients were treated with DMARDs with 36% having biologics, primarily ETN and INF. 63% of ERA patients received a DMARD, with 26% later receiving a biological.

**Conclusion:** Over a three-year period almost all patients with a polyar- ticular presentation received treatment with MTX and almost 50% also received a biological therapy. A high proportion of children with an oligoar- ticular presentation also went on to receive DMARDs and biologics, with many children receiving this treatment for persistent oligoarthritis. This is despite the lack of clinical trial evidence for effectiveness in this subtype. Further studies on the efficacy/effectiveness in this subtype should be undertaken to ensure appropriate use of advanced therapies in this population.
in first year of life, daycare attendance, household pets, urban residence or family stressors and development of JIA in this case control study.

Disclosure: S. Shenol, None; K. B. Whitlock, None; C. A. Wallace, None.

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Growth during Tocilizumab Therapy for Polyarticular-Course Juvenile Idiopathic Arthritis: 2-Year Data from a Phase 3 Clinical Trial. Kamal N. Bhrucha1, Hermine I. Brunner2, Nicola Ruperto1, David A. Cabrál3, Abraham Gedalia4, Valeria Gerlons3, Christian Jorgensen5, Athalaipalatham Ramanan6, Daniel Lovell7, Alberto Martini8, James Crane3, Chris Wells9, and Fabrizio De Benedetti S. 1. Genetech, South San Francisco, CA; 2. PRCSG, Cincinnati, OH; 3. PRINTO, Genoa, Italy; 4. Istituto Giannina Gaslini, Genoa, Italy; 5. Consultant, Santa Monica, CA; 6. Roche Products Ltd., Welwyn Garden City, United Kingdom; 7. Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy.

Background/Purpose: Elevated interleukin-6 (IL-6) levels have been associated with low growth velocity in patients with juvenile idiopathic arthritis (JIA). 1 The efficacy of tocilizumab (TCZ), an IL-6 receptor inhibitor, in patients with polyarticular-course JIA (pJIA) was demonstrated up to 104 weeks in the phase 3 CHERISH trial. 2 Growth was evaluated in patients with pJIA treated with TCZ for up to 104 weeks in CHERISH.

Methods: Patients with active pJIA for ≥6 months and inadequate responses to methotrexate received open-label (OL) TCZ intravenously every 4 weeks (randomly assigned 1:1 to receive 8 or 10 mg/kg for body weight [BW] <30 kg or 8 mg/kg for BW ≥30 kg) for 16 weeks. At week 16, patients with ≥JIA ACR30 response were randomly assigned 1:1 to receive placebo or to continue TCZ double-blind for 24 weeks. At week 40, all patients entered an OL extension and received TCZ according to BW through week 104. Height velocity and height standard deviation scores (SDS) were measured in patients with Tanner stage <4 (the subset of study patients with the highest growth potential) provided they did not receive the growth hormone somatropin during the study.

Results: Of 188 patients who received ≥1 dose of TCZ, 123 patients with Tanner stage <4 were included in the growth population (1 patient received somatropin and was excluded from the growth population). At baseline, the growth population had a mean World Health Organization (WHO) height SDS ± SD of −0.5 ± 1.2. The baseline height SDS was not related to age or disease duration (Spearmen’s rank correlations r = 0.08 and r = −0.12, respectively). For patients with Tanner stage <4 at baseline and height data at year 2 of the study (n = 103), baseline mean height SDS increased significantly (by 0.40) from baseline to year 2 of treatment (p < 0.0001 vs baseline). At year 2, 71.8% (74/103) of these patients had an increased height SDS compared with their baseline height SDS, with a mean height velocity of 6.7 ± 2.0 cm/year (n = 103). For patients with available data at year 2 (n = 103), the mean daily oral corticosteroid doses (≥ SD at baseline and year 2 of treatment were 0.05 mg/kg (± 0.08) and 0.02 mg/kg (± 0.05), respectively.

Conclusions: Mean height SDS of patients with pJIA was below normal at baseline. The majority of patients who were Tanner stage <4 at baseline (71.8%) had an increased height SDS at year 2 (end of study).

References:

Disclosure: K. N. Bhrucha, Genentech/Roche, 1. Roche Pharmaceuticals, 3; H. I. Brunner, Janssen R & D, LLC, 2; N. Ruperto, Abbott, AstraZeneca, BMS, Centocor, Eli Lilly, Francesco Angelini s.p.a., GlaxoSmithKline, Italfarmaco, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 2; Abbott, AstraZeneca, BMS, Centocor, Eli Lilly, Francesco Angelini s.p.a., GlaxoSmithKline, Italfarmaco, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 5; D. A. Cabrál, Roche Pharmaceutical, 4; A. Gedalia, None; V. Gerlons, AbbVie, Novartis, 2; C. Jorgensen, None; A. Ramanan, Roche, Chugai, 5; D. Lovell, Genentech, Roche, Novartis, 8; AstraZeneca, Centocor, Angen, Bristol Meyers Squibb, Abbott, Pfizer, Regeneron, Roche, Novartis, UBC, Horizon, Johnson & Johnson, 5; A. Martini, AbbVie, AstraZeneca, BMS, Centocor, Eli Lilly, Francesco Angelini s.p.a., GlaxoSmithKline, Italfarmaco, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, Schwarz Biosciences, Xoma, Wyeth, 5; J. Crane, None; C. Wells, Roche Pharmaceuticals, 3; F. De Benedetti S., Novartis, Novimmune, Hoffmann-La Roche, SOBI, AbbVie, 2; AbbVie Novartis, Novimmune, Hoffmann-La Roche, SOBI, 5.

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Nearly 20% of CHILDREN ARE NOT Correctly Classified According to Current ILAR Classification in a Printr Dataset of More THAN 12,000 Juvenile Idiopathic Arthritis Patients. Alessandro Consolaro1, Francesca Bovis5, Ekaterina Alekseeva1, Violeta Vladislava Panaviciene1, Jordi Anton1, Susan Nielsens2, Gordana Thai3, Maria Trachana1, Nico Wulffraat4, Pavla Dolezalova5, Josef Uziel6, Nahid Shafran5, Ingrida Rumba-Rozenfelde1, Valda Stanenicka1, Nicolina Ruperto1, Daniel Lovell7, Angelo Ravelli8 and Alberto Martini7. 1. Istituto Giannina Gaslini, Genova, Italy; 2. PRINTO - Istituto Giannina Gaslini, Genova, Italy; 3. Istituto Giannina Gaslini, Genova, Italy; 4. Aristotle University, Thessaloniki, Greece; 5. Aarhus, Genoa, Italy; 6. Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel; 7. PRCSG, Cincinnati, OH; 8. Istituto Giannini-PRINTO, Genova, Italy.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is an exclusion diagnosis that encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown origin. In the ILAR classification, this heterogeneous group of chronic arthritides has been categorized on clinical and laboratory grounds to try to identify homogeneous, mutually exclusive categories suitable for etiopathogenic studies. However, the ILAR classification is complex and includes several inclusion and exclusion criteria. As a result, the correct placement of a patient in a specific category is not simple.

Methods: Patients enrolled in the multinational study of the EPidemiology, treatment and Outcome of Childhood Arthritis (EPOCA study) and in the Pharmacovigilance in patients treated with biologics (Pharmachild) were merged in a single database, after exclusion of overlapping patients. Therosa patients were considered to be "provisional" (i.e. not fitting into an ILAR category despite ILAR category attribution by the attending physician) in the two datasets and the queries regarding classification raised to the investigators by the PRINTO staff were analyzed and grouped into major categories according to the inclusion or exclusion criterion involved.

Results: A total of 12,141 patients were included in the study. The Table shows, for each JIA subtype, the most frequent drawbacks leading to a provisional classification. Most problems were related to the lack of 2 determinations of rheumatoid factor (RF) at least 3 months apart, the missing data in the indication of the presence or absence of psoriasis in the patient or in the presence or absence of a history of psoriasis in a first degree relative, the lack of assessment of HLA-B27 antigen, or the discrepancies in data results in the indication of a family history of spondyloarthropathies.

<table>
<thead>
<tr>
<th>N</th>
<th>Provenential diagnosis N (%)</th>
<th>Reasons for provisional diagnosis N (%)</th>
<th>Rheumatoid factor</th>
<th>Psoriasis</th>
<th>Spondyloarthropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>12141</td>
<td>2396 (19.7)</td>
<td>1776 (14.1)</td>
<td>580 (46.4)</td>
<td>264 (21.1)</td>
</tr>
</tbody>
</table>

Conclusion: In current clinical practice nearly 20% of JIA patient were categorized according to physician diagnosis attribution despite the lack of fulfillment of the ILAR exclusion criteria. Most frequently, this was related to the lack of assessment of RF or the inconsistency in indication of the presence of psoriasis in a first-degree relative.

Disclosure: A. Consolaro, None; F. Bovis, None; E. Alekseeva, Roche Pharmaceuticals, 2; A. Martini, None; A. Ravelli, None; A. Martini, None.

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Is It Worth Allowing the Presence of Morning Stiffness in the Definition of Inactive Disease in Juvenile Idiopathic Arthritis? Alessandro Consolaro1, Maikaela Allegri1, Maria C. Gallo1, Benedetta ScippaMentra2, Serena Calandra3, Cristina Robbiano1, Federica Mongelli2, Cecilia Bava2, Alberto Martini3 and Angelo Ravelli1. 1. Istituto Giannina Gaslini, Genova, Italy; 2. University of Genova, Genova, Italy, 3. Istituto Giannina Gaslini and University of Genova, Genova, Italy.
Background/Purpose: Morning stiffness is a major symptom of juvenile idiopathic arthritis (JIA) and it is usually associated with active disease. However, it is common view that children with disease quiescence may have some degrees of residual morning stiffness. The 2004 preliminary criteria for inactive disease (ID) in JIA did not include the assessment of morning stiffness, whereas the 2011 revision of the criteria has allowed the presence of morning stiffness lasting ≤15 minutes. However, it is still uncertain whether the disease status of children with ID who have or do not have morning stiffness is comparable. Aim of the study was to compare the disease status of children with JIA who meet the 2011 revised criteria for ID and have or do not have a morning stiffness lasting ≤15.

Methods: A database at the study center including 785 patients who had undergone a total of 2957 visits, which included a parent report of the presence and duration of morning stiffness, was analyzed to identify all visits in which patients met the criteria for ID. In each visit, the duration of morning stiffness was categorized as follows: ≤15 min, 15-30 min, 30-60 min, 1-2 hr, >2 hr. Clinical assessments included demographic features, and parent-reported outcomes. In case a patient met the ID criteria in more than 1 visit, only the first visit was retained.

Results: A total of 460 visits in which the patient met the criteria for ID were evaluated. Absence of morning stiffness was reported in 390 (84.8%) visits, whereas in 70 visits (15.2%) there was morning stiffness. Among the visits with morning stiffness, in 41 (8.9%) duration was ≤15 min, and in 29 (6.3%) duration was >15 min. Table shows the comparison of disease duration and parent-reported outcomes between patients with absence or presence of morning stiffness.

Conclusion: Among patients who met the 2011 criteria for ID, those with morning stiffness ≤15 min had worse parent-reported outcomes than those without morning stiffness. This finding suggests that patients may not perceive their child’s disease state as true remission when lower degrees of morning stiffness are present. Notably, a sizeable proportion (6.3%) of children meeting the 2004 ID criteria had morning stiffness lasting >15 min. The change of the criterion “Duration of morning stiffness of ≤15 minutes” to “Absence of morning stiffness” in the definition for ID should be considered.

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Background/Purpose: National registry cross-sectional data show significant differences in patient-reported outcomes (PROs) across juvenile idiopathic arthritis (JIA) subtypes. This study aimed to assess predictors of patient-reported outcomes (PROs) in JIA in a tertiary care clinic setting.

Methods: This is a retrospective study of children meeting ILAR JIA criteria evaluated in a tertiary pediatric rheumatology clinic between 2010-2012. Pain over the past week was assessed with a visual analogue scale (VAS; 0-10). Function was estimated with the childhood health assessment questionnaire (CHAQ; 0-3). Physician global disease activity was measured using a VAS (0-10). We tested the association of clinical characteristics with pain and function using multivariable linear and ordinal logistic regression, accounting for clustering by subject. Pair-wise correlation was used to compare the associations of physician disease assessment and each PRO.

Results: During the study period there were 542 subjects evaluated at 2,689 visits. The distribution of JIA categories was oligoarticular (37%), polyarticular RF+ (3%), polyarticular RF- (19%), systemic (8%), psoriatic (9%), enthesis-related arthritis (ERA) (18%), undifferentiated (6%). Patients with ERA and undifferentiated reported higher pain intensity (p<0.01), higher pain prevalence (p<0.01), and poorer function (p<0.01) than other JIA categories. In multivariable analyses, older age, female sex, higher active joint count, NSAID use, DMARD use, and the ERA and undifferentiated categories were associated with higher pain scores (Table). Higher active joint count, NSAID use, glucocorticoid use, and ERA were associated with worse function. In patients with ERA, higher tender enthesitis count and female sex were significantly associated with higher pain intensity and poorer function.

Conclusion: Patients with undifferentiated arthritis, higher active joint count and glucocorticoid use were associated with worse function. Correlation between the physician assessment of disease activity and patient-reported pain intensity and function were low (r=0.5, 0.4, respectively).

Disclosure: A. Taxter, None; K. Maughn, None; E. M. Behrens, None; P. F. Weiss, None.

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Biologic Treatment of Adult Patients with Juvenile Idiopathic Arthritis Followed in the National Registry. Katerina Jarosova1, Karel Hejduk2, Michal Uher2 and Jiri Vencovsky, MD, DSc. 1Institution of Rheumatology, Prague, Czech Republic, 2Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, 3Charles University Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: To analyze the efficacy and safety of biologic agents in adult patients with juvenile idiopathic arthritis (JIA).

Methods: ATTRA is the Czech national registry of patients with different forms of chronic arthritis who are treated with biologic drugs. Using this registry, we have analyzed adult JIA patients, who switched their treatment biologic agents in the 1st instance. Patients were treated in recommended doses for RA and the first drug was infliximab (44.3%), etanercept (36.7%), adalimumab (18.1%), or golimumab (0.9%). Those patients, who failed to improve in DAS28 by at least 1.2 after 3 months at 2 consecutive visits, who lost the response during the treatment, or who had to be discontinued due to adverse event, were switched to an alternative TNF inhibitor (TNFi) or to rituximab, abatacept or tocilizumab. Survival on therapy after 1st and 2nd biologic event, were switched to an alternative TNF inhibitor (TNFi) or to rituximab, abatacept or tocilizumab. Survival on therapy after 1st and 2nd biologic agents was calculated. Clinical efficacy was assessed with DAS28. Safety assessments were done for all patients during the whole follow-up period. No guidelines have been issued for the preference between the 1st or 2nd drug type and this was left solely to treating physician decision and was based on the assessment of overall clinical situation.

Results: Two hundred and ten adult JIA patients were treated with anti-TNF agents in the 1st instance. Mean age of patients was 22.4 years, duration of disease was 12.7 years and 62% were women. Ninety (42.9%) patients received more than one biologic agent. DAS28 showed excellent and persistent improvement for those patients who remained on the first drug. The treatment responses to a second biologic agent were also significant, although with smaller differences to baseline DAS28 values. DAS28 at the initiation of the first TNFi was 6.01±1.28 and decreased significantly to 2.69±1.47 after 12 months and to 2.21±1.46 after 24 months; DAS28 at initiation of the
second TNFi or other biologic agent was 5.59±1.53 and decreased to 2.77±1.39 and 2.74±1.00 after 12 and 24 months, respectively. Survival on the treatment was shorter in patients who switched the biologic agent in comparison with the first users (p = 0.017). The survival on the drug in first users and in switched patients was as follows: 0.93 (95% CI: 0.90–0.97) and 0.89 (95% CI: 0.82–0.95) in the first year; 0.87 (95% CI: 0.83–0.92) and 0.77 (95% CI: 0.68–0.86) in the second year. Adverse events that lead to treatment discontinuation were seen in 4% and 6% after one year and in 6% and 10% after 2 years therapy in the first and subsequent biologic agents groups, respectively. Treatment discontinuation due to inefficacy was observed in 1% and 6 %, and in 5% and 12% with the 1st and 2nd line treatment in years 1 and 2.

**Conclusion:** biologic treatment in adult patients with juvenile idiopathic arthritis is effective and safe. Similarly to patients with RA, it is possible to regain efficacy after switching to second biologic drug in a majority of patients, although with somewhat lower difference between the entry and 2 years DAS28 evaluations. Good adherence to therapy was observed for both first and second biologic agents.

Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 00023728 (Institute of Rheumatology).

**Disclosure:** K. Jarosova, None; K. Hejduk, None; M. Uher, None; J. Vencovsky, MD, DSc, None.

### Table

<table>
<thead>
<tr>
<th>CHOP</th>
<th>TSRHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splinted post injection (%)</td>
<td>Splinted post injection (%)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>9.1</td>
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<tr>
<td>Race</td>
<td>White</td>
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<tr>
<td></td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
</tr>
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<td></td>
<td>Other*</td>
</tr>
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<td>Not Hispanic</td>
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<tr>
<td>Labs</td>
<td>ANA</td>
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<td>ESR</td>
</tr>
<tr>
<td></td>
<td>Irnis present</td>
</tr>
<tr>
<td></td>
<td>Injection dose (mg/kg)</td>
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<tr>
<td></td>
<td>Hexacetonide</td>
</tr>
<tr>
<td>Total joint activity (mean)</td>
<td>Arthritis not occurred</td>
</tr>
<tr>
<td></td>
<td>Patients receiving re-injection</td>
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</tbody>
</table>

**Legend:** CHOP—The Children’s Hospital of Philadelphia, TSRHC—Texas Scottish Rite Hospital for Children, NSAID-nao-stroildal anti-inflammatory drug, BDM—range of motion, CHAQ—Children’s Health Assessment Questionnaire. *Includes: Native American, Hawaiian, other, not specified.

**Disclosure:** E. Ramsay, None; H. Benham, None; J. Tress, None; J. Diaz, None; D. Sherry, None.

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**Retrospective Review of Immobilization Vs. Immediate Resumption of Activity in Patients with Oligoarticular Juvenile Idiopathic Arthritis and Corticosteroid Knee Injections.** Elaine Ramsay1, Heather Benham2, Jenna Tress3, Janille Diaz4 and David D. Sherry5. 1The Children’s Hospital of Philadelphia, 2Philadelphia, PA, 3Texas Scottish Rite Hospital for Children, 4Dallas, TX, 5Children’s Hospital of Philadelphia, Philadelphia, PA. 6The Children’s Hospital of Philadelphia, Philadelphia, PA.

**Background/Purpose:** Intrarticular corticosteroid injection (IACI) is one of the most common treatment modalities in oligoarticular Juvenile Idiopathic Arthritis (JIA). There is widespread use of IACI in the treatment of arthritis, but recommendations following the procedure vary, as there are no published studies on splinting patients post-IACI. Post-injection, Texas Scottish Rite Hospital for Children (TSRHC) splints patients for 24 hours while The Children’s Hospital of Philadelphia (CHOP) does not. The aim of this study was to compare the number of cases of recurrent arthritis and re-injection following IACI.

**Methods:** Data (see Table) were retrospectively collected at CHOP and TSRHC. All patients diagnosed with oligoartricular JIA according to ILAR criteria (2nd revision, 2001) between 2008–2010 were included. Chi square and T test were utilized for preliminary analysis.

**Results:** 131 patients at CHOP and 70 patients at TSRHC received a knee IACI. The average age was 9.1 (CHOP) v. 6.7 (TSRHC) (p=0.0002). There were no significant differences in the gender ratio. At TSRHC (6 v. 10, p=0.055), and a higher number of ANA positive patients (54 v. 74, p=0.003). Overall mean joint disease severity scores (sum of range of motion restriction, joint swelling and tenderness) at CHOP were higher (3.4 v. 2.3, p <0.001). Mean dose of triamcinolone hexacetonide was higher at CHOP (1.4 mg/kg v. 0.8 mg/kg, p<0.001). Arthritis reoccurred in 37 (28%) at CHOP v. 30 (43%) at TSRHC (p=0.041). 37 patients at CHOP received re-injection of the same knee v. 5 at TSRHC (p <0.001).

**Conclusion:** TSRHC patients were younger and more frequently ANA positive and Hispanic. Joint disease severity scores were higher at CHOP, and patients received a higher mean dose of triamcinolone hexacetonide IACI.

The number of recurrent arthritis cases was similar between institutions and there was a trend toward more recurrent arthritis at TSRHC, but CHOP completed a larger amount of repeat injections. This may indicate that TSRHC begins systemic immunosuppression if IACI fails to clinically remit the knee. Future plans include comparison of time to recurrent arthritis to see if splinting extends remission. If it does, the practice of splinting knees following IACI may be beneficial in children with oligoarticular JIA. Examining co-variables such as age, ethnicity, ANA status, disease activity, steroid type and dose, and concomitant medications are planned. Limitations of this study include: 1) possibility that some subjects with oligoarticular JIA were missed; 2) some subjects were lost to follow-up; 3) variation in recording and practice styles. Also, the study only examined knee IACIs, splinting duration was less than reported in adults, and adherence was not monitored.

Disclosure: K. Jarosova, None; K. Hejduk, None; M. Uher, None; J. Vencovsky, MD, DSc, None.

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**Pharmacovigilance in Juvenile Idiopathic Arthritis Patients (PHAR-MACHILD) Treated with Biologic Agents and/or Methotrexate. Consolidated Baseline Characteristics from Pharmachild and Other National Registries.** Joost F. Swart1, Alessandro Consolario2, Gerd Hornfei2, Kimmie L. Hynrich3, Francesca Bosv3, Bo Magnusson1, Jose Melo-Gomes1, Ekaterina Alexeeva4, Stefano Lanni5, Gerd Ganser10, Violeta Vladislava Panajevi6, Jori Anto17, Ioan Foeldvari13, Valda Stanjevica14, Susan Nielsen15, Ralf Traudzedd16, Constantin Ailioaie17, Pierre Quartier18, Toni Hospach9, Gordana Susic19, Maria Trachana20, Frank Weller-Heinemann21, Alberto Martini22, Nico Wulfraat23 and Nicoloino Ruperto1. 1Wilhelmina Children’s Hospital/ UMC Utrecht, Utrecht, Netherlands, 2Istituto Giannina Gaslini, Genova, Italy, 3Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, 4Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, 5PRINTO - Istituto Giannina Gaslini, Genoa, Italy, 6Karolinska University Hospital, Stockholm, Sweden, 7Pediatric Rheumatology, Lisbon, Portugal, 8Scientific Centre of Children’s Health of RAMS, Moscow, Russia, 9Istituto Giannina Gaslini, Genoa, Italy, 10Sankt Joseph Stift, Sendenhorst, Germany, 11Children’s Hospital, Affiliate of Vilnius University Hospital Santarvitas Klinika, Vilnius, Lithuania, 12Hospital Sant Joan de Déu, Barcelona, Spain, 13Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany, 14Riga Stradins University, Riga, Latvia, 15University Clinic of Pediatrics II, Rigshospitalet, Copenhagen, Denmark, 16Helios Clinics, Berlin, Germany, 17Al-exandru Ioan Cuza University, Iasi, Romania, 18Necker-Enfants Malades Hospital, Paris, France, 19Olgahospital, Stuttgart, Germany, 20School of Medicine, University of Belgrade, Belgrade, Serbia, 21Aristotle University, Thessaloniki, Greece, 22Klinikum Bremen-Mitte, Bremen, Germany, 23PRINTO-IRCCS, Genova, Italy.

**Background/Purpose:** The availability of methotrexate (MTX) and biological agents has provided a major change in the treatment of children with juvenile idiopathic arthritis (JIA). However, limited information exists on the safety of the current available treatments. An international registry named Pharmachild (European Union grant 260353) has been set up by the Pediatric Rheumatology International Trials Organisation (PRINTO)/Paediatric Rheumatology European Society (PRE$). In parallel several national registries with the same purpose have been set up in different European Countries for the follow-up of these patients.

**Methods:** We merged into a unified database the baseline demographic data of JIA patients treated with MTX or biologicals coming from the Pharmachild registry and from the national registries of Germany, United Kingdom, Sweden and Portugal. Events of special interest (ESI) and moderate/severe serious adverse events (AE) related to the drugs were
Results: About 61% of the patients have been treated with biologicals alone or in combination with MTX, and 29% only with MTX. The events of special interest ranged from 0.1 to 15.0% and the other adverse events from 4.8% to 69.9%.

Conclusion: Combination of information from different data sources is a recommended task and will provide a powerful tool for the future analysis of safety events coming from different registries.

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Agreement Between Enthesitis Evaluation By Manual Palpation and Dolorimetry in Juvenile Spondyloarthropathy. Lauren Minor, Keith Sikora, Robert A. Colbert, Sarah Minor, and Hemalatha Srinivasulu. 1NIAMS, NIH, Bethesda, MD, 2NIAMS, NIH, Bethesda, DC, 3NIAMS NIH, Bethesda, MD, 4Children’s National Medical Center, Washington, DC.

Background/Purpose: Enthesitis is a characteristic feature of spondyloarthritis (SpA). Clinical evaluation of enthesitis by palpation is subject to differences in pressure used at different sites or by different examiners over time. Use of a dolorimeter allows calibration of the exact pressure used in assessment of tenderness. The purpose of this study was to assess agreement between manual and dolorimetric testing of enthesal points in juvenile SpA (JSpA).

Methods: Patients less than 18 years of age and diagnosed with JSpA based on ILAR criteria for ERA (over 75%), and Psoriatic arthritis and ESSG criteria for undifferentiated arthritides were included in the study. Forty JSpA patient encounters (age range 7–18 y) and 10 healthy controls (range 10–25 y) were included in the study. Thirty-three entheseal sites were assessed by manual palpation by the same examiner. Three different examiners participated in the study. Tenderness elicited at less than 4 kg pressure using a 20 lb dolorimeter was considered positive by dolorimetry; tenderness with thumb pressure with blanching of the examiner’s nail bed was considered positive by manual palpation. Kappa statistics were performed by SPSS to assess agreement between manual and dolorimetric testing. Kappa value (k) > 0.6 indicates substantial agreement; 0.4 < k < 0.6 is considered moderate, and 0.21 < k < 0.4 shows fair agreement.

Results: The table displays kappa values for all 33 enthesal sites indicating the degree of agreement, for all 40 JSpA encounters. Substantial agreement between manual and dolorimetric assessment was noted in 42% of sites (14/33); moderate agreement was seen in 39% of sites (13/33) and fair agreement in 12% (4/33). Kappa values of corresponding right and left entheseal sites showed no statistical difference (paired t-test = 0.6). Of a total of 10 positive enthesal sites by manual palpation and 5 sites by dolorimetry in the 10 healthy controls, only one entheseal site showed agreement by both methods. Similar analysis on 30 adult SpA patients yielded 57% sites with substantial and 15% with moderate agreement.

Conclusion: There was substantial to moderate agreement between clinical enthesitis evaluation by manual and dolorimetric methods in 81% of sites, with fair agreement in another 12% in JSpA. Since a single exam was performed at each visit, inter-rater reliability was not assessed. Although manual testing standardized for nail blanching and dolorimetry exhibited considerable agreement, use of dolorimetry may enhance objectivity for enthesitis evaluation among JSpA patient in clinical trials. Future studies are needed to address inter-rater reliability between the two methods and to correlate with ultrasound and/or MRI.

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coauthors, methotrexate as well as other DMARDS were allowed to be given concomitantly.

Results: Methotrexate (without a biologic agent) was applied to a total of 1517 patients, Etanercept (ETA) to 1925, Adalimumab (ADA) to 498 and Tocilizumab (TOC) to 104 patients for a total exposure time of 3019; 3958; 561 and 103 years, respectively. A total of 1272 adverse events (AE) were reported. In the control group (406/1000 PY [389–424]) with 44 classified as serious (15/1000PY[11–20]). In the ETA cohort there were 1131 AE (286/1000PY [272–300]) and 149 SAE (38/1000PY[32–44]), in the ADA cohort 373 AE (665/1000 PY [625–703]) and 28 SAE (50/1000 PY [35–71]) and in the TOC cohort there were 97 AE (941/1000 PY [878–973]) with 10 SAE (97/1000 PY [54–170]). In the control cohort, a total of 252 AE qualified as ESI, upon ETA 234, upon ADA 60 and upon TOC 13 (table).

Conclusion: This progress report from the ongoing BiKeR-registry showed a higher incidence for several adverse events of interest including autoimmunity, uveitis, anaphylaxis and MAS while the total rate is surprisingly low. In general, JIA patient tolerated biologic treatment very well. Differences between the cohorts are at least in part biased by differences in JIA category distribution and preexisting uveitis risk.

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Using the 2011 ACR Recommendations for the Treatment of Juvenile Idiopathic Arthritis (JIA) to Evaluate a Single Centre Treatment Pathway: A Feasibility Study. Katherine Green1, Marinka Twilt2 and Taunton R. Southwood1, 1Birmingham Children’s Hospital, Birmingham, United Kingdom, 2Aarhus University Hospital, Aarhus, Denmark, 1Institute of Child Health, University of Birmingham and Birmingham Children’s Hospital, Birmingham, United Kingdom.

Background/ Purpose: The 2011 ACR recommendations for the treatment of Juvenile Idiopathic Arthritis (ACR-JIA) are evidence based, consensus-approved therapeutic pathways for the safe and effective treatment of JIA. Our aim was to determine the feasibility of applying ACR-JIA to evaluate the treatment pathway in a single centre JIA polyarticular cohort.

Methods: We conducted a retrospective analysis of a single-centre paediatric JIA cohort by reviewing case notes, investigations and treatment databases of all newly diagnosed JIA polyarthritis patients in the 2 years after ACR-JIA publication. 35 patients with multiple joint arthritides fulfilled ILAR criteria for the diagnosis of JIA: systemic arthritis (n=5), analysed separately), polyarthritis (n=25) and Extended Oligoarthritis (n=5, analysed together with polyarthritis (total n=30) as these groups are managed similarly in the ACR Recommendations.

Using the Recommendations, disease severity and poor prognostic features were used to categorize the patients and critical therapeutic time points (disease duration of 8–12 weeks from diagnosis to starting methotrexate use defined as Failure. Methotrexate was ineffective, 14–28 weeks from starting methotrexate to starting etanercept) were calculated. Drug monitoring frequency was also determined.

Results: 25 females and 10 males (median age at onset 13, range 1.5–15 years) were included in the evaluation. Median age at disease onset for
poly/extended oligoarthritis was 10 years (1.5–16), with a median of 12 joints (12–38) active at presentation, and for the systemic group median age at onset was 6 years (2–7), with a median number of 6 active joints (2–10). 3 polyarthritis patients were rheumatoid factor positive. In the polyarthritis/extended oligoarthritis group, 2 patients with polyarthritis had poor prognostic features, 23 had moderate and 6 had high disease severity. None of the systemic patients had poor prognostic factors, 2 had moderate and 2 had high disease severity.

22/30 patients with polyarthritis/extended oligoarthritis followed the ACR recommendations for treatment according to their disease severity, commencing methotrexate therapy within a median of 6 weeks (3–32 weeks) of diagnosis. Etanercept was commenced in a total of 9 patients (30%) within a median of 6 months (1.5–24 weeks) subsequent to commencing methotrexate. This was due to intolerance in 5 patients (56%), inefficacy in 2 cases (22%) and both intolerance and inefficacy in 2 cases (22%). A total of 7 patients did not follow ACR-JIA guidelines due to excessive length of time between diagnosis and commencing methotrexate or etanercept treatment, most commonly due to delays in funding approval or insufficient regular drug monitoring tests. All patients with systemic arthritis followed the ACR-JIA recommendations.

Conclusion: Overall, 28/35 patients followed ACR-JIA. This study demonstrates the feasibility of using the ACR-JIA recommendations to evaluate a clinical pathway. It also highlights the potential influence of the local health economy in achieving rapid commencement of new JIA therapies and the challenges of ensuring regular drug monitoring in all patients.


Role of Joint Status in Decreased Accelerometer-Assessed Daily Physical Activity in Juvenile Idiopathic Arthritis. Mette Noergaard, Marinka Twilt and Troels Herlin. Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is often associated with decreased physical activity (PA). Although improved disease control has opened up the possibilities for JIA-children to participate in dynamic sport activities, various limitations secondary to the disease seem to restrict an adequate integration in sport activities. Accurate, objective measurements of PA and identification of specific factors limiting PA in JIA-children are therefore needed.

This study aimed to: 1. Compare accelerometer-assessed PA in JIA-children with normative data of age- and gender-matched healthy controls. 2. Relate accelerometer-assessed PA to joint status in the lower extremities (LE) in JIA-children regarding active arthritis as well as persistent LOM (contractions) and exceeded range of motion (ROM) (hypermobility).

Methods: In 61 patients with JIA PA was assessed using the hip-worn GT1M Actigraph accelerometer during waking hours for one week, providing at least 3 separate days each of 8 hours of valid recording accelerometer using 10 second intervals of recording (epochs).

Joint status was evaluated using a joint activity count of 71 joints. Also, LE-joints (hips, knees, ankles, toes) were examined for persistent LOM and exceeded ROM (Beighton score-items including alternative items to cover all LE-joints). Demographic, disease- and pain-related parameters were also obtained.

Results: For each age-group between 10–16 years accelerometer data of the 61 JIA patients were compared with 239±93 normative controls. Values of mean counts per minute (c/min), recorded minutes with moderate and high PA (>1000 c/min) and high PA (>2500 c/min) were significantly lower in patients than in normative controls (p=0.004), with the more severe JA-subcategories having the lowest values.

PA of JIA-children was significantly correlated to joint swelling (p=0.004) and LOM of the hips and the ankles, but not the knees; no matter if due to active arthritis or contractions. No significant correlations were found between PA of JIA-children and reported pain (p=0.59) and hypermobility (p=0.58).

Conclusion: Accelerometer-assessed PA-levels of JIA-children were significantly lower than those of normative controls. LOM of hips and ankles, but surprisingly not the knees, were significantly associated with impaired PA. This emphasizes the importance of obtaining full ROM specifically in hips and ankles of JIA-children for the purpose of adequately participating in sport activities.

Disclosure: M. Noergaard. None; M. Twilt. None; T. Herlin. None.

Establishing Clinical Meaning and Defining Important Differences in Patient Reported Outcome Measures of Physical Function, Fatigue and Pain Interference in Juvenile Idiopathic Arthritis. Esi Morgan DeWitt1, Bin Huang2, Kimberly Barnett3, Adam Carle4, Constance Mara5 and Karen Cook6. 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Cincinnati Children’s Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH; 3Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Patient reported outcome measures (PROMs) are used increasingly in clinical care. A framework to interpret scores according to degree of clinical severity would enhance their practical use. Furthermore, use of PROMs in evaluation of treatment effectiveness over time requires establishment of minimal important differences (MID) in change scores.

Methods: We identified clinical severity thresholds and MID for measures of mobility, upper extremity function, fatigue, and pain interference working with patients with juvenile idiopathic arthritis (JIA) and parents of JIA patients using standard setting methodology modified from educational testing. Data from Patient-Reported Outcomes Measurement Information System (PROMIS) item bank longitudinal validation collected on 121 JIA patients was used to develop clinical vignettes across a range of symptom severity. Vignettes were created based on most likely item responses at different levels on the T score metric [mean = 50; SD = 10]. Vignettes were anchored at 5-point intervals (0.5 SDs). Parents and patients participated in separate one-day meetings. Vignettes were ordered and placed on cards. Panelists identified adjacent vignettes considered to represent upper and lower boundaries separating category cut points (i.e., none / mild problems, mild/ moderate, moderate/severe). Cut scores were defined as mean score for boundary vignettes. To define MIDs panelists responded to items to represent "just enough improvement to make a difference". Average change scores served as estimates of MID.

Results: For pain interference, mobility, and upper extremity function patients set higher cut points for severity than parents, typically by 0.5 SD. Parents tended to set higher MID scores than JIA patients. Size of MID varied according to severity classification of the symptom. MIDs estimated by the panelists were typically larger than the MIDs determined using statistical methods.

Conclusion: We used a modified educational standard setting method to estimate clinically relevant cut points to classify severity for PROMIS measures of mobility, upper extremity, fatigue and pain interference. Parallel exercises identified these cut points from the perspectives of patients with JIA and parents of a child with JIA. We explored a novel means of determining MID from the patient/parent perspective. This allows for meaningful interpretation of PROMIS measures in a clinical setting. In summer 2014, the method will be repeated with clinicians serving as panelists. Results will be compared across panel groups. MIDs generated by the 3 panelist groups and those generated statistically from the longitudinal study sample will be compared.


Patient-Reported Outcomes in Children with Moderately to Severely Active Polyarticular or Polyarticular-Course Juvenile Idiopathic Arthritis Who Are Prescribed and Treated with Adalimumab, Gerd Horneff7, Carol A. Wallas8, Pierre Quartert1, Daniel J. Kingsbury9, Kirsten Minden1, Mareike Bereswilk1, Vishvas Garg9, Hartmut Kupper6 and Jasmina Kalabic1. 1Asklepios Klinik Saar Augustin, Saar Augustin, Germany; 2University of Washington School of Medicine and Seattle Children’s Hospital, Seattle, WA, 3Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases of childhood and adolescents, and improvement in health-related quality of life and functional disability is an important therapeutic goal in the treatment of patients (pts) with JIA. The objective was to evaluate pt-reported outcomes (PROs) in pts with moderately to severely active polyarticular or polyarticular-course JIA (pJIA) who are prescribed and treated with adalimumab (ADA) ± methotrexate (MTX) in routine clinical practice.

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Methods: This is an ongoing, multicenter, non-interventional observational registry of pts diagnosed with moderately to severely active pJIA that are prescribed and treated in a routine clinical setting with either ADA ± MTX or MTX alone. Pts with resistant disease, that had received prior MTX treatment, were prescribed and treated with ADA as second line therapy. A cohort of pts with prescribed MTX, naïve to biologics, served as controls. Physical function was measured by the Disability Index of Childhood Health Assessment Questionnaire (DICHQAQ), which ranges from 0 (no disability) to 100 (best possible health state). The currently study is limited using data up to 12 months, and all data are as observed.

Results: 842 pts (540 in ADA arm/302 in MTX arm) were enrolled and treated in the registry. The majority of the pts were female (76% and 69% for MTX and ADA, respectively). The mean age at baseline was 9.6 and 12.2 yrs and the mean pJIA disease duration at baseline was 1.3 and 3.7 yrs for MTX and ADA arms, respectively. At baseline mean DICHQAQ was 0.62 for both MTX and ADA treatment arms. For those pts with data at both baseline and 12 months, the mean change in DICHQAQ was -0.24 and -0.22 for the MTX and ADA arms, respectively, indicating a clinically meaningful difference. From baseline to 12 months, the scores of the individual health concepts in the CHQ-PF50 increased for both the MTX and ADA treatment arms, with the exception of Family Cohesion, as the scores had little change over time (Table). Parental emotional impact had a substantial increase as mean scores changed from 57.8 to 73.0 and 57.0 to 68.8 in the MTX and ADA treatment arms from baseline to 12 months, respectively.

### Table Summary of Child Health Questionnaire Parent Form (CHQ-PF50)

<table>
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<th>Baseline MTX</th>
<th>ADA ± MTX</th>
<th>Month 12 MTX</th>
<th>ADA ± MTX</th>
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<td>80.8 (17.6)</td>
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<td>68.8 (25.6)</td>
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<td><strong>Parental Impact – Time</strong></td>
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</table>

Conclusion: Over the course of 12 months of treatment, pts with pJIA in the ADA treatment arm demonstrated clinically meaningful improvements in functional disability as well as an increase in the scores of the individual health concepts, indicating an improvement in health-related quality of life. The extent of improvement was comparable to that in the MTX treatment arm.

Disclosure: G. Hornoff, AbbVie, Pfizer, and Roche, 2, AbbVie, Novartis, Pfizer, and Roche, 8; C. A. Wallace, Pfizer and Amgen, 2, Amgen and Novartis, 5; P. Quartier, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 2, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 5; D. J. Kingsbury, AbbVie, 9; K. Minden, Pfizer and Abbvie, 2, Pfizer, Abbvie, Roche/Chugai, Novartis, Medica and PharmAllergan, 5; M. Bereswill, AbbVie, 1, AbbVie, 3; V. Garg, AbbVie, 1, AbbVie, 3; H. Kupper, AbbVie, 1, AbbVie, 3; J. Kalabic, AbbVie, 1, AbbVie, 3.

290 Patterns of Active Joint Involvement in JIA. Simon W.M. Eng1, Mira Van Veenendaal2, Alan M. Rosenberg3, Kiem Oen4, Quaid Morris1 and Rae S.M. Yeung5. 1University of Toronto, Toronto, ON, 2The Hospital for Sick Children, Toronto, ON, 3University of Saskatchewan, Saskatoon, SK, 4University of Manitoba, Winnipeg, MB.

Background/Purpose: JIA encompasses a set of heterogeneous diseases with chronic joint inflammation. Although the ILAR criteria consider joint counts, they do not reflect specific joint involvement patterns. We sought to study these patterns, through unsupervised pattern recognition techniques, to better characterize homogeneous subpopulations of children with JIA.

Methods: Principal component analysis was conducted on baseline joint involvement data from 807 treatment-naive patients satisfying the ILAR criteria to identify composite variables, or principal components (PCs), that distinguish patients from each other. Cluster analysis was conducted on patient PC scores to identify signatures of joint involvement.

Results: 4 PCs were identified that explained 46% of variance among patients. The PCs summarized (1) overall joint count, (2) finger vs. toe involvement, (3) large vs. small joint involvement, and (4) SI joint involvement. On these PCs, 12 distinct signatures were identified whose “fingerprints” or defining characteristics are depicted in Figure 1. These signatures described joint involvements based on clinically meaningful combinations of characteristics given by the PCs. The signatures were clearly able to distinguish homogeneous patient subpopulations both within and between ILAR subtypes based on joint involvement (Figure 2).

Conclusion: Our analysis recovered distinct patterns of joint involvement in an assumption-free manner that will be useful in defining homogeneous patient subpopulations within and across the ILAR subtypes in JIA.

Figure 1: “Fingerprints” or joint co-involvement frequencies for each signature. Vertical heat maps represent overall frequencies of joint involvement among patients in each signature. Square matrices represent frequencies of involvement of joints in columns given the involvement of joints in rows.
Figure 2: Relationships between the signatures and ILAR subtypes. Heat maps (outermost rings) depict PC scores for each patient. The innermost ring depicts the ILAR subtype composition of each signature and signature composition of each ILAR subtype. Ribbons link patients between signatures (left) and ILAR subtypes (right).

Disclosure: S. W. M. Eng, None; M. Van Veenendaal, None; A. M. Rosenberg, None; K. Oen, None; Q. Morris, None; R. S. M. Yeung, Novartis Pharmaceutical Corporation, 2.

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Development of a Serious Game Designed for Children with Juvenile Idiopathic Arthritis. Jean-David Cohen1, Damien Bentayou2, Marcantoine Bernard-Brune1 and Sonia Trope3. 1CHU LAPEYRONIE, MONTPELLIER, France, 2CG Artist, PESSAC, France, 3ANDAR, Paris, France.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is the most common chronic paediatric rheumatic disease and cause of physical and psychological disability, with family and school consequences.

If the advances in therapeutics as biologicals have revolutionized the outcome of children with JIA, it is necessary to develop educational materials to increase their independence and improve their quality of life.

Information about the disease and treatments, the ability to cope with difficult situations, having good reflexes concerning biotherapies are all skills needed to live well the disease every day.

Democratization of computers and smart phones has led us to develop a serious game for children as an educational learning instrument.

Methods: The game was developed according to the steps of Assessment, Design, Development, Implementation, and Evaluation (ADDIE model).

A steering committee was formed with a pediatric rheumatologist, a patient organization and an agency of video game developers including an art director, a lead programmer and a graphist.

Decisions were strained by a limited budget support.

The National Association against Rheumatoid Arthritis initiated the project and provides funding, manages logistics and monitoring.

The pediatric rheumatologist initially established a series of themes to be developed in accordance with the association and transmitted scientific data to developers.

The developers have proposed animations and graphics, game plays.

The committee has defined the specifications at different points during physical meetings and conference calls:

- Format
- Themes and key messages
- Graphics (places, people)

The committee has decided to create an adventure game with different interactives activities.

The following directions have been validated:

- Development of a serious game powered by Unity for computers, smartphones and tablets to allow use in all places (waiting rooms), designed to run on the IOS (apple) and Android operating systems.

- Definition of key messages and themes: family, school, sport, hospital, rehabilitation, treatment, further investigations.

- Graphic choices:
  - a Hospital (single place with the greatest number of possible themes)
  - Two avatars (one boy, one girl) to facilitate the identification of players.

Conclusion: To our knowledge, this is the first application dedicated to JIA.

To ensure the appropriateness of its speech, its ergonomics and ease of use, the global level of satisfaction, a neuropsychiatrist and the KOURIR organization (parents of children with JIA), will evaluate the beta version.

Adaptations would be made prior to the release of the game. Eventually, other game trays could complement this version in the future (adding school and home).

Disclosure: J. D. Cohen, None; D. Bentayou, None; M. Bernard-Brune1, None; S. Trope3. None.

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Flares in Children with JIA: Results from the Reach-out Cohort. Lori B. Tucker1, Jaime Guzman1, Kiem Oen2 and ReACCh Out Investigators3. 1BC Children’s Hospital and University of British Columbia, Vancouver, BC, 2Children’s Hospital of Winnipeg and University of Manitoba, Winnipeg, MB, 3BC Children’s Hospital, Vancouver, BC.

Background/Purpose: Disease flares are a concern to patients with JIA, their parents, and caregivers alike; but little is known of disease manifestations during a flare in children who have achieved inactive disease (ID) or whether flares differ among subtypes. The aim of this study is to describe flares in children with JIA and determine differences in flare characteristics among JIA subtypes.

Methods: We studied children diagnosed with JIA between 2005 and 2010 who had at least one visit with ID (no active joints, no extra-articular manifestation, and a physician global assessment < 10mm) while being prospectively followed in the Research in Arthritis in Canadian Children
emphasizing Outcomes (ReACCh-Out) cohort. They received usual pediatric rheumatology care at 16 Canadian centres. Flare was defined as loss of any criteria for ID. In addition a flare was imputed on the basis of an intra-articular injection alone in absence of other documentation of disease activity. Treatment of flares were recorded if there was a change, addition, or restart of anti-rheumatic or anti-uvetis treatment.

Results: Of 1492 children recruited in ReACCh-Out, 1146 had at least one visit with ID, with median follow-up of 24 mo (IQR 12.39) following first record of ID. A total of 1,191 flares were observed in 531 children (46.3%) after their first ID episode: 31% with systemic JIA and 44–50% with other subtypes. Arthritis was a feature of the majority of flares but there were significant differences in frequencies across subtypes (p=0.001). Frequencies of nonarticular flares also differed among subtypes (p<0.001) and were most common in children with systemic, enthesitis related arthritis and undifferentiated subtypes. Flares due to uveitis were seen in patients with oligoarticular, rheumatoid factor negative, and undifferentiated subtype most commonly. The majority of flares occurred while patients were still on treatment for their JIA and overall 45% were not associated with treatment changes (Table).

Table: Characteristics of disease flare across JIA subtypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Systemic Oligo RF neg RF pos Psoriatic ERA Undiff</th>
</tr>
</thead>
<tbody>
<tr>
<td># subjects</td>
<td>1146</td>
</tr>
<tr>
<td>Flares signs (% of flares):</td>
<td></td>
</tr>
<tr>
<td>Arthritis flares</td>
<td>79</td>
</tr>
<tr>
<td>Non-articular flares</td>
<td>18</td>
</tr>
<tr>
<td>PGA ≥ 1 without other signs</td>
<td>10</td>
</tr>
<tr>
<td>Treatment at time of flare (% of flares):</td>
<td></td>
</tr>
<tr>
<td>Flare on treatment</td>
<td>70</td>
</tr>
<tr>
<td>Flare off treatment</td>
<td>27</td>
</tr>
<tr>
<td>No change in treatment following flare</td>
<td>45</td>
</tr>
</tbody>
</table>

Conclusion: Flare characteristics in JIA differ among disease subtypes. An increase in PGA alone accounts for flare some patients, suggesting that PGA includes consideration of disease manifestations not included in our flare definition. Our results suggest that while disease flares occur in approximately half of children with JIA managed with usual care, many are mild and require no treatment change.

Discussion: L. B. Tucker, None; J. Guzman, None; K. Oen, None; R. O. Investigators, None.

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Long Term Functional Outcome and Quality of Life of Patients with Refractory Juvenile Idiopathic Arthritis Treated with Etanercept: Results of the Dutch Arthritis and Biologicals in Children Register. Janneke Anink1, Femke Prince1, Maryanne Dijkstra1, Marieke H. Otten1, Marinka Twilt2, Rebecca ten Cate3, Simone Gorter4, Yvonne van Breemen, Amsterdam, Netherlands, 7Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Juvenile idiopathic arthritis patients refractory to methotrexate (MTX) are eligible for treatment with biologic agents. A longitudinal sub-analysis (n=53) of the Dutch Arthritis and Biologicals in Children register previously showed that disability and health related quality of life (HRQoL) improved shortly after treatment with etanercept. Our aim was to investigate long term functional outcome, HRQoL and treatment changes in the same patients, who started etanercept >5 years ago.

Methods: Patients were traced and questioned on education and employment. Data on recent disease status, comorbidities and structural damage were retrieved. Disability was assessed by (Child) Health Assessment Questionnaire (C/HAQ). HRQoL was measured by Child Health Questionnaire, Short Form 36 and Health Utilities Index Mark 3. Linear mixed models were used to analyze changes over time.

Results: 43 patients (81% response) started etanercept median 8.5 years (IQR: 7.7–10.3) ago. Median age was 22 years (IQR: 18–24). 42% had a (C)HAQ of 0.00. HRQoL was similar to HRQoL shortly after start of etanercept, except for the domains bodily pain and general health perception, which deteriorated to levels comparable to those at start of etanercept. VAS pain also worsened (median 12 (IQR 2–43)), but not to the extent as the bodily pain domain on the SF-36. The unemployment rate (12%) was comparable to the general population; educational level was higher (77% of patients >17 years had achieved at least upper secondary education). 40% of patients switched to other biologic agents, 40% were still using etanercept and 20% were off anti-rheumatic treatment. 14% had had joint surgery. There were no reports of malignancies.

Conclusion: The improvement in HRQoL after start of etanercept was sustained after 8.5 years. Disability was low. On many aspects of daily life, patients functioned comparably to or better than the general population. The need for surgery for 14% of patients stresses the importance of early treatment of JIA. Chronic pain - even when the disease is inactive - remains an important issue that should not be overlooked.

Disclosure: J. Anink, None; F. Prince, None; M. Dijkstra, None; M. H. Otten, None; M. Twilt, None; R. ten Cate, Pfizer Inc, 2; Pfizer Inc, 5; S. Gorter, None; Y. Koopman-Keemink, None; M. A. J. Van Rossum, None; E. P. A. Hoppenreijis, None; L. W. A. van Suijlekom-Smit, Pfizer Inc, 2.

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Background/Purpose: To assess the pharmacokinetics (PK) and PK-efficacy correlations of body surface area (BSA)-adjusted dosing of 30 mg/m² golimumab administered subcutaneously (SC) every 4 weeks (q4w) + methotrexate (MTX) through Week 48 for 53 patients (ages 2 to <18 years) with juvenile idiopathic arthritis (JIA).

Methods: GO-KIDS is a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 trial of SC golimumab 30 mg/m² (maximum 50 mg) q4w + MTX (10–30 mg/m²/week) in pediatric patients with active JIA despite current MTX therapy (median 15 mg/week). PK, safety, and efficacy evaluations were performed q4w through week 16. At Week 16, patients who were ACR JIA 30 responders were randomized (1:1) to 30 mg/m² golimumab or placebo q4wks through Week 48 with GLM reinstituted upon flare (defined as per JIA ACR flare criteria) or initiation of new DMARDS, biologics, systemic immunosuppressors. Serum trough concentrations were also obtained at Weeks 16, 24, and 48. Serum golimumab trough concentrations for 154 patients were determined via a validated immunoassay. The relationships of ACR pediatric 30 response and disease flare status with steady-state trough levels at Week 48 were assessed.

Results: Trough serum golimumab concentrations in patients receiving SC 30 mg/m² golimumab q4w through Week 48 were maintained over time. Steady-state trough golimumab levels were similar across different age groups, and were also similar to those seen in adult RA patients who received 50 mg SC q4w in Phase III clinical trials. There were no apparent differences in pediatric ACR JIA 30 response rates and disease flare rates among the 4 groups of JIA patients categorized by the 4 quartiles of steady-state trough golimumab levels at Week 48. In addition, there were no apparent PK differences between patients who did and did not experience disease flares in the randomized golimumab group. Mean (SD) and median trough serum golimumab concentrations (mg/mL) by age groups and body weight quartiles are presented in the table.

Conclusion: Treatment with 30 mg/m² SC golimumab q4w + MTX resulted in sustained steady-state trough serum golimumab concentrations over time. The PK/efficacy correlation analyses demonstrated that the BSA-adjusted dosing regimen of 30 mg/m² SC golimumab q4w provided adequate drug exposure for the desired efficacy.

Age Groups (Years) 2–6 ≥6 to 12 ≥12 Combined

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Mean (SD)</th>
<th>1.42 (0.744)</th>
<th>0.95 (0.593)</th>
<th>1.21 (0.711)</th>
<th>1.14 (0.685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.77</td>
<td>0.92</td>
<td>1.29</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>Mean (SD)</td>
<td>1.17 (0.650)</td>
<td>0.96 (0.721)</td>
<td>1.24 (0.836)</td>
<td>1.13 (0.780)</td>
</tr>
</tbody>
</table>
### Background/Purpose: Intra-articular corticosteroid injections in juvenile idiopathic arthritis (IACI) are a standard treatment in juvenile idiopathic arthritis (JIA). This study assessed response to IACI in a large prospective cohort of children and young people (CYP) recruited at initiation of treatment.

### Methods: Participants were in the Childhood Arthritis Prospective Study (CAPS), an on-going prospective inception cohort study in 7 UK paediatric rheumatology centres, recruiting CYP <16 years with new inflammatory arthritis persisting for ≥ 2 weeks. Demographics, disease features, joint count, treatment details, Childhood Health Assessment Questionnaire (CHAQ), physician’s global assessment (PGA), parent’s general evaluation of well-being (PGE), ESR are collected at first presentation, 6 months, then yearly.

### Results: Of 1477 CYP recruited to CAPS 759 completed 3 years of follow-up and 603 (79.5%) were treated with IACIs. 185 (24.4%) required IACI alone (with a single episode of injection as the only treatment in 100, (13 % of the total cohort) usually the knee in 80 %. Most injected patients required additional treatments, 393 (69.3%) commenced a DMARD or biologic agent. Of these, 93 patients received both DMARD/ biologic and IACI at the same time. Of the 185 patients treated only with IACI 85 had more than one episode of injections. For this group the median time to first injection was 14 days (IQR 6.36) and time from first to second injection was 318 days (IQR 62.52) illustrating a prolonged effect from the first injection.

### Conclusion: Approximately one quarter of patients required monotherapy with IACI alone. Only 13% of all patients and 25% of oligo-articular course patients were managed with a single injection. Higher measures of disease activity were significantly associated with the need for DMARD therapy in addition to IACI.
Methotrexate dose, MISS and countermeasures instituted by the parents were determined at 4 time points (at inclusion, at 6 weeks, 3 months and 6 months). Countermeasures were classified into 4 criteria: antiemetic drugs, covert dosing, taste masking and complementary medicine. Results were analyzed using descriptive statistics and non-parametric testing (Wilcoxon signed rank test).

Results: 38 patients were included (63% female, median age at inclusion 11.7 years, median disease duration 7.1 years). Average MISS at inclusion was 10.8 ± 4.1, and after 6 months 12.2 ± 7.2 (p = 0.316). In 6/38 patients (16%), MTX was reduced or discontinued during the study. In 89 time intervals between study visits, 40 countermeasures were introduced by the parents.

Countermeasure n MISS before introduction MISS after introduction p
Antiemetic drugs 9 10.56 13.78 0.080
Covert dosing 11 12.64 12.64 0.766
Taste masking 9 11.67 13.22 0.120
Complementary medicine 11 12.73 14.18 0.089

Conclusion: If MTX intolerance is present, symptoms will not decrease over the course of 6 months. Various modalities used by the parents as countermeasures against nausea show no discernible effect.

Disclosure: A. Scheuern, None; N. Fischer, None; J. P. Haas, None; B. Hugle, None.

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S100 Proteins in Oligoarticular Juvenile Idiopathic Arthritis. Alexandra R Aminoff1, Carol A Wallace1, Sarah Ringold2, Anne Stevens1 and Jessica M Foster3. 1Seattle Children’s Hospital/Univ of Washington, Seattle, WA, 2Seattle Children’s Hospital, Seattle, WA, 3Seattle Children’s Research Institute, Seattle, WA.

Background/Purpose: There is a lack of reliable biomarkers that correlate with active juvenile idiopathic arthritis (JIA). The S100A8/A9 heterodimer (calprotectin) and S100A12 are proinflammatory molecules that have been shown to correlate with risk of relapse in JIA. Our objectives were to compare calprotectin and S100A12 levels in children with newly diagnosed oligoarticular JIA to those of healthy controls and to determine whether baseline levels of these proteins in oligoarticular JIA are associated with disease course.

Methods: This was a prospective, observational cohort study of newly diagnosed oligoarticular JIA patients at Seattle Children’s Hospital. Plasma calprotectin and S100A12 levels were measured using commercially-available enzyme-linked immunosorbent assay (ELISA) kits and compared to healthy pediatric controls using the Wilcoxon rank sum test.

Results: The oligoarticular JIA cohort (n=25) was 68% female, with a mean age of 5.6 years (range 2.1–14.4 years) and the historic pediatric control group (n=30) was 67% female, with a mean age of 9.1 years (range 1.3–13.4 years). The oligoarticular JIA cohort had significantly elevated calprotectin levels (median 1246 ng/ml, range 202–5694) compared to controls (median 730 ng/ml, range 124–1668), p value 0.005. For S100A12, the oligoarticular JIA cohort again had significantly elevated levels (median 48,800 pg/ml, range 0–350,400) compared to controls (median 13,400 pg/ml, range 0–178,700), p value =0.002.

Conclusion: Patients with oligoarticular JIA have significantly higher calprotectin and S100A12 levels at the time of diagnosis compared to healthy controls. A longitudinal analysis is underway to determine if these baseline S100 protein levels correlate with subsequent disease course. A reliable biomarker to aid in the prediction of disease course at diagnosis would potentially allow providers to identify children who would benefit from earlier aggressive therapy.

Disclosure: A. R. Aminoff, None; C. A. Wallace, Amgen; 2Pfizer Inc; 2Amgen; 5Novartis Pharmaceutical Corporation; 5S. Ringold, None; A. Stevens, None; J. M. Foster, None.

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Long-Term Impact of Juvenile Idiopathic Arthritis in the Greek adults’ Psychosocial Life. Despoina Dimopoulou1, Maria Trachana, Polychroni Pratsidou-Gertzis2, Giorgia Garyfallos1, Prodromos Sidiropanos1, Athina Theodoridou1 and Alexandros Garyfallos1. 14th Department of Internal Medicine, Aristotle University, Hippocratio Hospital, Thessaloniki, Greece; 2Aristotle University, Thessaloniki, Greece, 31st Department of Pediatrics, Aristotle University, Thessaloniki, Greece, 42nd Department of Psychiatry Aristotle University, Thessaloniki, Greece, 5University of Crete, Heraklion, Greece.

Background/Purpose: Juvenile idiopathic arthritis (JIA) seems to have a negative impact on patients’ life style mostly due to the disease chronicity. No relevant data have been published for Greek young adults so far. To capture the impact of disease burden in the psychosocial profile of adults with JIA, 17.2 years after disease onset.

Methods: A total of 96 (66 females) patients were enrolled. Psychosocial distress was assessed by the Greek version of the self-completed paper-based General Health Questionnaire (GHQ-28). A second questionnaire regarding marital status, education level and employment status was completed by all patients. Disease activity status at the last follow-up visit was assessed according to the Wallace’s criteria while the level of disease activity by the Disease Activity Score-28 (DAS-28). The patient’s assessment of global disease activity was measured on a Visual Analogue Scale (VAS) 0 to 10. Structural damage was scored by the the Juvenile Arthritis Damage Index-Articular (JADI-A) and by the Total modified Sharpvan der Heijde Score (TmSvdHS). Physical ability was assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Results: The GHQ-28 case score depicted impaired psychosocial status in 18 patients (18.7%). The level of psychosocial distress was significantly correlated with DAS28 at the last follow up visit (r=0.446, p<0.001). The presence of disease activity was correlated with higher degree of depression (p=0.032) and social dysfunction (p=0.008). Interestingly, patients without or with mild physical disability (HAQ-DI=0–0.49) differed from those with moderate-to-severe disability (HAQ-DI=0.5–3) in the fields of somatization (p=0.004) and social dysfunction (p<0.001), but not of depression. Higher degree of depression was recorded in the unemployed patients (p=0.018) and in those with mandatory education (p=0.018). In contrast, structural damage (JADI-A, TmSvdHS), marital status and current use or duration of corticosteroid treatment didn’t find to influence patients’ psychosocial profile. Global disease activity rated by the patient was found to be the only significant predictor of psychosocial distress in the multivariate analysis [B=0.057 95%CI (0.017, 0.097), P=0.005].

Conclusion: Psychosocial distress is evident in a considerable proportion of the patients (~19%), indicating a constant impact of the disease on every-day life. The tight control of disease activity is therefore crucial in order to prevent symptoms of depression in these JIA adults.

Disclosure: D. Dimopoulou, None; M. Trachana, None; P. Pratsidou-Gertzis, None; G. Garyfallos, None; P. Sidiropanos, None; A. Theodoridou, None; A. Garyfallos, None.

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A Controlled Trial of Intra-Articular Corticosteroids with or without Methotrexate in Oligoarticular Juvenile Idiopathic Arthritis. Angelo Ravelli1, Giulia Bracciolini2, Sergio Davi2, Angela Pistorio2, Alessandro Consolaro2, Sara Verazzat3, Bianca Lattanzi2, Giovanni Filicarno2, Sara Dalprà2, Maurizio Gattinara2, Valeria Gerlioni2, Antonella Insalaco4, Fabrizio de Benedetti2, Adele Civino2, Luciana Breda2, Loredana Lepore2, Maria Grazia Maggio1, Franco Garofalo1, Silvia Magni-Manzoni2, Donato Rigante11, Antonella Buoncompagni2, Marco Gattorno2, Clara Malattia1, Stefania Viola2, Paolo Picco2, Nicollino Ruperto2 and Alberto Martinili1. 1Istituto Giannina Gaslini and University of Genova, Genova, Italy, 2Istituto Giannina Gaslini, Genova, Italy, 3Istituto Ortopedico Gaetano Pini, Milano, Italy, 4Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 5Ospedale Pediatrico Bambino Gesù, Roma, Italy, 6Ospedale Cardinale G. Panico, Tricase, Italy, 7Ospedale Policlinico, Chieti, Italy, 8Istituto Burlo Garofolo, Trieste, Italy, 9University of Palermo, Palermo, Italy, 10Ospedale degli Infermi, Biella, Italy, 11Università Cattolica Sacro Cuore, Rome, Italy, 12Istituto Giannina Gaslini, Genoa, Italy.

Background/Purpose: In contrast with the numerous randomized controlled trials conducted in polyarticular or systemic juvenile idiopathic arthritis (JIA), little evidence-based information is available for oligoarticular JIA. As a result, the management of children with this subtype, which is the most prevalent in Western countries, is largely empiric. Intra-articular corticosteroid (IAC) injection is the therapy of first choice for oligoarthritis in many pediatric rheumatology centers. However, although IAC injections are usually highly efficacious, relapses of synovitis are common and sometimes occur only a few months after the procedure. It is still unclear whether concomitant administration of methotrexate (MTX) may increase and prolong the effectiveness of IAC injections. The aim of the study was to compare the efficacy of IAC injection administered as monotherapy or in association with MTX in children with oligoarticular JIA in a phase II, randomized, actively controlled, multicenter trial.
Methods: Inclusion criteria were oligoarticular JIA by ILAR criteria, age < 18 years, and parent informed consent. Patients who were previously treated with synthetic or biologic DMARDs, had undergone an IAC injection < 3 months, were newly injected only in 1 knee, or had active uveitis were excluded. Patients enrolled were randomized 1:1 to receive either IAC therapy alone (Arm 1) or IAC therapy plus MTX (Arm 2). MTX was given orally at 15 mg/m²/week (maximum 20 mg/week). All patients were followed for 12 months and were assessed at 3, 6 and 12 months. The primary outcome was synovitis flare, defined as recurrence, persistence or new onset of synovitis in 1 or more injected or uninjected (i.e. previously unaffected) joints. Flare rate/probability was compared by chi-square and Kaplan-Meier methods.

Results: A total of 207 patients (50 boys and 157 girls) were enrolled, 102 in Arm 1 and 105 in Arm 2. Fifteen patients lost to follow-up <6 months were included only in the intention-to-treat (ITT) cohort. Patients in arms 1 and 2 were comparable for demographic features and median number of injected joints (2 vs. 2). In the ITT cohort (n=207) flare of synovitis occurred in 133 patients (64.2%), 69 (67.6%) in Arm 1 and 64 (60.9%) in Arm 2 (p=0.31), whereas in the as-observed (AO) cohort (n=192) flare of synovitis occurred in 118 patients (61.4%), 64 (66%) in Arm 1 and 54 (56.8%) in Arm 2 (p=0.19). By Kaplan-Meier analysis, the probability of synovitis flare in the 2 treatment arms was comparable in both ITT and AO cohorts (log-Rank test: p=0.18 and 0.07, respectively). However, among the 118 patients who flared in the AO cohort, flare in injected joints occurred more frequently in Arm 1 than in Arm 2 (46/64, 71.9% vs. 29/54, 53.7%; p=0.04).

Conclusion: Flare of synovitis in injected joints occurred less frequently in patients who received concomitant MTX. However, the association of oral MTX did not increase the overall effectiveness of IAC therapy, owing to the high frequency of new onset of synovitis in uninjected joints. Trial registration identifying number: FARMY279L, AIFA, Italy.

Disclosure: A. Ravelli, None; G. Braccioli, None; S. Davi, None; A. Pistorio, None; A. Consolaro, None; S. Verazza, None; B. Lattanzii, None; G. Filocamo, None; S. Dalpra, None; M. Gattorno, None; V. Gerloni, None; A. Insalaco, None; F. De Benedetti, None; A. Civino, None; L. Breda, None; L. Lepore, None; M. C. Maggio, None; F. Garofalo, None; S. Magni-Manzoni, None; D. Rigante, None; A. Buoncompagni, None; M. Gattorno, None; C. Malattia, None; S. Viola, None; F. Pico, None; N. Ruperto, None; A. Martini, None.

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Patient-Reported Joint Count in Juvenile Idiopathic Arthritis: The Reliability of a Mannequin Format. Maryanne Dijkstra1, Janneke Anink1, Philomine A. van Pelt2, Johanna M.W. Hazes2 and Lisette W.A. van Suijlekom-Smit1. 1Erasmus MC Sophia Children’s Hospital, Rotterdam, Netherlands, 2Erasmus MC, Rotterdam, Netherlands.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is a common chronic disease, requiring regular monitoring. Patient-reported outcomes can assist monitoring, may promote patient self-management and can be useful in epidemiological surveys. Our objective was to evaluate the reliability of a mannequin-format patient-reported joint-count in JIA, and to detect changes in agreement at a follow-up visit.

Methods: JIA patients aged 12–21 marked joints with active arthritis on a mannequin (see Figure 1) before their regular clinic visit. The physician performed a joint-count without having seen the patient’s assessment. For two subsequent clinic visits, agreement between the physician and patient-reported joint-counts was assessed using Intraclass Correlation Coefficient (ICC) and kappa statistics. The ability of the patient-reported joint-count to discriminate between active and inactive disease was evaluated using positive and negative predictive values. Sensitivity to change was estimated using discriminative features and median number of injected joints (2 vs. 2). In the ITT cohort. Patients in arms 1 and 2 were comparable for demo-

Results: Out of 875 JIA patients followed into adulthood, 91 pregnancies were reported in 70 patients (58 females patients, 12 partners of male patients). Until June 2014, reports on pregnancies were evaluable for 50 females with 60 pregnancies. The majority had polyarticular JIA (72%), another 16% enthesitis-related arthritis. The median age at conception was 20.9 years (ys, range 13.8–29.0), the median disease duration 11.6 ys (range 3.3–26.1).

All patients were ever treated with bDMARDs (94%) and/or nbDMARDs (100%), 48% were exposed at conception (10 to
Conclusion: This study begins to characterize the factors that pediatric rheumatologists use to define a successful disease outcome for JIA in young adulthood. Physicians prioritized physical outcomes, function and medication adverse effects in the definition of successful JIA management. Further studies are needed to characterize the factors that the patients prioritize. With additional studies, the definition of a gold standard based on physician and patient input will enable patients to be better informed about their treatment options and expected future outcomes.

Disclosure: M. L. Mannion, None; M. Williams, None; G. McGwin Jr., None; K. G. Saag, None; T. Beukelman, Novartis Pharmaceutical Corporation, 5, Genentech and Biogen IDEC Inc., 5, UCB, 5, Pfizer Inc, 2.

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Predicting Chronic Pain in Children with Juvenile Idiopathic Arthritis: Results from the Childhood Arthritis Prospective Study. Amir Rashid1, Kate Holliday1, Lis Cordingley1, Roberto Carrasco1, Bo Fu1, Helen E. Foster1, Eileen Baldiam2, Alice Chieng3, Joyce Davidson1, Lucy Wedderburn4, Kimme Hynie3 and Wendy Thomson3. 1The University of Manchester, Manchester, United Kingdom, 2The University of Manchester, Manchester, United Kingdom, 3University of Manchester, Newcastle upon Tyne, United Kingdom, 4Alder Hey Children’s Foundation NHS Trust, Liverpool, United Kingdom, 5Royal Manchester Children’s Hospital, Manchester, United Kingdom, 6Royal Hospital for Sick Children, Glasgow, United Kingdom, 7University College London (UCL), London, United Kingdom, 8Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, 9Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Pain is the most common symptom of JIA and has been associated with disease activity. However, disease activity has only accounted for a small amount of the variance in pain. This suggests predictors beyond clinical factors may be important in determining pain. The objectives of this study were to predict, at first presentation, children who are likely to have poor pain outcomes and how these children differ from those that improve.

Methods: Participants were children with new inflammatory arthritis who were recruited into the CAPS cohort and followed systematically with baseline data for the 100mm visual analogue scale (VAS) for pain available. A two-stage approach was used for the analysis. Firstly, pain trajectories were modelled in children with pain at presentation and at one or more follow-up visits (up to five years post baseline) using a discrete mixture-model. Secondly, multinomial logistic regression was used to determine the association between baseline variables and trajectory groups (95% CI). These variables included the core outcome variables (active and limited joint counts, physician’s global assessment (PGA), parent/patient general evaluation (PGE), childhood HAQ (CHAQ) score), gender, age at onset and disease duration.

Results: 957 children were included. A three group trajectory model of pain was selected as the most clinically relevant model (Figure) and included a Low-Low pain group (trajectory 1), a High-Low pain group (trajectory 2) and a High-High pain group (trajectory 3). Children in the High-Low group and High-High group had significantly older age at onset, longer disease durations, more involved joints, higher PGE, PGA, pain and CHAQ scores at presentation, compared to children in the Low-Low group. Higher pain at baseline predicted membership of the High-High group (RRR 1.1 (95% CI 1.05, 1.1)) and High-Low Pain (RRR 1.1 (95% CI 1.1.1,1) compared to Low-Low group; and predicted membership in the High-Low group compared to the High-High group (RRR 0.98 (95% CI 0.97, 0.99)). Both Higher CHAQ scores and older age at onset predicted membership in the High-High group compared to both the Low-Low group and the High-Low group. Longer disease duration at presentation predicted membership in the High-High group (RRR 1.03 (95% CI 1.01, 1.04) and the High-Low group (RRR 1.02 (95% CI 1.001, 1.03) compared to Low-Low group.

Conclusion: Even when adjusting for core outcome variables at presentation, participants who present earlier in their disease, are younger at disease onset and report less pain and functional problems upon presentation are less likely to report pain over time. Age at onset, functional problems and pain at presentation differentiated between high levels of pain which improved or persisted over time.
Background/Purpose: Several studies suggest an increased frequency of cardiovascular disease (CVD) in patients with rheumatoid arthritis, but little is known about CVD risk in patients with juvenile rheumatoid arthritis (JRA). The objective of this study was to evaluate the frequency of CVD and CVD risk factors in adults with a prior diagnosis of JRA compared to controls.

Methods: A retrospective, partly population-based cohort study was independently conducted utilizing patients at two major academic institutions (Cohorts 1 and 2). Each institution employed a unique methodology to evaluate for the common endpoint of clinical CVD outcomes and risk factor development with comparison to control groups of similar age and sex. Cohort 1 was an inception cohort of residents of a geographically defined area who were diagnosed with JRA in 1960–1993. CVD and CVD risk factors were ascertained via medical record review and telephone survey for the subset of patients currently aged ≥30 years. Cohort 2 included patients diagnosed with JRA in 1980–1985 who participated in a clinical exam or completed a survey in 2011–2012 (i.e., 29 year follow-up).

Results: Among 41 patients with JRA and 28 controls in cohort 1, 3 patients (7%) had CVD, compared to 0 controls (p = 0.43). Of these, 1 patient had CVD prior to age 30 with ages at time of CVD diagnosis ranging from 21–39 years. Types of CVD included 1 patient with venous and arterial thrombosis, 1 patient with coronary artery disease and myocardial infarction, and 1 patient with angina pectoris. Analysis for the presence of CVD risk factors in Cohort 1 demonstrated 15 patients (56%) with hyperlipidemia, compared to 0 controls (p = 0.019). Twenty patients (49%) were ever smokers, compared to 10 controls (36%) (p = 0.004). Other risk factors including hypertension, diabetes mellitus, and family history of CVD were elevated in the JRA cohort but did not obtain statistical significance. Among 170 JRA patients with 29 year follow-up and 91 controls in Cohort 2, 2 patients (2%) had CVD, compared to 0 controls (p = 0.29). Types of CVD included 1 patient with myocardial infarction and 1 patient with angina pectoris and myocardial infarction. Analysis for the presence of CVD risk factors in Cohort 2 demonstrated 14 patients (8%) with hypertension, compared to 2 controls (2%) (p = 0.049). Ninety patients (54%) were ever smokers, compared to 36 controls (40%) (p = 0.028). Other CVD risk factors measured and elevated in the JRA cohort included use of antilipemic medication, use of antihypertensive medication, and CVD in first degree relative, but statistical significance was not obtained. The presence of diabetes mellitus was equal in the JRA cohort and control group for Cohort 2.

Conclusion: Certain CVD risk factors including hyperlipidemia, hypertension, and smoking appear to be more common among patients with JRA than in age-matched controls. There may be a trend toward increased numbers of CVD events, and occurrence of CVD at younger ages in patients with JRA, although statistical significance was not demonstrated in this study. Continued longitudinal follow-up of these cohorts and larger population-based studies are needed to establish a definitive relationship between JRA and CVD.

Disclosure: J. Anderson, None; K. Anderson, None; H. Aulie, None; C. S. Crowson, None; T. Mason II, None; S. P. Ardoin, None; A. M. Reed, None; B. Flato, None.
306 Association of Kawasaki Disease with Tropospheric Winds in Central Chile: Is Wind-Borne Desert Dust a Risk Factor?1. Arturo Borzutzky1, Alvaro García1, Rodrigo Hoyos-Bachiloglu1 and Hector Jorquera1. 1Millenium Institute on Immunology and Immunotherapy, Pontificia Universidad Católica de Chile, Santiago, Chile; 2Pontificia Universidad Católica de Chile School of Medicine, Santiago, Chile; 3Centro de Desarrollo Urbano Sustentable (CEDEUS), Santiago, Chile.

Background/Purpose: Kawasaki disease (KD) has been reported to have seasonal variations in many different countries, as well as geographical and temporal clustering. It has been found that KD cases diagnosed in Japan, Hawaii and San Diego, USA increase when tropospheric wind patterns arrive from central Asia, suggesting a common, wind-borne causal agent.

Methods: We analyzed KD cases hospitalized in Santiago, Chile to look for associations with local, regional and large scale meteorological variables. We compiled monthly data of KD incidence rates, local meteorological variables, regional winds and several El Niño Southern Oscillation (ENSO) indices for 2001-2010; we considered standardized anomalies in all analyses.

We used dynamic linear regression models to account for data autocorrelation.

Results: Zonal (U) winds at 1000 and 925 mb above Santiago show a strong correlation with KD data on univariate linear regression (P < 0.001), but no significant association was observed for other unlagged meteorological variables. We then fitted multivariate dynamical regressions using time series ARX models; model selection was carried out by minimizing Akaike’s Information Criterion (AIC) and several model structures — using different lags in meteorological variables — were explored. This multivariate dynamic regression showed that meteorological variables explain 38% of variance in KD rates. A unit increase in northerly wind at 3 lagged months, temperature at 1 and 3 lagged months and monthly change of ENSO 4 index are associated with changes in KD rates of 0.203 (95% CI 0.049 – 0.358), 0.181 (95% CI 0.014 – 0.347), 0.192 (95% CI 0.030 – 0.353) and -0.307 (95% CI -0.458 -0.156), respectively.

Conclusion: We found a statistical association of KD at Santiago, Chile with tropospheric, northerly wind patterns suggesting dust transported from the Atacama Desert could include a causative agent. A novel result is that ENSO dynamics also explain part of KD variability with a decrease in KD when La Niña is dissipating or El Niño is on the rise; hence climate scale dynamics might be taken into account in future studies worldwide — at least as a potential explanatory variable that may confound KD seasonality on a global scale.

Disclosure: A. Borzutzky, None; A. García, None; R. Hoyos-Bachiloglu, None; H. Jorquera, None.

References

307 Sibling Exposure and Risk of Juvenile Idiopathic Arthritis. Jessica Miller1, Anne-Louise Ponsonby2, Angela Pezic3, Jonathan Akikusa1, Roger Allen4, Jane Munro1 and Justine Ellis1. 1Murdoch Childrens Research Institute, Parkville, Australia; 2The University of Melbourne, Parkville, Australia; 3Royal Childrens Hospital, Parkville, Australia; 4Royal Children’s Hospital, Melbourne, Australia.

Background/Purpose: Susceptibility to juvenile idiopathic arthritis (JIA) is presumed to be determined by the interplay of genes and environment. Our understanding of the genetic basis of JIA risk has increased markedly over the last few years, but the environmental factors remain largely unknown. The hygiene hypothesis suggests that exposure to microbes in early life may protect against the development of immune disorders. Measures of early life hygiene have been associated with asthma, allergy, multiple sclerosis (MS) and type 1 diabetes. Exposure to siblings may be a marker of exposure to childhood infection, and we have previously shown that higher infant sibling exposure prior to school age is associated with a decreased risk of MS. We therefore hypothesised that sibling exposure may also be associated with JIA.

Methods: Participants were drawn from the CLARITY JIA biobank in Victoria, Australia. Cases (n = 302; mean age 8.5y ± 4.7 SD; 67% female) were children born in Victoria who were diagnosed with JIA by a paediatric rheumatologist at the Royal Children’s Hospital (RCH), Melbourne. Systemic JIA cases were excluded. Controls (n = 676; mean age 7.1y ± 4.1 SD; 41% female) were healthy children born in Victoria and visiting the RCH day surgery unit for a minor surgical procedure. At recruitment, families completed a questionnaire that collected birthdates of the index child and siblings, along with data on other potential confounders including index child age and sex, maternal age at birth, gestational age at birth, child sleeping arrangements and socio-economic status. We compared birth order, only-child status, total number of siblings, and cumulative years of sibling exposure by age six, between cases and controls using logistic regression.

Results: We found that, compared to being an only child, having any siblings conferred a protective effect on JIA risk (adjusted OR = 0.46, 95% CI 0.28 - 0.74, p = 0.001). The protective effect appeared to increase with increasing number of siblings (Table 1).

Table 1: Total number of siblings born within 18 years of the index child

<table>
<thead>
<tr>
<th>JIA Cases No. (%)</th>
<th>Controls No. (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 47 (16.5)</td>
<td>79 (12.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1 123 (43.3)</td>
<td>327 (49.8)</td>
<td>0.46 (0.28, 0.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>2 86 (30.3)</td>
<td>165 (25.1)</td>
<td>0.50 (0.29, 0.87)</td>
<td>0.014</td>
</tr>
<tr>
<td>≥ 3 28 (9.9)</td>
<td>86 (13.1)</td>
<td>0.25 (0.13, 0.48)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

A protective effect of siblings was also observed when we considered cumulative sibling years by age 6 (e.g. ≥ 3y exposure vs no exposure, adjusted OR = 0.49, 95% CI 0.30 – 0.79, p = 0.003). There was no association between birth order and JIA risk. We also compared cases to a second control sample (n = 341, mean age 8.1 years ± 3.6 SD; 45% female) collected from the community and weighted to represent the Victorian child population. JIA odds ratios were found to be similar by this approach, although confidence intervals were wider, reflecting the smaller size of the community control sample.

Conclusion: In the CLARITY JIA case-control sample, increased exposure to siblings is associated with a reduced risk of disease. This suggests that increased microbial exposure in childhood may confer protection against the development of JIA.

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308 Tenascin-C, a TLR4 Ligand Levels in Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis: Cross-Sectional and Longitudinal Study. Anuj Shukla, Priyanka Gaur and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Tenascin-C (TNC) is an extracellular matrix glycoprotein, which binds to TLR4 and leads to its activation. Monocytes of children with Enthesitis related arthritis (ERA) show TLR4 overexpression. TNC may serve as an endogenous stimulator of TLR4 in ERA. Thus we...
studied the serum and synovial fluid levels of TNC in children with ERA and its association with disease activity.

**Methods:** TNC levels were measured in serum of 80 children with ERA satisfying ILAR criteria. 15 children were followed-up while on regular NSAID treatment and levels were reassessed at 3 months. 17 paired serum-synovial fluid samples and 25 healthy control serum samples were also analyzed. Disease activity was assessed by physician global assessment; tender, swollen and damaged joint counts; enthesitis score, ESR and CRP.

**Results:** Patients were mainly boys (9:1) with average age at disease onset of 11.2 years and duration of disease of 4.4 years. 80% had peripheral arthritis, 63% active enthesitis, 43% clinical sacroiliitis, 39% inflammatory back-pain, and 8% had a history of acute anterior uveitis. Most of the children were HLA-B27 positive (90%, n=72) and 29% had positive history of JIA-ERA or spondyloarthritis in the family.

The average physician global assessment (0–10) was 4.5±±2.2. Average early morning stiffness was 50±57 minutes with 4:2-tender and 3±3 swollen joints. Average ESR and CRP were 72±37 mm at 1 hour and 6.9±5.6 mg/dl. 25% children had at least one damaged joint with an average count of 2±2. 16 children out of 80 had no tender and swollen joints and were classified as inactive disease.

The mean serum TNC level in children with active disease was 67.1±44.9 ng/ml and was significantly higher than the inactive 40.6±36.7 ng/ml (p=0.01) and healthy control 21±15.2 ng/ml (p<0.001). Median levels were higher in HLA-B27 positive 70.1 ng/ml vs. negative disease 22.8 ng/ml (p=0.003).

Serum levels correlated positively with disease activity parameters like physician global assessment (r=0.4, 95% CI=0.2 to 0.6, p=0.005), tender joint count (r=0.4, 95% CI=0.27 to 0.6, p=0.0001), swollen joint count (r=0.46, 95% CI=0.2 to 0.6, p=0.0001), ESR (r=0.42, 95% CI=0.21 to 0.6, p=0.002) and CRP (r=0.32, 95% CI=0.1 to 0.5, p=0.007) and negatively with duration of disease (r=-0.33, 95% CI=-0.5 to -0.17, p=0.003). TNC levels did not correlate with enthesitis scores and damaged joint counts. In ROC analysis for active vs. inactive disease, TNC (AUC=0.754) was equivalent to ESR (AUC=0.787) and CRP (AUC=0.789).

Treatment with regular and adequate dose of NSAIDs lead to a significant fall in the serum levels at 3 months of follow-up (p=0.0003). The median synovial fluid TNC level in JIA-ERA was 17.39 ng/ml. Synovial fluid levels were significantly lower than the paired serum values (p=0.01).

**Conclusion:** Circulating TNC levels are significantly raised and correlate with various clinical and laboratory parameters of disease activity in children with ERA. It is equivalent to ESR and CRP as a measure of disease activity. Regular NSAID treatment results in significant fall in the levels at 3 months probably related to control of disease activity.

Disclosure: A. Shukla, None; P. Gaur, None; A. Aggarwal, None.

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**Clinical Significance of Cytokine Profile with Interleukin-18 and -6 in Systemic Juvenile Idiopathic Arthritis.** Masaki Shimizu, Natsumi Inoue, Yuko Tatsuki, Sayaka Ishikawa, Kazuyuki Ueno and Akira Yachie. School of Medicine, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, Kanazawa, Japan.

**Background/Purpose:** Innate proinflammatory cytokines interleukin (IL)-6 and IL-18 are critical for perpetuating the inflammatory processes in systemic juvenile idiopathic arthritis (s-JIA) and macrophage activation syndrome (MAS). To assess the role of IL-6 and IL-18 in the pathogenesis of s-JIA and MAS, and to investigate the clinical significance of serum cytokine profile with IL-18 and IL-6 might be useful to predict disease course. Furthermore, serum IL-18 levels reflect the biological activities of the immune system in s-JIA and may predict the development of MAS and the prognosis of s-JIA.

Disclosure: M. Shimizu, None; N. Inoue, None; Y. Tatsuki, None; S. Ishikawa, None; K. Ueno, None; A. Yachie, None.

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**Differential Expression of microRNA in Monocytes from Children with Systemic Juvenile Idiopathic Arthritis: Implications for Polarized Phenotype.** Grant Schulter1, Ndate Fall1, Nan Shen2 and Alexei Grom1.

1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Shanghai Institutes for Biological Sciences Chinese Academy of Sciences & Shanghai Jiao Tong University School of Medicine, Shanghai, China.

**Background/Purpose:** Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease of childhood, and the predominant effector cells are monoclonal phagocytes rather than lymphocytes as in autoimmune diseases such as rheumatoid arthritis (RA). Previous gene expression data has shown monocytes in SJIA have a novel phenotype with clear proinflammatory activation as well as features of alternative activation. This aberrant phenotype may contribute to the potential of these children to develop macrophage activation syndrome (MAS). What controls monocyte/macrophage differentiation in SJIA is unknown. MicroRNA are small, non-coding RNA that serve as transcriptional negative regulators to fine-tune gene expression programs involved in cell differentiation, metabolism and immunity.

There is growing evidence that miRNA contribute to the pathogenesis of human disease, including RA. These regulators have also been implicated in controlling differentiation of monocytes and macrophages. However, miRNA expression in SJIA has not been examined. Here, we examine miRNA expression profiles in peripheral blood monocytes from children with SJIA.

**Methods:** We enrolled children with active SJIA, defined as presence of active arthritis or systemic features, as well as those with new-onset disease or clinically inactive disease (CID). Freshly isolated CD14+ monocytes were isolated by magnetic beads separation, and used to generate RNA which in turn was used to quantify the expression of 384 miRNA and controls on the TaqMan™ MicroRNA Array A.

**Results:** We found that monocyte expression of mir-125a-5p was significantly elevated in children with active SJIA compared to those with CID (relative expression 16.8 vs. 3.0, p<0.05). In addition, expression of mir-125a-5p was significantly correlated with markers of disease activity including ferritin (R=0.73, p<0.001) as well as presence of systemic features such as hepatosplenomegaly. Recently mir-125a-5p has been suggested to play an essential role in monocyte polarization. We also found several specific microRNA with differential expression in monocytes from children with new-onset disease compared to those with active established disease. One of these, miR-187, has been implicated in negative regulation of cytokines including IL-6. We find that miR-187 expression strongly correlates with markers of disease activity including C-reactive protein (R=0.813, p<0.05), ferritin (R=0.644, p<0.05) and soluble IL-2 receptor (R=0.779, p<0.05) as well as presence of systemic features. Interestingly, while monocyte expression of mir-146a has been correlated with disease activity in RA, we found no difference in expression between monocytes from patients with active SJIA and those with CID.

**Conclusion:** These results provide the first report of miRNA expression profiles in children with SJIA. Taken together, these data suggest that differential miRNA expression contributes to the phenotype of monocyte/macrophages in SJIA, and may have implications for disease pathogenesis and development of MAS. Further work will examine impact of miRNA expression on monocyte function and differentiation.
Inhibition of Natural Killer (NK) Cell Cytotoxicity By Interleukin-6 (IL-6): Implications for the Pathogenesis of Macrophage Activation Syndrome. Loredana Cifaldi1, Giusi Prencipe2, Ivan Caiello2, Claudia Bracaglia2, Raffaele Strippoli1 and Fabrizio De Benedetti Sr. 2. 2Pediatric Haematology/Oncology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 2Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 3Cellular Biotechnologies and Haematology, Sapienza Rome University, Rome, Italy.

Background/Purpose: MAS occurs frequently in patients with active systemic juvenile idiopathic arthritis (sJIA) and because of the similarities with Haemophagocytic Lymphohistiocytosis (HLH) is classified among secondary HLH. s-JIA is characterized by high levels of Interleukin-6 (IL-6). Impairment of natural killer (NK) cell function and decrease perforin expression have also been reported in sJIA. Aim of this study was to evaluate the effect of IL-6 on NK cell cytotoxic function.

Methods: Following in vivo treatment with poly(I:C), splenic NK cell cytotoxic activity from wild-type (WT) or IL-6 transgenic (IL-6TG) mice was evaluated using the chromium51 release assay. NK cell number, perforin, granzymeB, CD69 and CD107a expression were evaluated by flow cytometric analysis. Human polyclonal NK cells were expanded from peripheral blood mononuclear cells (PBMCs) in co-cultures with the feeder cell line RPMI8866 in the presence of tocilizumab, an IL-6 receptor blocker, or isotype control. IL-6 production in the supernatants of human polyclonal NK cells was measured by ELISA. PBMCs from healthy donors were treated with IL-6. NK cell cytotoxic activity, perforin and CD107a expression were evaluated as above.

Results: Following poly(I:C) administration, in vivo generation of splenic NK cell cytotoxicity was markedly reduced in IL6TG mice compared to WT mice. In IL6TG mice number of NK cells, number of CD69+ NK cells and degranulation were comparable to WT mice. Defective expression of both perforin and granzymeB were found in NK cells from IL6TG mice. High levels of IL-6 were found in the supernatants of human polyclonal NK cells. Neutralization of IL-6 effects with tocilizumab in co-cultures of human PBMCs increased human NK cell cytotoxicity and perforin expression. Addition of IL-6 to human PBMCs decreased perforin expression in NK cells.

Conclusion: Both in vivo and in vitro in humans, IL-6 inhibits NK cytotoxicity down-regulating perforin expression. In patients with prominent inflammatory response, such as that present in s-JIA, high levels of IL-6 may contribute to the induction of MAS also by inhibiting cytotoxicity inducing a defect similar to that of primary HLH.

Disclosure: L. Cifaldi, None; G. Prencipe, None; I. Caiello, None; C. Bracaglia, None; R. Strippoli, None; F. De Benedetti Sr., Novartis, Novimmune, Hoffmann-La Roche, SOBI, AbbVie, 2, AbbVie Novartis, Novimmune, Hoffmann-La Roche, SOBI, 5.

Mutations in the MTHFR Gene Are Not Associated with Methotrexate Intolerance in Patients with Juvenile Idiopathic Arthritis. Andrea Scheuern, Nadine Fischer, Johannes-Peter Haas and Boris Hugle. German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany.

Background/Purpose: Methotrexate (MTX) is the drug used most frequently in the therapy of juvenile idiopathic arthritis (JIA). However, long-term treatment in children frequently leads to intolerance, with marked revulsion and refusal of treatment. Mutations in the gene for methylenetetrahydrofolate reductase (MTHFR) can lead to increased toxicity of MTX and could possibly represent an initial stimulus for this conditioned response.

The objective of this study was to investigate the relation of common mutations in the MTHFR gene and occurrence of MTX intolerance in pediatric patients with juvenile idiopathic arthritis treated with MTX.

Methods: Consecutive patients admitted to the German Center for Pediatric and Adolescent Rheumatology from October 2012 until April 2014 were included in this study. Inclusion criteria were 1) diagnosis of JIA and 2) treatment with MTX for at least 3 months prior to inclusion. Exclusion criteria were other diseases leading to nausea and/or abdominal complaints, and concomitant medications possibly inducing nausea (excepting biologics and non-steroidal anti-inflammatory drugs). Intolerance to MTX was determined using the validated Methotrexate Intolerance Severity Score (MISS) questionnaire; presence of MTX intolerance was assumed for MISS values of ≥ 6. Presence of the two most common mutations in the MTHFR gene (C677T and A1298C) was tested using a polymerase chain reaction assay, as described previously. Results were analyzed using descriptive statistics and univariate analysis.

Results: 114 patients were included (71% female, median age at inclusion median 12.6 years, median disease duration 4.1 years). Of those, 49 (43%) showed MTX intolerance. 42% of patients were heterozygous, and 7% homozygous for the C677T mutation of the MTHFR gene, 45% of patients were heterozygous, and 12% homozygous for the A1298C mutation; frequencies of both mutations are comparable to published data. Compared to the homozygous wild type, MTX intolerance was not found significantly more frequent in patients with hetero- and homozygous (p = 1.000) or homozygous (p = 0.125) C677T mutations, nor in patients with hetero- and homozygous (p = 0.775) or homozygous (p = 0.444) A1298C mutations. Compound heterozygous mutations for C677T and A1298C were also not found significantly more frequently in patients with MTX intolerance (p = 0.809).

Conclusion: Mutations in the MTHFR gene are not found significantly more frequently in JIA patients with intolerance to MTX. Development of MTX intolerance appears not to be causally related to toxicity associated with the MTHFR gene.

Disclosure: A. Scheuern, None; N. Fischer, None; J. P. Haas, None; B. Hugle, None.

Elevated Cardiovascular Disease Burden and Inflammatory Biomarker Levels in Adults with Juvenile Idiopathic Arthritis. Siobhan Crittenden1, Elizabeth Coulson1, Vijay Kunadian1, Wan-Fai Ng1 and H. E. Foster1. 1Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom, 2Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, 3Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom.

Background/Purpose: Rheumatoid Arthritis (RA) is associated with a 50% greater cardiovascular mortality rate than the general population, attributable to the increased prevalence of traditional risk factors and inflammatory molecules involved in coronary atherosclerosis. Many young people with Juvenile Idiopathic Arthritis (JIA) have their disease persisting into adulthood. Since persistent systemic inflammation is known to accelerate the atherosclerotic process, individuals with JIA and especially those with persistent inflammation may have a greater cardiovascular risk. This study was to assess the prevalence of traditional cardiovascular risk factors and carotid artery Intima-Media Thickness (cIMT) as a surrogate cardiovascular outcome. Additionally, potential biomarkers for predicting and monitoring of cardiovascular risks will be sought.

Methods: 51 adults with JIA (median age: 34.0 years, range: 18 – 63 years) were recruited from an adult continuity clinic along with 27 age- and gender-matched controls (median age 35.5 years, range: 18 – 62 years). JIA subtypes were defined by ILAR classification. After informed consent, cIMT was examined using B-mode ultrasound by one observer (EJC), and clinical data and blood samples were collected. cIMT images were analysed using the M’ath software package (Intelligence in Medical Technologies). Serum levels of potential cardiovascular risk biomarkers previously indentified in other adult inflammatory arthritis, such as systemic inflammation and adhesion molecules, were quantified using ELISA kits (R&D Systems) or Cytometric Bead Arrays (BD Biosciences). Data were analysed using FCAP Array software.

Results: A significantly higher proportion of adults with JIA compared to controls had a pre-existing diagnosis of hypertension (12 % vs. 1 %, p = 0.029). Mean CRP and cIMT were significantly greater in patients than in controls (9.0 mg/ml vs. 5.6 mg/l, p = 0.006, and 0.540 mm vs. 0.492 mm, p = 0.039 respectively), especially among those with systemic JIA and RF+ polyarticular JIA. cIMT correlates with age (Pearson’s coefficient 0.67, p < 0.001). Serum levels of MPO, IL-12p70, IL-12/23p40, IL-4, IL-8, TNFα and IL-21 were significantly different between the adult JIA and control group. Among the JIA subgroups, the polyarticular JIA group has the highest level of E-LAT, while the oligoarticular JIA group has the highest level of CD40L. Extended oligoarticular JIA has higher levels of IP10 and IL-8. After correcting for age, hypertension and smoking, IL-12/23p40 (p < 0.01) and IL-12p70 (p = 0.035) remain independent predictors for the differences in cIMT between patients and controls.
Conclusion: Adults with JIA have increased cIMT, as well as serum levels of CRP and several pro-inflammatory cytokines compared to healthy controls. Furthermore, IL-12p70 and IL-12/23p40 could potentially be used as biomarkers for cardiovascular risk. IL-12 plays an important role in JIA pathogenesis, promoting Th1 response and inflammatory cytokines such as TNFα. It is noteworthy that MPO, which is linked with plaque development, thrombus formation and is a predictor of CVD in healthy individuals, is upregulated in adults with JIA.

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Next Generation Sequencing Reveals Restriction of the Treg Cell Repertoire and an Abundance of Shared Synovial Treg Clonotypes in JIA.

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Background/Purpose: Regulatory T cell (Treg) dysfunction has been documented in juvenile idiopathic arthritis (JIA), but the basis for this lapse in suppressive capacity is incompletely understood. Animal models of autoimmunity demonstrate that a diverse and polyclonal Treg repertoire is essential for immune system homeostasis and Treg cell function. We therefore employed next generation sequencing (NGS) to analyze the repertoires of synovial fluid (SF) and peripheral blood (PB) Treg and effector T cells (Teff) in JIA.

Methods: Paired SF and PB samples were obtained from patients with JIA. Control samples included PB from age-matched, healthy children and SF from patients with Lyme arthritis. Treg (CD4+/CD25+/H9252) and Teff (CD4+/CD25+/H9252) cells were isolated from SF and PB mononuclear cells by fluorescence-activated cell sorting. The T cell receptor (TCR) β chain was amplified by multiplex PCR with genomic DNA serving as the template (ImmunoseqTM). The PCR products were sequenced using the Illumina HiSeq platform. The data was processed using the ImmunoSEQSTM set of online tools, the International ImMunoGeneTics system (IMGT) HighV-QUEST platform, and the Immunglobulin Analysis Tool (IgAT). The pre-specified primary aim was to evaluate the clonality of SF and PB Treg and Teff populations in JIA patients. Based on data evaluating the Treg repertoire and autoimmunity in animal models, we calculated that a sample size of 5 JIA patients would provide sufficient power for this study.

Results: 5 patients with JIA, 3 healthy controls, and 2 patients with Lyme arthritis were studied. In the PB of controls, the Treg and Teff repertoires were equally polyclonal. In contrast, JIA PB Treg cells were more clonal than control PB Treg, control PB Teff, and JIA PB Teff cells (ANOVA p<0.0001 with Bonferroni correction). JIA disease severity, as measured by the active joint count, correlated with the PB Treg clonality (r=0.95, p=0.005). Clonal abnormalities were not observed in the JIA PB Treg repertoire. In SF, JIA Treg cells were significantly more clonal than JIA PB Treg and Teff cells, JIA SF Treg cells, and control PB Treg and Teff cells (ANOVA p=0.0001 with Bonferroni correction). JIA patients shared a substantial portion of SF Treg clonotypes, significantly more than SF Teff cells (Wilcoxon p=0.0002). In some JIA patient pairs, up to 19% of SF Treg clonotypes were shared. Further, these shared SF Treg clonotypes were private to JIA patients and were not identified in Lyme arthritis. In further support of disease specific TCRs in JIA SF, convergent recombination was seen preferentially in the SF Treg compared to the PB Treg compartment (Wilcoxon p=0.0002). Skewed TCRβ variable family and joining gene usage, including overuse of gene segments that have been associated with other autoimmune conditions, was observed in JIA Treg and Teff cells.

Conclusion: Our data identified an unexpected restriction of the SF and PB Treg repertoires in JIA with sharing of SF Treg clonotypes across arthritis patients. These findings suggest that inadequacy in the Treg repertoire may contribute to Treg cell dysfunction and the perpetuation of inflammation in JIA, possibly in response to shared antigenic triggers.

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NLRRC4-Related Macrophage Activation Syndrome (NLRC4-MAS): A Novel Primary Autoinflammatory Syndrome Caused By Activating Mutations in NLRC4.

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Background/Purpose: Macrophage Activation Syndrome (MAS) is a life-threatening systemic inflammatory complication of many rheumatic diseases and its causes are unknown. While genetic defects causing impaired cytotoxicity result in a similar entity called primary Hemophagocytic Lymphohistiocytosis (HLH), MAS has no known primary genetic cause.

Methods: We performed detailed clinical, genetic, and immunologic evaluation of a patient with early onset, recurrent MAS-like disease including whole exome sequencing, serum cytokine analysis, and whole blood transcriptional profiling. We also tested monocyte and macrophage inflammasome activation, cytokine production, and cell death. We also evaluated the inflammatory effects of this mutation in a transduced monocytic cell line.

Results: We identified a 7 year-old female with recurrent MAS-like episodes, including pancytopenia and hyperferritinemia, since 2 months of age. Genetic testing identified a de novo threonine to serine conversion in NLRC4, a cytosolic danger sensor, Nod-like Receptor (NLR), and component of the NLR4 inflammasome. The patient’s serum and transcriptional profiles were distinct from NOMID and similar to MAS-prone diseases, with high, constitutive IL-18 elevation. Patient monocytes and monocyte-derived macrophages showed over-production of IL-1β and IL-18, enhanced cell death, and spontaneous ASC aggregate formation. These findings were reproduced in THP1 monocytes constitutively expressing mutant NLRC4. The patient has weaned from steroids and colchicine and has been flare-free after six months of IL-1 receptor antagonist (anakinra) therapy.

Conclusion: Like mutations in NOD2 causing Blau Syndrome and in NLRP3 causing the cryopyrinopathies, activating mutations in the nucleotide-binding region of NLRC4 cause a novel “inflammasomopathy”. However, NLRC4 mutations uniquely manifest as recurrent MAS. Strengthening the NLRC4-MAS association, our findings have been independently corroborated in an unrelated kindred[1]. Ongoing investigation of NLRC4-MAS to determine its unique inflammatory characteristics will shed light on the pathogenesis of MAS and related systemic inflammatory disorders.


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Cytokines in Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome: Tipping the Balance Between Interleukin-18 and Interferon-Gamma. Karen Put, Amneelene Avau, Ellen Brisse, Tania Mitera, Stephanie Put, Paul Proost, Brigitte Bader-Meunier, René Westhovens, Benoît Van den Eynde, Ciriana Orabona, Francesca Fallarino, Lien De Somer, Thomas Tousseyn, Pierre Quartier, Carine Wouters, and Patrick Mathys. 1University of Leuven, Laboratory of Immunobiology, Rega Institute, Leuven, Belgium, 2University of Leuven, Laboratory of Molecular Immunology, Rega Institute, Leuven, Belgium, 3University of Leuven, Laboratory of Rheumatology, University Hospital Leuven, Leuven, Belgium, 4Institut de Duve, Université catholique de Louvain, Brussels, Belgium, 5Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Perugia, Italy, 6University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium, 7University of Leuven, Department of Imaging and Pathology, Leuven, Belgium.

Background/Purpose: To study the role of interferon-gamma (IFN-γ) in the pathogenesis of systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS) by searching for an IFN-γ profile and assess its relation with other cytokines.

Methods: Patients with inactive (n=10) and active sJIA (n=10), MAS (n=5) and healthy controls (n=16) were enrolled in the study. Cytokines and IFN-γ-induced proteins were determined in plasma by ELISA and H9253 MS, in patient peripheral blood mononuclear cells (PBMCs) (qPCR, flow cytometry, western blot and ELISA) and in lymph node biopsies of one patient during both sJIA and MAS episodes (immunohistochemistry). IFN-γ responses were investigated in healthy donor PBMCs, primary fibroblasts and endothelial cells.

Results: Plasma IFN-γ, IL-6 and IL-18 were elevated in active sJIA and MAS. Levels of IFN-γ and IFN-γ-induced proteins (IP-10/CXCL-10, IL-18BP and IDO) in MAS were highly surpassing levels in active sJIA. Free IL-18 and ratios of IL-18/IFN-γ were higher in active sJIA versus MAS. MAS PBMCs showed a hyporesponsiveness to IFN-γ in vitro. Endothelial cells and fibroblasts expressed IFN-γ-induced proteins in situ in lymph node stainings of a MAS patient and in vivo upon stimulation with IFN-γ.

Conclusion: Patients with active sJIA and MAS show distinct cytokine profiles with highly elevated plasma levels of IFN-γ and induced proteins typically found in MAS. In addition to PBMCs, histiocytes, endothelial cells and fibroblasts may contribute to an IFN-γ profile in plasma. Increasing levels of IFN-γ compared to IL-18 may raise suspicion for development of MAS in sJIA.

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Background/Purpose: JIA is an umbrella term used to describe a heterogeneous group of diseases. To date no specific markers exist in clinical practice to predict disease activity & outcome. MRP8/14 are calcium-binding proteins secreted by infiltrating phagocytes in synovial inflammation. Studies have shown that their serum concentrations correlate sensitively & specifically with synovial inflammation in JIA. It is believed that they are predictive biomarkers that can indicate subclinical disease activity & identify patients at risk of relapse during times of clinically inactive disease. They have also been shown to identify patients more likely to respond to treatment with Methotrexate. To date there have been no studies looking specifically at their use in Down’s Arthritis (DA).

Objectives: To evaluate the use of standard (ESR&CRP) & novel (MRP8/14) inflammatory markers as biomarkers of disease activity in DA & JIA.

Methods: Between May 2013-May 2014 new cases of JIA & DA attending the NCPR had blood drawn to measure their CRP, ESR & MRP 8/14 levels at diagnosis. Corresponding Active Joint Count (AJoC) was documented. Paired synovial fluid (SF) samples were taken for analysis from children requiring steroid joint injections as treatment for their arthritis. Serum (Se) & SF concentrations of MRP 8/14 were determined by sandwich ELISA. The reader of laboratory assays was blinded for diagnosis & inflammatory activity. CRP & ESR were measured as part of routine clinical assessment.

Results: 32 children (20 JIA, 12 DA) had serum samples taken for CRP, ESR & MRP8/14 at diagnosis. 13 of these children had paired synovial fluid samples taken. The average AJoC was 4 (range 1-11). Table 1 highlights accuracy of each measurement as a marker of disease activity. In DA, a significant correlation was detected between AJoC & both ESR and MRP 8/14 (SF). Combining results for the DA & JIA cohort, a significant positive correlation was noted between paired samples of MRP8/14 in Se & SF.

Table 1 (n=32 Serum, n=14 Synovial Fluid)

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<th>Variable 2</th>
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<td>Positive</td>
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<td></td>
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<td>MRP 8/14 SF</td>
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<td>MRP 8/14 SF</td>
<td>ESR</td>
<td>Positive</td>
<td>p&lt;0.05</td>
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</table>

Conclusion: MRI with contrast remains the gold standard for diagnosis of synovitis. In reality, clinical assessment is the major diagnostic tool. DA is a more challenging condition than JIA, in light of confounding illness & the often-associated non-verbal state. In DA a simple biomarker of disease would be invaluable. We have shown that CRP is a poor marker of disease activity in JIA & DA so the need for a more specific biomarker is evident. Our preliminary results suggest that children with DA have elevated SF levels of MRP 8/14 that correlate to disease activity. SF concentrations of MRP 8/14 are significantly higher than their paired Se samples; however our results show significant positive correlation between the two. This suggests that Se MRP 8/14 levels are potential accurate markers of SF levels. MRP 8/14 may be a useful biomarker of disease activity in DA, aiding timely diagnosis & instigation of appropriate treatment, in turn, helping to improve clinical outcomes for this patient group.

Disclosure: C. Foley, None; O. Killeen, None; E. J. MacDermott, None.

HLA-B27 Subtypes in Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis. Rajni Srivastava, Shikha Agnihotry, Rakesh Aggarwal and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: HLA-B27 has a high degree of genetic polymorphism, with more than 105 known subtypes. Enthesitis Related Arthritis (ERA) is most common form of Juvenile Idiopathic Arthritis (JIA) in Asian and Indian population. It has strong association with HLA B27 similar to the adult anklyosing spondylitis (AS). Since the disease occurs in children and different HLA B27 subtypes confer different susceptibility to AS we studied the HLA B27 subtypes associated with ERA and AS to see if there is any difference.

Methods: Samples were collected from 135 patients with ERA and 121 patients with AS. Genomic DNA was isolated from whole blood using salting out technique and HLA B27 typing was done using ARMS-PCR. Primers for intronic region of HLA-DR were used as internal control. HLA B27 subtyping was done by sequencing using a group-specific amplification of the second and third exon region of HLA B27 gene.

Results: Hundred and seven out of 135 patients with ERA (79%) and 102/121 (84%) of AS patients were HLA B27 positive. HLA B*2705 and 04 were the most common subtypes. HLA B*2702 and 07 were seen rarely. The frequency of HLAB*2705 was 70% in ERA as compared to 56.8% in AS (p=0.032) whereas HLAB*2704 was 21.4% in ERA and 36.2% in AS (p=0.013). No correlation was seen between B*27 subtypes (B*2704 and B*2705) and clinical features of JIA-ERA.
Conclusion: HLAB*27 subtype frequencies are different in ERA and AS. It is possible that the presence of ancestral subtype HLA B*27:05 leads to early onset of disease.

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Systemic Juvenile Idiopathic Arthritis and Exposure to Fine Particulate Air Pollution. Andrew Zeft1, Sampath Prahalad2, Rayfel Schneider3, Alexei Grom2, Fatma Dedeglu4, Pamela F. Weiss5, Carter Mix6 and C. Arden Pope7. 1The Cleveland Clinic, Cleveland, OH, 2Emory University, Atlanta, GA, 3The Hospital for Sick Children, Toronto, ON, 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 5on behalf of CARRAnet Investigators, Palo Alto, CA, 6The Children’s Hospital of Philadelphia, Philadelphia, PA, 7Brigham Young University, Provo, UT.

Background/Purpose: Environmental factors are understood to play a pathogenic role in the etiology of Systemic Onset Juvenile Idiopathic Arthritis (SJIA). Fine particulate matter (aerodynamic diameter ≤2.5-mm cut point, PM_{2.5}) is a measurable component of ambient urban pollution, and positive associations of short-term PM_{2.5} exposure with the reported clinical presentation of SJIA in young children have been described in a regional cohort. Our objective was to further establish associations between short-term ambient pollution exposures and the reported clinical event dates of SJIA onset in cases residing from multiple metropolitan regions.

Methods: A case-crossover study design was used to analyze associations of short-term PM_{2.5} exposures with the event date of SJIA symptom onset from cases residing in the metropolitan regions of Boston, Philadelphia, Atlanta, Cincinnati, and Toronto. Time trends, seasonality, month, and weekday were controlled for by matching. Selected exposure windows (up to 14 days) of PM_{2.5} were examined.

Results: Positive, statistically significant associations between PM_{2.5} concentrations and elevated risk of SJIA were not observed. The most positive associations of short-term PM_{2.5} exposure with the reported clinical onset of SJIA were in children <5.5 years of age (RR 1.75, 95% CI 0.85–3.62). An ad hoc extended pooled analysis including previously reported cases residing from Utah’s metro areas identified an increased risk of SJIA for 0.85–3.62). An ad hoc extended pooled analysis including previously reported cases residing from Utah’s metro areas identified an increased risk of SJIA from 14 days) of PM_{2.5} were examined.

Conclusion: Even in this multi-city, multi-period study only small, statistically insignificant PM_{2.5}-SJIA associations are observed. However, similar to previously observed results, the PM_{2.5}-SJIA association is most suggestive in preschool aged children. More subjects with spatial and temporal specificity may be required by the analysis to demonstrate effects, and further research may be useful in larger numbers of SJIA cases and in geographic areas which experience a greater ambient particulate burden.

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Autoantibodies in Juvenile Systemic Sclerosis. Katharine Moore1, J. Lee Nelson1, Marvyn J. Fritzler2, Marisa S. Klein-Gitelman3, Ann M. Reed4, Tzielan C. Lee5 and Anne M. Stevens6. 1University of Washington, Seattle, WA, 2Moffitt Advanced Diagnostics Laboratory, Faculty of Medicine, University of Calgary, Calgary, AB, 3Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, 4Mayo Clinic, Rochester, MN, 5Stanford University School of Medicine, Stanford, CA, 6Seattle Children’s Research Institute, Seattle, WA.

Background/Purpose: There are no known biomarkers for organ involvement, response to therapy, or prognosis in juvenile systemic sclerosis (JSSc). In adults with systemic sclerosis, a number of serum autoantibodies have been described, many of which have been associated with clinical phenotypes. Knowing the pattern of organ involvement associated with a particular autoantibody can be of benefit, with implications for both treatment and screening. The objective of this study was to determine the frequency and clinical significance of an extended panel of both scleroderma-specific and scleroderma-associated autoantibodies in patients with JSSc.

Methods: Stored plasma samples from 28 pediatric patients with systemic sclerosis, 26 with localized scleroderma and 35 age-matched healthy controls were tested for antinuclear antibodies (ANA) as well as antibodies against Ro52, platelet-derived growth factor receptor, Ku, PM-Scl-70, PM-Scl-100, Th/TG, huF/NOR-90, fibrillarin, RPI55, RPI1, centromere proteins A/B (CENP-A, CENP-B), and topoisomerase I/Scl-70 RNA. The majority of the stored samples were obtained after the initiation of treatment. Line immunoassay was used, with the exception of Th/TG, which were assessed for by chemiluminescence.

Results: Of the 28 patients with JSSc, the most common antibodies detected were anti-PM-Scl-100 (17.9%), anti-Scl-70 (14.3%), anti-CENP-B (10.7%) and anti-CENP-A (7.1%). Anti-PM-Scl-70 and anti-RP155 were found in one patient each. By comparison, no autoantibodies were detected in the plasma from either healthy pediatric controls or juvenile localized scleroderma patients, except for ANA in five (17.9%) of the localized scleroderma cases and one control. Of the patients with JSSc, 15 (53.6%) were ANA positive but negative for both anti-Centromere (CENP-A/B) and anti-Scl-70. Of these, three carried antibodies to PM-Scl-100. There were no significant differences in antibody profile between limited and diffuse systemic disease, or with specific clinical disease manifestations.

Conclusion: In this cohort, the presence of autoantibodies targeting PM-Scl-100, Scl-70, and CENP-A/B were highly specific for systemic sclerosis compared to localized scleroderma or controls. Testing for PM-Scl-100 helped capture additional patients who were ANA positive but anti-Centromere/anti-Scl-70 negative, but there remained JSSc patients with ANA of unknown antigen specificity. Furthermore, the association of autoantibodies with systemic but not with localized scleroderma reinforces the concept of two distinct disease processes.

Disclosure: K. Moore, None; J. L. Nelson, None; M. J. Fritzler, Inova Diagnostics, Inc., San Diego, CA; S. M. Klein-Gitelman, None; A. M. Reed, None; T. C. Lee, None; A. M. Stevens, None.

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Mutations of Familial Hemophagocytic Lymphohistiocytosis (FHL) Related Genes and Abnormalities of Cytokitoxicity function tests in Patients with Macrophage Activation Syndrome (MAS) Occurring in Systemic Juvenile Idiopathic Arthritis (sJIA). Claudia Braocolia1, Elena Sieni2, Martina Da Ros3, Carmela De Fusco4, Concetta Micalizzi5, Valentina Cetica6, Benedetta Ciambotti7, Maria Luisa Congilio8, Antonella Insalaco9, Fabrizio Villa10, Benedetti Sr10, and Maurizio Arcese10. 1Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 2Department of Pediatric Hematology-Oncology, Meyer Children’s Hospital, Florence, Italy, 3Department of Pediatric Hematology-Oncology, Pausilipon Children’s Hospital, Naples, Italy, 4Department of Pediatric Hematology-Oncology, G. Gaslini Children’s Hospital, Genoa, Italy, 5Istituto Toscano Tumori (I.T.T.), Florence, Italy.

Background/Purpose: MAS is a severe complication of rheumatic diseases, mostly sJIA. Clinical and laboratory features are similar to those of FHL resulting from mutations in selected genes involved in the cytokitoxicity pathway. We investigated the presence of mutations of FHL-related genes and of abnormalities in degranulation and perforin expression, in patients with MAS occurring in the context of sJIA.

Methods: From the HLH Italian National Registry, we selected patients with MAS defined according to the HLH 2004 criteria and with confirmed diagnosis of sJIA based on ILAR criteria. Mutation analysis was performed by Sanger sequencing of FHL-related genes. Perforin expression and degranulation were analyzed using flow-cytometry.

Results: We identified 31 patients (17 females; 25 Southern European, 6 Indian) with MAS and sJIA. Eleven patients (35.5%) had 14 monoallelic mutations in PRF1 (n = 7), UNC13D (n = 1), STX11 (n = 1), STXBp2 (n = 4), and Rab27a (n = 1). Three patients had mutations in 2 genes. Both degranulation and perforin expression were evaluated in 18 patients. At least one test was defective in 11 patients (61%). The clinical and laboratory features of patients with monoallelic mutation and/or with abnormalities in at least one functional test, were not different from those of the remaining patients. However, re-occurrence of MAS tended to be more frequent in patients carrying mutations (mutated 27% versus non-mutated 10%) and in patients showing abnormalities in at least 1 functional test (abnormal 18% versus 0%). One patient died of MAS: she carried the N252S mutation in UNC13D. Familial mutations were not observed in patients with sJIA who develop MAS. Additional genetic studies are warranted to identify additional genes potentially linked to MAS development.
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Superior Therapeutic Efficacy of a Novel Oral Small Molecule Retinoic Acid Receptor-Related Orphan Receptor Gamma T (Rorgt) Inverse Agonist Inv-17: A Promising Safe & Efficacious Treatment for Rheumatoid Arthritis.

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Background/Purpose: T helper 17 (Th17) cells and their production of Th17 cytokines IL-17A and IL-17F play a critical role in the pathogenesis of RA and collagen-induced arthritis [CIA]. Retinoic acid receptor-related orphan receptor gamma t (RORgt) is a nuclear hormone receptor that specifically regulates Th17 cells by acting as a control switch for Th17 differentiation, function and cytokine production. Lead development efforts of several proprietary novel chemical scaffolds of the INV-17 portfolio of small molecule RORgt inverse agonists led to the identification of an INV-17 clinical compound candidate demonstrating potent in vitro pharmacological effects against Th17 cells and cytokines coupled with optimal druggable properties. To establish the preclinical Proof of Concept in RA prior to advancing to IND-enabling development, the in vivotreatmentefficacy of INV-17 was assessed in the mouse CIA model.

Methods: Disease was induced in DBA1 mice according to a standard protocol. Prior mouse in vivo pharmacokinetic [PK] studies determined the optimal oral bioavailability and drug exposure of INV-17 enabling p.o. dosing in this study. To assess the preclinical efficacy in a mouse CIA model, INV-17 was administered orally for 28 days as a therapeutic treatment regimen following chicken collagen CII/CFA disease induction on day 0 and CII/IFA booster immunization on day 15 in DBA1 mice. Upon disease-onset, mice with a clinical arthritis score > 1 (Scale: 0–16) were randomized to receive 28-day dosing with INV-17 at 30 mg/kg (n=10) or comparator controls: Vehicle (n=11) or Dexamethasone [Dex] (n=9).

Results: Successful disease amelioration following INV-17 and Dexamethasone treatment was observed with statistically significant reduction of cumulative arthritis score of 6.02 ± 0.26 [mean ± SEM] (p<0.0001) vs. 9.42 ± 0.24 (p=0.0001) cytokine CIA scores, respectively, in contrast to the vehicle group of 8.81 ± 0.43. Significant improvement in clinical disease scores in INV-17 treated mice was evident starting on arthritis day 13 (p=0.04) with maximal therapeutic effects observed on arthritis day 16 (p=0.0007) through day 26 (p=0.0003) until end of study (p=0.01). INV-17 drug levels were assessed in peripheral blood and hind joints confirming optimal INV-17 pharmacokinetic exposures and oral bioavailability. INV-17 was well tolerated and INV-17-treated mice were unremarkable with optimal body conditions.

Conclusion: The superior safety and therapeutic efficacy data following 28-day treatment of an orally bioavailable small molecule INV-17 clinical candidate compound provide the first report establishing the preclinical POC in RA with pharmacological intervention of RORgt inverse agonism. This compelling evidence supports advancing INV-17 into IND-enabling development stage and highlights the potential promise of INV-17 as a safe & efficacious novel RA DMARD treatment.

Disclosures: A. Gaweco, Innovimmune Biotherapeutics Holding, LLC, 3; S. Palmer, Innovimmune Biotherapeutics Holding, LLC, 3; C. Stremnitzer, Innovimmune Biotherapeutics Holding, LLC, 3; K. Matthews, Innovimmune Biotherapeutics Holding, LLC, 3; M. Fisher, Innovimmune Biotherapeutics Holding, LLC, 3; J. Blin, Innovimmune Biotherapeutics Holding, LLC, 3; E. M. Ginzler, Innovimmune Biotherapeutics Holding, LLC, 3; J. Tilley, Innovimmune Biotherapeutics Holding, LLC, 3.

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Anti-Inflammatory Marine Compound, Lyy-B2, Ameliorates Rheumatoid Arthritis through Inhibition of Osteoclast Differentiation.

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Background/Purpose: Osteoclasts are multinucleated giant cells of macrophage/megakaryocyte lineage, and are believed to play major roles in joint destruction caused by rheumatoid arthritis (RA). Nuclear factor of activated T cells, cytoplasmic 1 (NFATc1) is a key transcription factor which up regulates the osteoclast-specific protein expression of cathepsin K, matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and tartrate-resistant acid phosphatase (TRAP), and promotes osteoclast differentiation resulting in bone resorption. In recent years, a significant number of natural products with anti-inflammatory activity have been discovered from marine organisms, and several of these compounds are now under clinical trials. In the present study, we evaluated a culture of LYY-B2, a soft coral-derived compound with anti-inflammatory and anti-arthritis properties.

Methods: We used lipopolysaccharide (LPS)-stimulated marine macrophages to evaluate the anti-inflammatory and anti-osteoclast formation properties of LYY-B2, in vitro. Lewis rats (180–220g) were used to evaluate the possible effects of LYY-B2, in vivo, on adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA) animal models. We also examine the joint features of LYY-B2 attenuation of RA by histology and immunohistochemistry.

Results: LYY-B2 significantly inhibited pro-inflammatory induced nitric oxide synthase protein expression in LPS-stimulated macrophages. Moreover, it also attenuated multileucemic cell formation, osteoclast-related gene expression (MMP9 and cathepsin K) and expression of osteoclast-related proteins (TRAP and actin ring). Our animal experiments revealed that LYY-B2 (5mg/kg) significantly inhibited AIA and CIA joint characteristics in rats. Moreover, using histological analysis, we have found that LYY-B2 also improved the histopathological features of RA. Immunohistochemical results show that LYY-B2 inhibited expression of osteoclast-related proteins cathepsin K, MMP 2, MMP 9, CD11b, and NFATc1 in ankle tissues of AIA- and CIA-rats.

Conclusion: The present findings indicated that LYY-B2 could be of potential use as a therapeutic agent to treat rheumatoid arthritis through inhibition of osteoclast differentiation.

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Results: There were higher expression levels of Snail and Cad-11 with a positive correlation in synovial tissues from RA patients and CIA rats. Stimulation with TNF-α or activation of Wnt signaling up-regulated the expression levels of Snail, Cad-11 and α-SMA in SF, and TNF-α antagonist therapy down-regulated their expression levels in CIA joints. While Snail-overexpressed SF transfectants had increased expression levels of Cad-11 and α-SMA and enhanced TNF-α-mediated invasive capacity and IL-6 production, Snail-knockdowned CIASF transfectants had decreased expression levels and the opposite effect on these functions. In addition, Snail-overexpressed normal rat joints had hyperplastic synovium with increased expression levels of Cad-11 and α-SMA. In CIA joints, silencing the expression of Snail ameliorated arthritis with reduced Cad-11 expression and extracellular matrix (ECM) deposition, whereas overexpressing Snail exacerbated arthritis with increased Cad-11 expression and ECM deposition.

Conclusion: This study demonstrates for the first time that transcription factor Snail regulates TNF-α-mediated activation of rheumatoid SF, and these findings might contribute to the pharmacological development of therapeutics targeting SF in RA patients.

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Tadalafil Decreases Joint Inflammation in TNF-Tg Mice By Restoring Passive Lymphatic Transport. Echoe M. Bouta1, Igor Kuzin2, Ronald Wood3, Christopher T. Ritchlin4, Andrea Bottaro2 and Edward M. Schwarz5. 1University of Rochester Medical Center, Rochester, NY, 2Cooper Medical School, Camden, NJ, 3University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with enigmatic episodic flares. Using longitudinal imaging, we recently demonstrated that arthritic knee flare in tumor necrosis factor transgenic (TNF-Tg) mice is associated with the loss of the lymphatic pulse and B-cell clogging of the lymphatic sinuses in the adjacent popliteal lymph node (PLN), which is ameliorated by B-cell depletion therapy that restores passive lymphatic flow from inflamed joints. To test the hypothesis that similar efficacy can be obtained via vasodilatory therapy that opens lymphatic vessels parallel to the clogged PLN, we evaluated the effects of tadalafil, a FDA-approved PDE5 inhibitor, on lymphatic transport, synovitis and bone erosion in TNF-Tg mice experiencing knee flare.

Methods: TNF-Tg mice with collapsed PLN underwent contrast enhancement MRI (CE-MRI), power Doppler (PD) ultrasound, near infrared indocyanine green (NIR-ICG) imaging prior to and after treatment via gavage every other day with tadalafil or placebo for six weeks.

Results: Fold change in ICG clearance from the footpad, a marker of lymphatic transport, was found to be higher in tadalafil treated animals compared to placebo (15.62±23.25 vs. 2.77±1.17) (Figure 1A and B). As expected, lymphatic contraction frequency decreased over time in the placebo and tadalafil treatment groups, consistent with progression of the disease and lymphatic dilation respectively. Lymph node contrast enhancement (LNCE), an alternative biomarker of lymphatic transport to the PLN that is measured via CE-MRI, decreased slightly (0.87±0.10 fold change) in the placebo group, indicating further PLN collapse. In contrast, tadalafil induced a slight increase (1.05±0.12 fold change) in LNCE, indicating a halt in PLN collapse. Additionally, mice treated with tadalafil showed a greater PLN volume compared to placebo (15.56±10.15 mm3 vs. 9.97±6.09 mm3), indicative of increased transport to the PLN, PD within the joint, and after measure of transport, was found to be significantly lower after tadalafil treatment compared to placebo (0.011±0.001 mm2 vs. 0.08±0.02 mm2) (Figure 1C). Placebo treated animals were shown to have a 1.36±0.23 fold change in knee synovial volume, while tadalafil treatment showed a lower fold change, 0.95±0.28 (Figure 1D).

Conclusion: Tadalafil treatment increases passive lymphatic transport, as evidenced by increased ICG clearance, PLN volume and LNCE; in conjunction with decreased lymphatic contraction. In addition, this increase in lymphatic transport results in decreased PD volume within the joint, indicative of decreased joint inflammation. These results in addition to flow cytometry and histology of joints and PLNs will be presented.

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IL-1 Receptor Antagonist (IL-1Ra)-Fc Ameliorate Autoimmune Arthritis By Regulation of the Th17 Cells/Treg Balance and Arthrogenic Cytokine Activation. Hong Ki Min1, Sung Hwan Park2, Mi-La Cho2, Ji Hyeon Ju1, Seung-Ki Kwok1, Seon-Yeong Lee1, Seung Min Jung2, Kyung-Su Park3 and Jennifer Lee4. 1Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, 2The Catholic University of Korea, Seoul St. Mary’s Hospital, Seoul, South Korea, 3Catholic University of Korea, Seoul, South Korea, 4St. Vincent Hospital, SuWon Gyeonggi-do, South Korea.
Background/Purpose: IL-1β signalling has critical role on pathogenesis of various inflammatory arthritis including rheumatoid arthritis (RA). We aimed to investigate the therapeutic effects of human IL-1 receptor antagonist with Fc fragment (hIL-1Ra-Fc) on autoimmune arthritis and find out the possible mechanisms by which hIL-1Ra-Fc has anti-arthritis effects in a murine model of RA and arthritis patient.

Methods: Collagen-induced arthritis (CIA) murine model was induced in DBA/1J mice. The levels of various cytokines were determined by using enzyme-linked immunosorbent assay. The joints of mice were assessed for clinical arthritis score and histologic features. Th17 cells and Treg cells were stained using antibodies specific for CD3, CD4, CD25, CD17, CD45, and FoxP3. Osteoelasticogenesis was determined by TRAP stain and real-time PCR.

Results: hIL-1Ra-Fc reduced the clinical arthritis, histological inflammation and cartilage score in CIA model. The expression of proinflammatory cytokines, VEGF, and RANK were reduced in affected joint of hIL-1Ra-Fc treated mice. hIL-1Ra-Fc treated mice showed decreased number of Th17 cells with increased Treg cells in spleens. hIL-1Ra-Fc reduced Th17 cell differentiation by inactivation of STAT-3 signalling, reciprocally induced Treg cell differentiation through STAT-3 signalling. In addition, Suppression of gene expression of IL-17, TNF-α, RANKL and VEGF were decreased, while increased Foxp3 gene expression in PBMC of RA patients after administration of hIL-1Ra-Fc.

Conclusion: The anti-arthritis effects of hIL-1RA-Fc are associated with regulating balance between Th17 cells and Treg cells and with suppressing osteoelasticogenesis and angiogenesis affected joints.

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AMPK Activation in Inflammatory Arthritis. Monica Guma1, Yun Wang2 and Ru Liu-Bryan2. 1University of California, San Diego, La Jolla, CA, 2UCSD/VAMC, La Jolla, CA.

Background/Purpose: AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase involved in the regulation of cellular energy homeostasis. It is a central regulator of both lipid and glucose metabolism. Many studies have suggested that AMPK activation can also exert significant anti-inflammatory and immunosuppressive effects. We evaluated whether modulating this pathway altered pathogenic mechanisms in inflammatory arthritis.

Methods: The AMPK agonist A-769662 (60mg/kg/bid) was tested in two arthritis models: In antigen induced arthritis (AIA), mice were primed with sBsa in complete Freund’s adjuvant and then given an intraarticular challenge with mBsa in the knee on day 21. In passive serum arthritis, K/BxN sera was injected on day 0. Joints were harvested and prepared for histological assessment. IL-6 expression in joints and sera was measured by ELISA. Human fibroblast-like synoviocyte (FLS) and bone marrow derived macrophage (BMDM) function was tested using A-769662 (250μM) as follows: 1) phosphorylation of p65 NF-kappaB by Western Blot, 2) IL-6 secretion by ELISA, 3) NO secretion by Griess method, 4) cell survival in FLS.

Results: AMPK pathway activation by A-769662 reduced inflammatory infiltration and joint damage in both animal models. In passive K/BxN model, day 8 scores were 8.2±3 and 2.4±3 (p<0.05) for vehicle and A-769662-treated mice, respectively. In AIA model joint histology scores for vehicle and A-769662-treated mice for synovial hypertrophy were 2.9±0.9 and 1.6±1.1 (p=0.01), bone erosion scores were 2.2±1 and 1.5±1 (p<0.05), and cartilage damage scores were 2.0±0.6 and 1.2±0.6 (p<0.05), respectively. IL-6 expression in serum and arthritic joints was significantly decreased in A-769662 treated mice. The mechanism of AMPK action was evaluated in FLS and BMDM. AMPK activation with A-766244 reduced IL-6 and NO secretion by 52%±5.6% and 76%±7.5 %respectively (p<0.05), and p65 NF-kappaB phosphorylation after TL stimulation in BMDM. Additionally, AMPK activation also significantly increased H2O2-induced apoptosis in FLS.

Conclusion: Activating AMPK pathway suppressed inflammatory arthritis in mice as well as IL-6 expression in serum, arthritic joints and cultured BMDM. These data suggest that AMPK signaling activation could be an effective therapeutic strategy for IL-6 dependent inflammatory arthritis.

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Background/Purpose: We developed a novel mono-arthritic multi-flare Rat Streptococcal Cell Wall (SCW) model which captures certain aspects of disease with flares and remission of inflammation similar to Rheumatoid Arthritis (RA). To delineate the role of TNF, T cells, and IL-1 in pathogenesis of SCW-induced arthritis, we investigated the activity of clinical agents, Etanercept, Abatacept and Anakinra. Comparative evaluation of these targeted therapies was also performed in the rat Collagen Induced Arthritis (CIA) model.

Methods: SCW arthritis was induced in female Lewis rats with an intra-articular injection in the hind ankle joint on day 1 (flare 1) followed by two intravenous challenges on days 21 (flare 2) and 42 (flare 3) of SCW extract PG-PS 100p. CIA was induced using methods previously described in literature. Inflammation and pain were monitored by measuring paw swelling (mechanical calipers) and withdrawal threshold (von-Frey assay) respectively. Additional biomarkers assessed by cytokine profiling, cell phenotyping, bioluminescence/μCT imaging and histopathology were also performed in the local joint.

Results: In the SCW model late prophylactic administration of Etanercept, Abatacept and Anakinra significantly inhibited paw swelling by ≥60% (p<0.001), ≥60% (p<0.001), 88% (p<0.001) and pain by 37% (p<0.05), ≥28% (p<0.05) and 64% respectively in flare 2. Etanercept in flare 3 inhibited paw swelling by 60% (p<0.001) and partially inhibited pain by 27%. Interestingly, prior treatment with Etanercept in flare 2 followed by a wash out period of 14 days and re-administration in flare 3 led to a loss in efficacy, potentially due to immunogenicity. Abatacept administration in flare 3 had no effect on either paw swelling or pain in rats that were treated in flare 3 alone or in rats that were treated previously in flare 2. In the CIA model, both late prophylactic and therapeutic treatment with Etanercept inhibited paw swelling by 50% (p<0.001). A loss of efficacy with Etanercept was also observed in the CIA model when administered prophylactically possibly due to immunogenicity. Prophylactic, late prophylactic and therapeutic administration of Abatacept in the CIA model significantly inhibited paw swelling by 100% (p<0.001), 42% (p<0.001) and 34% (p<0.001) respectively. The additional biomarkers corroborated with efficacy in both models.

Conclusion: We developed a novel multi-flare SCW model that can be used to evaluate clinically relevant parameters of inflammation and pain simultaneously. Using clinical agents Etanercept, Abatacept and Anakinra targeting TNF, T cells and IL-1 respectively we have delineated distinct pathogenic mechanisms of inflammation and pain at different stages of disease in the SCW model. We also show similar profiles of efficacy in late prophylactic and therapeutic regimens in the CIA model. The flaring mechanism in the SCW model allows for drug washout periods in between compound administration. This might provide useful pre-clinical insights on potential immunogenicity mechanisms that may be relevant in a clinical setting. Our novel model can facilitate innovative assessment of anti-rheumatic agents in multiple flares and offers a powerful tool for drug discovery.

Disclosure: K. Chakravarthy, Merck Pharmaceuticals, 3; R. Faltus, Merck Pharmaceuticals, 3; A. Murtaza, Merck Pharmaceuticals, 3; M. Cicmil, Merck Pharmaceuticals, 3.

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A Novel, Small Molecule Cyclin-Dependent Kinase 4/6 Inhibitor As the New Option for Treatment of Rheumatoid Arthritis. Hiroshi Takahashi1, Tsuyoshi Mizuno1, Toshinichi Nakamura1, Yuri Sakai1, Yumiko Muroga1, Kyohei Horie1, Naoki Hase1, Hitoshi Koisaka1 and Tsuyoshi Kimura1. Teijin Pharma Limited, Hino, Tokyo, Japan, 2Tokyo Medical and Dental University (TMDU), Tokyo, Japan.

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is characterized by infiltration of immune cells to the synovial tissues and their hyperplasia. Therapeutic strategies to inhibit proin-
flamatory cytokines or immune cells with biological agents and methotrexate are the mainstay in the current treatment of RA. However, they cannot induce complete remission in all of the patients. Combination therapy of two biologics such as etanercept and abatacept failed to show the synergistic effects. Cyclin-dependent kinases (CDK) are key regulators of the cell cycle progression, and several CDK inhibitors have been developed for treatment of cancer. Recently, it was reported that cell cycle inhibition of synovial fibroblasts with a small molecule CDK4/6 inhibitor ameliorated progression of arthritis without attenuating acquired immune responses in an animal model of RA. Although CDK4/6 is thus an attractive target for treatment of RA, its inhibitors have not yet been developed for clinical use in RA treatment. In this study, we show that we have developed a novel and potent CDK4/6 inhibitor, Compound T and its derivatives for RA treatment. We examined Compound T for its anti-arthritic effects in monotherapy and in combination therapy with TNF blockade in animal models of RA.

Methods: Novel synthetic compounds were evaluated in kinase assays to determine in vitro CDK4/6 inhibitory activity and selectivity for CDKs and other kinases. The effects of these compounds on cell cycle were tested by the SubG1 method. Pharmacokinetic (PK) studies and hERG channel binding assay were performed to determine PK and safety profiles of the test compounds. In vivo efficacy of Compound T was tested in collagen induced arthritis (CIA) as well as anti-collagen antibody induced arthritis (CAIA) of mice. Compound T was orally administered to both models to see the effects on the arthritis score. The effect of combination treatment of Compound T with etanercept was tested in the CAIA model.

Results: Compound T inhibited CDK4 and 6 potently (IC50 is about 1 nM) and selectively to other kinases in the cell free assay. Compound T inhibited cell cycle at the G0/G1 phase without inducing cell death in the cell based assay. Oral administration of Compound T alone suppressed the arthritis score, compared to vehicle treatment, in the CAIA and CIA models. In the CAIA model, combination of oral Compound T with intraperitoneal etanercept synergistically suppressed the progression of arthritis compared to monotherapy with Compound T or with etanercept at maximum effective dose. In hERG binding assay, Compound T had binding activity at the high concentration range, but several compounds among its derivatives showed low binding affinity against hERG.

Conclusion: Compound T we synthesized is a potent inhibitor of CDK4/6 and selective to other kinases. Oral treatment with Compound T suppressed the arthritis score in both CAIA and CIA models of mice. CDK4/6 inhibitors should offer a new option for better treatment of RA.

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330 Prolactin Reduces Bone Erosion in Adjuvant-Induced Arthritis. Maria G. Ledesma-Colunga, Norma Adan, Ana L. Reyes-Lopez, Fernando Lopez-Barrera, Gonzalo Martinez de la Escalera and Carmen Clapp, Institute of Neurobiology, National University of Mexico (UNAM), Queretaro, Mexico.

Background/Purpose: Bone erosion is an important feature of rheumatoid arthritis (RA) that frequently results in lifelong crippling. The receptor activation of NFκB ligand (RANKL)/osteoprotegerin (Opg)/RANK receptor (RANK) system triggers bone loss in arthritis and is activated by proinflammatory cytokines such as TNFα. Prolactin (PRL), the hormone essential for reproductive function and frequently increases in the circulation of patients with RA. Moreover, hyperprolactinemia reduces chondrocyte apoptosis, proinflammatory cytokine expression, pannus formation, joint swelling, and pain in adjuvant-induced arthritis (AIA) rats (Adan et al., J Clin Invest 123:3902, 2013). Here, we investigate whether eliciting hyperprolactinemia before or after inducing AIA reduces the systemic levels of TNFα and inhibits the expression of the RANKL/OPG/RANK system and bone erosion in arthritic ankle joints.

Methods: Progression of inflammation (joint swelling) was analyzed in rats implanted or not with osmotic minipumps delivering PRL beginning 3 days before or of 15 days after the injection of Complete Freund’s adjuvant (CFA). At maximal inflammation (21 days post CFA), bone erosion was evaluated histochemically, RANKL/OPG/RANK, TNFα, and PRL receptor (PRLR) mRNA levels in arthritic joints were quantified by qRT-PCR; and systemic TNFα protein levels were determined by ELISA.

Results: Expression of the PRLR was significantly elevated in the joints of AIA rats. Treatment with PRL before or after inducing AIA reduced local (hind paw) expression and serum levels of TNFα. Moreover, PRL reduced the AIA-induced increase of RANKL and RANK expression in joints, but did not modify that of the RANKL inhibitor OPG. Consistent with these findings, treatment with PRL before inflammation onset significantly reduced the AIA-induced loss of cortical and trabecular bone.

Conclusion: PRL-induced down-regulation of TNFα/RANKL/RANK expression may protect against bone destruction in arthritis, supporting the therapeutic potential of hyperprolactinemia in RA. Funded by UNAM grant IN200312.

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332 Improvement of the Stability of RNA Aptamers Against Interleukin-17A. Natsuki Otaki1, Asako Sasaki1, Shinsuke Hiramoto1, Masakazu Nagamine1, Shigeyuki Mori1, Tomoyoshi Kayo1, Kuniyoshi Hota1, Masayuki Takahashi1, Kazuhiro Haruta1 and Yoshikazu Nakamura1. 1Zenyaku Kogyo Co., Ltd., Tokyo, Japan, 2RIBOMIC Inc., Tokyo, Japan.

Background/Purpose: Aptamers are RNA or DNA oligonucleotides selected for their capacity to specifically bind and inhibit the function of a target protein. The effect is similar to neutralizing antibodies that defend the body against pathogenic antigens. These potentially therapeutic oligonucleotides often have short half-lives, however, because they are rapidly degraded by nucleases in peripheral blood and excreted by the kidneys. Here we describe an RNA aptamer against IL-17A that resists degradation in serum and decreases the severity of collagen-induced arthritis in DBA/1 mice.

Methods: In vitro assay of serum stability. After substituting a methoxy group for the 2' hydroxyl group of ribose, we incubated the RNA aptamers in mouse serum for 0.5 to 72 hours at 37°C. Controls were incubated in phosphate buffered saline. Next, samples were added to quenching buffer (8 M urea, 10 mM EDTA, 0.05% bromophenol blue). Then, the RNA fragments were electrophoresed in 20% polyacrylamide gels that contained 8 M urea in TBE buffer. Bands were visualized by staining the gel with SYBR Green II. Each fraction of intact aptamer was normalized to its corresponding control.

Pharmacokinetic studies in mice. Aptamers were PEGylated with 40-kDa polyethylene glycol and conjugated with 3'-inverted deoxymyidine. Then, these aptamers were infused as a single bolus into the tail vein of a C57BL/6 mouse at 1 mg/kg. Aptamer concentrations in plasma were measured by enzyme-linked oligosorbent assay. Collagen-induced arthritis in mice. Mice were immunized with bovine type II collagen in Freund’s complete adjuvant on day 1. On day 22, they were boosted with bovine type II collagen in Freund’s complete adjuvant. PEGylated aptamers were injected intraperitoneally at 5 mg/kg once a day from day 22 to day 37. Objective signs of arthritis for each paw were scored using a scale of 0 to 4.

Results: In vitro assay of aptamer 17M-340 for serum stability showed very little degradation after 72 hours incubation. By contrast, prototype aptamer Apt21-2 or 17M-4 were rapidly degraded within 24 hours. In vivo, the plasma half-life of 17M-340 was 9.3 hours, more than ten-fold that of 17M-4. Finally, intraperitoneal injection of 17M-340 but not 17M-4 reduced the objective score of collagen-induced arthritis significantly (p < 0.05).

Conclusion: The anti-IL-17A aptamer is 31-base oligoribonucleotide that forms a stem-loop structure. Substitution of a methoxy group for the 2' hydroxyl group of ribose at three positions in the stem and one position in the loop markedly increased stability of the aptamer in vivo. Our findings raise the
Deletion of the Prolactin Receptor Aggravates the Course of Antigen-Induced Arthritis. Norma Adan, Maria G. Ledesma-Colunga, Ana L. Reyes-Lopez, Fernando Lopez-Barrera, Gonzalez Martinez de la Escalera and Carmen Clapp. Institute of Neurobiology, National University of Mexico (UNAM), Queretaro, Mexico.

Background/Purpose: Prolactin (PRL), the hormone essential for lactation, may protect against joint damage in rheumatoid arthritis. PRL frequently increases in the circulation of patients with rheumatoid arthritis, and eliciting hyperprolactinemia in rats before or after inducing the adjuvant model of inflammatory arthritis reduced chondrocyte apoptosis, proinflammatory cytokine expression, pannus formation, joint swelling, and pain (Adan et al., J Clin Invest 123:3902, 2013). Methods: To better understand the role of PRL in inflammatory arthritis, antigen-induced arthritis (AIA) was induced in PRL receptor-deficient (Prlr−/−) mice from two susceptible genetic backgrounds (C57BL/6 and 129Svj). On day 0, preimmunized or control animals were injected into the knee joint with methylated-BSA antigen (mBSA) or vehicle, respectively, and parameters of inflammation were evaluated at days 1-, 1+3, and 3+ post-mBSA.

Results: In the 129Svj strain, Prlr−/− mice showed an earlier onset of AIA but similar clinical severity (joint swelling and pain) compared to wild type mice. However, PRLR-deficient mice had a two-fold increase in synovial hyperplasia and higher levels of circulating IL-6. In the C57BL6 strain, Prlr−/− mice displayed similar joint swelling but increased mechanical allodynia compared to Prlr−/+ mice. Consistent with augmented pain, a two-fold enhanced synovial hyperplasia occurred in the absence of the PRLR, although circulating levels of IL-6 were similar between Prlr−/− and Prlr−/+ mice.

Conclusion: Loss of the PRLR correlates with an aggravated AIA phenotype with different symptoms depending on the genetic background. These findings support the protective role of the PRL system in inflammatory arthritis. Work supported by UNAM-Grant IN200312.

Deletion of the Prolactin Receptor Aggravates the Course of Antigen-Induced Arthritis. Norma Adan, Maria G. Ledesma-Colunga, Ana L. Reyes-Lopez, Fernando Lopez-Barrera, Gonzalez Martinez de la Escalera and Carmen Clapp. Institute of Neurobiology, National University of Mexico (UNAM), Queretaro, Mexico.

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Interleukin-33 Suppresses Experimental Arthritis through Promoting Fopx3+ Regulatory T-Cells and Type-2 Immune Responses in Mice. Jerome Biton1, Allan Thiolat1, Sara khalghparast Athari1, Delphine Le-meieter1, Roxanne Herve1, Patrice Decker1, Jean-Philippe Girard1, Stephanie Roga2, Andre Herbelin1, Anais Levascot1, Marie-Christoze Boissier2 and Natacha Bessis1. 1INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cite and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hopitaux de Paris (AP-HP), Bobigny, France, 2Centre National de la Recherche Scientifique, Institut de Pharmacologie, Université de Toulouse, Université Paul Sabatier, Institut de Pharmacologie et de Biologie Structurale et de Biologie Structurale, toulouse, France.

Background/Purpose: Interleukin (IL)-33 is a new member of the IL-1 family that exerts pleiotropic activities in innate and adaptive immunity. With its receptor ST2, they have newly emerged as key molecules strongly involved in several inflammatory and autoimmune disorders. Recent evidence suggests that the IL-33/ST2 axis is strongly involved in the pathophysiology of rheumatoid arthritis (RA). However in RA models, the role of IL-33 and its receptor is still controversial. We aimed at deciphering IL-33 mode of action after administration in an experimental model of RA, namely collagen-induced arthritis (CIA).

Methods: CIA was induced by immunization of C57Bl6 mice with type 2 collagen. IL-33 was ip administered in CIA mice and cells were analyzed by flow cytometry on day 28 after CIA induction.

Results and Conclusion We show a previously unshown dramatic inhibition of mouse collagen-induced arthritis (CIA) development after repeated administration of IL-33. This therapeutic effect was related to an enhanced type-2 immune response, including the expansion of eosinophils, Th2 cells, innate type 2 lymphoid cells (ILC2, defined as CD25+ cKit−Lin−Sca-1− ST2L+) and an increase in Th2 cytokines levels in the serum of treated mice. Moreover, our work brings out the interplay between Treg and IL-33. Since IL-33 acts directly on Treg via ST2L, we showed that IL-33 treatment of CIA major Treg frequency and increases the suppressive capacities of those cells. IL-33 also induces the emergence of a CD39+ high Treg population in a ST2L dependant manner. In the light of our present study, IL-33 can exert powerful anti-inflammatory properties in CIA, integrating the establishment of a type-2 immune response, the expansion and the activation of Treg. Our study reveals an undescribed mechanism by which IL-33 inhibits arthritis development, thus updating and strengthening the crucial role of IL-33 in RA.

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addition, the additive effects of IL-7 and TSLP in human RA in vitro dendritic cell (DC)/T-cell co-cultures were studied.

Methods: Proteoglycan-induced arthritis was induced in wildtype mice (WT) and mice deficient for the TSLP receptor subunit (TSLPR) and mice of both genotypes were treated with anti-IL-7R or PBS. Arthritis severity was assessed and paw lysate and serum were collected for cytokine analyses. CD1c DCs and CD4 T-cells were isolated from blood of RA patients and were co-cultured in presence of IL-7, TSLP or the combination of both cytokines and proliferation and cytokine production were assessed.

Results: Arthritis severity and synovitis were significantly decreased in TSLP−/− mice treated with anti-IL-7R compared to control mice (Arthritis severity; mean area under the curve ± SEM: 25 ± 5.9 vs. 50.7 ± 6.9; p < 0.01). This was associated with strongly reduced radiographic joint damage and osteoclast activity, which were significantly lower in TSLP−/− mice treated with anti-IL-7R compared to WT mice treated with anti-IL-7R. PBS treated TSLP−/− mice or PBS treated WT mice (Radiographic joint damage: Mean score ± SEM: 0.1 ± 0.1; 0.6 ± 0.1; 0.3 ± 0.1, 1.4 ± 0.2 respectively; all p < 0.001). This was associated with decreased levels of IL-17, IL-6, IL-1β and CD40L, which were all robustly downregulated by combined blockade of IL-7 and TSLP signaling (all p < 0.05). In DC/CD4 T-cell co-cultures from RA patients, TSLP and IL-7 additively increased T-cell proliferation (p < 0.001) and production of Th17-associated cytokines (IL-17, IL-22, IL-6; all p < 0.05) and T-cell attracting chemokines (all p < 0.05).

Conclusion: TSLP and IL-7 additively promote production of Th17-specific and Th17-associated cytokines, linked with enhanced inflammation and immunopathologies. As both cytokines signal via the IL-7Ra, these data emphasize the need for drugs that target this subunit to abrogate activity of both ligands and prevent immunopathology in RA.

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Effect of Etanercept on Endothelial Dysfunction in Rat Adjuvant-Induced Arthritis. Perle Totoson1, Katy Maguin-Gaté1, Daniel Wendling2 and Céline Demougeot1. 1EA 4267 « Fonctions et Dysfonctions Epithéliales de la Peau », Faculté de Médecine-Pharmacie, Besançon, France; 2CHU J Minjoz, Besançon, France.

Background/Purpose: Growing evidence indicate that Rheumatoid Arthritis (RA)-associated increase in cardiovascular risk is secondary to the presence of endothelial dysfunction (ED). Although Tumor Necrosis Factor inhibitors are unanimously approved for the treatment of RA, their effect on ED is still controversial. The present study aimed to determine the impact of etanercept on ED as well as the mechanisms involved in the model of adjuvant-induced arthritis (AIA) rats.

Methods: AIA was induced by an intradermal injection of Mycobacterium butyricum in the tail of male Lewis rats. At the first signs of arthritis, AIA rats received etanercept (10 mg/kg 3 days, s.c) or saline (controls AIA) for 21 days. Arthritis score was daily evaluated. At the end of experiment, preconstricted isolated aortic rings were relaxed with acetylcholine (Ach, 10−11–10−6 M) in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), cyclooxygenase-2 (NS398), arginase (nor-NOHA), endothelium-derived hyperpolarizing factor (EDHF) (apamin/charybdotoxin) and superoxide anions production (Tempol). Blood pressure was measured by invasive method.

Results: Compared to controls AIA, etanercept significantly reduced arthritis score (~34%, p < 0.001). This was associated with an improvement of Ach-induced relaxation (p < 0.05). Beneficial effects of etanercept or ED were mediated by a decrease in cyclooxygenase-2 and arginase activity, a decrease in superoxide anions production and an increase in NO synthase activity. EDHF production was unaffacted by the treatment. Surprisingly, no correlation was found between the arthritis score and Ach-induced relaxation (Emax) (r = -0.195; p = 0.246). Last, etanercept significantly increased systolic blood pressure (125.2 ± 5.7 vs 107.1 ± 5.5 controls AIA; p < 0.05), but not diastolic blood pressure.

Conclusion: Our study demonstrated that etanercept decreases endothelial dysfunction in conduit arteries despite increasing blood pressure. The beneficial effects involved the modulation of vascular NO synthase, cyclooxygenase-2, arginase and superoxide anions production pathways. Our data suggested that these effects are, at least in part, independent on arthritis severity reduction.

Disclosure: P. Totoson, None; K. Maguin-Gaté, None; D. Wendling, None; C. Demougeot, None.

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Bombina Variegata peptide8/Prokineticin 2: A Novel Arthritis-Inducible Chemokine. Haruyasu Ito, Ken Yoshida, Kentaro No da and Daitaro Kurosaka. Jikei University School of Medicine, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by the joint destruction. Chemokines play important roles as monocyte and neutrophil recruiters in RA. Bombina variegata peptide 8 (Bv8), one of such chemokines is highly expressed in various tissues including the brain, testis, and bone marrow. Bv8 has a diversity of functions, being involved in angiogenesis, neurogenesis, circadian rhythm, and pain threshold. We have previously reported that Bv8 expression level was elevated in the synovial tissue of collagen induced arthritis (CIA) mice. However, it is still unknown whether Bv8 can induce arthritis. Therefore, in this study, we investigated the expressions of Bv8 and its receptors (PKR1, PKR2) in CIA mice. And, we also examined whether Bv8 recruits polymorphonuclear neutrophils (PMNs) and monocytes in vivo and induces inflammatory arthritis in vivo.

Methods: CIA was induced in 6-week-old DBA/1j male mice. PKR1 and PKR2 mRNA expression levels of joints in CIA mice were measured by real-time PCR on days 28 and 35 and compared to those in normal mice. Immunohistochemical (IHC) staining was performed to semi-quantitate PKR1 or PKR2 expression on day 28 in the synovial tissue. We performed monocyte and neutrophil chemotaxis assays in response to recombinant Bv8 (rBv8) using Boyden chambers. Results were expressed as the fold increase of the number of migrated cells compared to PBS. Test Bv8 for inflammatory activity in vivo, we injected PBS or rBv8 (10−10M, 20µl) into knee joints. The knee circumference measurements were taken in a blinded manner before and 24 hours after the intraarticular injection for all mice. IHC stainings for PMNs (Gr-1/Ly6G) and monocytes (F4/80) were performed on paraffin sections from mouse knee joints to quantify Gr-1/Ly6G and F4/80 positive cells in the Bv8 group compared to the PBS group, respectively.

Results: In the CIA group, PKR1 mRNA expression level was significantly higher on days 35 than the control group (p < 0.05), and PKR2 mRNA expression level was significantly higher on days 28 and 35 than the control group (p < 0.05). IHC stainings for PKR1 and PKR2 both showed significantly higher expressions of receptors in synovial tissue in the CIA group compared to the control group. PMN chemotaxis assays showed that rBv8 has significantly increased PMN chemotactic activity at 10−12 M compared to PBS (p < 0.05). Joints injected with rBv8 had significantly increased knee circumference than those injected with PBS (p < 0.05). The number of Gr-1/Ly6G positive cells was significantly higher in mouse knee joints injected with rBv8 compared to PBS (p < 0.05). There was no significant difference in the number of F4/80 positive cells in both groups.

Conclusion: As well as Bv8, PKR1 and PKR2 expression levels were elevated in the synovial tissue of the CIA group. Bv8 recruited PMNs in vitro and induced neutrophil-driven inflammatory arthritis. These results indicate that Bv8 may have a previously unrecognized pathogenesis in RA by recruiting neutrophils. Targeting Bv8 may provide a new therapeutic strategy to treat inflammatory arthritis.

Disclosure: H. Ito, None; K. Yoshida, None; K. Noda, None; D. Kurosaka, None.

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Background/Purpose: A variety of animal models suggest that TLR signaling is important in the pathogenesis of RA and the generation of specific autoantibodies. This study was conducted with sera from patients with rheumatoid arthritis, as well as with arthritis animal models to identify autoantigens dependent on TLR 7 and 9 in human and animal models for disease modifying use. Moreover TLR2 and TLR 9 modulating bacterial vesicles from P gingivalis containing PAD (Peptidyl-Aarginine Deiminase) which is involved in citrullination was used to study the TLR2/4 in arthritis.

Methods: Using protein filter technology (28000 human protein filter) the autoantigen profile of RA patients, mouse collagen and zymosan induced
arthritis, as well as collagen and pristan induced arthritis in rats and TLR7, TLR9 deficient double-deficient and MyoD88 and Tlr8 deficient mice of the MRL-lpr/lpr background were obtained. Cationic liposomes transferring siRNAs, bacterial vesicles, lipomannan and LPS were used for the validation of their potential as therapeutic target in collagen or collagen antibody induced arthritis (CAIA).

Results: We found 18 identical proteins targeted in human and animal situations of arthritis. These data identify mRNA binding hnRNP proteins which are part of P bodies, stress granules and components of messenger RNA stability complex as well as CRP binding proteins as target molecules in mice, rats and humans with RA. Moreover, we found MyoD88 independent autoantigens which are not expressed in the thymus or proteins such as high mobility group box proteins 1 and 2 which are MyoD88 independent sensors of nucleic-acid-mediated innate immune responses. Systemic administration of siRNAs with cationic liposomes inhibiting expression of Toll dependent autoantigens overexpressed and targeted by autoantibodies in the human and mouse synovial tissue were used for the validation of their potential to inhibit collagen induced arthritis in C57BL/6j mice. Moreover P. gingivalis vesicles containing the the PAD induce a mild inflammatory response in the CAIA model of arthritis. P. gingivalis LPS and lipomannan treated animals show a 80% reduction of arthritis score compared to E. coli LPS in a C57BL/6j CAIA model.

Conclusion: Systemic blocking of common RNA or DNA binding proteins overexpressed in synovial target tissue appears to modify arthritis. P. gingivalis vesicles evolved the ability to interrupt and undermine a subset of TLR2/4 signalling events for corrupting innate immune and modulate RA.

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340 Role of Beta-catenin Signalling to Control Dendritic Cell Function in Collagen-Induced Arthritis. Celso Henrique Alves1, Julia L. Ober-Blöbaum2, Inge Brouwers-Haspel3, Patrick S. Asmawidjaja4, Anne-Marie Mus5, Björn E. Clausen4 and Erik Lubberts5. 1Erasmus MC, University Medical Center, Rotterdam, Netherlands, 2Institute for Molecular Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany, 3Erasmus Medical Center, Rheumatology, Rotterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and synovial infiltration of immune cells. T-cell priming by activated dendritic cells (DCs) contributes to the pathogenesis of RA. DCs are professional antigen presenting cells that have the dual ability to stimulate immunity and maintain tolerance. Microbial and pro-inflammatory stimuli trigger their maturation into immunostimulatory DCs that express high levels of MHC peptide complexes, costimulatory molecules and pro-inflammatory cytokines to induce an adaptive immune response. DCs are also important to establish self-tolerance either via the generation of regulatory T cells (Tregs) or via the induction of apoptosis or anergy of auto-reactive effector cells. However, the signaling pathways mediating the tolerogenic DC function in vivo remain largely unknown. Recently, the b-catenin pathway has been suggested to promote a regulatory DC phenotype in vitro. While activation of b-catenin causes the phenotypic maturation of bone marrow-derived DCs, these cells fail to produce immunogenic cytokines and instead drive Treg differentiation in vitro and protection from autoimmune disease in mice.

The aim of this study was to unravel the in vivo role of b-catenin signaling to control DC function in collagen-induced arthritis (CIA). Our preliminary data indicate that changes in the levels of b-catenin expression in DCs did not alter the course and severity of CIA. However, the increase in IL-10 and in the Treg frequency during arthritis suggests that activation of b-catenin signaling may enhance the regulatory function of DCs.

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341 Death Receptor 3 Causes Vascular Dysfunction in a Murine Model of Rheumatoid Arthritis. Jessica O Williams1, Eddie C.Y. Wang2, Derek Lang3 and Anwen S. Williams. 1Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, United Kingdom, 2Institute of Infection and Immunity, Cardiff University School of Medicine, Cardiff, United Kingdom.

Background/Purpose: Increased cardiovascular (CV) risk is prevalent in several forms of inflammatory arthritides. The mechanisms that regulate CV disease during early inflammatory arthritis are ill-defined. Studies in humans and animal models identify matrix metalloproteinase 9 (MMP-9) as a potential regulator of CV pathology. Macrophages are early sentinels of both joint inflammation and vascular dysfunction. They are considered a major source of MMP-9 and can be induced in vitro to produce this metalloproteinase in response to Death Receptor 3 (DR3) signaling. Ablation of DR3 expression reduces MMP-9 levels in arthritic joint tissues during experimental arthritis. Here, for the first time, we measure DR3-dependent vascular dysfunction, associated macrophage infiltration and MMP-9 expression in vascular and perivascular adipose tissues (PVAT) with a view to understanding DR3’s role in initiating early CV damage during inflammatory arthritis.

Methods: Murine collagen-induced arthritis (mCIA) was induced in DBA/1 mice (WT). Constriction responses to serotonin (5HT) were used to assess vascular function in isolated sections of thoracic aorta (±PVAT) in non-mCIA and mCIA mice with mild disease. DR3-dependent changes in vascular function were analysed using age-matched DBA/1 DR3 deficient mice (DR3-/-). Region specific (thoracic aorta and PVAT) leucocyte infiltration was determined using haematoyxlin and eosin staining, whilst localisation of F4/80 macrophages were visualised and MMP-9 expression quantified after immunohistochemical staining.

Results: The onset of mild arthritis was associated with inflammatory changes in the aortic vessel wall, characterised by increased macrophage infiltration (p<0.05) and DR3 expression (p<0.001). Total MMP-9 expression was unaltered (non-mCIA vs. mCIA mice). Macrophages (F4/80+), DR3 and total MMP-9 expression were all significantly elevated in PVAT (p<0.05 for all). The mCIA vascular tissues (±PVAT) exhibited significant contractile dysfunction compared to non-mCIA controls (p<0.001). The presence of PVAT was associated with a significant (p<0.001) dextral shift in constriction response curves but had no effect on maximal constriction. In DR3-/- non-mCIA mice, leukocyte infiltration (p<0.05) and total MMP-9 (p<0.001) levels were elevated in PVAT but not in the aortic vessel wall. Vascular function was unaltered (WT versus DR3-/-) and PVAT retained its ability to shift the constriction response curve to the right (p<0.001) in both genotypes. mCIA had no impact on the leukocyte ingress or MMP-9 production in the aortic vessel wall or PVAT (WT versus DR3-/-). However, loss of DR3 further impaired vascular function (±PVAT) in comparison to WT (p>0.001).

Conclusion: The onset of mCIA drives an inflammatory response in the PVAT; associated with macrophage infiltration, increased expression of DR3 and MMP-9, and is detrimental to vascular function. Loss of DR3 perpetuates vascular dysfunction independently of leukocyte ingress and MMP-9 production. Further studies are justified to deduce the impact of DR3 on vascular function, in particular, the potential link with cardiovascular co-morbidities allied to arthritis.

Disclosure: J. O. Williams, None; E. C. Y. Wang, None; D. Lang, None; A. S. Williams, None.
Vascular Permeability As an Imaging Biomarker for Chronic Inflammatory Arthritis: A Dynamic Contrast Enhanced Magnetic Resonance Imaging Study. Eun Jeong Nam1, Yongmin Chang2, Jung-Woo Park2, Shijin Sung3, Jungwan Hong1, Md. Hasan Al Faruque1, Jongmin Lee1 and Young Mo Kang4. 1Kyungpook National University School of Medicine, Daegu, South Korea; 2Kyungpook National Univ Hosp, Daegu, South Korea.

Vascular permeability as an imaging biomarker for chronic inflammatory arthritis: A dynamic contrast enhanced magnetic resonance imaging study.

**Background/Purpose:** Rheumatoid arthritis (RA) is a chronic inflammatory disease in which adequate diagnosis of disease activity is particularly important for optimizing treatment outcomes. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is used to detect inflammatory changes in synovial joints, and to discriminate active and inactive stages of disease. However, DCE-MRI has not been previously used to evaluate changes quantified using DCE-MRI was consistent with the vascular densities reached, and thereafter declined gradually. The pattern of permeability changes quantified using DCE-MRI was consistent with the vascular densities and disease activity. Furthermore, vascular permeability and densities decreased significantly in a dose-dependent manner after treatment with MTX.

**Conclusion:** Vascular permeability assessed by DCE-MRI can be used as an imaging biomarker for tracking disease progression, and for monitoring therapeutic efficacy in inflammatory arthritis.

**Results:** Permeability maps on the knee joint revealed less heterogeneity during the acute stage, compared to early and late stages of arthritis. Vascular permeability increased progressively until the active stage of arthritis was reached, and thereafter declined gradually. The pattern of permeability changes quantified using DCE-MRI was consistent with the vascular densities and disease activity. Furthermore, vascular permeability and densities decreased significantly in a dose-dependent manner after treatment with MTX.

**Conclusion:** Vascular permeability assessed by DCE-MRI can be used as an imaging biomarker for tracking disease progression, and for monitoring therapeutic efficacy in inflammatory arthritis.

**Reduced Macrophages in the Synovium Contribute to the Effective Treatment of Spontaneous Arthritis Observeded in Human TNF-Transgenic Mice.** Robert Birkett, Qi Quan Huang, Bo Shi and Richard Pope. Northwestern University Feinberg school of Medicine, Chicago, IL.

**Background/Purpose:** Macrophages in rheumatoid arthritis (RA) synovial tissue (ST) produce high levels of inflammatory cytokines/chemokines and exhibit enhanced differentiation into osteoclasts in the pannus, playing the pivotal role in promoting inflammation and joint destruction. Recent observations demonstrate that effective therapy employing a TNF inhibitor results in a selective reduction of sublining RA ST macrophages within 24 hours. However, neither ingress of monocytes into the tissue nor apoptosis of macrophages in the RA tissue accounted for the reduction of macrophages. Therefore, employing a murine model, studies were performed to define the role of CCR7 expression to promote macrophage egress from inflamed joints as a potential mechanism for therapeutic response.

**Methods:** CCR7 expression in RA synovial macrophages was determined by two color immunohistochemistry employing anti-CCR7 and anti-CD68, RT-PCR and immunoblotting. A human TNF transgenic (hTNF-tg) mouse line which spontaneously develops arthritis was employed, and treated with infliximab, administered intraperitoneally (10mg/kg, i–3 doses). The clinical severity of the arthritis was defined as the sum score of joint swelling, inflammation, deformity and grip strength. Ankle histology was performed. The immune cell phenotypes and apoptosis were determined by flow cytometry. Ankle cell migration was tracked by PKH26 intra-articular injection and cell identification by flow cytometry.

**Results:** CCR7 was increased in macrophages in RA ST and synovial fluid. CCR7 expression on normal human macrophages was significantly increased at the mRNA and protein levels following incubation with TNFa, Pam3 or LPS. As expected the hTNF-tg mice developed arthritis beginning at week 4, progressing through week 12. The hTNF-tg mice treated with infliximab for 72 or 168 hours demonstrated significant clinical improvement. Histologic analysis identified significant reduction of inflammation, bone erosion and pannus formation after 168 hours of therapy. Flow cytometric analysis demonstrated that ST macrophages were significantly reduced at 24 hours, prior to clinical improvement, and 72 and 168 hours following the initiation of therapy. In contrast, other cell types including granulocytes, B or T lymphocytes and dendritic cells were not consistently or not significantly reduced. No increase of macrophage apoptosis or necrosis in ankle ST was
observed following treatment. Futher, although there was a reduction of PKH26 labeled macrophages in the ankles following therapy, there was also a reduction of macrophages in the poplitael lymph nodes and no increase in the percentage of PKH26 labeled macrophages was detected.

**Conclusion:** These observations demonstrate increased CCR7 on macrophages in the RA joint and that CCR7 on macrophages was increased by inflammation. Macrophages, but not other cell types, in the inflamed synovium of hTNF-Tg mice were reduced early prior to clinical or histologic improvement, but we have yet to document egress as the mechanism. The role of CCR7 in the therapeutic reduction of macrophages is being pursued by crossing hTNF-Tg mice with those deficient in CCR7.

**Disclosure:** R. Birkett, None; Q. Q. Huang, None; B. Shi, None; R. Pope, None.

345 A Low Salt Diet Ameliorates Clinical Manifestations in Collagen-Induced Arthritis. Bettina Sehnert1, Sandy Pohle2, Agnes Schröder2, Jens Titze2 and Reinhard E. Voll1. 1University Hospital Freiburg, Freiburg, Germany, 2University of Erlangen-Nürnberg, Erlangen, Germany, 3Vanderbilt University School of Medicine, Nashville, TN.

**Background/Purpose:** A genetic predisposition, but also environmental factors including infections and smoking modulate manifestation and severity of inflammatory autoimmune disease like rheumatoid arthritis (RA). Recently, the induction of pathogenic Th17 cells as a consequence of increased salt intake was demonstrated in an animal model of multiple sclerosis. The impact of dietary factors such as low salt consumption on the inflammatory status in arthritis has not yet fully characterized. The aim of the study was to investigate the association between salt intake and clinical manifestations in a mouse model of arthritis.

**Methods:** DBA/1 mice were immunized with bovine type II collagen (CII) in complete Freund’s adjuvant (CFA). Two weeks before immunization experimental diet was started and the mice were divided in two groups. The LS (low-salt) group (n=9) received a diet containing a sodium content <0.03% and tap water. The HS (high-salt) group (n=10) were fed with a diet containing 4 % NaCl in combination with 0.9% NaCl supplemented tap water. The feeding lasted 62 days. Arthritis severity was assessed by clinical scoring to a graded scale (0–4). At the end of the experiment hind paws were removed for histological analysis. The stained sections (hematoxylin/eosin, toluidine blue and tartrate-resistant acid phosphatase) were graded on a scale from 0–3. Levels of IgG1 and IgG2a antibodies against bovine collagen type were measured by ELISA.

**Results:** Administration of a low salt diet resulted in a decreased arthritis severity compared to the HS-group. Further, the incidence of arthritis was significantly lower in the LS group. The histopathological analysis revealed reduced infiltrations with inflammatory cells in the group fed with the low salt diet. Also the destruction of cartilage and bone was less pronounced in the LS group compared to the HS group. ELISA experiments showed that the level of pathogenic IgG2a antibodies against CII was markedly increased in HS-mice, whereas low salt consumption reduced anti-CII IgG2a levels significantly. The titers of CII-specific IgG1 were similar in both groups. This result in decreased IgG2a/IgG1 ratio in the LS group and indicates a shift toward a more Th2-dominated immune response.

**Conclusion:** Low salt diet ameliorates clinical and histological signs in murine collagen-induced arthritis. The low salt consumption inhibits the humoral IgG2a response against CII and protects against antibody-mediated joint destruction. We conclude that a low salt diet might ameliorate RA and support treatment of immune-mediated arthritides.

**Disclosure:** B. Sehnert, None; S. Pohle, None; A. Schröder, None; J. Titze, None; R. E. Voll, Investigator, 5.

346 Treatment of Collagen Induced Arthritis with Human Embryonic Stem Cell-Derived Multipotent Mesenchymal Stromal Cells (hESC-MSC). Gabriel Criado1, María J. Pérez-Lorenzo2, María Galindo1, Jose L. Pablos1, Pablo Menéndez3 and Elena Gonzalez-Gil4. 1Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, 2Josep Carreras Leukemia Research Institute, Barcelona, Spain, 3Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain.

**Background/Purpose:** Inhibition of TGFβ signaling in human Embryonic Stem Cells (hESC) generates mesenchymal stromal cells (hESC-MSC) with osteogenic, adipogenic and chondrogenic potential. These cells have immunosuppressive and anti-inflammatory properties in vitro and have shown a protective effect in experimental models of acute inflammation. The aim of the present study was to test their therapeutic potential in an experimental setting of chronic inflammation, the collagen-induced arthritis model (CIA).

**Methods:** Arthritis was induced in 8–10 weeks old male DBA/1 mice by intradermal immunization with 200 mcg of chicken type II collagen (CII) in Complete Freund’s Adjuvant (CFA). Mice were treated starting on the day of arthritis onset with three doses of 10⁶ cells / mouse hESC-MSC every other day and arthritis severity was evaluated daily during ten days. Effect of in vivo treatment was assessed by flow cytometry to detect Treg (FoxP3⁺), Th1 (IFNγ⁺) and Th17 (IL17⁺) CD4 T cells in lymph nodes. To analyze T cell responses in vitro, lymph node cells were stimulated with CII, proliferation was measured by incorporation of the colorimetric reagent WST-1 and IFNg and IL17 levels were quantified by ELISA. Serum levels of anti-CII antibodies were determined by ELISA. Detection of hESC-MSC mouse tissues was performed by quantitative PCR (qPCR) of HLA-C and quantification of murine and human indoleamine 2,3 dioxygenase (IDO) was performed by quantitative PCR. Statistical differences were analyzed by ANOVA and Mann-Whitney U-test using GraphPad Prism software. P values < 0.05 were considered significant.

**Results:** Treatment of CIA mice with hESC-MSC reduced disease severity compared to control-treated mice. Differences appeared the first day after treatment and were significant and sustained in the group receiving 3 doses. Therefore, administration of 3 doses was the schedule used for subsequent experiments. Anti-CII antibodies levels were not affected by treatment. Analysis of CD4 T cell populations in treated mice showed an enrichment in FoxP3⁺ Treg cells (8.56 ± 0.89 % vs 5.89 ± 0.81 % in control mice, *P=0.026*) in inguinal lymph nodes. IFNg producing cells were also increased (0.88 ± 0.09 % vs 0.54 ± 0.02 %, **P=0.008**) but not IL17 producing cells (0.93 ± 0.09 % vs 0.84 ± 0.05 %, P=0.54). In vitro stimulation with CII caused higher production of IFNg and IL17 in lymph node cultures from hESC-MSC-treated mice although not statistically significant (IFNg: 539.0 ± 219.3 pg/ml vs 147.8 ± 93.35 pg/ml, P=0.09; IL17: 258.3 ± 134.1 pg/ml vs 72.39 ± 72.39 pg/ml, P=0.24) and proliferation was not affected. hESC-MSC treated mice that showed MSC colonization in lymph nodes, as detected by HLA- expression, had significantly higher expression of murine indoleamine 2,3 dioxygenase than their treated non-colonized and not treated counterparts (6.88 ± 0.94 Units vs 1.049 ± 0.36 in non-colonized and 1.82 ± 0.24 in non-treated mice, **P<0.009 and *P=0.004**, respectively).

**Conclusion:** Treatment with hESC-MSC ameliorates CIA by inducing IFNg and indoleamine 2,3 dioxygenase.

**Disclosure:** G. Criado, None; M. J. Pérez-Lorenzo, None; M. Galindo, None; J. L. Pablos, None; P. Menéndez, None; E. Gonzalez-Gil, None.

347 Salt Aggravates Arthritis By Th17 Polarization. Seung Min Jung1, Hong Ki Min1, Jung Hee Koh1, Jin Young Kang1, Jennifer Lee2, Seung-Ki Kwok3, Kyung-Su Park2, Hyeok-Jae Ko1, Wan-Uk Kim1, Hyeok-Jae Ko1, Seung-Hun Jung2, and Ji Hyon Park2. 1Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, 2St. Vincent Hospital, SuWon Gyeonggi-do, South Korea, 3Division of Rheumatology, Department of Internal Medicine, Daejeon St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea, 4Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea.

**Background/Purpose:** Sodium chloride (NaCl) recently has been shown to drive autoimmune diseases through the induction of pathogenic interleukin 17-producing T helper (Th17) cells. This study investigated the effect of NaCl on Th17 cell differentiation in human and murine arthritis.

**Methods:** To evaluate in vivo arthritogenic effect of NaCl, collagen-induced arthritis (CIA) mice were fed a normal or high-salt diet ad libitum, and paw swelling was scored visually. Splenocytes were analysed by flow cytometry for RORgt expression, and splenic CD4⁺ T cells were differentiated into Th17 cells. Peripheral blood mononuclear cells obtained from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) were cultured under high-salt-fed CIA mice expression and were analysed by flow cytometry for quantifying Th17 cell population.

**Results:** NaCl increased murine and human Th17 cell differentiation in a dose-dependent manner and aggravated arthritis in CIA mice. Joint inflammation was more severe in the high-salt-fed CIA mice. T cells from high-salt-fed CIA mice expressed a higher level of RORgt and were more...
likely to differentiate into Th17 cells. Th17 cells were located primarily in arthritic joints, and also observed the intestinal tract of high-salt-fed CIA mice. Na+ and IL-17 concentrations were higher in synovial fluid from RA patients than in fluid from OA patients. There was a tendency towards increased RORgt expression after NaCl treatment in arthritic patients.

**Conclusion:** This study suggests that NaCl can aggravate arthritis by affecting Th17 differentiation. Limiting salt intake might be helpful in the management of arthritis.

**Disclosure:** S. M. Jung, None; H. K. Min, None; J. H. Koh, None; J. Y. Kang, None; J. Lee, None; S. K. Kwok, None; K. S. Park, None; H. J. Ko, None; W. U. Kim, None; H. Y. Kim, None; S. H. Park, None; J. H. Ju, None.

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**ACR Poster Session A**

**Rheumatoid Arthritis - Clinical Aspects: Novel Biomarkers and Other Measurements of Disease Activity**

**Sunday, November 16, 2014, 8:30 AM-4:00 PM**

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**Smoking Status Is Associated with Inflammatory Cytokine Profile and Disease Activity: Decreased Inflammation and Disease Improvement with Smoking Cessation**

Jeremy Sokolove1, Harlan Sayles2, Catriona Wagner1, Lauren J. Lahey1, Geoffrey M. Thiele2, William H. Robinson1, Andreas Reimold1, Gail S. Kerr3, Grant W. Cannon4 and Ted R. Mikuls2.

1VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, 2Dallas VA and Univ of TX Southwestern Med Ct, Dallas, TX, 3Washington DC VAMC, Georgetown and Howard University, Washington, DC, 4Salt Lake City VA and University of Utah, Salt Lake City, UT.

**Background/Purpose:** Cigarette smoking is a risk factor for RA and has been associated with increased disease severity and lower rates of disease remission. We examined whether smoking cessation might be associated with reduced disease activity and investigated the association of autoantibody levels with smoking status.

**Methods:** RA patients from the Veterans Affairs RA (VARA) registry were studied (n = 1468, 76.9% anti-CCP2+, 90.7% male, median age 65 [IQR 57–72], median disease duration 8.45 years [IQR 2.8–18]). Baseline serum samples were evaluated for levels of 19 distinct ACPA and 17 cytokines using the BioPlex platform. Baseline smoking status was recorded as current, former, or never. Cross-sectional associations of baseline smoking status with disease activity (DAS28) and its constituents as well as levels of ACPA, and baseline levels of cytokines were assessed.

**Results:** Multiple measures of RA disease activity including DAS28 were significantly higher among current smokers compared with either former or never smokers (P<0.01), an effect limited to the seropositive (anti-CCP2 positive) population (Table 1). The number of inflammatory cytokines found in high concentration was significantly higher among current smokers compared with both former and non-smokers (FDR q-value <0.1%). Levels of both anti-CCP2 as well as ACPA subtypes were lower in never smokers but similar between current and former smokers while levels of RF were highest in current smokers, and lower in both former smokers and lowest in never smokers (Table 2).

**Conclusion:** Current smoking is strongly associated with increased RA disease activity as well as elevation in pro-inflammatory cytokine levels compared to both former and never smokers. Our findings suggest that continued tobacco exposure promotes greater RA disease activity, particularly in ACPA-positive patients though independent of titer or specificity. The observation of reduced disease activity among former smokers, approaching that of never smokers, suggests that the effects of smoking may be reversed by smoking cessation. Whether RF may be a mediator of this effect remains to be clarified.

**Table 1:** Measures of disease activity, ACPA, and cytokine expression among anti-CCP2 positive RA patients; *p*-values among smoking groups generated using Scheffe’s method for multiple comparisons.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Current smoker</th>
<th>Former smoker</th>
<th>Never smoker</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>24.3 ± 1.8</td>
<td>23.2 ± 1.1</td>
<td>19.7 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>0.8 ± 0.08</td>
<td>0.7 ± 0.07</td>
<td>0.6 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR bone marrow edema</td>
<td>22.9 ± 0.9</td>
<td>18.9 ± 0.9</td>
<td>16.6 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total joint count</td>
<td>80.0 ± 0.9</td>
<td>70.0 ± 0.8</td>
<td>60.0 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Disclosure:** J. Sokolove, None; H. Sayles, None; C. Wagner, None; L. J. Lahey, None; G. M. Thiele, None; W. H. Robinson, None; A. Reimold, None; G. S. Kerr, None; G. W. Cannon, AbbVie, 2; T. R. Mikuls, Genetech/Roche, 2.

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Galectin-3 in the Systemic Circulation Is Increased in Newly Diagnosed Rheumatoid Arthritis and Is Associated with Anti-CCP and Bone Marrow Edema.

Saida Farah Issa1, Anne Friesgaard Christensen2, Hanne M. Lindegaard3, Merete Lund Hetland1, Kim Hoeslven-Petersen3, Kirsten Junker3, Kristian Stengaard-Pedersen1, Tine Lottenburger1, Torkell Ellingsen1, B Hansen3, Jens Kristian Pedersen4, Ulrik B. Lauridsen3, Anders Svendsen3, Ulrik Tarp1, Jan Podenphant3, Mikkel Ostergaard3 and Peter Junker1.

1Department of Rheumatology, Odense University Hospital, Odense, Denmark, 2Department of Rheumatology, Vejle Hospital, Vejle, Denmark, 3DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, 4Research Unit at King Christian X Hospital for Rheumatic Diseases, Glostrup Hospital, Glostrup, Denmark.

**Background/Purpose:** Galectin-3 (Gal-3), a 26kD beta-galactoside binding protein, has been implicated as a pro-inflammatory mediator in animal arthritis and rheumatoid arthritis (RA) in humans. Thus, Gal-3 is overexpressed by fibroblast-like synoviocytes in the rheumatoid synovium, particularly upon adhesion to cartilage components. Moreover, Gal-3 is increased in serum in animal arthritis and in serum and synovial fluid in patients with long-standing RA as compared with osteoarthritics and healthy individuals.

**Methods:** Of this investigation we aimed to clarify the level by smoking status with disease activity (DAS28) and its constituents as well as baseline levels of ACPA, and baseline levels of cytokines were assessed.

**Results:** Multiple measures of RA disease activity including DAS28 were significantly higher among current smokers compared with either former or never smokers (P<0.01), an effect limited to the seropositive (anti-CCP2 positive) population (Table 1). The number of inflammatory cytokines found in high concentration was significantly higher among current smokers compared with both former and non-smokers (FDR q-value <0.1%). Levels of both anti-CCP2 as well as ACPA subtypes were lower in never smokers but similar between current and former smokers while levels of RF were highest in current smokers, and lower in both former smokers and lowest in never smokers (Table 2).

**Conclusion:** Current smoking is strongly associated with increased RA disease activity as well as elevation in pro-inflammatory cytokine levels compared to both former and never smokers. Our findings suggest that continued tobacco exposure promotes greater RA disease activity, particularly in ACPA-positive patients though independent of titer or specificity. The observation of reduced disease activity among former smokers, approaching that of never smokers, suggests that the effects of smoking may be reversed by smoking cessation. Whether RF may be a mediator of this effect remains to be clarified.

**Table 1 a.** Galectin-3 correlations according to autoantibody status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total RA (n = 159)</th>
<th>Anti-CCP positive (n = 93)</th>
<th>Anti-CCP negative (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPrho</td>
<td>0.22 p &lt; 0.01</td>
<td>0.26 p &lt; 0.01</td>
<td>0.25 p &lt; 0.04</td>
</tr>
<tr>
<td>ESRrho</td>
<td>0.27 p &lt; 0.01</td>
<td>0.29 p &lt; 0.01</td>
<td>0.32 p &lt; 0.04</td>
</tr>
<tr>
<td>MR bone marrow edemarho</td>
<td>0.27 p &lt; 0.05</td>
<td>0.28 p &lt; 0.05</td>
<td>0.32 p &lt; 0.06</td>
</tr>
<tr>
<td>MR erosionrho</td>
<td>0.03 p &lt; 0.05</td>
<td>0.03 p &lt; 0.05</td>
<td>0.05 p &lt; 0.05</td>
</tr>
<tr>
<td>MR synovinitrho</td>
<td>0.10 p &lt; 0.26</td>
<td>0.11 p &lt; 0.32</td>
<td>0.18 p &lt; 0.56</td>
</tr>
<tr>
<td>HAQ-scorerho</td>
<td>0.24 p &lt; 0.05</td>
<td>0.27 p &lt; 0.05</td>
<td>0.27 p &lt; 0.05</td>
</tr>
<tr>
<td>DAS28rho</td>
<td>0.14 p &lt; 0.08</td>
<td>0.20 p &lt; 0.06</td>
<td>0.27 p &lt; 0.05</td>
</tr>
<tr>
<td>Total joint countrho</td>
<td>0.00 p &lt; 0.06</td>
<td>0.05 p &lt; 0.64</td>
<td>0.01 p &lt; 0.06</td>
</tr>
</tbody>
</table>
Table 1. Galectin-3 correlations in RA subsets according to antibodies and smoking habits

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total RA (n=159)</th>
<th>Anti-crp-positive (n=93)</th>
<th>Anti-crp-negative (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers (n=108)</td>
<td>Never smokers (n=51)</td>
<td>Smokers (n=71)</td>
</tr>
<tr>
<td>CRP rho</td>
<td>rho = 0.23</td>
<td>rho = 0.18</td>
<td>rho = 0.24</td>
</tr>
<tr>
<td>ESR rho</td>
<td>rho = 0.34</td>
<td>rho = 0.22</td>
<td>rho = 0.25</td>
</tr>
<tr>
<td>MR bone erosion rho</td>
<td>rho = 0.03</td>
<td>rho = 0.06</td>
<td>rho = 0.21</td>
</tr>
<tr>
<td>MR erosion rho</td>
<td>rho = 0.14</td>
<td>rho = 0.19</td>
<td>rho = 0.59</td>
</tr>
<tr>
<td>MR synovitis rho</td>
<td>rho = 0.14</td>
<td>rho = 0.15</td>
<td>rho = 0.05</td>
</tr>
<tr>
<td>HAQ-score rho</td>
<td>rho = 0.22</td>
<td>rho = 0.00</td>
<td>rho = 0.40</td>
</tr>
<tr>
<td>DAS28 rho</td>
<td>rho = 0.12</td>
<td>rho = 0.23</td>
<td>rho = 0.15</td>
</tr>
<tr>
<td>Total joint count rho</td>
<td>rho = 0.17</td>
<td>rho = 0.53</td>
<td>rho = 0.06</td>
</tr>
</tbody>
</table>

Table 1: Clinical Characteristics of RA Patients, n=26

<table>
<thead>
<tr>
<th>Mean Age, ±SD, range</th>
<th>57.5±13.8 (23–79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n, (%)</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>Race, n, (%)</td>
<td>White 15 (57.7)</td>
</tr>
<tr>
<td></td>
<td>Black 3 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Mixed 4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Asian 4 (15.3)</td>
</tr>
</tbody>
</table>

Table 2: Disease Duration in months, ±SD, range

| Mean Disease Duration in months, ±SD, range | 56.0±55.3 (3–240) |

Table 3: Erosive Disease, n, (%) [imaging available on 15 patients]

<table>
<thead>
<tr>
<th>Autoantibody Status</th>
<th>IgM RF or ACPA positive, n, (%)</th>
<th>IgM RF and ACPA negative, n, (%)</th>
<th>IgM RF and ACPA positive, n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (11.5)</td>
<td>3 (11.5)</td>
<td>20 (76.9)</td>
</tr>
</tbody>
</table>

Table 4: Mean ACPA titer (IU/mL), ±SD, range

| Mean ACPA titer (IU/mL), ±SD, range | 195.1±67.9 (60–250) |

Table 5: Mean IgM RF titer (IU/mL), ±SD, range

| Mean IgM RF titer (IU/mL), ±SD, range | 143.8±166.8 (21.1–587) |

Table 6: Disease Activity Parameters

| Mean CRP (mg/dL), ±SD, range | 1.2±0.5 (1–3.2) |

Table 7: Mean CDAL (Mean ± SD, Range

| Mean CDAL (Mean ± SD, Range | 13.0±7.3 (6–30) |

Table 8: Current smokers, n, (%) |

| Current smokers, n, (%) | 4 (15.4) |

Table 9: Current Medications, n, (%) |

| Current Medications, n, (%) | 8 (30.8) |

Table 10: Hydroxychloroquine alone |

| Hydroxychloroquine alone | 1 (3.8) |

Table 11: Conventional DMARDs (Methotrexate ± Leflunomide) |

| Conventional DMARDs (Methotrexate ± Leflunomide) | 8 (30.8) |

Table 12: Anti TNF agents (Etanercept, Adalimumab) |

| Anti TNF agents (Etanercept, Adalimumab) | 8 (30.8) |

Table 13: Prednisone |

| Prednisone | 1 (3.8) |

Table 14: Rho-Associated Protein Kinase (ROCK) Activity Is Elevated in Rheumatoid Arthritis (RA) Patients and May be Responsive to RA Therapies.

Rho-Associated Protein Kinase (ROCK) Activity Is Elevated in Rheumatoid Arthritis (RA) Patients and May be Responsive to RA Therapies

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Total RA (n=159)</th>
<th>Anti-crp-positive (n=93)</th>
<th>Anti-crp-negative (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>4.73±0.3</td>
<td>4.00±0.3</td>
<td>5.04±0.5</td>
</tr>
</tbody>
</table>

Table 15: S147

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Total RA (n=159)</th>
<th>Anti-crp-positive (n=93)</th>
<th>Anti-crp-negative (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>4.32±0.5</td>
<td>4.53±0.5</td>
<td>4.52±0.5</td>
</tr>
</tbody>
</table>

Table 16: Sunday, November 16

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Total RA (n=159)</th>
<th>Anti-crp-positive (n=93)</th>
<th>Anti-crp-negative (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>4.32±0.5</td>
<td>4.53±0.5</td>
<td>4.52±0.5</td>
</tr>
</tbody>
</table>

Table 17: S147

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Total RA (n=159)</th>
<th>Anti-crp-positive (n=93)</th>
<th>Anti-crp-negative (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>4.32±0.5</td>
<td>4.53±0.5</td>
<td>4.52±0.5</td>
</tr>
</tbody>
</table>
Background/Purpose: Fatigue is an important issue for patients with rheumatoid arthritis (RA). The ACR/EULAR Boolean definition of remission comprises values ≤1/10 for joint counts, CRP and patient global assessment; fatigue is not specifically assessed. Near-remission (defined as remission for counts and CRP but with patient global assessment >1/10) is a status which may, or may not, be an acceptable objective for patients. Fatigue levels in this status are unknown.

Objectives: To assess fatigue levels and other aspects of impact, in patients in ACR/EULAR remission, compared to patients in near-remission and not in remission.

Methods: Ancillary analysis of the RAID database, based on an international multicenter cross-sectional study of consecutive RA patients from 12 European countries, and the baseline data in COMEDRA, a French national study in stable RA patients (refs 1, 2). Remission, near-remission and non-remission were assessed cross-sectionally and patient-reported impact of RA including fatigue was assessed using the RA Impact of Disease (RAID) score (ref 1). The RAID assesses pain, function, fatigue, sleep, coping and well-being; each component of the RAID score ranges from 0 (no impact) to 10 (high impact). Patients in remission were compared to those in near-remission and not in remission for mean levels and the proportion of patients with a score ≤1/10, in each of the RAID components. The discriminant capacity of fatigue and of the other RAID components for the status of remission was assessed by Cohen's effect size.

Results: In total, 1284 patients had complete data for this analysis: mean (±standard deviation) age 57±11 yrs, disease duration 13±10 yrs, 78% women. Mean RAID score was 3.3±2.2. Mean fatigue in this population was 4.1±2.7. With the ACR/EULAR Boolean definition, only 87 (6.8%) were in remission and 84 (6.5%) were in near-remission. In remission patients, all the components of the RAID were very low (mean value below 1), except fatigue (mean value of 1.2±1.8; i.e., fatigue was above 1/10 in 25% of the patients in remission, versus 9–21% for the other aspects of RA impact. Near-remission was characterised by more impact of RA for all components of the RAID but particularly fatigue (mean fatigue 4.0±2.3), similar to patients not in remission: 4.3±2.7). Fatigue levels, psychological well-being and sleep had the lowest discriminant capacity to distinguish patients in remission versus not.

Conclusion: The ACR/EULAR definition of remission is extremely stringent and rarely attained for patients with long-standing RA. Fatigue was the only aspect of the impact of RA to remain at significant levels for many patients in Boolean remission, and was much higher in patients in near-remission. More work is needed to understand the link between fatigue and disease activity.

Disclosure: L. Gossec None; B. Fautrel None; J. Kirwan None; A. Balasasew None; M. de Wit None; B. A. C. Dijkmans None; M. Englundhe None; P. Gaudin None; F. Gogus None; T. Heiberg None; T. K. Kiven None; E. Martin-Mola None; M. Mattucci-Cerinic None; K. Otta None; A. Ryussen-Witrand None; T. Sokka-Isler None; M. Soubrier None; M. Dougados None.

Background/Purpose: Patients with rheumatic diseases have significantly better clinical status in recent years than in previous decades, including rheumatoid arthritis (RA)1 and systemic lupus erythematosus (SLE).2 These improvements in many of the health assessment domains are linked to the estrogen environment in women, which was almost always elevated in 1980 when the HAQ3 was reported normal at this time. In 1999, 16% of patients were reported to have HAQ scores of zero, suggesting “no difficulty” in function, but most nonetheless reported problems with function as well as psychosocial issues reflecting “floor effects.” Therefore, a multidimensional HAQ (MDHAQ) was developed to include 13 queries in the user-friendly HAQ format, 3 simple activities of daily living (ADL) from (and identical to) the HAQ, and 5 not on the HAQ: 2 complex activities – “walk 2 miles or 3 kilometers” and “participate in recreation and sports as you would like”, and 3 “psychological” queries – sleep quality, anxiety and depression. We analyzed mean scores for each of the 13 MDHAQ items in patients with RA and SLE in routine care in an academic rheumatology setting.

Methods: An MDHAQ is completed in an academic rheumatology setting by each patient at each visit. The MDHAQ queries 13 items (Table) in the patient-friendly HAQ format, all scored 0–3, with 4 response options: without any difficulty=0, with some difficulty=1, with much difficulty=2 and unable to do=3. Mean scores were analyzed in 140 female patients, 70 who met criteria for RA and 70 for SLE. Mean scores for each item were computed and compared using a t-test with a p-value of ≤0.05 considered significant on 2-tailed tests. Exploratory factor analysis (Principal Component analysis with varimax rotation) on the 13 items was performed.

Results: Mean scores for the 8 items a-h found on the HAQ were <0.70 in patients with RA and <0.50 in patients with SLE (Table), but scores were

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Conclusion: Scores of 0 are seen on considerably more HAQ items than MDHAQ items. The MDHAQ identifies patient problems, which are not captured by the HAQ, similar in RA and SLE. Documentation of improvement is not possible when baseline scores are zero. The MDHAQ might be considered for usual clinical care as well as in clinical trials.

References:

Disclosure: N. Annappareddy, None; D. Giangreco, None; L. Castrejon, None; N. Shetty, None; T. Pincus, None; J. Block, None; M. Joly, None.

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Increased Vascular Wall Inflammation in Patients with Active Rheumatoid Arthritis As Measured By an 18F-FDG-PET/CT Scan. Rabiga A1, Alper M. van Sijl1, Yvo M. Smulders1, L. van der Laken1, Ronald Boellaard1, Karel-Jan D.F. Lensen1 and Michael T. Nurmohamed2. 1VU University Medical Center, Amsterdam, Netherlands, 2St. Marianna University School of Medicine, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have an elevated risk of developing cardiovascular disease (CVD). Like active RA, atherosclerosis is an inflammatory process. There are indications that aortic inflammation in atherosclerosis can be detected on 18F-Fluorodeoxyglucose-positron emission tomography/computed tomography scan (18F-FDG-PET/CT).

Objective: To quantify 18F-FDG uptake in large arteries of RA patients using PET/CT, as potential reflection of vascular wall inflammation in areas of atherosclerosis, and its association with disease activity in patients with RA as compared to controls.

Methods: 18F-FDG-PET/CT scan was performed in patients with active RA (DAS28 > 4.0; n=29) and in controls with osteoarthritis (n=11). Semi-quantitative FDG-uptake was determined by calculation of the mean standardized uptake value (SUV) and tissue-to-background ratio (TBR) using 18F-FDG activity in the vena cava as background. One volume of interest (VOI) of each arterial segment with maximum 18F-FDG uptake was used for SUV calculation (focal arterial uptake). Total arterial uptake was estimated by using the mean of all focal arterial uptakes in all arteries.

Results: Focal as well as total arterial uptake of 18F-FDG was the highest in patients with RA. SUV was significantly higher in RA for the thoracic aortic tract, the abdominal aorta and the femoral arteries as compared to OA controls. C-reactive protein was associated with an increased total arterial uptake as well as an increased focal arterial uptake in the thoracic aortic tract, the abdominal aorta, the iliac arteries and the femoral arteries. DAS28 >2.6 was also correlated to total arterial uptake and uptake in the thoracic aortic tract, the abdominal aorta and the iliac arteries. There were no significant differences in TBR between RA and OA.

Conclusion: Increased focal vascular wall uptake of 18F-FDG as sign of vascular inflammation was found in several arterial segments of RA patients. C-reactive protein and clinical RA activity were correlated with 18F-FDG uptake in most of these arteries. Overall, total arterial uptake was higher in RA patients and it was correlated with C-reactive protein and disease activity. The lack of differences in TBR measurements requires further study.

Disclosure: R. Agca, None; A. M. van Sijl, None; Y. M. Smulders, None; A. E. Voskuyl, None; J. van der Laken, None; R. Boellaard, None; K. J. F. Lensen, None; M. T. Nurmohamed, Abbie, 2.

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Increased Left Ventricular Mass Index and Decreased Ejection Fraction Are Associated with Disease Activity in Rheumatoid Arthritis Patients without Cardiac Symptoms: Comparison Between Non-Biologic and Biologic Dmards Treatment Groups, Using a Cardiac Magnetic Resonance Imaging. Kotolik J. Block1, Nozaki1, Ikumi1, Takei3. 1Nihon University School of Medicine, Tokyo, Japan, 2St.Marianna University School of Medicine, Kawasaki, Japan, 3Nihon University School of Medicine, Itabashi Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) experience an excess risk of congestive heart failure (CHF), but effects of disease-modifying anti-rheumatic drugs (DMARDs) on cardiac structure and function are uncertain. Cardiac magnetic resonance imaging (CMR) has been used to identify early functional and structural changes in the left ventricle (LV) before development of clinically overt CHF. We evaluated LV function and structure using a CMR in RA patients (pts) without cardiac symptoms, and determined the impact of non-biologic and biologic DMARDs (bDMARDs).

Methods: Consecutive RA pts and healthy control without a history or clinical findings of hypertension, cardiovascular disease, diabetes, or dyslipidemia were enrolled. RA pts received biologic or non-biologic DMARDs (nbDMARDs). All subjects underwent evaluation of LV function and structure using non-contrast CMR. LV function was based on LV ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO). LV hypertrophy was measured by absolute LV mass (LVM) and LV mass index (LVMi) determined by LVM/body surface area. Subjects were classified into four categories based on LVMi and LVM/EDV of control subjects, with the mean + 2 SD of each measure defined as elevated LVMi and LVM/EDV.

Results: We compared 90 female RA pts (mean age, 55.9±7.1 years) with a matched 20-patient control group (mean age, 52.7±4.6 years). 46 RA pts received nbDMARDs [43, methotrexate (MTX) (8.1±2.1mg); 3, other drugs] and 44 RA pts received bDMARDs [(18, infliximab (3 mg/kg); 26, tocilizumab (8 mg/kg) plus MTX (8.0±1.4 mg)]. Among the RA groups, there were no significant differences in characteristics such as age, cardiovascular risk factors, RA duration, MTX dose, and proportion of corticosteroid users. The Simplified Disease Activity Index (SDAI) was significantly
higher in the nbDMARDs group than in the bDMARDs group (22.3 ± 1.5, 5.6 ± 1.9, p = 0.002). Compared to the control group, the nbDMARDs group showed significantly higher LVM and lower EF (p < 0.001, p = 0.003, respectively). There were no significant differences in LVM and EF between the control and the bDMARDs groups. LV structure was classified as (1) concentric remodeling (LVMi < 66.9 and LVM/EDV > 1.02); (2) concentric hypertrophy (LVMi > 66.9 and LVM/EDV > 1.02); (3) eccentric hypertrophy (LVMi > 66.9 and LVM/EDV < 1.02); and (4) normal geometry (LVMi < 66.9 and LVM/EDV < 1.02). Among those with abnormal LV geometry, 32% of RA patients in the nbDMARDs group showed eccentric hypertrophy, 98% of RA patients in the bDMARDs group showed normal geometry. LVM and EF were significantly associated with SDAI (r = 0.567, p < 0.001; r = −0.312, p = 0.003, respectively). Mass/EDV tended to be associated with SDAI (p = 0.07). Adjusting for SDR did not modify the association of SDAI with EF and LVMi (p = 0.017, p = 0.005, respectively).

Conclusion: The RAID score was associated with objective measured and subjective disease measures in this inception cohort of DMARD naïve RA patients. These findings support the use of RAID as a valid PROM in patients with early RA, covering a wide variety of disease manifestations and reflecting the patient perspective.

Disclosure: L. B. Nordberg None; E. Lie None; A. B. Aga None; M. T. Maehlen None; I. Olsen C; T. Uhlig None; T. K. Kvien None; E. H. Haavardsholm AbbVie; Pfizer, MSD, Roche, UCB; 2; T. A. study Group AbbVie; Pfizer, MSD, Roche, UCB, 2.

Background/Purpose: The RAseq program, which used RNAseq to profile the peripheral blood mononuclear cell (PBMC) transcriptomes of 80 early RA (≤6 mo duration) patients, identified 694 differentially expressed genes (DEGs) (FDR < 0.05). We aimed to identify DEGs that are associated with clinical features (fatigue, swelling, and pain) of RA and developed an integrated biomarker and clinical scoring system that includes simple and laboratory measures. The goal was to select three validated biomarkers (BV) for a clinical scoring system (SS) that can predict low, moderate, and high disease activity in early RA patients.

Methods: A total of 102 early RA patients (≤6 mo duration) were included in the study. All patients completed the 28-joint count DAS (DAS28-CRP), patient-reported outcomes (Patient Global [PG], Patient Benefit [PB], American College of Rheumatology [ACR] remission, ACR20, ACR50, ACR70, ACR90), HADS (anxiety and depression), and the DASS-21 (depression, anxiety, and stress). The disease activity was scored using the Disease Activity Score (DAS), the Health Assessment Questionnaire (HAQ), the Short Form-36 (SF-36) Health Survey, and the tender and swelling joint counts. A biomarker loading value (BV) was calculated as the ratio of the biomarker level in the RA group to that in the healthy control group.

Results: Among the 694 DEGs, 304 were upregulated (FDR < 0.05) and 390 were downregulated. The biomarkers were selected using the following criteria: (1) univariate analysis of the BV and clinical measures (p < 0.05); (2) BV were normalized using a log2 transformation; (3) for each BV, the distributions were compared across the disease activity groups (FDR < 0.05); and (4) the BV were incorporated into the SS, and the final SS was selected using 10-fold cross-validation (CV) and the area under the receiver operating characteristic curve (AUC) score. The SS, when compared with clinical measures, was able to distinguish between low, moderate, and high RA disease activity with an AUC of 0.79/0.92/0.93 against SLE. Omitting sensitivity/specificity/area under the curve (AUC) were 0.9/0.9/0.97 against RA patients and 0.79/0.92/0.93 against SLE. Omitting ACPA resulted in slightly weaker test performance with sensitivity/specificity/AUC of 0.9/0.86/0.95. When only seronegative (ACPA and RF negative) patients were considered, sensitivity/specificity/AUC was 1.0/1.0/1.0 and higher against healthy controls. In the validation phase on early RA patients from the HIT-HARD study, the panel showed sensitivity/specificity/AUC of 0.71/0.53/0.68 with ACPA and only slightly weaker performance at 0.71/0.52/0.67 without ACPA. Seronegative patients were detected with sensitivity/specificity/AUC of 0.09/0.60/0.78.

Conclusion: The multiplex bead-based approach showed promising results concerning the identification of potential diagnostic markers for seronegative RA. The need for rigorous validation of such exploratory approaches to control for over-fitting is clearly demonstrated. Future improvements of the technology such as citrullination of recombinant antigens may further enhance detectability of "seronegative" patients.

Disclosure: S. Vordenbäumen; None; A. Lucking; Protagen AG, 3; C. Theek; Protagen AG, 3; R. Brinks; GlaxoSmithKline, 9, UCB, 9; R. Fischer-Betz; None; J.
Parity and Severity of ACPA-Positive/Negative Rheumatoid Arthritis. Results from the Swedish EIRA Study. 

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Background/Purpose: Female sex and older age are known risk factors for rheumatoid arthritis (RA). The disease is however heterogeneous, and a common division occurs between the presence/absence of autoantibodies to citrullinated peptide antigens (ACPA) where ACPA-positive disease generally has a worse outcome. In a recent study we reported that parous women of reproductive age (18 to 44 years at diagnosis) had an increased risk of ACPA-negative, but not of ACPA-positive RA, and that this association was stronger closer to partum[1]. There are diverging results regarding the effect of parity on the severity of RA.

Our purpose was to explore if parity has impact on disease severity of RA, stratified into different phenotypes.

Methods: We studied female RA cases ages 18–70, who participated in the Epidemiological Investigation of Rheumatoid arthritis, EIRA, a population-based case-control study from the middle and southern parts of Sweden. All patients included fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA and were diagnosed by a rheumatologist, and included within 1 year of diagnosis. Information on disease severity (Health Assessment Questionnaire, HAQ and disease activity score 28, DAS28) was gathered from the Swedish Rheumatology Register, SRQ at inclusion, 3, 6, 12 and 24 months after diagnosis. Mixed models for repeated measurements over time were used to take account of the variation at different time point at individual level and to compare mean DAS28 and HAQ-scores over time. ANCOVA analysis was used to compare mean differences of clinical outcome measures at all time points.

Results: A total of 1237 female cases, with complete information, were included in the study with a mean age of 51 at inclusion. In all, 82% had ever given birth to a child before diagnosis and 65 % were ACPA-positive. Mixed models analysis showed associations between parity and ACPA negative but not ACPA positive disease. Parous women, aged 18–44, who would develop ACPA negative disease, had on average 1.17 higher DAS 28 (p<0.001) and 0.46 lower HAQ (p<0.01) compared to parous women in the follow up time, adjusted for age. These findings remained after individually adjusting for smoking, living area and level of education. There was an opposite trend among parous ACPA negative women (aged 45 to 70), were parous women had 0.26 lower DAS 28 (p=0.14) and 0.06 lower HAQ (p=0.46). ANCOVA analysis for different time points noted an association between higher DAS 28 and HAQ levels and parity in the ACPA negative reproductive age group at all time points, except at baseline. In ACPA negative disease, we observed a milder disease in parous women, although only significant at baseline.

Conclusion: Parity influenced ACPA negative disease, where parous women who developed RA during their fertile years had on average higher DAS 28 and HAQ compared to nulliparous women. Parity was not a predictor of severity in ACPA positive disease.

References


Disclosure: M. Pikwer, None; C. Orellana, None; H. Källberg, None; A. Pikwer, None; C. Turesson, None; L. Klareskog, None; L. Alfredsson, None; S. Saevarsdottir, None; C. Bengtsson, None.

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14-3-3pled Cit/Arg Antibody Ratios: Are We Overlooking the Prognostic Utility of Citrullinated Antibodies By Only Looking at Titers? Anthony Marotta1, Samina Turk2, Mairead Murphy3, WP Maksymowych4 and Dirkjan van Schaardenburg5. 1Augurex Life Sciences Corp., North Vancouver, BC, 2Reade, Amsterdam, Netherlands, 3University of Alberta, Edmonton, AB.

Background/Purpose: Citrullination is a post-translational modification whereby arginine (Arg) is degenerated by PAD enzymes to form citrulline (Cit). In RA, there are auto-antibodies (AAb) to Cit and native proteins1-2. With other types of PTM, such as phosphorylation, modifications are assessed as a degree of change in reactivity from the native state to inform biological relevancy and potentially deleterious events. Current ACPA antibodies are designed to measure reactivity to the Cit form of a peptide without accounting for the relative change in Cit:Arg reactivity. This may overlook important information related to citrullination and its relationship with clinical outcomes. 14-3-3ε is a ubiquitous intracellular protein whose extracellular expression in RA leads to its citrullination and the development of specific cit-reactive AAb. In this study we investigated whether anti-cit 14-3-3ε AAbs inform joint damage progression in early RA.

Methods: Anti-cit 14-3-3ε levels were measured in 139 DMDA-naïve early RA patients from the READE cohort using the MSD ECL platform, 4 highly reactive 14-3-3ε cit/arg peptides formed the basis of the assay. For each of the 4 sites, citrullination reactivity was defined as a %0 increase in Cit:Arg read units. Overall anti-cit-14-3-3ε positivity was defined as reactivity to at least one of the four sites. Contingency analysis was used to assess the association between ACPA and 14-3-3ε anti-cit-cit arg ratio positivity. Univariate and stepwise multivariate analyses were performed to identify predictors of radiographic damage progression (DSHS year 3 ≥ 3.0).

Results: Of 139 patients, 71% were ACPA positive and 51% were 14-3-3ε anti-cit-arg ratio positive. A univariate analysis evaluating the association of anti-cit-14-3-3ε titres and cit:arg ratios with radiographic progression revealed that the ratios were significantly associated (p<0.01) while titres were not. Contingency analysis revealed a strong association between ACPA and 14-3-3ε anti-cit-cit arg ratios, LR = 19.1, p<0.0001. By Fisher Exact test, ACPA and 14-3-3ε anti-cit-cit arg ratios were associated with radiographic progression at yr 3; LR = 5.3 p=0.02 and 6.4 p=0.01, respectively. In a model incorporating ACPA and 14-3-3ε anti-cit-cit arg ratio controlling for baseline total sharp score, the ratios independently predicted radiographic progression Chi-Sq = 6.4 p<0.01, while ACPA did not. In a multivariate model including baseline TSS, disease duration, age, ESR, gender together with RF, 14-3-3ε and 14-3-3ε anti-cit-cit arg ratio positivity, the only independent predictors of radiographic damage progression were 14-3-3ε protein and the cit:arg ratios; Chi-Sq = 5.2 (p=0.02) and 4.0 (p<0.05), respectively.

Conclusion: Both the 14-3-3ε protein and 14-3-3ε anti-cit-cit arg ratios are independent predictors of radiographic progression. The ratios (but not anti-cit-14-3-3ε titres) are a stronger predictor than ACPA. These data underscore 1) the potential benefit of accounting for cit:arg ratios rather than only cit titres in cit assays and 2) that the prognostic utility of 14-3-3ε anti-cit-cit arg ratios should be further investigated.


Disclosure: A. Marotta, Augurex Life Sciences Corp.; S. Turk, None; M. Murphy, Augurex Life Sciences Corp; 3 W. Maksymowych, Augurex Life Sciences Corp; 5 D. van Schaardenburg, Augurex Life Sciences Corp, 5.

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88% of Recent Onset Polymyelitis Patients Are Positive for 14-3-3 ε Markers and 14-3-3 ε Auto-Antibodies Inform a Favourable Prognosis. Gilles Boire1, Nathalie Carrier2, Artur Jose de Brum-Fernandes2, Patrick Liang3, Ariel Masetto4, Yuan Gui5, Mairead Murphy6, WP Maksymowych7 and Anthony Marotta8. 1Centre Hospitalier Universitaire de Sherbrooke, Universite de Sherbrooke, Sherbrooke, QC, 2Universite de Sherbrooke, Sherbrooke, QC, 3CHUS, Sherbrooke, QC, 4CHUS, Fleurimont, QC, 5Augurex Life Sciences Corp., North Vancouver, BC, 6University of Alberta, Edmonton, AB.

Background/Purpose: The 14-3-3 ε protein has been described as a mechanistic marker that is detectable in serum during the very early stages of RA development. A specific anti-14-3-3 ε autoantibody response is present in RA serum and is postulated to be protective when it effectively clears systemic 14-3-3 ε. This study examined the baseline expression of 14-3-3 ε
markers (protein and pan-autoantibodies) in a recent onset polyarthritis cohort and their association with the progression of joint damage.

Methods: 335 subjects were evaluated: 40 DMARD-naïve patients from the Sherbrooke EUPA cohort and 295 controls. Median age was 50 yrs, 2 months median disease duration, 75% were female and 60% were positive for RF and 55% for ACPA. Controls included 106 healthy and 189 disease controls consisting of connective tissue disease, OA, AS or autoimmune disorders. 14-3-3-η protein levels were previously tested in this cohort using the Ausab assay (cut off =19 ng/ml) and 50% of the recent onset polyarthritis patients were positive. 14-3-3-η AAb levels were measured on the MSD ECL platform using an established positive cut-off ≥380 U/ml. The group that was 14-3-3-η AAb-only positive, in whom the 14-3-3-η protein would have been cleared, was compared to the remainder of the cohort in terms of differences in radiographic progression over 30 months using the Mann-Whitney U-test. The Fisher Exact test was used to determine the association between marker positivity and radiographic progression (SHS±3 at 30 months).

Results: Median (IQR) 14-3-3-η AAb values were significantly higher in early RA 617 U/ml (473–742) vs all controls 264 U/ml (200–348), p<0.0001 delivering a ROC AUC of 0.89 (95% CI:0.85–0.94). When compared to healthy subjects, the ROC AUC was 0.95 (95% CI:0.92–0.99), p<0.0001 delivering 93% specificity and 85% sensitivity with a likelihood ratio (LR) of 11.3. Thirty-four patients (85%) were 14-3-3-η AAb positive, 88% were positive for either of the 14-3-3-η markers and a Pearson correlation between the two the 14-3-3-η markers of r<0.01 highlighted their complementary nature. Of the 40 patients, 15 (38%) were only positive for the 14-3-3-η AAbs and had significantly less joint damage progression at 30 months, median (IQR) ΔSHS 0 (0–3.5) vs the rest of the cohort, 5 (0–11.5), p<0.03. The Fisher exact test revealed that 14-3-3-η AAb positivity (in the absence of the 14-3-3-η protein) remains a high unmet need for biomarkers in the earliest stages of RA to assist prediction models for the risk of RA development in arthralgia patients. There were 60) ACPA -ve (n=130) ACPA +ve (n=60) ACPA -ve (n=27) ACPA +ve (n=88)

Citrullinated 14-3-3-η Antibodies Are Specific for Early and Established RA and Are Complementary to ACPA. Anthony Marotta1, Dirkjan van Schaardenburg1, Gilles Boire2, Desirée van der Heijde3, René Tervaert4, Maarten Boers4, C.F. Allaart4, Mairead Murphy4, Katherine A. Siminovich4 and WP Maksymowych4. 1Augurex Life Sciences Corp., 2; Leiden University Medical Center, Leiden, Netherlands, 3Academic Medical Center, Amsterdam, Netherlands, 4; University of Alberta, Edmonton, AB.

Background/Purpose: RF and ACPA are used for early diagnosis and in prediction models for the risk of RA development in arthralgia patients. There remains a high unmet need for biomarkers in the earliest stages of RA to assist with detection and prognosis to enable therapy initiation within the first 6–12 weeks of symptom onset. The 14-3-3-η serum protein and its corresponding auto-antibodies are early complementary markers to RF/ACP A. This study describes their expression and diagnostic utility as well as their complementarity to RF/ACPA in early RA.

Methods: 14-3-3-η plasma protein levels were measured on the Augurex ELISA and 14-3-3-η auto-antibody levels on the Meso-Scale-DISCO electro-chemiluminescent platform in 409 consecutive early RA patients (Reade cohort) according to the 2010 ACR/EULAR RA classification criteria. Patients were DMARD-naïve, had a rheumatologist-confirmed diagnosis, median symptom duration was 4 months, mean age was 54 years and 73% were female. For 14-3-3-η auto-antibody level determination, a composite score of six (6) peptides was generated. Peptides were selected based on their individual highest sensitivity for 100% specificity and their complementarity to maximize patient capture. An auto-antibody score of ≥380 U/ml was determined to be the best positive cut-off. Serum 14-3-3-η protein levels were previously determined in these subjects with a positive diagnostic cut-off of > 0.18 ng/ml. Positive baseline status for each of the 14-3-3-η markers and RF and ACPA were compared to examine the extent of early RA patient capture rate versus RF/ACPA.

Results: In the 409 patients, 67% (n=275) were positive for the 14-3-3-η protein with median (IQR) titres of 0.63 (0.10–5.13) ng/ml

14-3-3-η Early RA Biomarkers: Does Seronegative RA Exist? Dirkjan van Schaardenburg1, WP Maksymowych4, Maarten Boers4, C.F. Allaart4, Mairead Murphy4, Katherine A. Siminovich4, Anthony Marotta1. 1Reade, Amsterdam, Netherlands, 2University of Alberta, Edmonton, AB, 3Jan van Breemen Research Institute/Reade, Amsterdam, Netherlands, 4Augurex Life Sciences Corp., North Vancouver, BC.

Conclusion: RF, AAbs exist against 14-3-3-η native and citrullinated protein. Anti cit-14-3-3-η AAbs are expressed in early and established RA and complement ACPA as a diagnostic aid. Relative cit/arg AAb reactivity should be accounted for in citrullination assays to properly assess the burden of citrullination in RA.
and 77% (n = 313) were positive for 14-3-3 auto-antibodies with median (IQR) values of 527 (387–753) U/ml. RF and ACPA positive rates in this cohort were 63% (n = 259) and 69% (n = 282), respectively. 76% (n = 310) of patients were positive for one or both of RF and ACPA, 93% (n = 394) were positive for either of the 14-3-3 markers and 96% for any one of the four markers. This represents 23% more patients identified by 14-3-3 markers alone compared to RF/ACPA, and 27% more when the four markers are used together.

Combined 14-3-3 markers identify 93% of early RA patients compared to RF/ACPA alone at 76%. The combination of all four markers captures 96% of early RA patients which creates the opportunity to treat more patients within the therapeutic window and improve clinical outcomes.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 5; W. Maksymowycz, Augurex Life Sciences Corp, 5; M. Boers, Augurex Life Sciences Corp, 5; S. Turk, None; M. Murphy, Augurex Life Sciences Corp, 3; A. Marotta, Augurex Life Sciences Corp, 3.

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Increased Prevalence of Plasma Anti-Nuclear, Anti-SSA, and Connective Tissue Disease Associated Antibodies in African American Patients with Rheumatoid Arthritis. Rayford R. June¹, Douglas P. Landsittel², Bruce Rabín², S. Louis Bridges Jr. ³, CLEAR Investigators, TEAR Investigators, Thomas A. Medsger Jr. ¹ and Larry W. Moreland ¹. ¹University of Pittsburgh, Pittsburgh, PA, ²University of Pittsburgh, Center for Healthcare Research Data Center, Pittsburgh, PA, ³University of Pittsburgh Medical Center, Pittsburgh, PA, ⁴University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: African American (AA) patients with rheumatoid arthritis (RA) have been shown to have worse disability scores, increased disease activity scores, and reduced use of disease modifying anti-rheumatic drugs. The frequency of antinuclear antibodies (ANA) in Caucasian (CAU) RA has been reported, but ANA occurrence in AA RA patients is unknown. ANA positive CAU RA patients have an increased autoimmune genetic risk score and this phenotype is associated with coexistent Sjögren syndrome (SS). There is a high frequency of anti-SSA antibodies in SS. We hypothesized that AA RA patients have an increased frequency (compared to CAU RA patients) of ANA, anti-SSA, and other connective tissue disease (CTD) associated autoantibodies.

Methods: We assayed plasma samples from two published RA cohorts: (1) AA patients in the Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR II) and (2) CAU patients from the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial. All patients met the revised 1987 American College of Rheumatology classification criteria for RA. A total of 587 CLEAR and 390 TEAR samples were tested for ANA by indirect immunofluorescence (IIF) and the multiplex bead array (MBA) Bioplex 2200 ANA Screen. Differences in prevalence between AA and CAU RA patients was assessed using tests of proportions with chi-square and Fisher’s exact tests. Multivariable logistic regression was used to adjust results for age, sex, body mass index (BMI), race (AA vs. CAU), anti-CCP positivity, and the multiplex bead array (MBA) Bioplex 2200 ANA Screen. Differences in prevalence between AA and CAU RA patients was assessed using tests of proportions with chi-square and Fisher’s exact tests. Multivariable logistic regression was used to adjust results for age, sex, body mass index (BMI), race (AA vs. CAU), anti-CCP positivity, and the multiplex bead array (MBA) Bioplex 2200 ANA Screen.

Results: ANA by IIF was positive (≥ 1:80) significantly more frequently in AA RA patients (187/587 or 32%) compared with CAU RA patients (65/390 or 17%; p < 0.001). The pattern of nuclear staining among patients with a positive ANA significantly differed by racial/ethnic group (p < 0.001), with AA RA patients having higher frequencies of speckled staining (64% vs. 46%; p = 0.001) where as CAU RA patients had higher frequencies of nucleolar staining (10% vs. 3%; p = 0.03). Anti-SSA was detected in twice as many AA RA patients (80/587 or 14% vs. 22/390 or 6%; p < 0.001). Systemic lupus associated antibodies (anti-Sm, anti-RNP, anti-Sm/RNP, and anti-Chromatin) were also higher in this population (see Table 1). Higher prevalence of ANA and anti-SSA remained significant (p < 0.001) after adjustment. In the AA RA patients, logistic regression showed only RF was associated with ANA and anti-SSA without previous TNF use or disease duration significant.

Conclusion: We found that the prevalence of ANA, anti-SSA, and other CTD associated autoantibodies is higher in AA RA patients than in a CAU RA cohort. The increase in ANA prevalence is greater than the published difference in ANA by race (15% vs. 3%) and suggests the existence of a meaningful serological subset of AA RA patients beyond the currently recognized serologic subsets identified by RF and anti-CCP antibodies.

Table 1

<table>
<thead>
<tr>
<th>AA % Positive</th>
<th>CAU % Positive</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>ANA IIF (≥1:80)</td>
<td>31.9</td>
<td>16.7</td>
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<tr>
<td>SSA</td>
<td>13.6</td>
<td>5.6</td>
</tr>
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<tr>
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<tr>
<td>Sm</td>
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<td>RNP</td>
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In Early Rheumatoid Arthritis, the Multi-Biomarker Disease Activity Score at Different Time-Points Is Predictive of Subsequent Radiographic Progression. Karen Hambardzumyan¹, R.J. Bolce², Saedis Saevardsdottir³, Kristina Forslund⁴, Ingemar F. Petersson⁵, Pierre Geborek⁶, Eric H. Sasso², David Chernoff², Scott Cruckshank⁷ and Ronald F. van Vollenhoven⁸. ¹the Karolinska Institute, Stockholm, Sweden, ²Crescendo Bioscience Inc., South San Francisco, CA, ³Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, ⁴Karolinska Institutet, Stockholm, Sweden, ⁵Lund University, Lund, Sweden, ⁶Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, ⁷Scott Cruckshank and Associates, Inc., Santa Barbara, CA, ⁸Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The prediction of radiographic progression in early rheumatoid arthritis (eRA) patients is important for optimal treatment. We previously demonstrated that a multi-biomarker disease activity (MBDA) score (Vectra DA®) at baseline (BL) was predictive for radiographic progression over the first year of treatment of eRA patients from the Swedish Faracochemistry (SWEFOT) trial. The objective of this study was to evaluate the MBDA score, at different time-points and its change during treatment, as a predictor of radiographic progression over the first two years of treatment in eRA patients.

Methods: The analyses were performed on radiographic progression of patients from the SWEFOT trial, assessed by van der Heijde modified Sharp scores (SHS) from BL to years 1 and 2 (n = 220) and from Year 1 to Year 2 (n = 133); and on the MBDA and disease activity scores (DAS28) and C-reactive protein (CRP) at BL (n = 220), Month 3 (n = 220) and Year 1 (n = 133). Radiographic progression was defined as SHS ≥ 5, Mann-Whitney U and Chi-square tests were used for comparisons of disease activity measures between progressors and non-progressors, and for determining significance of proportion of radiographic progressors.

Results: The median values for year 1-progressors (n = 41) and non-progressors (n = 179) were MBDA score, 70 and 58 (p = 0.001); CRP (mg/L) 28 and 18 (p = 0.049); and DAS28, 6.1 and 5.7 (p = 0.136), respectively. After 3 months of MTX therapy the corresponding values were 48 and 40 (p = 0.001), 9 and 9 (p = 0.213), and 4.8 and 4.0 (p = 0.009), respectively. At BL, 3 months and 1 year, patients with low MBDA score had a lower mean score and a smaller proportion of subsequent radiographic progressors than those with low CRP or low DAS28 (table).

The highest risk for progression from BL to year 1 or 2 (25% and 41%, respectively), or from year 1 to year 2 (32%), was observed among patients with high MBDA score at BL which remained high at 3 or 12 months. In contrast, much lower risk of radiographic progression from BL to year 1 and 2 was detected among those patients whose BL high MBDA score dropped to low by month 3 (6% and 18% respectively) and very low risk of radiographic progression from Year 1 to Year 2 was among those patients who achieved low MBDA score by month 12 (4%). All patients with persistent low MBDA score throughout 1 year did not progress radiographically over 2 years. Those who had a moderate MBDA score at BL and achieved low MBDA at months 3 or 12 did not progress either.
Conclusion: MBDA scores at BL and at 13 months of treatment as well as change in MBDA category were predictive of subsequent radiographic progression during up to 2 years. At all measured time points, having a low MBDA score was associated with low risk for subsequent radiographic progression.

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Differential Relative Contribution of Individual Components on DAS28 over Time: An Analysis from the Prospective, Observational, Biological Treatment Registry Across Canada. Denis Choquette1, Dalton Sholter2, Isabelle Fortin1, Michael Starr3, Carter Thorne5, Milton Baker4, Regan Arendse1, Philip Baer4, Michel Zumz2, Jude Rodrigues4, Maqbool Sheriff1, Emmanuel Ramakapikas1, John S. Sampalis5, Francois Nantel13, J. S. Sampalis5, None; J. E. Sasso, Crescendo Bioscience, 4; Crescendo Bioscience, 3; A. Otawa, Crescendo Bioscience, 4; Crescendo Bioscience, 3; P. Criscuoli, Crescendo Bioscience, R. van Vollenhoven, AbbVie, BMS, GSK, Pfizer, Roche, UC, 2; AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UC, Vertex, 5.

Background/Purpose: DAS28 is an important outcome for clinical research and practice assisting with therapeutic decisions. The main contributors to DAS28 are joint tenderness and acute-phase reactants. A simulation analysis showed that, due to its logarithmic transformation in the DAS28 formula, the ESR contribution is greater in the lower than in the higher DAS28 range. This analysis assessed the relative contribution of individual DAS28 components and examined its clinical properties in rheumatoid arthritis (RA) patients treated with infliximab in a Canadian real-world setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after treatment with a biologic for <6 months (M). RA patients treated with infliximab between 2002–2012 and with ≤60M of follow-up were included. The association between treatment duration and parameter improvement was assessed using linear regression. Slope correlation was assessed with the Pearson's correlation coefficient.

Results: 832 patients evaluated over 4,002 visits were included. Longer treatment duration was associated with significant (P < 0.001) improvements in DAS28, TJC28, SJC28, PtGA, ESR, and CRP. Correlation analysis of the rate of change over time showed a high correlation (0.7–0.9) of DAS28 with TJC28, SJC28, and PtGA but low correlation with ESR (r = 0.418) and CRP (r = 0.111).

Overall, the relative contribution of TJC28, SJC28, PtGA, and ESR in DAS28-ESR was 22%, 9%, 12%, and 57%, respectively. For DAS28-CRP, the relative TJC28, SJC28, PtGA, and CRP contributions were 25%, 10%, 12%, and 20%. Over 60M of treatment, the mean relative contribution of TJC28 (M0:31%, M60:17%), SJC28 (M0:15%, M60:5%), and PtGA (M0:15%, M60:9%) significantly (P < 0.001) decreased whereas the weight of ESR contribution increased (M0:39%, M60:69%). Similar results were obtained with DAS28-CRP although the CRP contribution was lower compared to ESR.

Increased DAS28-ESR was associated with higher relative contributions (per unit of DAS28-ESR increase) of TJC28 [parameter estimate (B) = 5.3], SJC28 (B = 2.1), and PtGA (B = 0.7) but lower ESR contribution (B = −8.1). Similarly, increased DAS28-CRP was associated with lower relative CRP contribution (B = −2.0).

Conclusion: This analysis shows that TJC28 and acute-phase reactants have a greater weight than SJC28 and PtGA within DAS28. Furthermore, the relative contribution of acute-phase reactants is greater with lower DAS28, due to their logarithmic nature. These findings suggest that biologic variability and variability in laboratory techniques may have significant impact on classifying remission or DAS28 changes among patients with low DAS28 and on therapeutic plan changes.

Disclosures: D. Choquette, Notre-Dame Hospital, Quebec, Canada, 3; AbbVie, 5; Amgen, 5; Celgene, 5; BMS Canada, 5; Janssen-Pharmaceutica Product, L.P., 5; Pfizer Inc., 5; D. Sholter, Janssen Inc., 5; I. Fornt, Janssen Inc., 5; M. Starr, Janssen Inc., 5; C. Thorne, Janssen Inc., 5; M. Baker, Janssen Inc., 5; R. Arendse, Janssen Inc., 5; P. Baer, Janssen Inc., 5; M. Zummer, Janssen Inc., 5; J. Rodrigues, Janssen Inc., 5; M. Sheriff, Janssen Inc., 5; E. Ramakapikas, None; J. S. Sampalis, None; F. Nantel, Janssen Inc., 5; J. A. Leham, Janssen Inc., 3; S. Otawa, Janssen Inc., 3; M. Shawi, Janssen Inc., 3.

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Soluble 4-1BB is a Marker of Joint Involvement and Disease Activity in Rheumatoid Arthritis. Morten Aagaard Nielsen1, Thomas Andersen1, Kristian Stengaard-Pedersen2, Kim Hoerslev-Petersen3, Merete Lund Hetland4, Peter Junker5, Miekkel OStergaard6, Malene Hv1 and Bent Deleuran1.

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Background/ Purpose: 4-1BB is induced on T cells after antigen encounter and promotes clonal expansion and accumulation of high numbers of antigen-specific effector-type T cells primarily in the joint. This leads to survival of CD4 T cells and CD8 T cells and enhance TCR-dependent activities such as cytokine production. 4-1BB has previously been linked to rheumatoid arthritis (RA). We examined the role of 4-1BB in early treatment naïve RA (eRA, the OPERA cohort) and chronic RA (cRA).

Methods: Soluble 4-1BB was measured by ELISA in plasma from 77 treatment naïve eRA patients (disease <3 months), at baseline, after 3 months, and after 12 months of treatment in addition to age and gender matched healthy volunteers (HV) (n=54). Treatment was methotrexate + placebo (MTX) (n=41) or MTX + Adalimumab (ADA) (n=36). Clinical disease was assessed by: DAS28, CRP, number of swollen (SJ40) and tender joints (TJ40), IgM-RF and ACPA. In addition s4-1BB was also measured by ELISA in both plasma and synovial fluid (SF) from 8 cRA patients (disease duration >6 years (24 (7–48) years) with active disease.

Membrane bound 4-1BB was measured on peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC) by flow cytometry in cRA, and in PBMC from HV (n=9). Paired samples were compared with Wilcoxon signed rank test, non-paired samples by Mann-Whitney rank sum test. Correlations were tested using Spearman’s rho (r).

Data are expressed as median (IQR).

Results: In eRA plasma levels of s4-1BB were significantly elevated at baseline (9.8 (4.0–23.0) pg/ml compared with HV (4.0 (4.0–4.9) pg/ml) (P < 0.01). After 12 months treatment 4-1BB levels were similar to levels in HV. No differences were seen in the s4-1BB plasma levels over time between the ADA and MTX group. We observed correlation with baseline s4-1BB with SJ40 (r = 0.3) and DAS28 at 24 month (r = 0.3) (both p<0.05). A significant association with the presence of IgM-RF was observed.

In cRA patients significantly elevated levels were measured in the SF (102 (44.9–134.4) pg/ml compared with plasma (5.24 (3.91–40.3) pg/ml) (P < 0.01). Further, plasma s4-1BB showed a strong correlation with the corresponding levels in the synovial fluid. (r=0.7, P<0.01).

In cRA the expression of 4-1BB on the total number of T cells was significantly higher in SFMCs (4.12% (2.24–12.52) % compared with PBMCs (1.55% (0.93–3.57) %) and PBMCs from HV (0.91 (0.53–2.35) %)
In Early Rheumatoid Arthritis Patients with Non-Response to Methotrexate Monotherapy the Change in Multi-Biomarker Disease Activity Score Is Differentially Associated with Subsequent Response to Non-Biological Versus Biological Therapy. Karen Hambardzumyan1, R.J. Bolce2, Saedis Saevardottir3, Kristina Forslind4, Ingemar F. Petersson5, Pierre Geborek6, Eric H. Sasso2, David Chernoff2, Ronald F. van Vollenhoven7, 1The Karolinska Institute, Stockholm, Sweden, 2Creando Biotech, San Francisco, CA, 3Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 4Karolinska Institute, Stockholm, Sweden, 5Lund University, Lund, Sweden, 6Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, 7Scott Cruickshank and Associates, Inc., Santa Barbara, CA, 8Unit for clinical therapy research ClinFrid, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: For patients with early RA (eRA), methotrexate (MTX) is recommended as first-line treatment and in non-responders both the addition of conventional non-biological disease modifying anti-rheumatic drug therapy (triple DMARD therapy) and of biological (anti-TNF) therapy are supported by data. Identification of patients with a higher likelihood of responding to one or the other of these options would lead to more personalized medicine and an increased effectiveness of therapy. The objective of this study was to evaluate the change in the multi-biomarker disease activity (MBDA) score (Vectra DA®) during MTX monotherapy as a predictor of response to subsequent non-biological triple versus biological therapy.

Methods: Patients with eRA and DAS28 >3.2 entered the Swedish Farmacotherapy (SWEFOT) clinical trial and received MTX monotherapy for 3 months, at which time clinical non-responders (DAS28 >3.2) were randomized to receive non-biological triple DMARD therapy (arm A) or anti-TNF (infliximab) therapy with MTX (arm B). For this study, 62 responders and 129 non-responders at month 3 (n=62 from arm A and n=67 from arm B) were analyzed by MBDA score at baseline (BL) and month 3. The assessment of changes in the MBDA score (ΔMBDA) from BL to month 3 as a predictor for response (according to DAS28 and EULAR response criteria) to triple or anti-TNF therapy at year 1 was done by defining small (≥60), medium (7–20) and large (>20) decreases by tertiles. Small and moderate decreases were combined together (small/moderate) and compared versus large decreases for arms A and B. The proportion of patients in arm A versus arm B with response at year 1 was evaluated by the odds ratio (OR) for patients with small/moderate versus large decreases. Homogeneity of the odds ratios between the two cohorts was assessed by Breslow-Day test.

Results: The mean (median) decreases in MBDA score from BL to month 3 for year 1 responders (n=66) and non-responders (n=63) were 12.9 (10) and 10.8 (9), respectively (p=0.431), and Month 3 mean (median) MBDA scores were 47.1 (45) and 50.3 (47), respectively (p=0.336). Of patients who had small/moderate decreases in MBDA score during MTX monotherapy, 43% responded to subsequent triple therapy and 57% responded to anti-TNF (OR=0.577). In contrast, among patients with a large decrease in MBDA score, 67% responded to triple therapy and 37% to anti-TNF treatment (OR=3.33). Thus the relative treatment effect of arm A versus arm B differed according to the degree of change in the MBDA score from BL to 3 months (p=0.032). Similarly, good EULAR response was achieved by the majority (67%) of patients from arm A, who had large decrease in MBDA score and also the majority (57%) of patients from arm B, who had small/moderate decrease of the MBDA score.

Conclusion: Among patients with early RA who did not achieve low disease activity on MTX monotherapy, those patients with the greatest decrease in MBDA score were more likely to respond to triple therapy whereas patients with lesser decrease of the MBDA score were more likely to respond to anti-TNF therapy. These findings suggest that in MTX non-responders, the changes in MBDA score may help guide subsequent therapy.
Validation of Snapshot, a Rheumatoid Arthritis Assessment Tool, Against CDAI, DAS28 (ESR), and DAS28 (CRP) in Canadian Patients with Rheumatoid Arthritis. William G Bensen1, Wynn Bensen2, Melissa Deamude3, Cynthia Mech4, Robert Bensen5, Arthur N. Lau6 and Alpesh Shah2. 1St Josephs Hospital and McMaster University, Hamilton, ON, 2Rheumatology Health Team, Dr. Bensen’s Rheumatology Clinic, Hamilton, ON. 3Division of Rheumatology, McMaster University, Hamilton, ON, 4MSc in Clinical Epidemiology, University of Western Ontario, London, ON.

Background/Purpose: Measuring disease activity in Rheumatoid Arthritis (RA) remains an elusive goal. Both DAS and CDAI have an inherent weakness because similar numbers can result from dissimilar clinical situations. Snapshot, a hands-on immediate clinical tool, shows where a patient stands with SJC, TJC, MD and Patient Global, and visualizes the discrepancies between MD and patient assessments. We have validated Snapshot Traditional (SS-T) (SJC-PtGlobal, TJC-PtGlobal, MD-PtGlobal), Snapshot MD (SS-M) (SJC-MD global) and Snapshot Patient (SS-P) (TJC-Pt, global) to DAS28 (ESR), DAS28 (CRP) and CDAI in 96 Canadian RA patients, at onset, and disease control.

Methods: We validated Snapshot (SS-T, SS-M and SS-P) in data from 96 patients of active RA using SAS version 9.3. The Snapshot scores were validated against DAS28 (ESR), DAS28 (CRP) and CDAI scores. We used Pearson correlation coefficients to assess the correlation (r) and ordinary linear regression analysis to estimate regression coefficients (β) between Snapshot and other measures (DAS28 and CDAI). We also assessed the extent of agreement between Snapshot and other measures DAS28 using Bland-Altman plots.

Results: The results revealed direct significant linear correlation of Snapshot with DAS28 and CDAI (r = 0.83 with DAS28 (ESR), 0.92 with DAS28 (CRP), 0.94 with CDAI for SS-T, r = 0.82 with DAS28 (ESR), 0.91 with DAS28 (CRP), 0.91 with CDAI for SS-P and r = 0.70 with DAS28 (ESR), 0.79 with DAS28 (CRP), 0.89 with CDAI for SS-M). In a linear regression model with DAS28 (ESR) as a predictor, regression coefficients (β) were 1.33 (p < 0.001), 0.98 (p < 0.001) and 1.27 (p < 0.001) for SS-T, SS-M and SS-P respectively with good model fit. Bland-Altman plots showed high degree of agreement between Snapshot and DAS28 (ESR) with 96.7% (SS-M) and SS-P respectively with good model fit. Bland-Altman plots showed high degree of agreement between Snapshot and DAS28 (ESR) with 96.7% (SS-T), 96% (SS-M) and 95.6% (SS-P) of the observations of the difference between Snapshot and DAS28 lying between mean±2SD. Similar results were observed for change score data (for disease control).

Conclusion: All Snapshots (SS-T, SS-M, SS-P) validated well with DAS28 and CDAI in measuring RA disease activity with the benefit of one second visual recognition for patient and MD at the clinical visit and without calculation. The discrepancy between MD and patient values is obvious and prompts an alternative therapeutic decision. Some patients understated their disease as compared to their SJC and need more RA therapy, while others overstate because of soft tissue pain, or depression. We prefer Snapshot Traditional. Snapshot offers an immediate and validated clinical tool for doctors and patients allowing better understanding of disease activity and need for therapeutic intervention.

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Double Positivity of RA Serologies More Prevalent Yet Associated with Clinical Response in Ethnic Minority Patients with Rheumatoid Arthritis. Mercedes Quinones1, Sharon Dowell1, Ignacio Garcia-Valladares2, Gail S. Kerr4, Christopher Swearingen3, Luis R. Espinoza6, Yusuf Yazici2, Edward L. Treadwell8, Theresa Lawrence Ford6, Yvoone Sherre7, Angelia Mosley-Williams11, Rodolfo Perez Alamin612, Chunqiao Luo13, Aguun Ince114, Adrian Godoy2 and John Amatruda3. 1Howard University Hospital, Washington, DC, 2Howard University, Washington, DC, 3Hospital General de Occidente, Zapopan, Jal., Mexico, 4Washington DC VAMC, Georgetown and Howard University, Washington, DC, 5University of Arkansas, Little Rock, AR, 6LSU Medical Center, New Orleans, LA, 7New York University School of Medicine, New York, NY, 8East Carolina University, Greenville, NC, 9North Georgia Rheumatology Group, PC, Lawrenceville, GA, 110Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, 111Detroit VAMC, Detroit, MI, 112LSUHSC, New Orleans, LA, 113University of Arkansas for Medical Sciences, Little Rock, AR, 114St. Louis University, St. Louis, MO.

Double Positivity of RA Serologies More Prevalent But Associated with Clinical Response in a Diverse Ethnic Cohort with Rheumatoid Arthritis

Background/Purpose: The presence of both the anti-citrullinated peptide antibody (ACPAs) and a rheumatoid factor (RF) are associated with RA disease severity and portend a poor prognosis. Whether ethnic minorities differ in the prevalence of RA-related serologies from Caucasian RA counterparts is unknown, as is their role as determinants of a clinical response in this patient subset.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with at least one follow up visit were evaluated. Comparisons of demographic (age, gender, race, education, smoking), RA disease status (RF, ACPA, nodules/erosions), RA treatment (prednisone, DMARD, biologics) variables amongst ethnic subsets were made as well as frequencies of clinical response (D MDHAQ – 0.3 and D RAPID3 –3.6) from baseline. Baseline differences between ethnic subsets were compared using Chi-square for categorical and Kruskal-Wallis for continuous variables. Logistic regression associating outcome at follow up and between ethnic subsets were estimated, adjusting for age, smoking, race, education, baseline RAPID3, and double positivity of RA-related serologies.

Results: Follow up visits in 671 EMRAC patients provided data for analyses (Table). African American patients were older (p=0.02), and had longer follow up compared to either Caucasians or Hispanics (p<0.001). Either a positive ACPA (60%, 46.3% vs 14.3%, respectively, p<0.001) or RF (79.6%, 71.7%, respectively vs 42.1%, p<0.001) were more frequent in AA and Hispanics versus Caucasian patients. In patients who were double positive, the odds ratio for a clinical response was 2.7 (95% CI 1.37, 5.35) for MDHAQ and 3 fold (95% CI 1.37, 6.76) for RAPID3. There was a greater frequency of both ACPA+/RF+ in ethnic subsets who had a clinical response in both MDHAQ (AA 57.9%, Hispanics 46.9% vs Caucasian 16.7%) and RAPID3 (AA 64.9%, Hispanic 55% vs Caucasian 17.9%). Hispanic patients with RF+/ACP- had a 67% increased odds of a RAPID response compared to Caucasians and 8% to AA, while AA had a 55% increase in odds for clinical response compared to Caucasians – but none achieving statistical significance.

Conclusion: In a diverse cohort, double positivity of RA-related serologies while more prevalent, are associated with increased odds of a clinical response regardless of ethnicity.

RAPID3 Outcomes by Race and Double Positive RA Serology Status

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>HAQ Response</th>
<th>African-American</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF-ACP-</td>
<td>40 (66.7%)</td>
<td>15 (15.8%)</td>
<td>11 (34.4%)</td>
<td></td>
</tr>
<tr>
<td>RF+ACP-</td>
<td>10 (16.7%)</td>
<td>20 (21.1%)</td>
<td>5 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>RF-ACP+</td>
<td>0 (0%)</td>
<td>5 (5.3%)</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>RF+ACP+</td>
<td>10 (16.7%)</td>
<td>55 (57.9%)</td>
<td>15 (46.9%)</td>
<td></td>
</tr>
<tr>
<td>RAPID Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF-ACP-</td>
<td>27 (69.2%)</td>
<td>11 (19.3%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>RF+ACP-</td>
<td>4 (10.3%)</td>
<td>6 (10.5%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>RF-ACP+</td>
<td>1 (2.6%)</td>
<td>3 (5.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>RF+ACP+</td>
<td>7 (17.9%)</td>
<td>37 (64.9%)</td>
<td>11 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

1. seropositive (rheumatoid factor positive (RF+)/H11001 Analyses were adjusted for age, sex, symptom duration, and smoking status seronegative (RF−/ACPA-) and 3. missing ACPA (RF negative [RF−]).

T. Lawrence Ford, 2, Bristol-Myers Squibb, 2, Pfizer Inc, 2; E. L. Treadwell, 5, Celgene, 5; R. Perez Alamino, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol-Myers Squibb, 2, A. Morey, Williams, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol-Myers Squibb, 2; R. Perez Alamino, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol-Myers Squibb, 2; C. Luo, None; A. Inc. Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol-Myers Squibb, 2; A. Godoy, None; J. Amatruda, None.

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Background/Outcome: The aim of this study was to determine if failure to perform ACPA testing could cause a care gap.

Methods: 2,191 patients recruited to CATCH were allocated to 3 groups: 1. early treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or DMARDs, 2. early treatment with DMARDs (NSAIDs or methotrexate (P<0.00002), but there were no significant differences in DAS28, HAQ-DI, proportion receiving corticosteroids, or physician/patient global assessments. See Table for full results.

Conclusion: Patients with missing ACPA were less likely to fulfill RA criteria and were treated differently with fewer medications but had similar outcomes at 3 months. Cost-effectiveness of ensuring ACPA testing availability in suspected RA is unknown. Imputed data did not alter results. There could be a care gap in the unknown ACPA group who were RF negative, but there were no significant differences in DAS28, 3 month change in DAS28, or HAQ-DI despite less treatment. We cannot determine whether performing ACPA in RF positive suspected ERA adds value as we combined the seropositive group into any seropositive result. The cost effectiveness of performing ACPA in RF negative patients could be debated if early RA is already suspected.

Total 2191 1276 (58.2) 497 (22.7) 225 (10.3) N/A
Number of Participants (N)
Baseline 3 months 1745 1062 (60.9) 359 (20.6) 171 (9.8) N/A
Age, mean ± SEM 53.04 ± 0.34 51.61 ± 0.44 54.04 ± 0.67 55.58 ± 0.80 0.000009*
Rheumatoid factor serology at baseline, no. (%) 1110 (50.7) 813 (37.1) 268 (12.2) N/A
Anti-CCP serology at baseline, no. (%) 736 (33.6) 724 (33.0) 731 (33.4) N/A
Female, no. (%) 1445 (72.6) 958 (75.5) 336 (76.7) 151 (67.4) 0.0007*
Symptom duration at baseline, mean ± SEM (months) 6.04 ± 0.08 6.24 ± 0.11 5.89 ± 0.18 5.62 ± 0.26 0.0008*
Swollen joint count (ACR 20, no. ± SEM) 7.23 ± 0.14 7.05 ± 0.17 7.44 ± 0.30 7.74 ± 0.38 0.19
RSI, mean ± SEM 0.96 ± 0.03 1.00 ± 0.02 0.98 ± 0.03 0.97 ± 0.05 0.57
Baseline 3 months 0.63 ± 0.16 0.61 ± 0.02 0.67 ± 0.04 0.66 ± 0.07 0.12
Mean days (N)
Baseline 3 months 1569 (78.8) 1138 (89.7) 293 (59.0) 138 (61.6) 0.00001*
On Methotrexate, no. (%) 1296 (64.9) 889 (69.7) 253 (56.9) 124 (55.1) 0.00001*
Baseline 3 months 1194 (75.0) 830 (78.2) 250 (69.6) 114 (66.7) 0.0002*
Number of DMARDs, mean ± SEM 1.31 ± 0.02 1.41 ± 0.02 1.17 ± 0.04 1.05 ± 0.05 0.00001*
Baseline 3 months 1.60 ± 0.02 1.67 ± 0.03 1.51 ± 0.05 1.36 ± 0.06 0.00001*
On cortico- steroid, no. (%) 966 (48.3) 614 (48.1) 234 (47.1) 111 (52.4) 0.40
Baseline 3 months 559 (35.1) 370 (34.8) 133 (37.0) 56 (32.7) 0.59

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Diagnostic Accuracy and Associated Costs of Rheumatoid Factor Testing in Primary Care: A Population-Based Cohort Study in Spain. Raashid Luqmani, Kiara Morsley, Anne Miller, Christopher J. Edwards, M. Kasmim Javid, Daniel Prieto-Alhambra, Rafael Pinedo-Villanueva, Manuel Medina Peralta, Sebastian Calero Munoz, Nigel Arden, Francesca Fina-Aviles and Cyrus Cooper.


Background/Outcome: To assess the sensitivity, specificity, and predictive values of rheumatoid factor (RF) as a test for rheumatoid arthritis (RA) in primary care, and to estimate the costs associated with the use of RF in primary care settings.

Methods: Design: a retrospective cohort study using electronic data from the Information System for the Development of Research in Primary Care (SIDIPAD database), which contains the complete primary care records and laboratory results of more than 5 million people (over 80% of the population) in Catalonia, Spain.

Setting: primary care. Participants: patients aged 18 or above registered in the SIDIPAD database with at least one RF test performed between 01/01/2006 and 31/12/2011, excluding those who had a diagnosis of RA at the start of the study period. Outcome measures: RA diagnosis (as coded in medical records) within the first year after RF testing, and cost of RF testing per case of RA.

Results: 495,434 patients out of an eligible 4,766,498 (10.3%) people were tested for RA at least once during the study period. 107,362 (21.7%) were sero-positive of which 2,768 (2.6%) of these were diagnosed with RA in the following year. Similarly, 1,414,388,072 (3.3%) sero-negative participants were subsequently diagnosed with RA. RF testing had a sensitivity of 70.8% (95% CI 69.4 to 72.2), specificity 78.7% (78.6 to 78.8), and positive and negative predictive values of 2.6% (2.5 to 2.7) and 99.7% (99.6 to 99.7) respectively. An estimated €3,963,472 was spent on RF testing in the duration of the study, with a cost of €1,432 per true positive case.
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Biomarkers of Cardiac Dysfunction and Inflammation in Plasma Predict Occult Coronary Plaque Burden and Composition in Rheumatoid Arthritis. George A. Karpouzas1, Joel Estis2, John Todd2 and Matthew Budoff1. 1Habor-UCLA Medical Center, Torrance, CA, 2Singulex, Alameda, California, Alameda, CA.

Background/Purpose: Rheumatoid arthritis (RA) is associated with accelerated coronary atherosclerosis, myocardial infarction, and mortality. We previously reported a higher prevalence, severity, and different composition of occult coronary plaque in patients with RA compared to age and gender matched non-rheumatic disease controls (NRD). We now explore whether various plasma inflammatory biomarkers, or their combinations, predict occult coronary plaque presence, various burden outcomes, and composition in the same cohort of patients with RA.

Methods: One hundred and fifty RA subjects without symptoms or prior diagnosis of cardiovascular disease underwent 64-slice computed tomography angiography (CTA). Coronary artery calcium score (CAC), segment involvement score (SIS- n of segments with plaque), stenosis severity score (sum of segmental plaque burden- PBS) were computed. Plaques were further characterized as non-calcified (NCP), mixed (MP), or calcified (CP). High-sensitivity cardiac Troponin-I (cTnI) and inflammation (IL-6) may predict the presence, various burden outcomes, and composition score (SIS- n of segments with plaque), stenosis severity score (sum of segmental plaque burden- PBS) were computed. Plaques were further characterized as non-calcified (NCP), mixed (MP), or calcified (CP). High-sensitivity cardiac Troponin-I (cTnI) and inflammation (IL-6) may predict the presence, various burden outcomes, and composition score.

Results: Higher tertiles of cTnI correlated with plaque prevalence, as well as increasing CAC, SIS, and PBS (p-values 0.006, 0.005, 0.01, and 0.009 respectively- not shown). IL-6 and cTnI independently and individually predicted various plaque parameters after age and gender adjustments (model 1, table 1). The combination of high CAC with high IL-6 predicted plaque burden after adjustments both for age and gender, as well as additional CRFs (model 2- table 1). Very high-risk plaque outcomes for future cardiac events (CAC >100, SIS >5, SSS >5, obstructive plaque, or composite outcome) were best predicted by cTnI alone. Similarly, cTnI was the only biomarker predicting presence of higher-risk NCP or MP [OR (95% CI) of 2.37 (1.13–4.94)]; however, significance was lost after age and gender adjustments [1.97 (0.92–4.24)].

Conclusion: In patients with RA, biomarkers of cardiac dysfunction (cTnI) and inflammation (IL-6) may predict the presence, various burden outcome severity, and composition of occult coronary plaque as evaluated by CTA. Their associations and prognostic implications for atherosclerosis deserve further evaluation.

Table 1. Multivariable analysis for remission of disease and progression of carotid plaques

<table>
<thead>
<tr>
<th>Events at month 12</th>
<th>Factors*</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-TnI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC (&gt;0 vs. 0)</td>
<td>Unadjusted</td>
<td>2.5</td>
<td>(1.2–5.2)</td>
<td>1.7</td>
</tr>
<tr>
<td>CAC&gt;100 vs. ≤100</td>
<td>Model 1</td>
<td>7.5</td>
<td>(2.5–20.7)</td>
<td>6.0</td>
</tr>
<tr>
<td>SIS (&gt;0 vs. 0)</td>
<td>Model 2</td>
<td>2.6</td>
<td>(0.8–4.8)</td>
<td>2.3</td>
</tr>
<tr>
<td>SIS&gt;5 vs. SIS≤5</td>
<td></td>
<td>4.3</td>
<td>(1.2–13.6)</td>
<td>2.5</td>
</tr>
<tr>
<td>SSS (&gt;0 vs. 0)</td>
<td></td>
<td>2.8</td>
<td>(0.8–4.8)</td>
<td>2.3</td>
</tr>
<tr>
<td>SSS&gt;5 vs. SSS≤5</td>
<td></td>
<td>2.9</td>
<td>(1.1–7.7)</td>
<td>2.6</td>
</tr>
<tr>
<td>PBS (&gt;0 vs. ≤2)</td>
<td></td>
<td>3.6</td>
<td>(1.7–7.7)</td>
<td>3.2</td>
</tr>
</tbody>
</table>

**Number of event in the multivariate analysis after cases with unavailable data excluded, may be different from total number/percentage in the text.**
Evaluation of RAPID3 with Minimal Joint Count and ACR/EULAR Provisional Remission Definitions As Predictors of Future Good Radiographic + Functional Outcome in a Double-Blind, Phase 3, Randomized Controlled Trial of Tocilizumab. Martin J. Bergman1, Jeffrey Yourish2, Jinglan Pei3, Jenny Devenport4, William Reiss2, and Edward Keystone5. 1Taylor Hospital, Ridley Park, PA, 2Genentech, South San Francisco, CA, 3University of Toronto and Mount Sinai Hospital, Toronto, ON.

Background/Purpose: Based on treat-to-target guidelines, the goal of treatment should be remission. Definitions for remission recommended by the ACR/EULAR task force include joint counts and a laboratory test and were selected to predict later good radiographic and functional outcomes. 1 Despite these guidelines, rheumatologists still do not regularly measure disease activity. RAPID3, developed as a tool for monitoring disease activity, is advantageous because it requires only patient input. This analysis evaluated the performance of RAPID3 with minimal joint count (for physician input), compared with ACR/EULAR proposed remission definitions, to predict future good radiographic + functional outcome.

Methods: LITHE was a 5-year, double-blind, phase 3 study of tocilizumab (TCZ) in patients with moderate to severe RA who had inadequate responses to MTX therapy. 2 Patients were randomly assigned 1:1:1 to receive placebo + MTX, TCZ 4 mg/kg + MTX, or TCZ 6 mg/kg + MTX for 24 weeks, with an option to escape starting at week 16. Associations between various year 1 measures were evaluated against rates of good radiographic + functional outcome at year 2, specifically no worsening of Genant-Sharp Score (GSS) and HAQ-DI, and HAQ-DI ≤0.5. 1 Logistic regression was used to estimate odds ratio (OR), positive predictive value (PPV), negative predictive value (NPV), and sensitivity/specificity of the measures. Results: In total, 690 patients had sufficient 2-year data to evaluate year 2 outcome: 73% of patients had no worsening of GSS score, 58% had no worsening of HAQ-DI, 22% had HAQ-DI ≤0.5, and 15% met all 3 criteria. ORs with 95% confidence intervals (CIs) for all year 1 measures were >1, indicating that all were statistically significantly associated with year 2 outcome, though no one measure had superior association (p < 0.05 for all, overlapping 95% CIs for OR). NPV and specificity were high (≥80%), but PPV and sensitivity for all measures were low (range, 28–49% and 16–39%, respectively), which meant the measures could successfully identify patients who did not achieve the year 2 outcome but were not very good at identifying patients who achieved the outcome (Table).

Conclusion: Consistent with publications on other therapies/populations, 3 these results suggest the RAPID3 plus ≤1 joint count performed similarly to more complex measures. However, given that no single measure had especially high PPV or sensitivity, it is important that the patient be fully evaluated to understand what individual factors might contribute to his or her long-term prognosis.

References:

Table. Performance of Year 1 Measures for Predicting Year 2 Outcome of Good Radiographic + Functional Outcome

<table>
<thead>
<tr>
<th>Year 1 Measure</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>n</th>
<th>PPV %</th>
<th>NPV %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPID3 ≤6 with SJC6 ≤1</td>
<td>3.461</td>
<td>2.098, 5.692</td>
<td>683</td>
<td>28.8</td>
<td>87.5</td>
<td>34.0</td>
<td>84.6</td>
</tr>
<tr>
<td>RAPID3 ≤3 with SJC6</td>
<td>3.973</td>
<td>2.182, 7.148</td>
<td>683</td>
<td>35.3</td>
<td>86.7</td>
<td>22.6</td>
<td>92.4</td>
</tr>
<tr>
<td>RAPID3 ≤6 with SJC6 ≤1</td>
<td>3.149</td>
<td>1.951, 5.068</td>
<td>681</td>
<td>28.5</td>
<td>87.9</td>
<td>38.7</td>
<td>82.1</td>
</tr>
<tr>
<td>RAPID3 ≤3 with SJC6 ≤1</td>
<td>4.257</td>
<td>2.403, 7.486</td>
<td>681</td>
<td>36.8</td>
<td>87.1</td>
<td>26.4</td>
<td>91.7</td>
</tr>
<tr>
<td>SDAI &gt; 3 only</td>
<td>3.956</td>
<td>2.230, 6.969</td>
<td>623</td>
<td>37.3</td>
<td>86.0</td>
<td>26.7</td>
<td>90.9</td>
</tr>
<tr>
<td>ACR/EULAR Boolean criteria only</td>
<td>5.246</td>
<td>2.539</td>
<td>687</td>
<td>47.4</td>
<td>86.4</td>
<td>17.0</td>
<td>96.6</td>
</tr>
</tbody>
</table>

Disclosure: J. Shen, None; Q. Shang, None; Y. Y. Leung, None; S. L. Yu, None; C. K. Wong, None; E. Li, None; T. Y. Zhu, None; L. S. Tam, None.
radiographic progression at Month 12 for the DMARD-naïve and MTX NR groups.

Table: Mean changes in disease activity measures from BL to 3 months for DMARD-naïve patients and from Month 3 to 12 months for MTX non-responders

<table>
<thead>
<tr>
<th>Response Measurement</th>
<th>CRP ≤1 mg/dL and MBDA ≤12</th>
<th>CRP ≤1 mg/dL and MBDA &gt;12</th>
<th>CRP &gt;1 mg/dL or MBDA &gt;24</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD-Naïve Patients</td>
<td>N=29</td>
<td>37</td>
<td>154</td>
</tr>
<tr>
<td>MBDA</td>
<td>−5.5</td>
<td>−11.9</td>
<td>−16.4</td>
</tr>
<tr>
<td>DAS28</td>
<td>−1.5</td>
<td>−1.6</td>
<td>−1.8</td>
</tr>
<tr>
<td>TJC</td>
<td>−5.2</td>
<td>−5.0</td>
<td>−4.6</td>
</tr>
<tr>
<td>SJC</td>
<td>−5.0</td>
<td>−5.9</td>
<td>−5.8</td>
</tr>
<tr>
<td>CDAI</td>
<td>−12.2</td>
<td>−12.9</td>
<td>−13.2</td>
</tr>
<tr>
<td>ΔSHS &gt;3 at Year 1 (%)</td>
<td>10%</td>
<td>35%</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MTX Non-responders</th>
<th>N=55</th>
<th>23</th>
<th>49</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBDA</td>
<td>−4.2</td>
<td>−15.4</td>
<td>−23.2</td>
<td>−20.7</td>
</tr>
<tr>
<td>DAS28</td>
<td>−1.1</td>
<td>−1.4</td>
<td>−2.0</td>
<td>−1.8</td>
</tr>
<tr>
<td>TJC</td>
<td>−3.0</td>
<td>−4.3</td>
<td>−4.0</td>
<td>−4.1</td>
</tr>
<tr>
<td>SJC</td>
<td>−3.3</td>
<td>−4.2</td>
<td>−6.7</td>
<td>−5.9</td>
</tr>
<tr>
<td>CDAI</td>
<td>−8.0</td>
<td>−10.5</td>
<td>−13.6</td>
<td>−12.6</td>
</tr>
<tr>
<td>ΔSHS &gt;3 at Year 1 (%)</td>
<td>24%</td>
<td>39%</td>
<td>53%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Conclusion: These analyses suggest that if a clinical trial of DMARD-naïve or MTX-NR patients with RA were to include patients with MBDA score >44 even though CRP was ≤1mg/dL, the number of eligible patients would be increased by 24% and 47%, respectively, compared with the conventional approach to enrollment based on CRP >1mg/dL alone, while maintaining clinical and radiographic outcomes.

Disclosure: R. F. van Vollenhoven, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 5, R. J. Bolce, Crescendo Bioscience, 3; K. Bardhuzmumyan, None; S. Saevarsdottir, None; K. Forslind, Abbvie, BMS, 9, I. Peterson, None; E. H. Sasso, Crescendo Bioscience, 3; C. Hwang, Crescendo Bioscience, 3; O. Segurado, Crescendo Bioscience, 3; P. Geborek, None.

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Fatigue Fluctuates Substantially over Time in Rheumatoid Arthritis Patients Despite Stable Disease Activity during Treatment with Biological Agents.

Emilie Lund Egsmose, Renee Cordtz and Ole Rintek Madsen. Copenhagen University Hospital Gentofte, Hellerup, Denmark.

Background/Purpose: Fatigue (FTG) is a symptom commonly reported by patients with rheumatoid arthritis (RA). Little is known about its nature and etiology. The number of studies including FTG as an outcome measure has increased rapidly during recent years and FTG is considered a potential marker of RA disease activity in the clinic (1). In order to judge whether a given change in any disease marker in the individual patient is due to “measurement error” or to real change it is essential to know how large the natural variation of the disease marker is when the disease activity is constant.

The purpose of the present study was to examine intra-individual FTG fluctuations in patients with stable RA during treatment with a biological agent.

Methods: 233 RA patients treated with a biological agent and with stable disease activity were identified in the Danish registry for biological treatment in rheumatology (DANBIO). Stable disease activity was defined as a change in DAS28-CRP ≤0.6 between two consecutive visits with complete clinical data sets available including FTG. Paired data from a single set of such two consecutive visits were extracted for each patient. Data comprised DAS28-CRP and its individual components, HAQ and global assessment of the patient (PaGl) and the physician (PhGl) as well as patient reported FTG scored on 0–100 visual analogue scales (VAS). Bland-Altman analyses were used to assess the lower and upper 95% limits of agreement between the two consecutive FTG assessments and the corresponding bias (the mean of individual differences). Associations between intra-individual inter-visit differences (Δ) in FTG and in other measures of disease activity were evaluated using Pearson’s linear correlation analyses and by stepwise multiple regression with ΔFTG as the dependent variable. A p-value ≤ 0.05 was considered statistically significant.

Results: Mean age was 60±15 years, female/male ratio 3.2, mean time from treatment start to the first visit 136.1±117.8 (range 0–485) weeks, mean inter-visit duration time 22.3 ± 27.6 weeks, mean DAS28-CRP 5.2 and mean FTG 43.3±27.6. Mean ΔDAS28-CRP was 0.0±0.3 (range −0.6 to 0.6) (NS). The bias for FTG was 0.9±21.8 (NS) and the lower and upper limits of agreement −35.9 and 37.7, respectively. No significant correlation was found between the absolute value of ΔFTG and the inter-visit duration time (r = 0.043, NS). ΔFTG was weakly correlated with ΔPaGl (r = 0.33, p < 0.01) and ΔPaGl (r = 0.39, p < 0.001) and were not significantly correlated with change in any other single measure of disease activity or ΔDAS28-CRP.

In a multiple regression analysis including Δ of all disease activity measures including DAS28-CRP as independent variables, ΔFTG was significantly predicted by only ΔPaGl (beta = 0.26, p < 0.001) and ΔPaGl (beta = 0.15, p < 0.05). No statistically significant difference in FTG or ΔFTG was found between males and females.

Conclusion: In individual RA patients, large fluctuations in FTG were observed over time although the disease activity was stable. If FTG is considered to reflect disease activity, changes in FTG less than approximately 35 on a VAS-scale may be interpreted as natural variation or pure measurement error.

Disclosure: E. L. Egsmose, None; R. Cordtz, None; O. R. Madsen, None.

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The Use of Week 12 CDAI, RAPID3 and DAS28(CRP) Responses to Predict Optimal Response to MethotreXate.

Gerd Burmester1, Gurjit S. Kacley2, Jeffrey R. Curtis3, Yusuf Yazici4, Benoit Guerette5, Xin Wang5, Alan Friedman2 and Vibeke Strand6. 1Charite ´ University Medicine, Berlin, Germany, 2University of Florida, Jacksonville, FL, 3University of Alabama at Birmingham, Birmingham, AL, 4New York University School of Medicine, New York, NY, 5AbbVie, Inc., North Chicago, IL, 6Stanford University, Palo Alto, CA.

Background/Purpose: The prediction of treatment outcomes based on early response could guide treatment decisions in patients (pts) with rheumatoid arthritis (RA). The objective was to determine if disease state at wk 12 in pts treated with a lower dose of methotrexate (MTX) + adalimumab (ADA), assessed by CDAI, DAS28(CRP) and RAPID3, was predictive of an SDAI response at a later time point, comparable to that achieved by pts receiving a high dose of MTX+ADA.

Methods: Data for this post hoc analysis originated from 2 randomized controlled trials. In CONCERTO, pts with early RA received ADA + 2.5, 5, 10 or 20 mg/wk MTX. In MUSICa, pts with moderate to severe RA and an inadequate response to MTX, received ADA + 7.5 or 20 mg/wk MTX. “Achievers” were defined as pts achieving optimal SDAI responses comparable to those in the top 40th percentile (pct) receiving 20 mg/wk MTX + ADA. For CONCERTO, achievers had SDAIs at wk 16 ≥ 5.5; wk 20 ≥ 5.0 and wk 26 ≥ 4.2; for MUSICa, achievers had SDAIs at wk 16 ≥ 5.4, wk 20 ≥ 5.1 and wk 24 ≥ 5.1. The following outcomes at wk 12 were compared in achievers vs non-achievers: CDAI, DAS28(CRP) and RAPID3. The likelihood of predicting optimal SDAI responses was assessed by ROC analysis using logistic regression with wk 12 CDAI, DAS28(CRP) and RAPID3 as predictors. Optimal ROC thresholds based on sensitivity and specificity, as well as those with satisfactory negative and positive predictive values (NPV, PPV), were calculated.

Results: In CONCERTO, 11/98 (11.2%), 10/100 (10%), 21/99 (21.2%) and 21/98 (21.4%) of pts receiving 2.5, 5, 10 and 20mg/wk MTX, respectively, were achievers; in MUSICa, 29/154 (18.8%) and 28/155 (18.1%) in 7.5 and 20 mg/wk MTX groups, respectively, were achievers. ROC-AUC, PPV and NPV indicated that wk 12 CDAI, DAS28(CRP) and RAPID3 were good predictors of optimal SDAI responses (table). Across selected thresholds, all three criteria provided good NPV for all MTX groups. In CONCERTO, non-achievers in CDAI remission/LDA at wk 12 achieved SDAI remission (≤ 3.3) or LDA (≤ 11) at wk 26; most pts in CDAI MDA or HDA at wk 12 did not. In MUSICa, in the 7.5 mg MTX treatment group, non-achievers in CDAI remission/LDA at wk 12 reached SDAI LDA (≤ 11) or MDA (11–26) at wk 24; 72.5% of pts in wk 12 CDAI MDA did not achieve optimal SDAI responses.
Table: AUC, PPV and NPV of wk 12 CDAI, RAPID3 and DAS28 (CRP) for prediction of optimal SDAI response

<table>
<thead>
<tr>
<th>MTX dose (mg/wk)</th>
<th>WK 12 criterion</th>
<th>Area under curve (95% CI)</th>
<th>ROC threshold</th>
<th>Sensitivity</th>
<th>1-specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONCERTO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>CDAI</td>
<td>0.907 (0.837, 0.977)</td>
<td>3.6</td>
<td>0.455</td>
<td>0.016</td>
<td>0.625</td>
<td>0.926</td>
</tr>
<tr>
<td>5*</td>
<td>CDAI</td>
<td>0.750 (0.692, 0.807)</td>
<td>7.3</td>
<td>0.700</td>
<td>0.100</td>
<td>0.704</td>
<td>0.956</td>
</tr>
<tr>
<td>10</td>
<td>RAPID3</td>
<td>0.873 (0.789, 0.952)</td>
<td>6.6</td>
<td>0.459</td>
<td>0.014</td>
<td>0.625</td>
<td>0.925</td>
</tr>
<tr>
<td>5*</td>
<td>RAPID3</td>
<td>0.807 (0.711, 0.902)</td>
<td>6.5</td>
<td>0.900</td>
<td>0.265</td>
<td>0.290</td>
<td>0.944</td>
</tr>
<tr>
<td>10</td>
<td>DAS28</td>
<td>0.870 (0.795, 0.952)</td>
<td>2.6</td>
<td>0.570</td>
<td>0.100</td>
<td>0.600</td>
<td>0.872</td>
</tr>
<tr>
<td>5*</td>
<td>DAS28</td>
<td>0.755 (0.598, 0.944)</td>
<td>2.6</td>
<td>0.700</td>
<td>0.167</td>
<td>0.667</td>
<td>0.944</td>
</tr>
<tr>
<td>10</td>
<td>RAPID3</td>
<td>0.765 (0.633, 0.897)</td>
<td>4.1</td>
<td>0.222</td>
<td>0.190</td>
<td>0.600</td>
<td>0.872</td>
</tr>
<tr>
<td>5*</td>
<td>CDAI</td>
<td>0.822 (0.570, 0.989)</td>
<td>4.1</td>
<td>0.222</td>
<td>0.190</td>
<td>0.600</td>
<td>0.872</td>
</tr>
<tr>
<td>20</td>
<td>0.940 (0.908, 0.977)</td>
<td>8.7</td>
<td>0.853</td>
<td>0.058</td>
<td>0.703</td>
<td>0.962</td>
<td></td>
</tr>
<tr>
<td>7.5*</td>
<td>RAPID3</td>
<td>0.758 (0.673, 0.850)</td>
<td>7.0</td>
<td>0.740</td>
<td>0.243</td>
<td>0.464</td>
<td>0.919</td>
</tr>
<tr>
<td>20</td>
<td>0.839 (0.734, 0.944)</td>
<td>3.4</td>
<td>0.444</td>
<td>0.077</td>
<td>0.000</td>
<td>0.885</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>DAS28</td>
<td>0.814 (0.740, 0.888)</td>
<td>2.7</td>
<td>0.338</td>
<td>0.059</td>
<td>0.000</td>
<td>0.640</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For CONCERTO, optimal SDAI response was SDAI at wk 16 $\leq$ 6.8, wk 20 $\leq$ 6.0 and wk 25 $\leq$ 4.2; for MUSICA, optimal SDAI response was SDAI at wk 20 $\leq$ 6.0 and wk 25 $\leq$ 4.1. ROC thresholds with NPV $\geq$ 0.8 and PPV $\geq$ 0.8 are presented, except for the groups indicated by the asterisk, where the optimal ROC cut-off is presented.

Conclusion: CDAI and RAPID3 are quick, convenient tools to assess treatment response, and correlated well with DAS28(CRP) as predictors of later outcome in the CONCERTO and MUSICA trials. In pts with early RA receiving lower doses of MTX, the achievement of remission of LDA targets at wk 12 was predictive of a subsequent optimal SDAI treatment response comparable to pts receiving higher MTX doses. Based on these data, pts in MDA/HDA at wk 12 might benefit from an adjustment of therapy.

Disclosure: G. Burmester, AbbVie, Pfizer, UCB, Roche, 2; AbbVie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5; AbbVie, BMS, Pfizer, Merck, UCB, Roche, 8; G. S. Kaheel, AbbVie, 5; J. R. Curtis, AbbVie, Amgen, Genentech, BMS, Janssen and CORRONA, 2, Genentech, UCB, Janssen, Amgen and CORRONA, 5; Y. Yazici, AbbVie, BMS, Celgene, Genentech, Horizon, UCB and Pfizer, 5; B. Guerreau, AbbVie, 1, AbbVie, 3; X. Wang, AbbVie, 1, A. Friedman, AbbVie, Inc., 1, AbbVie, Inc., 3; V. Strand, AbbVie, Affrent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iiroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, S1K, Sakeda, UCB, Vertex, 5.

What Level of Disease Activity at 6 Months Predicts Achieving or Sustaining Remission at 12 Months? Edward Keystone, 1, PhD; Birger Baer, 2, Boulos Hararou, 2, J Antonio Avina-Zubieta, 2, Andrew Chow, 3, Dalton Sholter, 4, Denis Choquette, 5, Emmanouil Rampakakis, 6, John S. Sampalis, 7, Francois Nantel, 1, Allen J Lehman, 9, May Shawi, 9 and Susan Otawa, 9. 1Mount Sinai Hospital, University of Toronto, Toronto, ON, 2Private Practice, Scarborough, ON, 3University of Montreal Hospital Centre, Montreal, QC, 4University of British Columbia, Department of Experimental Medicine, Vancouver, BC, 5McMaster University, Hamilton and Credit Valley Hospital, Mississauga, ON, 6University of Alberta, Edmonton, AB, 7Institut de rhumatologie de Montréal (IRM), Montréal, QC, 8JSS Medical Research, Montreal, QC, 9Janssen Inc., Toronto, ON.

Background/Purpose: Achievement of clinical remission in rheumatoid arthritis (RA) is a process that may take several months. Identification of clinical signs predicting future remission may assist physicians in clinical decision making. The aim of this analysis was to describe the association between DAS28-ESR score at 6 months and the likelihood of achieving remission at 12 months in a real-world, clinical practice setting.

Methods: BioTRAC is an ongoing, prospective Canadian registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with IFX or golimumab as first biologics or after having been treated with a biologic for $<6$ months. Eligible patients for this analysis included RA patients treated with IFX who were enrolled between 2002 and 2012 and had available DAS28 data at 6 and 12 months of follow-up. The association between DAS28-ESR score at 6 months and remission achievement at 12 months was assessed with logistic regression. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off points for achieving and maintaining remission.

Results: A total of 293 patients were included with a mean (SD) age of 56 (13.5) years and disease duration of 10.0 (9.7) years. Mean (SD) DAS28 was 3.8 (1.5) and 3.5 (1.5) at 6 and 12 months, respectively, and the percent with DAS28-ESR remission was 24.6% and 27.0%. Of the patients in remission at 6 months, 65.3% sustained the remission at 12 months, while of those not in remission at 6 months, 14.5% achieved remission at 12 months ($P<0.001$). Logistic regression analysis showed a significant inverse association between DAS28-ESR score at 6 months and the likelihood of achieving remission at 12 months [for each increase in DAS28-ESR score by one unit there was a 64.6% lower probability of achieving remission; $P<0.001$]. ROC curve analysis identified a DAS28 score at 6 months $\leq$ 3.54 as most accurately predicting remission at 12 months with a sensitivity of 82% and a specificity of 70% (Figure 1A). Stratified analysis showed that, among patients in remission at 6 months, a DAS28 score of $\leq 3.13$ was the optimal cut-off for predicting sustained remission at 12 months (68% sensitivity, 64% specificity) (Figure 1B).

Conclusion: The results of this analysis demonstrate that a DAS28-ESR target of $\leq 3.54$ at 6 months maximizes the likelihood of remission at 12 months while a value of $\leq 3.13$ should be targeted for optimal sustainment of remission.

Figure 1. ROC curves showing the optimal DAS28-ESR cut-offs at 6 months for achieving (A) or sustaining (B) remission at 12 months.

Disclosure: E. Keystone, Abbott, Amgen, AstraZeneca, BMS, F. Hoffmann-La Roche, Janssen, Lilly, Novartis, Pfizer Sanofi-Aventis, UCB, 2, Abbott Laboratories, AstraZen-
In Palindromic Rheumatism, Older Age, Shorter Interval Between Attacks and Positive Anti-CCP Antibodies May Predict Progression to RA

Masatoshi Hayashi1, Jackie L. Nam2, Laura Hunt3, Elizabeth Hensor3, Toshihisa Kanamono1, Toshihisa Kojima3, Naoki Ishiguro3, Masatoshi Hayashi1, Jackie L. Nam2, Laura Hunt3, Elizabeth Hensor3, Toshihisa Kanamono1, Toshihisa Kojima3, Naoki Ishiguro3

Background/Purpose: Palindromic rheumatism (PR) is a clinical syndrome characterised by episodes of joint swelling that settle spontaneously. A proportion of PR patients progress to develop rheumatoid arthritis (RA). Understanding the factors associated with progression would have value for management and understanding pathogenesis. We therefore identified potential factors associated with the development of RA in these patients.

Methods: A retrospective analysis was done on 55 patients with PR followed up in our rheumatology early arthritis clinics. For inclusion, patients had either a history or physical examination findings consistent with synovial swelling that returned to normal between episodes in the absence of an alternative diagnosis. Medical history, clinical examination and laboratory findings were compared between the group that progressed to ACR/EULAR 2010 RA (progression) and the group that did not (non-progression).

Results: Of the 55 patients, 28 (51%) developed RA and 27 (49%) did not over a mean (SD) period of 28.3 (40.0) and 17.2 (19.0) months of follow-up. Factors that differed between the groups were: age at PR onset (non-progression vs. progression median 39 vs. 48 years; table), duration of interval between attacks (30 vs. 45 days), anti-cyclic citrullinated peptide (anti-CCP) positivity (96% vs. 73%), and anti-CCP titre (164 vs. 57 U/ml).

Conclusion: In our cohort of patients with PR, a relatively high proportion progressed to RA. Features on history and anti-CCP anti-body positivity, particularly high antibody titres, were found to be associated with evolution to RA. These data should be of value in managing therapy and follow-up of PR patients.

Table: Characteristics of patients with palindromic rheumatism who progressed to RA in comparison with those without progression to RA at the first visit.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-progression</th>
<th>Progression</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>27 (49)</td>
<td>28 (51)</td>
<td></td>
<td>0.009*</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>39 (32, 45)</td>
<td>48 (39, 59)</td>
<td></td>
<td>0.009*</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>17 (63)</td>
<td>19 (68)</td>
<td>1.2 (0.4–3.8)</td>
<td>0.703</td>
</tr>
<tr>
<td>Symptom duration, mo</td>
<td>57 (28.0, 108.5)</td>
<td>88 (56.0, 138.0)</td>
<td>0.418</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>9.0 (2.0, 22.0)</td>
<td>16.0 (10.3, 29.0)</td>
<td>0.107</td>
<td></td>
</tr>
<tr>
<td>Duration of one attack, hours</td>
<td>60.0 (30.0, 60.0)</td>
<td>36.0 (33.0, 51.0)</td>
<td>0.356</td>
<td></td>
</tr>
<tr>
<td>Interval of attacks, days</td>
<td>45.0 (30.0, 96.0)</td>
<td>30.0 (22.3, 56.3)</td>
<td>0.007**</td>
<td></td>
</tr>
<tr>
<td>Gout crystal arthropathy, no.</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td>1.2 (0.1–4.1)</td>
<td>0.041</td>
</tr>
<tr>
<td>Smoker (current or prevalent), no. (%)</td>
<td>16 (59)</td>
<td>22 (79)</td>
<td>2.5 (0.8–8.2)</td>
<td>0.121</td>
</tr>
<tr>
<td>Smoker (current), no. (%)</td>
<td>8 (30)</td>
<td>10 (36)</td>
<td>1.3 (0.4–4.1)</td>
<td>0.613</td>
</tr>
<tr>
<td>FDGRA, no. (%)</td>
<td>9 (33)</td>
<td>5 (18)</td>
<td>0.4 (0.1–1.5)</td>
<td>0.188</td>
</tr>
<tr>
<td>RF, no. (%)</td>
<td>13 (57)</td>
<td>15 (58)</td>
<td>1.6 (0.5–5.6)</td>
<td>0.420</td>
</tr>
<tr>
<td>Anti-CCP, U/ml</td>
<td>16 (71)</td>
<td>24 (96)</td>
<td>0.9 (1.0–82.0)</td>
<td>0.025**</td>
</tr>
<tr>
<td>Anti-CCP titre, U/ml</td>
<td>57.0 (3.0, 143.9)</td>
<td>164.0 (73.0, 500.0)</td>
<td>0.010**</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>3.0 (1.0, 11.7)</td>
<td>4.2 (2.2, 9.3)</td>
<td>0.637</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>1.0 (1.0, 11.7)</td>
<td>1.0 (1.0, 11.7)</td>
<td>0.637</td>
<td></td>
</tr>
<tr>
<td>ANA, no. (%)</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td>1.2 (0.3–5.1)</td>
<td>0.184</td>
</tr>
</tbody>
</table>

Disclosure: M. Hayashi, None; J. L. Nam, None; L. Hunt, None; E. Hensor, None; T. Kanamono, None; T. Kojima, None; N. Ishiguro, None; P. Emery, None.

381 Distribution and Clinical Significance of Anti-Heterogeneous Nuclear Ribonucleoprotein A2 Antibody in Connective Tissue Diseases

Background/Purpose: The heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2) has been described as an important autoantigen in rheumatoid arthritis (RA) since it is targeted by autoantibodies. To explore clinical significance of anti-heterogeneous nuclear ribonucleoprotein A2 (anti-hnRNP-A2) antibodies, we detect the distribution of anti-hnRNP-A2 antibody in 1888 patients with connective tissue diseases.

Methods: Serum anti-hnRNP A2 antibody level was measured by solid-phase enzyme linked immunosorbent assay (ELISA) in 1464 patients with RA, 209 patients with systemic lupus erythematosus (SLE), 63 patients with mixed connective tissue disease (MCTD), 60 patients with Sjogren syndrome (SS), 47 patients with polyomyositis/dermatomyositis (PM/DM), and 45 patients with systemic sclerosis (SSc). The positivity rate of anti-hnRNP-A2 antibody was compared among various patient groups, and its correlation to clinical and laboratory parameters and its diagnostic significance were analyzed.

Results: The positivity rate of anti-hnRNP-A2 antibody was 38.0% (556/1464), 36.8% (77/209), 52.4% (33/63), 5.0% (360), 4.3% (247), and 8.9% (45) in RA, SLE, MCTD, SS, PM/DM and SSc, respectively. The r value differed insignificantly between the RA, SLE and MCTD groups (P > 0.05), but was significantly higher than in other disease groups (P < 0.01). The titers of anti-hnRNP-A2 antibody were significantly higher in the RA, SLE, MCTD groups than in other disease groups (P < 0.01), but differed insignificantly between the RA, SLE, MCTD groups (P > 0.05). In RA patients, anti-hnRNP-A2 antibody weakly correlated negatively to anti-Cyclical citrullinated peptide (CCP) antibody (r = 0.135, P < 0.01), but correlated insignificantly to age, course of disease, time of morning stiffness, erythrocyte sedimentation rate, C reactive protein, rheumatoid factor (RF), anti-keratin antibody (AKA) and glucose phosphate isomerase (GPI) (P > 0.05).

Conclusion: Anti-hnRNP-A2 antibody can be found in various connective tissue diseases, and its positivity rate is relatively high in RA, SLE and MCTD. It is not a RA-specific antibody. In RA, anti-hnRNP-A2 antibody does not coincide with other RA-related serological indicators; hence, it may serve as an adjunctive indicator for RA diagnosis.

Key Words: heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2); Rheumatoid Arthritis (RA); Connective Tissue Diseases.

Disclosure: W. Yong Sr., None; M. Fangxiang, None; W. Hong, None; F. Yongfei, None.

382 What Is More Predictive of Achieving Remission at 12 Months: The Efficacy of Baseline Treatment or the Actual Disease State Achieved at 6 Months?

Edward C. Keystone1, Carter Thorne2, Michael Starr3, Jude Rodrigues4, Philip Baer5, Regan Arendse6, J. Antonio Avina-Zubieta7, Denis Choquette8, Emmanouil Rampakakis9, John S. Sampalis, May Shaw10, Francois Nantel11, Allen J. Lehman11, and Susan Outa10,11

University of Toronto, Toronto, ON, Southlake Regional Health Centre, Newmarket, ON, McGill University Health Centre, Montreal, QC, Private Practice, Scarborough, ON, University of Saskatchewan, Saskatoon, SK, Arthritis Research Centre of Canada, Richmond, BC, Institut de rhumatologie de Montréal (IRM), Montréal, QC, JSS Medical Research, Montréal, QC, Janssen Inc., Toronto, ON.

Background/Purpose: The aim of rheumatoid arthritis (RA) treatment is to optimize symptom control and, when possible, achieve sustained remission. Therefore, identification of clinical signs predicting future remission is valuable to clinical decision making. One question faced by clinicians is whether the achievement of a lower disease activity value or a higher rate of change of disease activity is indicative of better future disease outcomes. The purpose of this analysis was to determine whether change in disease activity measures or the actual values achieved at 6 months were more predictive of remission. Therefore, identification of clinical signs predicting future remission is valuable to clinical decision making. One question faced by clinicians is whether the achievement of a lower disease activity value or a higher rate of change of disease activity is indicative of better future disease outcomes.

Methods: BIOTRAC is an ongoing, prospective registry of patients initiating treatment for RA with IFX or golimumab as first biologics or after...
having been treated with a biologic for <6 months. Eligible people for this study included RA patients treated with IFX enrolled between 2002–2012 with available 12-month information on remission. Multivariate logistic regression models with the parametric Wald statistic and the log-likelihood ratio were used to assess the independent contribution of the actual value and the change at 6 months in predicting 12-month remission as defined by DAS28 (≤2.6), SDAI (≤3.3) and CDAI (≤2.8) criteria. These two statistics assess the extent of contribution of an individual predictor to an outcome of interest - higher values signify greater contribution - and can be used to compare the contribution of different predictors in a standardized fashion.

**Results:** 436 patients were included with mean age of 56.1 yrs and disease duration of 10.4 yrs. With respect to 12-month DAS28 remission, a stronger association was observed with the actual DAS28 score compared to the percent improvement in DAS28 at 6 months. The Wald statistic for the percent change and actual value of DAS28 at 6 months was 5.38 and 46.88, respectively, while the change in log-likelihood was 4.98 (P = 0.026) and 61.64 (P < 0.001), respectively, indicating that the actual DAS28 value achieved is significantly more predictive of remission when compared to percent change in DAS from baseline.

For SDAI remission at 12 months, the respective Wald values for percent change and actual value at 6 months were 0.075 and 18.28 and log-likelihood changes were 0.07 (P = 0.788) and 24.08 (P < 0.001). For CDAI remission at 12 months, the Wald statistic was 0.01 and 34.42 for 6 month percent change and actual value, respectively, and change in log-likelihood was 0.01 (P = 0.934) and 34.23 (P < 0.001). Similar results were obtained when predicting low disease activity at 12 months.

**Conclusion:** These results demonstrate that the actual disease outcome value achieved at 6 months is a stronger predictor of remission at 12 months than the percent change in disease activity. These findings suggest that the treatment target in a real-world setting should be set as specific endpoints and not as change over time.


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**How Low Is Low Disease Activity? an Analysis from a Prospective, Observational Registry, Edward C. Keystone1, Boulos Harauzi1, John Kelsall1, Carter Thorne1, Philip Baer2, William Benson1, Deniz Choquette2, Regan Alg1, A. Jovaisa3, Daniel Jones1, Algis Jovaisa1, Emmanuel Rampakakis11, John S. Sampalis11, Francois Nantel11, May Shawi12, Allen J. Lehman12 and Susan Otawa12. 1University of Toronto, Toronto, ON, 2University of Montreal Hospital Centre, Montreal, QC, 3The Mary Pack Arthritis Centre, Vancouver, BC, 4Southlake Regional Health Centre, Newmarket, ON, 5Private Practice, Scarborough, ON, 6St Josephs Hospital and McMaster University, Hamilton, ON, 7Institut de rhumatologie de Montréal (IRM), Montréal, QC, 8University of Saskatchewan, Saskatoon, SK, 9University of Alberta, Edmonton, AB, 10University of Ottawa, Ottawa, ON, 11JSS Medical Research, Montreal, QC, 12Janssen Inc., Toronto, ON.

**Background/Purpose:** Composite measures of disease activity can facilitate clinical decision-making to achieve treatment goals, and treatment-to-target has been shown to improve outcomes. Both CRA and ACR/EULAR recommend that treatment target should be remission or, when not possible, low disease activity (LDA). Low levels of acute phase reactants, patient-reported disease activity (PGA), or tender joints included in such measures may result in meeting LDA criteria while having significant residual disease activity. This analysis examined the levels of individual components of composite measures in RA patients with LDA.

**Methods:** BioTRAC is an ongoing, prospective registry of RA, AS, or PsA patients initiating treatment with infliximab or golimumab as first activity. This analysis examined the levels of individual components of composite measures in RA patients with LDA.

**Results:** 321 RA patients with mean age of 57.1 years and mean duration since diagnosis of 10.5 years were included, providing information from 488 instances of LDA among patients with DAS28 LDA, mean (min, max) TJC28 was 1.3 (0.9), SJC28 was 1.2 (0.7), Pga was 2.1 (0.0,10.0), and ESR was 21.0 (1.0,75.0). Similarly, disease parameters in patients with CDAI and SDAI LDA were, respectively: TJC28 [1.4 (0.6); 1.5 (0.8)], SJC28 [1.1 (0.7); 1.0 (0.6)], PGA [2.3 (0.0, 5.0); 1.6 (0.0,9.0)]; and CRP [6.7 (0.0, 68.0)]. More than two swollen joints were present in 18.2%/14.1%/14.5% of DAS28 / CDAI / SDAI instances, respectively, and MDGA was >2 in 24.0%/18.6%/18.2% of instances. With respect to HAQ-DI, patients with DAS28 and CDAI LDA had a mean (min, max) score of 0.96 (0.0,0.288), 1.00 (0.0,0.288), and 0.96 (0.0,0.288), respectively; with 8.5%, 11.3%, and 9.8% of cases having HAQ-DI ≥2 indicating severe (very) severe disability.

**Conclusion:** Despite meeting the LDA criteria, significant residual disease may exist as indicated by the number of swollen joints and MDGA. Furthermore, a significant proportion of patients in LDA may have severe to very severe disability, although this may be due to long disease duration and irreversible damage. Altogether, although targeting LDA results in improved outcomes, it may not be an appropriate target for a significant portion of patients. Furthermore, treatment decisions should not be based solely on composite measures, but also take into consideration the global patient picture.


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Using Patient Reported Outcome Measures to Classify Disease Activity States in Rheumatoid Arthritis: A Comparison of Patient Activity Score (PAS) and Routine Assessment of Patient Index Data (RAPID). Erin Carruthers1, Noura AL Osaimi2, Charles H Goldsmith3, Paul Adam4 and Diane Lacaille5. 1Arthritis Research Centre of Canada, Richmond, BC, 2University of Ottawa, Ottawa, ON, 3Simon Fraser University, Burnaby, BC, 4Mary Pack Arthritis Centre, Vancouver, BC, 5Arthritis Research Centre of Canada, Vancouver, BC.

**Background/Purpose:** In RA the target for treatment is clinical remission or minimal disease activity. Patient involvement in monitoring their disease activity could enhance treatment by providing early warning when targets are not met, indicating the need to re-evaluate treatment. Several patient reported outcome measures of disease activity have been developed and validated. The objective of this study is to compare the agreement between patient and rheumatologist (MD) derived disease activity states using these measures.

**Methods:** Consecutive RA patients seen by 7 rheumatologists were invited to participate. Patients completed a questionnaire before their visit. MD joint count and lab values were obtained from charts. We evaluated 4 patient reported disease activity measures: i) PASI; ii) RAPID with 3 measures (RAPID3); iii) RAPID with 4 measures (RAPID4); iv) modified-RAPID4 (m-RAPID4) using HAQII instead of MDHAQ. The following MD derived measures served as gold standards: i) Clinical Disease Activity Index (CDAI); ii) Simplified Disease Activity Index (SDAI); iii) Disease Activity Score 28 (DAS28). Disease states were categorized into remission, low, moderate or high, according to published cut points. Because change in treatment is recommended with moderate or high disease activity, we also compared two categories: remission or low vs. moderate or high. Agreement between patient and MD derived disease states was evaluated using Agreement Coefficient 1 (AC1) for two category comparisons and Agreement Coefficient 2 (AC2), weighted with quadratic weights, for four category.
comparisons. AC values > 0.62 were considered good agreement. Z tests were used to evaluate the significance of the difference between pairs of ACs.

Results: We recruited 150 RA patients [mean (SD) RA duration: 11.9 (11.3) y; age: 57.8 (16.3) y; 81% female]. See Table 1 for agreement between patient and MD derived disease activity states. Overall, PASII showed the best agreement with MD measures. When comparing ACs for four category disease activity states, all pairwise comparisons were significantly different (all but one p < 0.001), except when comparing agreement between RAPID4 and m-RAPID4 with CDAI (p = 0.054), and between RAPID3 and RAPID4 with SDAI (p = 0.075). When comparing ACs for two categories, significant differences were detected in the agreement between PASII and RAPID3 with CDAI, RAPID4, and 4 with CDAI, PASII and RAPID3 with DAS28, PASII and RAPID5 with DAS28, RAPID4 and 4 with DAS28, and RAPID4 and m-RAPID4 with DAS28 (all p < 0.05).

Table 1. Agreement between patient and MD derived indices measured across four and two disease activity categories.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>PATIENT MEASURES</th>
<th>RHEUMATOLOGIST MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI-MD</td>
<td>SDAI-MD</td>
<td>DAS28-MD</td>
</tr>
<tr>
<td>AC1 [95% CI]</td>
<td>AC1 [95% CI]</td>
<td>AC1 [95% CI]</td>
</tr>
<tr>
<td>PASII</td>
<td>0.67 [0.55, 0.79]</td>
<td>0.67 [0.54, 0.79]</td>
</tr>
<tr>
<td>RAPID3</td>
<td>0.54 [0.40, 0.68]</td>
<td>0.60 [0.46, 0.73]</td>
</tr>
<tr>
<td>RAPID4</td>
<td>0.60 [0.47, 0.73]</td>
<td>0.65 [0.52, 0.78]</td>
</tr>
<tr>
<td>m-RAPID4</td>
<td>0.58 [0.45, 0.71]</td>
<td>0.64 [0.51, 0.77]</td>
</tr>
</tbody>
</table>

A = comparison across two categories (remission vs. low vs. moderate vs. high) B = comparison across two categories (remission or low vs. moderate or high)

Table 2. Differences between MRI, disease activity, and functional outcomes in pts at high risk versus moderate risk of RRP

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDAI</td>
<td>Delta (high versus moderate risk)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Oerison (MRI)</td>
<td>10.84</td>
<td>7.03, 14.66</td>
</tr>
<tr>
<td>Synovitis (MRI)</td>
<td>2.63</td>
<td>1.54, 3.71</td>
</tr>
<tr>
<td>Edema (MRI)</td>
<td>1.06</td>
<td>0.90, 3.02</td>
</tr>
<tr>
<td>Joint space narrowing (MRI)</td>
<td>6.54</td>
<td>3.59, 9.50</td>
</tr>
<tr>
<td>Disease activity and functional outcomes</td>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>DAS28 (CRP) C</td>
<td>0.72</td>
<td>0.36, 1.09</td>
</tr>
<tr>
<td>SDAI</td>
<td>8.22</td>
<td>4.38, 12.05</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.43</td>
<td>0.25, 0.60</td>
</tr>
</tbody>
</table>

Each line represents a mutivariable linear regression model of outcomes

Conclusion: Our results suggest that patients can self-monitor disease activity. PASII shows the best agreement with all MD measures. Given the similarities in the components of the measures compared, this difference may be due to cut points used to categorize disease states.

Disclosure: E. Carruthers None; N. Al. Osami None; C. H. Goldsmith None; P. Adam None; D. Lacaille None.

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Validation of a Prognostic Model to Predict Structural Damage Assessed By X-Ray in Patients with RA Using MRI Data from a Clinical Trial. EA Alemao1, S Joo2, S Banerjee1, P Allison1, P Emery4, M Weinblatt5 and M. Weinblatt.

Methods: By X-Ray in Patients with RA Using MRI Data from a Clinical Trial. Validation of a Prognostic Model to Predict Structural Damage Assessed By X-Ray in Patients with RA Using MRI Data from a Clinical Trial. We applied our prognostic model for RRP to pts in this study. The model includes seropositivity status, body weight, disease duration, DAS28 (CRP) and Total Sharp Score to determine the probability of RRP for each pt. The external validity of the model was evaluated for discrimination (receiver operating characteristic [ROC]) and calibration (Hosmer–Lemeshow goodness-of-fit chi-square). Based on the calculated probability of RRP, pts were categorized by probability into low (0–0.25), moderate (>0.25–0.75) and high (>0.75) risk of RRP. Analysis of variance was used to study the association between predicted probability of RRP at baseline to MRI outcome at 12 wks. Additionally, we examined the association between RRP prediction and disease activity [SDAI, DAS28 (CRP)] and functional status (HAQ) at 12 and 24 wks.

Results: There were 418 pts in the clazakizumab Phase IIIb study; average age was 50.4 yrs (SD 12.3); 82.1% were female. The RRP model when applied to clazakizumab Phase IIIb had an overall ROC of 0.73 (95% CI 0.62, 0.83) and Hosmer–Lemeshow chi-square of 13.5 (df=8, p=0.11). Baseline probability of RRP was evaluated in 387 (92.6%) pts with available data. Of these, the majority (96.1%) were in the moderate- and high-risk (48.1%) RRP groups. Pts in the moderate-risk group, when compared with those in the high-risk group, tended to be younger (mean age [SD] 48.3 [12.9] vs 52.2 [11.0] yrs). Compared with the moderate-risk RRP group, pts at high risk of RRP had significantly higher MRI measures of erosion, synovitis and joint space narrowing. In addition, pts at baseline in the high-risk group compared with the moderate-risk group had significantly higher disease activity scores and higher physical activity scores as measured by HAQ at 12 and 24 wks (Table).

Table 1. Agreement between patient and MD derived indices measured across four and two disease activity categories.

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>PATIENT MEASURES</th>
<th>RHEUMATOLOGIST MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI-MD</td>
<td>SDAI-MD</td>
<td>DAS28-MD</td>
</tr>
<tr>
<td>AC1 [95% CI]</td>
<td>AC1 [95% CI]</td>
<td>AC1 [95% CI]</td>
</tr>
<tr>
<td>PASII</td>
<td>0.86 [0.83, 0.90]</td>
<td>0.86 [0.82, 0.90]</td>
</tr>
<tr>
<td>RAPID3</td>
<td>0.70 [0.63, 0.76]</td>
<td>0.73 [0.67, 0.79]</td>
</tr>
<tr>
<td>RAPID4</td>
<td>0.77 [0.71, 0.83]</td>
<td>0.78 [0.72, 0.84]</td>
</tr>
<tr>
<td>m-RAPID4</td>
<td>0.73 [0.66, 0.79]</td>
<td>0.75 [0.68, 0.81]</td>
</tr>
</tbody>
</table>

AC1 = agreement coefficient 1; AC2 = quadratic weighted agreement coefficient 2

All p-values 2 tailed, p < 0.05.

Disclosure: E. Alemao, BMS, 1, BMS, 3; S. Joo, BMS, 3, BMS, 1; S. Banerjee, BMS, 1, BMS, 3; P. Allison, None; P. Emery, AbbVie, BMS, Merck, Pfizer, Roche, Takeda, 5, AbbVie, BMS, Merck, Pfizer, Roche, 2; M. Weinblatt, BMS, Crescendo Bioscience, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2; K. Liao, None.

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Association of Pharmacogenetic Markers with Treatment Response in Patients with Rheumatoid Arthritis. Ute L. Schwarz6, Janet E. Pope1, Edward Keystone2, Boulos Hararui1, Carter Thorne3, Yun-Hee Choi4, Melanie Poulin-Costello5, Nabil Bayan3 and Richard B. Kim1, 1 Western University, London, ON, 2 Mount Sinai Hospital, University of Toronto, Toronto, ON, 3 University of Montreal Hospital Centre, Montreal, QC, 4 Southlake Regional Health Centre, Newmarket, ON, 5 Agena Canada Inc., Mississauga, ON.

Background/Protocol: In the CANadian Methotrexate and Etanercept Outcome Study (CAMEO) continued therapy with etanercept (ETN) and methotrexate (MTX) led to better outcomes at month 24 than the withdrawal of MTX in MTX inadequate responders (MTX-IR) with active rheumatoid arthritis (RA). Patients had to tolerate MTX at a dose of ≥ 15 mg/wk or 10 mg/wk if intolerant. Similar disease activity was observed in both treatment arms at 12 months in the subgroup of patients who achieved low disease activity (disease activity score [DAS28] < 3.2) at 6 months of combination therapy, whereas if not in low DAS28 combination therapy was more effective. Recent evidence suggests that polymorphisms in genes related to metabolism and cellular transport pathways of MTX and to the biological targets of ETN may help predict clinical response in RA. This pre-defined CAMEO sub-study explored pharmacogenetic markers as novel predictors of treatment outcome in patients failing MTX prior to starting ETN.

Methods: All patients were treated with ETN+MTX for 6 months, followed by randomization to either ETN+MTX or ETN alone for an
additional 18 months. After consent, DNA extraction and genotyping was performed using TaqMan Genotyping Assays. Fifteen genetic variants in 12 genes related to MTX and 4 variants in 3 genes related to TNF were analyzed. The contribution of genetic variants to therapeutic response (improvement in DAS28 [\Delta DAS28]) from baseline to months 6, 12, 18 and 24; total Sharp score [TSS] at 12 and 24 months) was assessed using mixed models with adjustments for age and sex. Results: Assessments were performed in 111 patients (mean age 55.2 years, 73% female, 98% Caucasians). Univariate analyses did not suggest an association of genetic variants related to response to ETN (p > 0.25). Patients receiving ETN+MTX after randomization (N=64) were included for multivariate analyses at 12, 18 and 24 months. Patients expressing the ATIC 347C allele were more likely to have an improvement with combined therapy as compared to patients receiving ETN alone (OR: 2.2, 95% CI: 0.97 – 4.9). Conclusion: Genetic polymorphisms in drug transporters and metabolic enzymes related to MTX pathways were associated with clinical response after combined treatment in MTX-IR patients. No association between enzymes related to MTX pathways were associated with clinical response. 

Conclusion: Genetic polymorphisms in drug transporters and metabolic enzymes related to MTX pathways were associated with clinical response after combined treatment in MTX-IR patients. No association between enzymes related to MTX pathways were associated with clinical response.

Table 1: Association of genotype with treatment response assessed as DAS28 improvement from baseline

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>LS Mean DAS28 (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6, N = 108</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCB1 3455C&gt;T</td>
<td>TT</td>
<td>23</td>
<td>1.90 (1.30, 2.50)</td>
</tr>
<tr>
<td>GGG</td>
<td>GG</td>
<td>57</td>
<td>2.70 (2.20, 3.20)</td>
</tr>
<tr>
<td>ATIC 347C&gt;G</td>
<td>CT and TT</td>
<td>24</td>
<td>2.00 (1.34, 2.66)</td>
</tr>
<tr>
<td>GGG 452C&gt;T</td>
<td>CT and TT</td>
<td>24</td>
<td>2.64 (2.18, 3.10)</td>
</tr>
<tr>
<td>Month 12, N = 61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGG 452C&gt;T</td>
<td>CT and TT</td>
<td>12</td>
<td>2.48 (1.87, 3.23)</td>
</tr>
<tr>
<td>Month 18, N = 58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGG 452C&gt;T</td>
<td>CT and TT</td>
<td>10</td>
<td>2.06 (1.14, 2.98)</td>
</tr>
<tr>
<td>ATIC 347C&gt;G</td>
<td>CC</td>
<td>48</td>
<td>3.09 (2.57, 3.61)</td>
</tr>
<tr>
<td>GGG 452C&gt;T</td>
<td>CC</td>
<td>21</td>
<td>2.81 (2.08, 3.54)</td>
</tr>
<tr>
<td>ATC 347C&gt;G</td>
<td>GA and AA</td>
<td>42</td>
<td>2.97 (2.32, 3.61)</td>
</tr>
<tr>
<td>SLCO1B1 521T&gt;C</td>
<td>TC and CC</td>
<td>43</td>
<td>3.02 (2.43, 3.89)</td>
</tr>
<tr>
<td>Month 24, N = 59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGG 452C&gt;T</td>
<td>CT and TT</td>
<td>11</td>
<td>1.10 (0.88, 1.23)</td>
</tr>
</tbody>
</table>
| CI, confidence interval; DAS28, disease activity score; LS, least squares *P values are from multivariate comparisons by genotype.

Table 2: Association of genotype with treatment response assessed as TSS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>LS Mean TSS (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12, N = 62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCB1 3455C&gt;T</td>
<td>CT and TT</td>
<td>48</td>
<td>18.7 (17.95, 19.47)</td>
</tr>
<tr>
<td>GGG</td>
<td>GG</td>
<td>49</td>
<td>20.1 (18.87, 21.38)</td>
</tr>
<tr>
<td>ATIC 347C&gt;G</td>
<td>CC and GG</td>
<td>54</td>
<td>18.7 (18.01, 19.32)</td>
</tr>
<tr>
<td>ABC2C 1249G&gt;A</td>
<td>GA and AA</td>
<td>16</td>
<td>20.1 (18.96, 21.32)</td>
</tr>
<tr>
<td>Month 24, N = 56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCB1 3455C&gt;T</td>
<td>CT and TT</td>
<td>43</td>
<td>20.7 (19.73, 21.62)</td>
</tr>
<tr>
<td>GGG</td>
<td>GG</td>
<td>49</td>
<td>22.2 (20.76, 23.68)</td>
</tr>
<tr>
<td>ATIC 347C&gt;G</td>
<td>CC and CC</td>
<td>56</td>
<td>20.4 (19.72, 21.17)</td>
</tr>
<tr>
<td>ABC2C 1249G&gt;A</td>
<td>GA and AA</td>
<td>14</td>
<td>21.2 (20.72, 23.51)</td>
</tr>
</tbody>
</table>
| CI, confidence interval; LS, least squares; TSS, total Sharp score. *P values are from multivariate comparisons by genotype.

Disclosure: U. I. Schwarz, None; J. E. Pope, Abbott/AbbVie, Amgen, Actelion, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Glaxo-Smith Kline, Hoffmann-LaRoche, Janssen, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, UCB, 2; AbbVie, Amgen, Actelion, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Glaxo-Smith Kline, Hoffmann-LaRoche, Janssen, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, UCB, 5; E. Keystone, Abbott/AbbVie, Amgen, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Centocor, F. Hoffmann-LaRoche, Genzyme, Merck, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, UCB, Genentech, Janssen, 2; AbbVie; Bristol-Myers Squibb, F. Hoffmann-LaRoche, Genzyme, Merck, Pfizer, Roche, UCB, 2.

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Levels of IgG Autoantibodies to Oxidation-Associated MDA Neo-Determinants Are a Biomarker for Systemic Inflammation and Disease Activity

Methods: Monitoring disease activity in patients with autoimmune rheumatic diseases is an essential part of clinical care. Highly reactive malondialdehyde (MDA) arise from reactive oxygen species and lipid peroxidation and can covalently modify proteins and increased levels of MDA may be associated with the inherent autoimmune pathogenic process. We therefore hypothesized that levels of IgG autoantibodies to MDA-modified proteins may reflect core disease activity.

Results: In the current study, serum IgG anti-MDA levels were compared in 71 healthy controls, 30 OA, and 15 PsA, 283 SLE and 162 RA patients identified by ACR criteria. IgG anti-MDA was measured by sandwich ELISA using MDA-modified BSA. Statistical differences were assessed by Mann-Whitney test and Spearman analysis.

Results: Compared to controls (5±3 RU/ml), IgG anti-MDA was significantly increased in patients with PsA (7±2 RU/ml; p<0.001), SLE (17±21 RU/ml, p<0.001) and RA (14±21 RU/ml, p<0.001). In SLE patients, IgG anti-MDA significantly correlated with the disease activity assessed by SELENA-SLEDAI (p<0.001, R=0.34, n=219) and levels were higher in SLE patients with active disease (SLEDAI≥6, 18.9±17.3 RU/ml, p=0.001) than with low disease activity (SLEDAI<6, 11.5±16.6). In RA, IgG anti-MDA was significantly higher in new onset RA (<6 mo, 21±13 RU/ml, p<0.001) than in chronic RA (>2 yr, 10±8 RU/ml, p<0.001). Notably, new onset RA patients had more active disease by DAS28 (5.7±1.2, p=0.01) than chronic RA patients generally on therapy (4.8±1.5). Importantly, IgG anti-MDA significantly correlated with DAS28-ESR (p<0.0001, R=0.35, n=157, with 16 seronegative), and compared to RA patients with more controlled disease (DAS28<3.2, 6±3) the levels were higher in moderate disease (DAS28 3.2–5.1, 12±11 RU/ml, p=0.005) and further elevated in active disease (DAS28 >5.1, 15±12 RU/ml, p<0.001). IgG anti-MDA also correlated with TNFα (p=0.002, R=0.39, IL-6 (p=0.03, R=0.27) and CRP levels (p=0.003, R=0.37) in DMARD naive RA patients (n=62).

Conclusion: IgG autoantibodies to MDA-modified determinants may provide a biomarker for disease activity in rheumatic autoimmune diseases. These autoantibodies may therefore provide a valuable early objective metric for diagnosis and for assessing disease activity. The potential mechanisms responsible for induction of IgG anti-MDA autoantibodies during the pathogenesis of systemic inflammation merits further study.

Disclosure: C. Grönwall, None; L. Getu, None; J. D. Greenberg, None; R. M. Clancy, None; G. J. Silverman, None.

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Soluble TREM-1 Is a Biomarker of Anti-CCP-Positive, DMARD-Naive Early Rheumatoid Arthritis

Shachar Ofer-Shiber1, Elisheva Pokroy-Shapira2, Yair Mola2, Sharily Oren1, Hagit Shay-Aharoni1 and Ilan Babai2.

1Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel Aviv University, Petach Tikva, Israel, 2Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel, 3Rabin Medical Center, Beilinson Hospital, Beilinson Hospital, Petach Tikva, Israel.

Background/Purpose: Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell-surface receptor, expressed mainly on monocytes and neutrophils and involved in amplification of the inflammatory response. Previous studies have shown an upregulation of TREM-1 in synovium of patients with rheumatoid arthritis (RA) as

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well as increased levels of soluble TREM-1 (sTREM-1) in synovial fluid and blood of patients and animal model of RA. We sought to determine the serum sTREM-1 levels in disease-modifying anti-rheumatic drug (DMARD)-naïve early rheumatoid arthritis (ERA), to investigate the association of serum sTREM-1 levels with Disease Activity Score in 28 joints (DAS28) and seropositivity for anti-cyclic citrullinated peptide (CCP) antibody, and to determine the predictive value of sTREM-1 with respect to clinical response to DMARD therapy.

Methods: Twenty-two consecutive patients with DMARD-naïve ERA were prospectively evaluated for serum sTREM-1 by means of ELISA at diagnosis and at the following clinic visit after low dose prednisone and/or DMARD have been administered, and related to DAS28 and serum level of anti-CCP Ab. We compared the sTREM-1 level to that of 31 patients with established RA as well as to 24 controls.

Results: Serum sTREM-1 level was significantly higher in the DMARD-naïve ERA group (2125±389 pg/ml) compared to established RA group (1478±280 pg/ml, p=0.001) and normal control (34.4±7.4 pg/ml, p<0.001). In the ERA group, elevated basal sTREM-1 level was significantly associated with DAS28-CRP (p=0.001, HR 1.4 - 8.12), DAS28-ESR (p=0.04, HR 2.34 95%CI 0.1-8.12), as well as predicted higher DAS28 at the following encounter after DMARD treatment was administered (p=0.001, HR 3.25 95%CI 1.1-7.2), as well as in patients with established RA. Higher serum sTREM-1 levels were significantly associated with higher titers of anti-CCP antibody (p<0.001).

Conclusion: Our results suggest that serum sTREM-1 may provide a novel biomarker of DMARD-naïve ERA as well as of disease activity and seropositivity for anti-CCP antibody in RA.

Disclosure: S. Ofer-Shiber. None; E. Pokroy-Shapira. None; Y. Molad. None; S. Oren. None; H. Shay-Aharoni. None; I. Babal. None.

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High 11B-HSD1 Activity Is Associated with Progression to Rheumatoid Arthritis in Patients with a New Onset of Inflammatory Arthritis. Dominika Nanus1, Andrew Filer2, Lorraine Yeo1, Dagmar Scheel-Toellner3, Rowan Hardy1, Gareth Lavery1, Paul Stewart4, Christopher Buckley1, Mark Cooper2 and Karim Raza1. 1University of Birmingham, Birmingham, United Kingdom, 2University of Leeds, Leeds, United Kingdom, 3ANZAC Research Institute, Sydney, Australia.

Background/Purpose: Inadequate endogenous glucocorticoid (GC) synthesis during inflammation has been proposed as an aetiological factor in the development of rheumatoid arthritis (RA). It has been shown that inflamed synovial tissue from patients with RA can generate active GCs through the expression of the 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1), which converts cortisone to cortisol. We examined whether the total body activity of 11β-HSD1 was associated with the risk of developing persistent arthritis in patients first presenting with joint inflammation.

Methods: Blood and urine, were obtained from 76 patients with early arthritis (symptoms ≤12 weeks duration). The final diagnostic outcome was determined after 18 months clinical follow up when patients were assigned to one of the following three outcome groups: (1) Persistent inflammatory arthritis that did not fulfil 1987 ACR classification criteria for RA, n=13. (2) Persistent RA, according to 1987 ACR classification criteria, n=18. (3) Resolving inflammatory arthritis, n=24. Patients were classified as having a resolving inflammatory arthritis if they had no clinically apparent joint swelling at final follow-up, were not receiving disease modifying drugs or steroids and had not received such drugs in the previous 3 months. In addition, patients who fulfilled 1987 ACR classification criteria for RA and had a symptom duration of more than 12 weeks at initial assessment were recruited as patients with ‘established RA’, n=20. Total body 11β-HSD1 activity was determined by urinary gas chromatography/mass spectrometry and calculated as the tetrahydrocortisol + allotetrahydrocortisol/tetrahydrocortisone (THF + alloTHF)/THF and the cortisols/cortolones ratios. Urinary 11β-HSD2 activity was measured as the UFF/UFE ratio. Arthritis severity was assessed by ESR, CRP and DAS28.

Results: Systemic measures of 11β-HSD1 activity were significantly higher in patients with early arthritis whose disease went on to persist, and also in the subgroup of patients with persistent disease who developed RA, when compared with patients whose synovitis resolved over time (persistent RA, 134 (0.013) and resolving inflammatory arthritis, 0.96 (0.07), P=0.012, mean (SEM). Levels of ESR at baseline were not significantly different between the different outcome groups. However the levels of CRP in patients with early synovitis that persisted were higher than that in patients whose synovitis resolved. We observed a significant positive correlation between systemic 11β-HSD1 activity and both ESR and CRP in patients with established RA but not in any of the early arthritis patients group.

Conclusion: The present study demonstrates that patients with a new onset of synovitis whose disease subsequently resolved had significantly lower levels of systemic 11β-HSD1 activity when compared with patients whose synovitis developed into RA or other form of persistent arthritis. This observation is contrary to that predicted on the basis of previous work and raises the possibility that a high total body 11β-HSD1 activity during early arthritis may reduce the probability of disease resolution.

Disclosure: D. Nanus. None; A. Filer. None; L. Yeo. None; D. Scheel-Toellner. None; R. Hardy. None; G. Lavery. None; P. Stewart. None; C. Buckley. None; M. Cooper. None; K. Raza. None.

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Background/Purpose: Patients with rheumatoid arthritis (RA) sometimes rate their global disease activity differently than their rheumatologists. Previous studies describing this ‘discordance’ have primarily included patients with established disease (i.e., mean disease duration >10 years). The objective of this study was to evaluate the prevalence and correlates of patient-physician discordance in patients with early disease (i.e., duration <3 years).

Methods: We conducted an observational study of consecutive patients with RA recruited between July 2008 and December 2010. RA was defined by the Leiden early RA prediction rule or the 1987 ACR criteria. A physician joint assessor, who was independent from treatment decision-making, performed a standardized clinical evaluation. Discordance was defined by a >25-mm difference between the patient and physician global assessments of disease activity. A higher patient-than-physician global assessment defined positive discordance, and a higher physician-than-patient global assessment defined negative discordance. Patients completed visual analog scales for pain and fatigue, the Health Assessment Questionnaire (HAQ), and the Medical Outcomes Study Short Form 36 (SF-36). We abstracted the electronic medical records to collect demographics, laboratory data, smoking status, and body mass index (kg/m²). Correlations between explanatory variables and the presence of positive or negative discordance were determined using Spearman methods.

Results: A total of 127 patients with RA were recruited. The mean age was 55.6 years, mean disease duration was 6.8 months, and 63% of patients were female. The prevalence of positive (i.e., patient high) and negative (i.e., physician high) discordance was 10.2% and 16.5%, respectively. Positive discordance was associated with higher pain (r = 0.37, p < 0.001), fatigue (r = 0.32, <0.001) and HAQ disability (r = 0.31, p < 0.001). Poor health-related quality of life on the SF-36 physical component scale (r = -0.29, p = 0.001) and mental component scale (r = -0.20, p = 0.02) also correlated with positive discordance. Notably absent were associations of discordance with age, sex, radiographic damage, body mass index, smoking, anti-CCP antibodies, or use of prednisone or disease-modifying medications. In contrast, negative discordance (i.e., physician high) was associated with higher numbers of swollen joints (r = 0.19, p = 0.03), positive rheumatoid factor (r = 0.18, p = 0.046), and with lower pain and better overall physical and mental health on the part of the patient.

Conclusion: The contribution of this study is that prevalence and correlates of patient-physician discordance is similar in early and established RA. Discordance with early RA take into account their pain, fatigue and adverse quality of life when making their global disease assessments whereas physicians emphasize objective inflammation and laboratory markers. As ‘treat-to-target’ algorithms increasingly focus on quantitative targets, these data behove clinicians to fully consider the disease experience to provide optimal patient care.
Self-Assessment Tool of Rheumatoid Arthritis Disease Activity: Handgrip Strength Measured By a Smartphone Connected to a Dynamometer. Pierre LeBlay Sr., Philippe Lartigau, Pierre LeBlay, and Christian Jorgensen. Rheumatology Department, Division of Internal Medicine, School of Medicine, University of Los Andes, Santiago, Chile. Clinical Immunology and Osteoarticular Diseases Therapeutic Unit, CHU Lapeyronie, Montpellier, France.

Background/Purpose: Patient self-management should become a key component of rheumatology care. Development of modalities using personal technologies resources represents an attractive way to assess periodic disease’s activity. We previously developed a Smartphone application and a software to measure the dominant handgrip strength in rheumatoid arthritis (RA) patients. This pilot-study was performed in healthy and RA volunteers for testing and calibrating the system with a classical dynamometer. Then using this novel handheld device, we conducted an exploratory study to correlate RA disease activity with handgrip strength. Here we present our preliminary results.

Methods: We included 50 patients with RA. All patients fulfilled the 2010 ACR/EULAR criteria for RA. We excluded patients with health issues that could affect the test (hand or wrist surgery, myopathy, carpal tunnel syndrome, etc.). Patients received visual and audio instructions from the Smartphone application and a trained observer was present. The 28-joint disease activity score (DAS28) and modified Health Assessment Questionnaire (mHAQ) were measured for all participants. Linear regression and Two-Way ANOVA test were performed. The results were adjusted by age and sex.

Results: 96% of patients were females. Mean age was 62.59 ± 12.9. Mean DAS28 was 3.41 ± 1.38 and 38% of patients were in remission (DAS28<2.6). 22% were treated with Methotrexate or Leflunomide and 76% were treated with a bDMARD in association or not with a bDMARD. No patients reported difficulties or pain performing the test. Mean duration of the test was 3.5 minutes ± 0.22 and handgrip strength level was 9.63 ± 5.49 Kg. A significantly negative correlation between the index of handgrip strength and DAS28 was identified (r = -0.79, p < 0.05, p<0.01). We observed a significant correlation with the mHAQ (r = 0.85, 0.67 to 0.96, p<0.01). In a subgroup of 15 patients we evaluated the handgrip strength after treatment modifications or disease flare-up exacerbations and we found a significantly correlation with DAS28 changes (r = -0.93, -0.76 to -0.54, p<0.001). Ultimately we observed a tendency to correlate index of handgrip strength, adjusted by age and sex, and the presence of ultrasonography synovitis in a subgroup of 10 patients (p = 0.076).

Conclusion: Our preliminary data showed that Smartphone self-evaluation of handgrip strength is a feasible way to assess RA disease activity. Moreover, we will continue to follow longitudinally our RA patients in order to determine if this test could be used to detect flare-up or response to treatment. Then, we will validate this simple tool of self-assessment RA activity in a larger outpatients cohort.

Disclosure: F. Espinoza Sr., None; Y. M. Pers Sr., None; P. LeBlay Sr., None; C. Jorgensen, None.

Neuroendocrine Hormone and Metabolic Peptide Levels in the Earliest Phases of Rheumatoid Arthritis – Do Free Fatty Acids Play a Role? Man Wai Tang1, Frieda A. Koopman1, Jan P.M. Visscher1, Margot E. de Haar1, Danielle M. Gerlag2 and Paul P. Tak1. 1Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 2Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with several neuroendocrine hormones and metabolic peptides. The crosstalk between the hormones and the immune system is important for homeostasis during inflammation. Therefore, we hypothesize that disturbances in hormones may gradually result in an inflammatory disease and hormones may be even disturbed years before onset of arthritis. The aim of this study is to determine the hormone levels in RA patients and individuals at risk for developing RA and compare those with the levels in healthy controls.

Methods: In total 18 neuroendocrine hormones and metabolic peptides (triglycerides (TG), free fatty acids (FFAs)) and pancreatic polypeptide (PP) were measured in fasting serum samples from 22 RA patients, 45 individuals at risk for developing RA by the presence of RA-specific autoantibodies and 16 healthy controls.

Results: The median (IQR) PP level was significantly higher in RA patients (34 (23–58) pmol/L) and individuals at risk (31 (24–45) pmol/L) compared to healthy controls (10 (6–27) pmol/L), respectively P = 0.004 and P = 0.002. The TG level was significantly higher in RA patients (1.03 (0.75–1.29) mmol/L) and a trend towards elevated TGs in individuals at risk (0.94 (0.72–1.15) mmol/L) compared to healthy controls (0.70 (0.59–1.02) mmol/L), respectively P = 0.036 and P = 0.09. The FFA level was significantly higher in RA patients (0.59 (0.47–0.65) mmol/L) compared to healthy controls (0.40 (0.35–0.50 mmol/L; P = 0.011) and a trend towards elevated FFAs in individuals at risk (0.53 (0.40–0.59) mmol/L; P = 0.06) compared to healthy controls. In RA patients, the FFA level was positively correlated with disease activity parameters, but not confounded by body mass index or other variables. All other hormones and peptides were comparable between the three study groups.

Conclusion: FFA, TG and PP levels were higher in RA patients than in healthy controls. PP levels were higher in at risk individuals than in healthy controls and FFA and TG levels showed a similar trend. Moreover, the FFA level was positively correlated with disease activity parameters. This may support a role for FFAs, TGs and PPs in the pathogenesis of RA and these peptides may contribute, even in the at risk phase of RA, to the increased risk of cardiovascular diseases. Furthermore, PPs and FFAs can be potential biomarkers to identify individuals in the at risk phase of RA, who may develop RA later on.

Disclosure: M. W. Tang, None; F. A. Koopman, None; J. P. M. Visscher, None; M. J. H. de Hair, None; D. M. Gerlag, GlaxoSmithKline, 3; P. P. Tak, GlaxoSmithKline, 3.

Influence of Body Mass Index on Disease Activity and Radiographic Joint Damage in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Celine Vidal, Thomas Barnetche, Jacques Morel, Bernard Combe and Claire Daire. 1Hospital Lapeyronie, Montpellier, France, 2Rheumatology department, Bordeaux University Hospital, Bordeaux, France, 3Hôpital Lapeyronie, Montpellier, France.

Background/Purpose: Overweight and obesity in patients with rheumatoid arthritis (RA) are rising conditions. Adipose tissue has pro-inflammatory properties by producing adipokines which could play a role in RA activity. The prognosis of overweight and obese patients with RA is not well established.

Methods: We conducted a systematic review and meta-analysis to assess the influence of body mass index on disease activity (DAS 28) and radiographic joint damage (RJD) in patients with RA. We searched Medline and The Cochrane Database publications up to April 2014 with MeSH terms (“body mass index” OR “obese”) AND “rheumatoid arthritis”. Studies reporting DAS 28 and/or its components, Health Assessment Questionnaire (HAQ) and RJD according to body mass index (BMI) were included. Two investigators abstracted data and rated study quality and applicability. Statistical analysis used weighted mean differences with a fixed or random effects model, except for radiographic analysis in which standardized means were used as different radiographic scores were assessed in studies.

Results: Among the 579 citations retrieved with MeSH terms, 52 articles suited inclusion criteria and 7 of them were included in meta-analysis. Activity was assessed in 4 studies, involving 1402 patients, and revealed an association between obesity in RA and higher DAS 28 (+ 0.14, p = 0.04, I2 = 0%). Health Assessment Questionnaire (HAQ) was evaluated in 2 studies, involving 1264 patients, and also revealed a positive association with obesity (+ 0.1, p = 0.03, I2 = 0%). RJD was reported in 4 studies, involving 1465 patients, revealing a negative association with obesity (p = 0.03, I2 = 38%). According to the systematic review, the increase of DAS 28 could be explained by an increased of tender joint counts and global health assessment.

Conclusion: Obesity in RA is associated with higher DAS 28 and HAQ. However, obese patients with RA have lower RJD. This increase of DAS28 in obese patients could be explained by pro-inflammatory fat cytokines or the general tendency of higher pain levels due to comorbidities resulting from obesity. Conversely, the increase of adiponectin observed in obese patients.
Table 2: Multivariate regression (GEE): Both high and low BMI were associated with a lower odds of achieving sustained remission

<table>
<thead>
<tr>
<th>Variables*</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Category 1 vs. 2**</td>
<td>0.55 (0.31–0.96)</td>
<td>0.0361</td>
</tr>
<tr>
<td>BMI Category 3 vs. 2</td>
<td>0.75 (0.63–0.90)</td>
<td>0.0022</td>
</tr>
<tr>
<td>BMI Category 4 vs. 2</td>
<td>0.82 (0.67–1.01)</td>
<td>0.0678</td>
</tr>
<tr>
<td>BMI Category 5 vs. 2</td>
<td>0.50 (0.37–0.67)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI Category 6 vs. 2</td>
<td>0.36 (0.24–0.53)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Function (HAQ-DI) 0–3</td>
<td>0.54 (0.44–0.66)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pain (0–10)</td>
<td>0.94 (0.89–0.99)</td>
<td>0.0369</td>
</tr>
<tr>
<td>Achieved LDAS by 6 months (DAS28&lt;3.2)</td>
<td>5.36 (4.57–6.29)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of ERA patients in CATCH based on WHO BMI Categories (Univariate Analysis)

<table>
<thead>
<tr>
<th>BMI Category Baseline Variables*</th>
<th>BMI 1 (≤ &lt;18.5)</th>
<th>BMI 2 (18.5-24.9)</th>
<th>BMI 3 (25)</th>
<th>BMI 4 (≥ 25)</th>
<th>BMI 5 (≥ 25 and ≤ 30)</th>
<th>BMI 6 (≥ 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Underweight</strong> (N=44)</td>
<td>10 (22.7%)</td>
<td>24 (54.4%)</td>
<td>4 (9.1%)</td>
<td>6 (13.6%)</td>
<td>3 (6.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normal (N=344)</td>
<td>45 (13.2%)</td>
<td>132 (38.7%)</td>
<td>98 (28.5%)</td>
<td>36 (10.5%)</td>
<td>16 (4.7%)</td>
<td>12 (3.5%)</td>
</tr>
<tr>
<td>Overweight (N=323)</td>
<td>19 (5.9%)</td>
<td>92 (28.6%)</td>
<td>91 (28.3%)</td>
<td>35 (10.8%)</td>
<td>14 (4.3%)</td>
<td>9 (2.8%)</td>
</tr>
<tr>
<td>Obese I (N=175)</td>
<td>13 (7.4%)</td>
<td>54 (30.8%)</td>
<td>44 (25.1%)</td>
<td>29 (16.6%)</td>
<td>16 (9.2%)</td>
<td>15 (8.5%)</td>
</tr>
<tr>
<td>Obese II (N=76)</td>
<td>10 (13.2%)</td>
<td>38 (50.0%)</td>
<td>26 (34.2%)</td>
<td>7 (9.2%)</td>
<td>4 (5.3%)</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Obese III (N=42)</td>
<td>6 (14.3%)</td>
<td>23 (54.8%)</td>
<td>12 (28.6%)</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;.0001</td>
<td>.0410</td>
<td>.0001</td>
<td>.0010</td>
<td>.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of BMI groups where normal BMI is referent

Background/Purpose: To determine if patients with a very low body mass index (BMI) (<18.5) or high BMI (≥25) are able to achieve sustained remission (susREM) in an early RA (ERA) cohort.

Methods: Initial BMI and disease activity (DAS28) were prospectively measured over 3 years in patients from CATCH (Canadian Early Arthritis Cohort). Patients were categorized into 6 groups based on World Health Organization BMI classifications (class 1–6) Differences between BMI groups in patients’ demographics and clinical outcomes were assessed using Chi-square/Fisher’s exact tests or Kruskal-Wallis tests. Multivariate regression based on generalized estimating equations (GEE) methods was used to compare the likelihood of achieving susREM between groups, where susREM was defined as DAS28<2.6 x 2 at consecutive visits 3–12 months apart.

Results: 944/2524 eligible patients with a measured BMI and ≥ 2 consecutively measured DAS28 scores over 3 years formed the study cohort. Only 15 (2%) patients were underweight (category Cat 1). Overall 65% were either overweight (34% in Cat 3) or obese (31% in Cat 4–6), representing a rate higher than the WHO reported 47% national average. Patient characteristics in the 6 BMI categories were studied (Table 1).

Univariate analysis, presented for BMI strata show patients with higher BMI were older (p<0.0001), more often female (p<.001) with worse function at baseline by HAQ-DI (p<0.001). Those with very low or high BMI had a higher CRP (p=0.0004) and ESR (p<0.0001), and those with low or normal BMI were more often smokers (p=0.0001). Patients in the highest BMI strata had higher Patient Global Assessments of disease (PGa) (p=0.03) and pain (p=0.04). Variables that did not differ among groups included Physician’s Global assessments (MDGa) (p=0.9), ACFA and RF positivity [(p=0.16), (p=0.26)], symptom duration (p=0.66), DAS28 (p=0.06) at study entry, or steroid (p=0.5) or methotrexate (MTX) use (p=0.9) over the first 3 months. In the multivariate analysis patients in all BMI categories except for class 4 (p-value=0.678) were significantly less likely to achieve susREM compared to normal BMI. Early MTX use, not smoking, being Caucasian and achieving a low disease activity state (LDAS) by 6 months increased the odds of achieving susREM (Table 2).

Conclusion: The chance of achieving sustained remission is decreased in underweight, and overweight/obese ERA patients, more so in the morbidity obese (class 5–6). Early use of MTX, an early response to treatment, and non-smoking status improve the odds of sustained remission independent of BMI category. Underweight BMI may play a role in joint damage.

Disclosure: C. Vidal, None; T. Barnetche, None; J. Mored, None; B. Combe, None; C. Daen, None.

References:
1. C. Hitchon, None; C. Vidal, None; T. Barnetche, None; J. Mored, None; B. Combe, None; C. Daen, None.

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2010 criteria (RA) and undifferentiated arthritis (UA). We then compared logOPG, logTRAIL, logOPG/logTRAIL using general linear model adjusted for DAS28, rheumatoid factor and anti-citritulinated protein antibodies positivity, and total Sharp score at M0. Logistic regression was used to determine predictive value for remission (DAS28 ≤ 2.6) and radiographic progression (DSharp score >0).

Results: TRAIL, OPG and TRAIL/OPG at M0 were not different between RA (n = 641) and UA patients (n = 53). Among RA patients, patients with remission at M12 had a significantly lower concentration of M0 logOPG than those with DAS28 >2.6 (2.92±0.18 vs 2.98±0.16 pg/ml (n=341), respectively, p=0.002 and p=0.026 after adjustment). M0 TRAIL and M0 OPG/TRAIL were not significantly different between patients in remission at M12 and others. Logistic regression adjusted for DAS28, rheumatoid factor and anti-citritulinated protein antibodies positivity, and total Sharp score at M0 showed that logOPG≥3.1 (=1259 pg/ml) was predictive of absence of M12 remission (B=0.55, CFE: 0.33–0.90, p=0.018), with a sensitivity of 21%, a specificity of 87%, a positive predictive value of 75% and a negative predictive value of 38%.

Patients with progression of Sharp score erosion at M24 had significant lower M0 logTRAIL (2.96±0.22 vs 3.00±0.19, p=0.009 and p=0.002 after adjustment). M0 OPG and M0 OPG/TRAIL were not significantly different between patients with or without radiographic progression at M24. Logistic regression adjusted for DAS28, rheumatoid factor and anti-citritulinated protein antibodies positivity, and total Sharp score at M0 showed that logTRAIL≤2.95 (891 pg/ml) was predictive of erosion progression (B=0.47, CFE: 0.30–0.72, p=0.001) with a sensitivity of 52%, a specificity of 63%, a VPP of 39% and a VPN of 74%.

Conclusion: Concentrations of TRAIL and OPG could not help in distinguish UA and RA. Low M0 OPG is associated with remission at VPP of 39% and a VPN of 74%.

Physician pre-post differences in global assessment were not significantly different across disease duration, gender, age and DAS scores. Similar results were observed in the patient assessments except for disease duration. Smaller differences were observed in subjects having a disease duration of two years or less. The GLM revealed that no factors other than rater (physician or patient) explained the observed differences.

Physician global activity scores showed moderate correlation, the change in these assessments exhibited a weak relationship. Both physicians and patients agree on disease activity improvement although their magnitudes differ. Of the factors explored, only rater (physician or patient) seem to explain these differences.

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Th9 Lymphocytes in Rheumatoid Arthritis. Rosella Talotta¹, Angela Berzi², Fabiola Atzeni¹, Donata Dell’Acqua¹, Piercarlo Sarzi-Puttini¹ and Daria Trabattoni². Rheumatology Unit, L. Sacco University Hospital, Milan, Italy. ²Chair of Immunology, Department of Biomedical and Clinical Sciences "L. Sacco, Milan, Italy.

Background/Purpose: Th9 cells are IL-9-secreting Th lymphocytes that are involved in the immunological responses underlying parasitic infections and allergic diseases. In the case of autoimmune diseases, Th9 cells seem to be involved in the pathogenesis of experimental autoimmune encephalomyelitis. No study has yet evaluated the effects of Th9 responses in rheumatic diseases such as rheumatoid arthritis (RA). The aim of this study was determine the prevalence of Th9 lymphocytes in RA patients and identify their possible association with the discontinuation of biological treatment with infliximab (IFX).

Methods: We enrolled 55 consecutive RA outpatients: 15 not receiving any immunosuppressive drug; 20 responders to IFX treatment; and 20 who had discontinued IFX because of adverse events or inefficacy and were being treated with other biological agents (ABA, TCZ, ETN or CTZ) and traditional immunosuppressive drugs. The matched control group consisted of 10 healthy subjects. After giving their informed consent, the subjects underwent blood sampling for the isolation of peripheral blood mononuclear cells (PBMCs). The PBMCs were cultured with/without IFX 50 μg/ml for 18 hours, and the percentage of Th9 cells was assessed by means of flow cytometry. Th9 lymphocytes were identified as IFNγ-, IL-4-, IL-17-, IL-9-secreting CD4+ T cells.

Results: Cytometric analysis revealed no significant decrease in the percentage of Th9 cells after IFX exposure in any of the groups, but there were significantly fewer cells in the healthy controls than the RA patients both before and after the IFX stimulation assay (Fig.1). The higher frequency of Th9 cells in the patients was not associated with higher levels of anti-nucleus autoantibodies or other auto-antibody subsets, or with a higher likelihood of experiencing an adverse event or lack of efficacy on IFX treatment.

Conclusion: IL-9 levels are increased in RA patients, in whom it plays a crucial role. Th9 cells are the major producers of IL-9, and their prevalence is higher in RA patients than in healthy subjects, although they do not seem to affect the outcome of biological therapies.
Anti-Rheumatic Therapy Decreases Syndecan-1 Shedding in Rheumatoid Arthritis (RA). Ivana Hollan1, Gunnbjørg Hjeltnes2, Torstein Lyberg2, Stefan Agewall3, Allan Wilk4, Knut Mikkelsen1, Øystein T. Førre5, Tram T. Vuong6 and Svein O. Kolset3.1Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, 2Innlandet Hospital Trust, Lillehammer, Norway, 3Department of Medicine, Kuopio University Hospital, Kuopio, Finland, 4Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, 5Computational Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland, 6NMR Metabolomics Laboratory, School of Pharmacy, University of Eastern Finland, Kuopio, Finland, 7Helsinki Medical Imaging Center, Helsinki University Hospital, Helsinki, Finland, 8Kuopio Municipal Hospital, Kuopio, Finland, 9Suonenjoki Health Center, Suonenjoki, Finland.

Background/Purpose: Intact glyocalyx is of importance for healthy endothelial function. Changes in the endothelial glyocalyx, characterized by increased levels of circulating syndecan-1, might be related to accelerated atherosclerosis in RA. The aim of this study was to examine the level of serum (s-) syndecan-1 in patients with RA, and the effect of anti-rheumatic treatment on the s-syndecan-1 levels.

Methods: We selected 32 patients with active RA from the Norwegian observational PSARA study. Due to clinical decision, the patients should start either with methotrexate or methotrexate (MTX) and anti-tumor necrosis factor (TNF) regimen. The patients were examined before the treatment initiation (visit 1) and after 6 weeks (visit 2) of the treatment. S-syndecan-1 was measured by ELISA.

Results: The mean age of the patients was 59 ± 8 years, and 27% were men. 12 patients received MTX and 20 received MTX and anti-TNF treatment. S-syndecan-1 levels significantly decreased from visit 1 (49 ± 52 ng/ml) to visit 2 (45 ± 50 ng/ml), p=0.047. The difference was independent of age, sex and difference in DAS28. The s-syndecan-1 reduction was greater in the MTX than MTX and anti-TNF group (10 ± 13 vs. 1 ± 1 ng/ml), p=0.048.

Conclusion: Anti-rheumatic treatment reduces s-syndecan-1 in RA. Thus, a glyocalyx ameliorating effect may contribute to the reduction of cardiovascular morbidity and mortality due to anti-rheumatic treatment. In theory, the greater reduction of s-syndecan-1 in the MTX than in the combined group might be due to differences in patient population, as patients starting with MTX are likely to have a less severe RA, with a shorter disease duration, than those starting with anti-TNF. Interestingly, although MTX is considered as a less potent anti-rheumatic drug than anti-TNF, it may have a protective effect on glyocalyx, which may explain its cardioprotective effect observed in previous studies. This effect might be at least partially independent of its anti-inflammatory properties.

Disclosure: I. Hollan, None; G. Hjeltnes, None; T. Lyberg, None; S. Agerwall, None; A. Wilk, None; K. Mikkelsen, None; T. Forre, None; T. T. Vuong, None; S. O. Kolset, None.

Lipid Concentrations and Particle Sizes in Drug Naive Patients with Rheumatoid Arthritis. Auliikki Kononoff1, Hannu Kautiainen2, Pasi Soiminen3, Antti Kangas3, Leena Laasonen3, Leena Arstila3, Pia Elving3, Elina Savolainen3, Helena Niinisalo3, Mika Ala-Korpela3 and Olli Kautiainen-Seppanen1.1Department of Medicine, Kuopio University Hospital, Kuopio, Finland, 2Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, 3Computational Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland, 4NMR Metabolomics Laboratory, School of Pharmacy, University of Eastern Finland, Kuopio, Finland, 5Helsinki Medical Imaging Center, Helsinki University Hospital, Helsinki, Finland, 6Kuopio Municipal Hospital, Kuopio, Finland, 7Suonenjoki Health Center, Suonenjoki, Finland.

Background/Purpose: Excess mortality attributed to cardiovascular causes has been described among patients with rheumatoid arthritis (RA). Atherosclerotic lipid profile has been reported in patients with drug naïve RA without comorbidities. In a European study on inflammatory and atherogenic lipoprotein markers, patients with RA had significantly higher levels of small, dense LDL and lower levels of large, light LDL than controls. The size of LDL particles was smaller in RA patients compared to controls. We have investigated lipid concentrations and particle sizes among patients with newly diagnosed RA in a population based cohort.

Methods: Concentrations and sizes of lipoprotein subclass particles were analyzed by proton nuclear magnetic resonance spectroscopy of native serum samples from patients with RA participating in Northern Savo 2010 Study. Results: Sixty-three drug naïve patients, 34 female and 29 male patients with RA satisfying the ACR/Eular 2010 classification criteria were divided into tertiles according to the disease activity measured by DAS28 (<3.9, 3.9–4.7, >4.7). Small LDL concentrations were lowest in the tertile with the highest disease activity, p=0.031, and the particle size in LDL also increased with increasing disease activity, p<0.001. In HDL, the total, medium and small particle concentrations showed a linear decrease along with the disease activity, p=0.0012, 0.0079 and <0.001, respectively.

Conclusion: Marked changes in lipid concentrations and particle sizes occurred in drug naïve patients with RA and they were associated with disease activity.

References

Disclosure: A. Kononoff, None; H. Kautiainen, Abbvie inc, Pfizer inc; 5; S. Soiminen, None; A. Kangas, None; L. Laasonen, None; L. Arstila, None; P. Elving, None; E. Savolainen, None; H. Niinisalo, None; M. Ala-Korpela, None; O. Kautiainen-Seppanen, None.

Clinical Utility of 14-3-3p in the Evaluation of Inflammatory Arthritis. Lance Feller1, Paul Tuttle IV2 and Terry L. Moore3.1Saint Louis University, St. Louis, MO, 2Saint Louis University, St. Louis, MO.

Background/Purpose: 14-3-3 proteins are chaperones found in all eukaryotic cells. There are multiple isoforms which are thought to be involved in intracellular signaling and transcription regulation. Among their targets are phosphatases, kinases and transmembrane receptors. There are seven known isoforms in mammals. Recent work has implicated the η (Eta) isoform as having diagnostic potential in inflammatory arthritis. In this study we investigated the utility of measuring 14-3-3p when evaluating inflammatory arthritis.

Methods: Measurements of 14-3-3p were obtained during evaluation of joint pain in patients presenting between July 2013 and May of 2014. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were measured. Joint imaging was evaluated for erosive changes. A chart review was later conducted to evaluate the utility of standard measures versus 14-3-3p.

Results: 120 patients were evaluated. 21 had RA, 8 had juvenile idiopathic arthritis (JIA), and 6 had psoriatic arthritis (PsA). 30 patients had connective tissue disease (CTD), 10 had fibromyalgia (FMS), 3 had mono-
clonal gammopathies, 1 had enteropathic arthritis, and 1 had erosive osteoarthritis (OA). 8 had only OA, 2 had benign hypothyroidism syndrome, 1 had amyopathic dermatomyositis, 2 had celiac disease, and 2 had crystal induced arthropathies. 7 were antinuclear antibody (ANA) positive without syonovitis or CTD. 3 patients had granulomatosis with polyangitis, 2 had suspected PSA, 2 had chronic urticaria, and 11 had no associated condition.

Of the 21 RA patients, 18 were RF positive, 16 were anti-CCP Ab positive, and 16 were 14-3-3 positive. All 16 14-3-3 positive patients with RA were RF positive, 9 had joint erosions, of which 8 were RF, anti-CCP Ab and 14-3-3 positive. 14-3-3 was 76.2% sensitive for RA, and 89% specific. Its positive predictive value (PPV) was 61.5%, and negative predictive value (NPV) was 94.2%. 4 of the 8 JIA patients were 14-3-3 and RF positive. 4 were also anti-CCP Ab positive, of which 2 had measurable 14-3-3. 3 JIA patients had joint erosions. When JIA and RA were considered together, the sensitivity and specificity of 14-3-3 was 68.9% and 89% respectively, while PPV and NPV were 93% and 70%. The correlation of 14-3-3 and RF titers in RA was 0.63 (p<0.001) and 0.65 (p<0.001) in the combined RA/JIA cohort.

All 6 patients with PSA were seronegative. 2 had joint erosions.

30 patients had CTD; 6 were RF positive, 2 were anti-CCP Ab positive, and 5 were 14-3-3 positive. 3 of the five 14-3-3 positive patients also produced RF, while 1 had anti-CCP Ab. All FMS patients were seronegative. Of the 8 patients with purely OA, 1 had 14-3-3. 1 patient with celiac disease had 14-3-3. 1 patient with a positive ANA and joint pain had 14-3-3. 1 patient with joint pain and no evidence of synovitis produced 14-3-3.

Of the 17 patients with RF without RA, 10 were positive for 14-3-3, while 7 were positive for anti-CCP Ab.

**Conclusion:** 14-3-3 protein titers are associated with RA. Their general trend follows RF. Based upon the results from our study, 14-3-3 is both sensitive and specific for RA, with value in evaluating JIA as well. A larger sample size is necessary to evaluate utility with JIA.

**Disclosure:** L. Feller, None; P. Tuttle IV, None; T. L. Moore, None.

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**Association of Anti-Thyroid Autoantibodies with Fibromyalgia in Rheumatoid Arthritis.** Joawantiya Ahmad1, Helena Blumen, Claudia George, Asha Shresthe4 and Clement Tagoe4, 1Albert Einstein College of Medicine/Montefiore Medical Centre, Bronx, NY, 2Albert Einstein College of Medicine/Montefiore Medical Centre, Bronx, NY, 3Albert Einstein College of Medicine/Montefiore Medical Centre, Bronx, NY, 4Albert Einstein College of Medicine/Montefiore Medical Centre, Bronx, NY.

**Background/Purpose:** Autoimmune thyroiditis has been linked independently with fibromyalgia and chronic widespread pain. We studied how the presence of autoimmune thyroiditis affects the clinical presentation of rheumatoid arthritis with particular reference to chronic pain syndromes.

**Methods:** We studied a cohort of 203 patients with a diagnosis of rheumatoid arthritis for whom the presence or absence of autoimmune thyroid antibodies was documented. The relationships between thyroid autoantibodies and the presence of fibromyalgia and chronic widespread pain were examined. Logistic regression analyses were performed to determine the statistical significance of these associations.

**Results:** In our sample of 203 patients, we identified 34% of patients who tested positive for anti-thyroid peroxidase antibodies (anti-TPO). Thirty five percent of patients tested positive for anti-thyroglobulin antibodies (anti-TG). Among the thyroid autoantibody-positive patients, 37% had a diagnosis of fibromyalgia or chronic widespread pain. Additional patient variables considered included age, sex, body mass index (BMI) and the presence of comorbidities, including type II diabetes.

Logistic regression analyses (adjusted by age, sex, diabetes and BMI) indicated that anti-TPO positive patients were more likely to be diagnosed with fibromyalgia and report the presence of chronic widespread pain, with an odds ratio of 3.42, 95% CI (1.665–7.017), p<0.001. The odds ratio between anti-TG and fibromyalgia was not significant, p>0.05. Patients who were either anti-TPO or anti-TG positive were more likely to be diagnosed with fibromyalgia with an odds ratio of 2.70, CI (1.193–6.082), p<0.05.

When adjusted for degenerative disc disease, patients who were either anti-TPO or anti-TG positive were more likely to be diagnosed with fibromyalgia with an adjusted OR of 3.56, CI (1.608–7.003), p<0.05.

**Conclusion:** There is a strong positive association between the presence of anti-thyroid autoantibodies and hence autoimmune thyroiditis, with fibromyalgia syndrome and chronic widespread pain in patients with established rheumatoid arthritis.

**Disclosure:** J. Ahmad, None; H. Blumen, None; C. George, None; A. Shrestha, None; C. Tagoe, None.

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**Can GP88 (Progranulin) be Used As A Biomarker for the Diagnosis and Therapy Evaluation of Rheumatoid Arthritis?** Masao Sato1, Masao Takemura1, Kuniaki Saito2 and Yasuko Yamamoto2, 1Matsunami Reserch Park, Gifu, Japan, 2Kyoto University, Kyoto, Japan.

**Background/Purpose:** GP88 (progranulin; PGRN), a glycoprotein with a molecular weight of approximately 88000, is suggested to play an important role in the immune response and growth of tumors. Recently, its high affinity for the tumor necrosis factor receptor has been reported and there have been studies on its anti-inflammatory effects in autoimmune diseases. The objectives of the present study were to measure serum GP88 levels in rheumatoid arthritis (RA) patients, to analyze the changes of GP88 levels in RA patients treated with biological products, and to analyze whether PGRN is useful as a biomarker for the diagnosis and therapy evaluation of RA.

**Methods:** Serum PGRN levels were measured using ELISA in 149 healthy subjects (78 men and 71 women) who underwent health checkups (controls) and in 68 RA patients and 24 knee osteoarthritis (OA) patients before the start of treatment, who met the 2010 ACR/EULAR classification criteria and visited the arthritis outpatient clinic. Among RA patients who were non-responsive to methotrexate (MTX), the cryopreserved serum samples of 11 patients who were administered infliximab (IFX) were analyzed to determine the PGRN levels during the course of treatment (at baseline, week 6, week 14, week 22, and week 48).

**Results:** PGRN levels in the controls were 40.5 ± 14.3 ng/mL in men (mean age, 54.2 years; range, 25–68) and 41.0 ± 10.9 ng/mL in women (mean age, 51.0 years; range, 28–69), and there were no sex and age differences. PGRN levels were significantly higher in RA patients (51.2 ± 12.5 ng/mL) than in OA patients (43.9 ± 5.8 ng/mL) (p<0.01) and controls (p<0.001). Among the RA patients, 10 women and 1 man (mean age, 62.0 years; range, 27.0–78.0) received IFX treatment. MTX was administered orally at 6–8 mg/week, and IFX was administered at 3 mg/kg. Mean PGRN levels at the different time points were as follows: baseline, 43.0 ng/mL; week 6, 46.4 ng/mL; week 14, 50.8 ng/mL; week 22, 48.9 ng/mL; and week 48, 50.4 ng/mL, and there were no significant changes. Because disease activity was high at week 48 and IFX was considered ineffective, 2 cases received a different biological product. Mean PGRN levels in these 2 cases were as follows: baseline, 60.1 ng/mL; week 6, 61.3 ng/mL; week 14, 68.3 ng/mL; week 22, 74.9 ng/mL; and week 48, 79.5 ng/mL, showing an increasing tendency with the treatment course.

**Conclusion:** Serum PGRN levels were found to be significantly higher in RA patients than in OA patients and controls. Further, no changes in the PGRN levels were found in the group that showed a good response to IFX treatment. However, in cases resistant to IFX, PGRN levels were high when IFX was introduced, followed by an increasing tendency with the treatment course. Owing to the small number of cases in the present study, it is difficult to obtain a clear result. However, the findings showed the possibility of using PGRN levels for the differential diagnosis of RA patients and the therapy evaluation of IFX.

**Disclosure:** M. Sato, None; M. Takemura, None; K. Saito, None; Y. Yamamoto, None.

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**Metalflammation, PEDF and Chemerin: Potential Systemic Factors Which Link Obesity to Response to Therapy in Early Rheumatoid Arthritis.** Elisa Gremese, Barbara Tolusso, Anna Laura Fedele, Maria Rita Gigante, Silvia Canestri, Clara Di Mario, Angela Carbonella and Gianfranco Ferraccioli, Division of Rheumatology, Institute of Rheumatology and Ailffe Sciences, Catholic University of the Sacred Heart, Rome, Italy.

**Background/Purpose:** Obesity per se is a systemic, low-grade inflammatory state and the adipose tissue is an endocrine organ that releases bioactive substances, including pro-inflammatory cytokines, like TNFα and IL6 and specific adipokines. There are only few data about early RA (ERA), suggesting that obesity associates with disease outcomes. In this work we aimed to evaluate whether the body weight, and fat metabolic (PEDF-Pigment Epithelium-Derived Factor) and...
meta-inflammatory parameters (Chemerin), could be associated with the outcomes in terms of disease remission and treatment in ERA patients (symptoms duration <12 months).

**Methods.** 164 ERA patients, treated according to a treat-to-target strategy, were enrolled. At each visit the ACR/EULAR core data set was registered. Baseline BMI was collected and baseline interleukin-6, PEDF and Chemerin plasma levels were evaluated by ELISA’s methods.

**Results.** Of the 164 ERA patients (75.5% female, age 55.4±14.6 years, 34.3% very ERA, 66.9% seropositive, baseline DAS 3.4±1.0), 75 (45.7%) were normal weight, 66 (40.2%) overweight and 23 (14.0%) obese. Overweight and obese patients showed a higher disease activity at baseline compared to normal-weight patients (DAS: 3.6±1.0 vs. 3.3±0.9, p=0.02). At baseline, BMI values correlated with baseline PEDF (r=0.35, p<0.001) and chemerin (r=0.31, p<0.001) plasma levels. Moreover, chemerin plasma levels were correlated with aminoterminal pro-BNP (IL-6: r=0.28, p<0.001), ESR: (r=0.39, p<0.001), CRP: (r=0.35, p<0.001), swollen joint count (r=0.26, p<0.001), tender joint count (r=0.23, p<0.001), HAQ (r=0.24, p=0.002), DAS (r=0.34, p<0.001), CDAI (r=0.28, p<0.001) and SDAI (r=0.32, p<0.001). On the other hand, PEDF plasma levels correlated only with age (r=0.35, p<0.001) and baseline inflammatory markers (ERs: r=0.17, p=0.03, CRP: r=0.22, p=0.01). At 6 and 12 months, none of the patients had a significant reduction of weight-body. A significant reduction of the disease activity at 6 and 12 months follow-up was observed in the three subgroup of ERA patients (normal-weight, overweight and obese patients). In the same manner, circulating chemerin levels significantly decreased over time; conversely, the circulating levels of PEDF remained unchanged. These findings were observed both in patients reaching and not reaching remission at 12 months of follow up.

Fourteen obese RA patients (BMI 35.3±3.2) with an active disease (DAS 3.5±0.7) underwent a dietary regimen for weight loss for six months, with no change in RA treatment. At the sixth month, the mean reduction in percentage of BMI was 8.9±5.3% and the average percentage of DAS reduction was 46.8±20.2% (DAS T0: 1.8±0.6, p=0.01 with respect to DAS T0).

**Conclusion.** In ERA patients, PEDF and chemerin seem to be biomarkers of obesity and metaflammation, respectively. Chemerin seems to be linked to RA disease activity and to treatment response, irrespective of body weight and meta-inflammatory parameters (Chemerin), could be associated with the outcomes in terms of disease remission and treatment in ERA patients (symptoms duration <12 months).

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**14-3-3-σ: A Mechanistic Biomarker That Supports the Concept of “Uncoupling” of Inflammation and Joint Damage.** Dirkjan van Schaardenburg1, Mairead Murphy2, Yuan Gui3, Samina Turk1, WP Maksymowych1, Kelly Young1 and Anthony Marotta2. 1Reade, Amsterdam, Netherlands, 2Augurex Life Sciences Corp., North Vancouver, BC, 3University of Alberta, Edmonton, AB, 4Rheumatoid Patient Foundation, Cocoa, FL.

**Background/Purpose:** In RA, irreversible joint damage often begins within the first year of symptom onset. A compelling and growing body of data describing the “uncoupling” of inflammation and joint destruction indicates that radiographic monitoring is important in all RA patients, regardless of clinical response. Uncoupling is an interesting phenomenon that may not be apparent with either the DAS 28 or CRP. Furthermore, since HMGB1 can also arise from cell death, the elevation of HMGB1 levels, even with remission or low disease activity, may reflect tissue destruction that persists even with inflammation restrained.

**Disclosure:** D. S. Pisetsky, None; D. Spencer, None; S. R. Wisniewski, None; J. Lyons, None; M. Saul, None; M. J. McGeachy, None; Y. G. Hwang, None; H. Eng, None; L. W. Moreland, None.

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**The Relationship Between Disease Activity and Levels of HMGB1 in Patients with Rheumatoid Arthritis.** David S. Pisetsky1, Diane Spencer2, Stephen R. Wisniewski3, Jason Lyons4, Melissa Saul5, Mandy J. McGeachy6, Yong Gil Hwang6, Heather Eng7 and Larry W. Moreland8. 1Durham VAMC, Durham, NC, 2Duke University Medical Center, Durham, NC, 3University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, 4University of Pittsburgh, School of Medicine, Pittsburgh, PA, 5University of Pittsburgh, Pittsburgh, PA, 6University of Pittsburgh, Pittsburgh, PA.

**Background/Purpose:** HMGB1 (High Mobility Group Box 1), a non-histone nuclear protein, is a prototypic alarmin that displays immunological activity following release during cell death or immune cell activation. As shown in studies of patients with rheumatoid arthritis (RA) and animal models, HMGB1 plays a key role in pathogenesis; HMGB1 has increased expression in synovial tissue and blockade of HMGB1 can attenuate disease in animal models. While the role of HMGB1 in mediating disease has been well studied, its role as a biomarker has received less attention. The present study therefore explored the expression of HMGB1 in the blood of RA patients, investigating correlations with various clinical features.

**Methods:** This study utilized samples from the RACER (Rheumatoid Arthritis Comparative Effectiveness Research) cohort. Patients varied in disease duration and received therapy determined by clinical response. Disease activity was assessed by DAS 28 scores using C-reactive protein as the acute phase reactant. The samples, selected to provide a range of disease activity, were divided into 4 groups: remission; low activity; moderate activity; and high activity. Levels of HMGB1 were determined by ELISA using the Shino-test kit. The concentrations of HMGB1 in the plasma from 10, non-RA control subjects were also measured.

**Results:** Among 100 patients with RA, HMGB1 levels varied from 1.1 to 19.3 ng/ml (median value = 5.73 ng/ml) which was significantly higher than those of the control population (range = 0.72–3.28; median value = 1.93 ng/ml). Despite the increase in HMGB1 levels in the RA population, the median values of the 4 disease activity groups were similar (remission, 5.98; low 5.09; moderate 5.64; high, 6.02). These differences did not reach statistical significance by a non-parametric ANOVA. In contrast, CRP levels showed a statistically significant association with disease activity by a non-parametric ANOVA (p = 0.001). As a previous study suggested a relationship with disease duration, the results were analyzed in terms of duration less than 5 years, 5-10 years, 15-20 years and greater than 20 years. This analysis failed to reveal a relationship with disease duration. Values of males and females were also similar.

**Conclusion:** These studies demonstrate that levels of HMGB1 are elevated in the blood of patients with RA and show a relationship to disease activity distinct from that of CRP. As HMGB1 levels were increased in patients either in remission or with low disease. Conjugate proteins suggest an ongoing inflammation that may not be apparent with either the DAS 28 or CRP. Furthermore, since HMGB1 can also arise from cell death, the elevation of HMGB1 levels, even with remission or low disease activity, may reflect tissue destruction that persists even with inflammation restrained.

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**Table 1**

| SHS Y1 | 0.00–3.131 | 1.0–5.733 | 0.02 |
| SHS Y2 | 10–5.133 | 2.0–817 | 0.02 |
| SHS Y3 | 1.5–6.128 | 3.0–10.204 | 0.01 |
| Δ SHS Y1 | 0.00–1.131 | 0.00–2.704 | 0.006 |
| Δ SHS Y2 | 2.0–5.133 | 1.0–6.701 | 0.008 |
| Δ SHS Y3 | 0.00–4.107 | 2.0–7.204 | 0.009 |
The Utility of HLA-DR Genotypification As a Complementary Tool to Discriminate Undifferentiated and Rheumatoid Arthritis Patients in Early Arthritis. Fernando Dal Pra1, Gustavo Citera2, Margarita Landi3, Christian A. Waimann4, Luis Alejandro Cayet4, Sergio Pará1, Federico Cecatto5, Teresa Alvarellos6, Luciana Mas7, Josefina Marcos8, Mercedes García8, A. Salas8, Alejandro Martínez9, Rafael Chaparro10, Oscar Luis Rílo1, Edison Veloso11, Ricardo V. Juárez12, Maria Elena Crespo13, Antonio Catalán Pellet13, Anastasia Secco14, Lucila Marino12 and V. Martire14 1Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, 2Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, 3Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, 4Hospital Olavarria, Olavarria, Argentina, 5Hospital General de Agudos Dr. E. Torri, Buenos Aires, Argentina, 6Hospital Gral. de Agudos “Dr. Juan arena”, Buenos Aires, Argentina, 7Sanatorio y Universidad Adventista Del Plata, Entre Ríos, Argentina, 8Hospital Señor del Milagro, Salta, Argentina, 9Hospital Señor Del Milagro, Salta, Argentina, 10Hospital Bernardino Rivadavia, Buenos Aires, Argentina.

Background/Purpose: Only half of patients with undifferentiated arthritis (UA) will progress to rheumatoid arthritis (RA) after two years of follow-up. Particular human leukocyte antigens class II-DR (HLA-DR) alleles have been associated with a higher risk to develop RA, however these alleles may vary among ethnic groups. The aim of our study was to investigate the frequency of HLA-DR alleles and evaluate the association with the development of rheumatoid arthritis in an early arthritis cohort in Latin America.

Methods: We designed a case-control study. Cases were defined as patients with diagnosis of RA from an early arthritis cohort (<2 years of disease duration). Two control groups were selected. First group was obtained from the mentioned cohort and included patients with UA. The second control group was obtained from the national register of cadaveric organ donors (Healthy Subjects, HS). HLA-DR genotypes frequencies were estimated for each group. We calculated the odds ratio (OR) to develop RA in general population and undifferentiated arthritis. Statistical analysis was performed with two-tailed Pearson’s chi-squared test with Bonferroni adjustment (p-value = 0.05). Logistic regression analysis was used to identify the association of HLA-DR alleles and RA development in patients with UA, adjusted by smoking, gender and presence of rheumatoid factor (variable significance entry criteria P < 0.15). A p-value less than 0.05 was considered statistically significant.

Results: We included a total of 1859 subjects: AR = 474; UA = 52; C's = 1406. When compared with HS, RA patients had an increased frequency of DR4 [RA = 50% vs HS = 31%; OR 2.3 (1.7 - 2.8), P < 0.0001], DR9 [RA = 12% vs HS = 7%; OR 1.9 (1.3 - 2.8), P = 0.02], and lower frequency of DR7 [RA = 1% vs 21%; OR 0.6 (0.4 - 0.8), P = 0.02], DR11 [RA = 10% vs 21%; OR 0.4 (0.3 - 0.6), P = 0.0001], DR15 [RA = 9% vs 15%, OR 0.5 (0.4 - 0.8), P = 0.04]. Among patients with early arthritis, being heterozygote or homozygote for DR-4 allele could not differentiate between patients with RA and UA. On the other hand, patients with UA showed a higher frequency of DR7, DR11 and DR15 than RA (23%, 21%, 17% vs 13%, 11% respectively), but did not reach statistical significance after adjustment for multiple comparisons. Stepwise regression indicated that the presence of DR15 was significantly associated with lower risk of RA [OR = 0.35 (0.12 - 0.97), p = 0.04].

Conclusion: In our cohort of patients with early arthritis, the genotyping of HLA-DR alleles was not useful to discriminate between RA and UA. Only the presence of DR15 allele was associated with a lower probability of RA, however the poor precision of the estimates makes it difficult to address the utility of this determination in daily clinical practice.
at baseline. Median patient age was 56 years and 73% were female. 14-3-3-γ protein levels were tested using the Augurex 14-3-3-γ ELISA (cut-off ≥0.19 ng/ml) and 67% of patients were positive. 14-3-3-γ AAb levels were measured on the MSD ECL platform and using a diagnostic cut-off of 380 U/ml, 77% of patients were positive. Patients were grouped into 4 groups: 1) Negative for both markers, 2) Positive for the 14-3-3-γ only, 3) Positive for the 14-3-3-γ AAb only and 4) Positive for both markers. Assessment of differences across these 4 groups was performed using Kruskal-Wallis Analysis of Variance (ANOVA) with Dunn’s post-hoc testing to identify differences between individual groups.

Results: Across the four 14-3-3-γ biomarker expression groups (table), ANOVA revealed significant differences in RF and CCP positive rates and titers (p<0.0001), baseline TSS, SJC28 and ESR (±0.01). Patients who were only 14-3-3-γ auto-antibody positive had significantly lower positivity rates and titers of RF and CCP (p<0.0001).

<table>
<thead>
<tr>
<th>ANOVA (4 groups)</th>
<th>Double +</th>
<th>Protein +</th>
<th>AAb +</th>
<th>Double +</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF +</td>
<td>&lt;0.0001</td>
<td>14%</td>
<td>81%</td>
<td>34%</td>
<td>79%</td>
</tr>
<tr>
<td>CCP +</td>
<td>&lt;0.0001</td>
<td>41%</td>
<td>79%</td>
<td>35%</td>
<td>87%</td>
</tr>
<tr>
<td>SJC28</td>
<td>0.0007</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>ESR</td>
<td>0.02</td>
<td>18</td>
<td>27</td>
<td>31</td>
<td>32</td>
</tr>
</tbody>
</table>

Over the 3 years, 14-3-3-γ auto-antibody +ve patients had significantly lower radiographic progression compared to patients who were double positive (p=0.004). 14-3-3-γ auto-antibody +ve patients also had significantly greater changes in response to treatment in SJC28 (p=0.0004) and DAS28 (0.006) compared to the double positive patient group.

Conclusion: At baseline, the combination of a positive 14-3-3-γ auto-antibody test and a negative 14-3-3-γ protein test is significantly associated with a less severe RA disease profile and a better prognosis in regards to radiographic progression, SJC and DAS outcomes at 3 years. This data supports a protective role for 14-3-3-γ auto-antibodies.

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Soluble CD163 Is a Marker of Disease Activity in Early Rheumatoid Arthritis and Reflects TNFα Levels. Stinne Greisen, Holger Jon Möller, Kristian Steengaard-Petersen, Merete Lund Hetland, Kim Hoerslev-Petersen, Peter Junker, Mikkel Ostergaard, Malene Hvid and Bent Deleuran, 1Aarhus University, Aarhus C, Denmark, 2Aarhus University Hospital, Aarhus, Denmark, 3DANBO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, Glostrup, Denmark, 4Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, 5Odense University Hospital, Odense, Denmark, 6Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, 7Aarhus University, Aarhus, Denmark.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and eventually destruction, where TNFα is a central mediator of both processes. Soluble CD163 is a plasma marker of macrophage activation. CD163 is a scavenger receptor specifically expressed by macrophages and responsible for binding hemoglobin-haptoglobin complexes. The soluble form is cleaved from the cell surface by TACE/ADAM17, the metalloproteinase also responsible for the cleavage of TNFα, suggesting a close association between sCD163 and TNFα. In RA, sCD163 has been suggested as a marker of disease activity and progression. We aimed to investigate plasma sCD163 in very early RA (eRA) patients.

Methods: Soluble CD163 was measured by ELISA in plasma samples from 154 eRA patients belonging to the OPERA cohort. Age 53.5 years (51–56), 70% females, average disease duration: 3 months. Patients were randomized to conventional methotrexate and placebo (MTX+PLA) or MTX and aladimumab (MTX+ADA) treatment. Clinical disease was assessed by: Disease activity index (DAS28), health assessment questionnaire (HAQ), CRP, swollen joints (SJC40), tender joints (TJC40), simple disease activity index (SDAI), clinical disease activity index (CDAI), visual analogue scale (VAS) for pain, total sharp score (TSS), IgM-RF and ACPA. Statistical analysis was performed by student’s t-test, Spearman’s Rank correlation and linear regression.

Results: Plasma concentration of sCD163 at baseline was 2.40 mg/l (CI: 2.21 mg/l-2.56 mg/l) corresponding to the upper part of the HV reference interval (0.69mg/l - 3.86mg/l). After three months of treatment sCD163 had decreased significantly in both treatment groups (to 1.81 mg/l (1.68mg/l – 1.95 mg/l), p<0.001). Though the decrease in the MTX+ADA group was more prominent than in the MTX+PLA group. Withdrawal of ADA after 12 months of treatment was followed by incremental sCD163 levels during the subsequent 12 months (1.73mg/l (1.55mg/l-1.94mg/l) to 2.07mg/l (1.88mg/l – 2.28mg/l) (p<0.001)). At baseline sCD163 correlated with CRP and all investigated markers of disease activity (p = 0.16-0.28, p<0.05). We observed no correlation with TSS, IgM-RF and ACPA. The correlation between sCD163 and CRP at baseline could be fitted to a linear regression model (β=8.28, p<0.001). In the MTX+PLA group, this linear regression was also observed after 6 months and 1 year of treatment (β=7.5 and 9.9, respectively, both p<0.001). In the MTX+ADA group the close association was only observed after 3 months of treatment (β=10.9, p<0.007).

Conclusion: Soluble CD163 correlated with markers of disease activity in eRA. The correlation with CRP was very close and followed a linear regression model. Our results also indicate that sCD163 is associated with TNFα, as withdrawal of anti-TNF treatment was clearly reflected in increased sCD163 levels and correlation with CRP is diminished in the MTX+ADA treatment group. Plasma sCD163 thus reflects anti-TNF treatment and is a potential new disease activity marker in eRA.

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Vascular Endothelial Function Changes during Treatment in Patients with Rheumatoid Arthritis. Johana Zacarías1, Eliana Lancioni1, Tomas Cazenave1, Florencia Marengo1, Emilce Edith Schneebeger2, Lucas Lapicicio1, Margarita Morales1, Jorge Norscini3, Gabriel Waisman3, Javier Rosa3, Gustavo Citera2 and Enrique R. Soriano1. 1Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Argentina, 2Instituto de Rehabilitación Psicosocial, Buenos Aires, Argentina, 3Hypertension Section, Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 4Neurology Department, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Rheumatoid Arthritis (RA) patients have an increased risk for accelerated atherosclerosis. Endothelial dysfunction and arterial stiffness, assessed by measurement of carotid-femoral pulse wave velocity (PWV) and common carotid artery intima-media thickness (CCA-IMT), respectively, are proven surrogate markers of premature and potentially reversible atherosclerosis. Disease modifying anti-rheumatic drugs (DMARDs), and particularly biologic treatments, because of their higher capacity for controlling inflammation, might improve these surrogate markers of atherosclerosis. To assess the short-term effect (1 year) of treatment with conventional synthetic DMARDs, TNF-inhibitors, or Abatacept, on endothelial function and arterial stiffness in RA patients.

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The objective of this study was to determine the activity of these transporters in patients with active and inactive rheumatoid arthritis.

**Methods:** We included patients with Rheumatoid Arthritis (2010 ACR/EULAR criteria) from the early rheumatoid arthritis cohort of our Institute. ABCB1 (P-gp) and ABCG2 (BCRP) functional activity was measured in peripheral mononuclear cells by flow cytometry. The percentage of cells able to extrude substrates for ABCB1 (daunorubicin) and ABCG2 (mitoxantrone) were recorded. The specificity of the assay was confirmed with specific inhibitors (verapamil for ABCB1 and KO143 for ABCG2). Thirty healthy controls were also evaluated to establish normal values. The study was approved by our local ethics committee. For the statistical analysis continuous variables were compared with Student t or Mann-Whitney U tests and categorical variables with chi square or Fisher exact test as appropriate.

**Results:** Thirty seven patients (all women) had been included. The mean age was 38.3 ± 12.3 years and a disease duration of 5 ± 3.3 years. Twenty patients had inactive and 17 active disease according to DAS28 (1.2 ± 1.5 vs 4.1 ± 1; p<0.001). There were no differences in age, disease duration or use of prednisone (76.5 vs 80%), methotrexate (94.1 vs 95%), antimalarials (41.2 vs 40%) or sulfasalazine (35.3 vs 25%) among active and inactive patients (respectively, all with p >0.05).

The median percentage value of cells able to extrude daunorubicin in active patient was 4.4% (IQR 0.7–19.7%) vs 0.9 (IQR 0.5–3.4) in inactive patients. The median percentage of cells that extruded mitoxantrone in active patients was 1.7% (IQR 0.4–11.4%) vs 0.7% (IQR 0.4–1.8) in the inactive patients. These differences were not statistically significant.

Only 20 of 10 (47%) active patients were positive for ABCB1 and 8 of 17 (47%) active patients were positive (p=0.023) while for ABCB1 9/17 (53%) of active patients were positive and 6/20 (30%) of inactive patients were positive (p=0.157).

**Conclusion:** Patients with active RA have a higher percentage of positivity for the ABCB1 transporter compared with those in remission independently of treatment and disease duration. Follow up of these patients is currently ongoing to determine if the functional activity of these efflux pumps entails a higher risk of persistent activity or risk of RA reactivation.

**Disclosure:** Y. Atisha-Fregoso, None; H. Fragoso-Loyo, None; J. Jaquez-Ocampo, None; G. Lima, None; M. Baios, None; V. Pascual-Ramos, None; I. Contreras-Yañez, None; L. Llorente, None.

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**Determinants of Radiological Progression in Rheumatoid Arthritis:** Relationship with Serum Levels of OPG, RANKL and DKK-1. Carmen Gómez-Vaquero1, Irene Martín-Esteve1, Jose Iovra2, Jose Antonio Narvaez3, Juan Carlos Cofán3,4,1 Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, 3Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, 4Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City.

**Background/Purpose:** Osteoprotegerin (OPG), RANKL, and DKK-1 act as regulators of bone resorption and formation. The uncoupling of bone remodelling that occurs in rheumatoid arthritis (RA) originates generalized bone loss and joint erosions. Our aims are: 1) In patients with RA, to determine the serum levels of OPG, RANKL and DKK-1 and its relationship with radiological progression in hands. 2) To assess their relations with the activity and disability parameters of RA.

**Methods:** From a previous study in which we had radiographs of hands and frozen sera from all patients (T0), we selected the ones controlled since the diagnosis of the disease in an Early Arthritis Clinic of a university hospital through a strategy of tight control. They came back to make radiographs of hands and collection of sera (T1). Study variables were: 1) Demographics: age, sex, body mass index (BMI); 2) RA history: duration, RF, anti-CCP antibodies; 3) Disease activity: mean DAS28 and CRP between T0 and T1; 4) Disability: meaning HAQ; 5) RA treatment; 6) Serum levels of OPG, RANKL and DKK-1; and 7) Sharp-van der Heijde Index (SHI) of hands, analyzing together and separately erosions (SHI-Ero) and joint space (SHI-Spa).

**Results:** Thirty-seven patients (60 women) were included with a mean age of 53 ± 14 years and a mean BMI of 25.9 ± 4.9 kg/m2. At T0, mean RA duration was 1.6 ± 1.5 years. Sixty-one percent of the patients had RF + and 62% anti-CCP antibodies +. Mean DAS28 was 2.61 ± 0.96; CRP, 5.9 ± 7.1 mg/L; and HAQ, 0.330 ± 0.331. Seventy-six percent of the patients had low activity (DAS28 < 3.2) and 23%, moderate activity (DAS28 ≥ 3.2 and <
Mean annual progression of SHI was 0.9 ± 2.2; SHI-Ero, 0.2 ± 0.6, and SHI-Spa, 0.7 ± 1.7. The annual progression of SHI, SHI-Ero and SHI-Spa correlated with CRP levels (p < 0.01) and with the titer of anti-CCP antibodies. SHI-Spa progression correlated also with age (p < 0.05). We found no relation between SHI and OPG, RANKL or DKK-1.

Patients whose ISH worsened (48%) were older and had higher BMI and RA activity than patients in which ISH didn’t worsen (52%).

Conclusion: The progression of radiological damage in a series of RA patients controlled in an Early Arthritis Clinic is dependent on the activity of the disease and the titer of anti-CCP antibodies. Serum levels of OPG, RANKL and DKK-1 do not seem useful to predict progression of radiographic damage.

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Association of Antinuclear Antibodies with Lung Disease, Malignancy and Joint Replacement in Rheumatoid Arthritis. Roshini Ravendran1, Bobby Kwanghoon Han2, Quan-Zhen Li3 and Nancy J. Olsen1. 1Penn State College of Medicine, Hershey, PA, 2Cooper Medical School of Rowan University, Camden, NJ, 3University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: Antinuclear antibodies (ANAs) are present in a significant proportion of patients with rheumatoid arthritis (RA). Positivity for ANA in RA has been associated with use of TNF inhibitor therapies and with the presence of overlapping disorders such as Sjögren’s syndrome. We hypothesized that ANA positivity might be associated with other clinical or immune markers of RA.

Methods: Peripheral blood samples were obtained from CCP-positive RA patients (N=50) and 8 patients with systemic lupus erythematosus (SLE) who were seen in outpatient clinics. Clinical and laboratory features of disease were determined by chart review. Serum was used for measurement of ANA by ELISA and for detection of IgG and IgM autoantibodies on an automated platform. Groups were compared using the Mann-Whitney U test.

Results: ANA positivity was present in 23/50 (46%) of the RA patients and this group tended to be older (60 vs 52 years; P=0.02), have longer mean disease duration (10 vs 7 years; P=0.09), a lower prevalence of smoking (30% vs 63%; P=0.027), and somewhat higher prevalence of TNF inhibitor therapies (48% vs 26%; p=0.14) than the ANA negative group. Gender distributions were similar. The erythrocyte sedimentation rate was modestly correlated with ANA level (R=0.3; P=0.038). Malignancies were exclusively seen in the ANA+ group (8 cancers in 6 patients; P=0.008 vs ANA-). Only 2 of these were after starting TNF inhibitor therapy. 9 patients had lung disease, including interstitial fibrosis and bronchiectasis, and 6 of these were in the ANA+ group (NS), but lung disease in nonsmokers was only observed in ANA+ patients (P=0.038). Two of the 27 ANA-negative patients had a single joint replacement each, compared to 6/23 ANA-positive patients, 4 of whom had more than one replaced joint (P=0.027). Other connective tissue diseases including Sjögren’s Syndrome and thyroid conditions were not different in the two groups. On the autoantigen array, ANA+ and – subgroups of RA did not show any significant differences for IgM autoantibodies while 12 IgG autoantibodies were higher in the ANA+ group (P £ 0.04). Compared to SLE, the ANA+ RA group had significant elevation of 13 IgM autoantibodies, but did not show any elevated IgGs. ANA positivity in the RA patients was not associated with elevation of the Type I IFN gene.

Conclusion: ANA positivity in patients with CCP+ RA may define a clinical subset that has a greater risk of lung disease, malignancy and joint replacement surgery. The presence of ANA was associated with elevation of the Type I IFN signature. The paradoxical observation that smoking was less prevalent in the ANA+ group that had higher malignancy rates is not explained. If ANA expression in RA is not associated with the Type I IFN signature as in SLE, then other pathogenetic pathways may be involved, possibly including those involved in immune surveillance.

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Relationship Between Range of Motion of Joints in Upper Limbs and Physical Function in Patients with Long-Standing Rheumatoid Arthritis: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical Function. Toshihisa Kojima1, Hajime Ishikawa2, Keiichiro Nishida3, Jun Hashimoto3, Hisaki Miyahara4, Sakae Tanaka5, Nobuhiro Haga5, Yasuo Niki6, Masayo Kojima7 and Naoki Ishiguro8. 1Nagoya University Graduate School of Medicine, Nagoya, Japan, 2Niigata Rheumatic Center, Niigata, Japan, 3Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama city, Japan, 4National Hospital Organization, Osaka Minami Medical Center, Kawachinagano, Japan, 5National Hospital Organization, Okayama Kyushu Medical Centre, Fukuoka, Japan, 6The University of Tokyo Hospital, Tokyo, Japan, 7Keio University School of Medicine, Tokyo, Japan, 8Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Background/Purpose: Even now, in clinical practice, most of RA patients have long-standing disease and structural damage in their joints. Reconstructive joint surgery should be needed for further improvements of physical function for long-standing RA patients. It is very important to understand how much range of motion (ROM) should be needed to gain better physical function in each case.

The purpose of this study is to explore the characteristics of functional impairment and relationship ROM of joints and physical function in RA patients who were needed joint surgery using multicenter prospective cohort.

Methods: We started the prospective study in September, 2012 (Study registration: UMIN000012649). We collected data on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations were made using the HAQ-DI, DASH (Disability of Arm, Shoulder and Hand; upper limb function), and JSSF-RA (foot and ankle function), and patient subjective evaluations using the EQ-5D (QOL) and BDI-II (depression). Joint range of motion was also measured as part of this evaluation. This study is supported by grant from the Japanese Ministry of Health, Labour and Welfare.

Results: 347 surgical patients were registered. Mean values for age, disease duration, and sex were 65.2 years, 18 years, and 88% female, respectively. Actually, even long-standing RA patients who were needed joint surgery had remission or low disease activity in this baseline data (median values for DAS28 (3.0) and CRP (0.33 mg/dl). 23.8% of the patients were treated with biologics. We confirmed the significant correlation between HAQ-DI and EQ-5D, BDI-II; DASH and BDI-II (P<0.05). Assistive use of upper limb was required for arising, climbing stairs, standing up from the sofa, and walking outside by 52%, 51%, 44%, and 29% of patients, respectively.

We found significant relationship between ROM of joints in upper limb (shoulder, elbow and wrist) and the level of disability in HAQ-DI: Question 2 (shampoo hair), Q4 (arising), Q11 (tub bathing), and Q16 (opening and closing a wide mouth jar).

ROMs of the joints [age-adjusted mean values (95% CI)] which represented nearly non-existent levels of disability in each questioner of HAQ-DI, are as follows; wrist: flexion-extension 69.9 (61.4–78.5); pronation and supination 151.0 (145.4–158.6); elbow: flexion 153.5 (131.9–138.7); and shoulder; flexion 129.6 (122.2–137.0). (Fig. A and B).

Conclusion: ROMs of the joints in upper limbs were significantly associated with many kinds of daily activity including arising and bathing. The information should be important for assessment of disability in patients with long-standing RA. The ROM as shown in this study could be target of surgical procedure. It will be validated by further analysis of longitudinal data of this study.
Background/Purpose: Tender Joint Count (TJC) is a vital quality measure to assess the progression of Inflammatory Arthritis both from a therapeutic and a diagnostic standpoint. To date no scientific instruments are available to validate and standardize a Joint Count and these assessments remain largely subjective to the Joint Assessor. Physican variability, depending upon the technique and the force used in Tender joint count assessments, can significantly impact the Disease Activity Scores. Both inter and intra-observer variability bias in assessing Tender Joint Count can be pivotal in impacting the outcome of a trial.

Objectives: Primary Objective Tender Joint Count Assessments are significantly accurate using the Smart JAG Device than with conventional Joint Assessments.

Secondary Objective Establishing a high degree of consistency over time to monitor therapeutic response and improved joint function.

Methods: We present a smart hand held glove device for Tender Joint Count Assessment. The first of its kind that allows standardizing a joint exam and has a high yield to assess therapeutic efficacy over time. It is also much less time consuming and standardizes tender joint exams by keeping the pressure as constant with less inter and intra observer variability.

Results: There was striking difference in consistencies between the 2 groups. We found only 4.5% discrepancy within the device users as compared to 15% in non-device users. We performed a “paired t-test” between the discrepancy measures from the 2 groups. We found strong statistical significance between the 2 groups. (p<9.8 × 10^-8). There were no significant differences in the overall mean tender joints in either group.

Conclusion: The device measures tender joints with high accuracy and has less discrepancy between different users. Can be used by other health care personnel as joint assessors and has a high yield to assess therapeutic efficacy over time.
Prevalence of Morning Stiffness in a US Registry Population of Rheumatoid Arthritis Patients. Vibeke Strand1, Robert J. Holt2, Katherine C. Saunders3, Jeffery D. Kent4, Ping Xu2, Amy Y. Grahn5, Marc Mason5 and Carol J. Eizel6. 1Stanford University, Palo Alto, CA, 2University of Illinois - Chicago, Chicago, IL, 3Corrona, LLC, Southborough, MA, 4Horizon Pharma, Inc., Deerfield, IL, 5Axio Research LLC, Seattle, WA.

Background/Purpose: Morning stiffness is a symptom of rheumatoid arthritis (RA) that is frequently reported and thought to reflect disease activity, but its etiology is poorly understood.

Methods: Using the Corrona RA registry, data from RA patients enrolled from October 2001–February 2014 were evaluated cross sectionally: at enrollment and last visit between January 2013 and February 2014 for those with at least one visit during that interval. Longitudinal data from 2003 to 2014 were summarized to estimate changes in prevalence of morning stiffness over time reported by all Corrona RA patients.

Results: Prevalence of morning stiffness at enrollment was 74.1% and at last visit was 69.9%; mean (SD) duration 1.7 hours (± 3.1) and 1.5 hours (± 3.0), respectively. Approximately 50% of patients reporting morning stiffness work a duration ≥ 1 hour at last visit. Patients with morning stiffness were significantly less likely to be working 39.2% vs 47.3% and were more likely to have a BMI ≥ 30 (42.2% vs 29.9%) at last visit. Similar rates of treatment with biologic DMARDs as mono therapy or in combination with non-biologic DMARDs were observed in patients with and without morning stiffness. Among patients with no reported morning stiffness at time of enrollment, time in months to first visit with reported morning stiffness was not significantly different between patients with or without prior biologic DMARD experience (Figure 1).

Conclusion: Morning stiffness continues to be reported by a high proportion of US patients despite treatment with non-biologic and biologic DMARDs and the overall prevalence has remained relatively stable over the past 10 years. Patients reporting this symptom were also more likely to be not working. More research is needed to better understand how to manage morning stiffness in clinical practice.

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Comparative Dynamics of Rheumatoid Arthritis Disease Activity and Disease Severity Measures Using Rabbris, Ciras and DAS28 in a Population Based Cohort of Patients with RA. Arun K. Chandran1, Cynthia S. Crowson1, Birkan Ilian2, C. John Michet1, Eric L. Matteson1 and Elena Myasoedova1. 1Mayo Clinic, Rochester, MN, 2Marmara University School of Medicine, Istanbul, Turkey.

Comparative Dynamics of Rheumatoid Arthritis Disease Activity and Disease Severity Measures Using Rabbris, Ciras and DAS28 in a Population Based Cohort of Patients with RA. Arun K. Chandran1, Cynthia S. Crowson1, Birkan Ilian2, C. John Michet1, Eric L. Matteson1 and Elena Myasoedova1. 1Mayo Clinic, Rochester, MN, 2Marmara University School of Medicine, Istanbul, Turkey.
Background/Purpose: There is an extensive list of composite scores of rheumatoid arthritis (RA) activity status for the use in clinical practice including Disease Activity Score (DAS) and DAS-28. Much less common are validated definitions and scores of RA activity and severity for use in healthcare databases. The Record based Index of Severity (RARBIS) and the Claims-based Index for RA Severity (CIRAS) are methods used for this purpose. Our objective was to assess the dynamics of the CIRAS and RARBIS as measures of RA disease severity over time and to assess their correlation with DAS28.

Methods: A population-based inception cohort of 525 patients with incident RA (as per the 1987 ACR Criteria) in 1988–2007 was retrospectively identified and followed until 7-1-2012. The available data to calculate the RARBIS (joint surgeries, erosions, extra-articular manifestations, arthritis flares, morning stiffness, rheumatoid factor [RF] positivity, acute phase reactants and antirheumatic medications) were collected at every visit via medical record review. Claims data were used to calculate the CIRAS at every visit using 1 year prior data on number of inflammatory marker tests, platelet counts, chemistry panels, rheumatology visits, rehabilitation visits, assessment of RF, and Feltys syndrome. DAS28 was also collected, when available. RA flare was defined based on OMERACT 9 definition. Scores were compared using Spearman’s correlation.

Results: The 525 patients (mean age 55; 71% female) in our cohort had 15,649 visits (mean 30 visits per patient) with an average of 10.3 years follow-up. The mean RARBIS with medication at RA incidence was 3.3 (SD 1.4) and the CIRAS was 4.5 (SD 1.9). There was an increase in both, CIRAS and RARBIS scores during the first year of disease (Figure). Thereafter, the CIRAS scores tended to decrease, but the RARBIS values showed little change over the disease course. The flare rate decreased significantly during the follow-up by 0.3 per 100 person-years per year (p<0.001). There was a statistically significant correlation between RARBIS and CIRAS scores (r=0.19, p<0.001). DAS28 was available in only 278 visits. There was a moderate correlation between DAS28 and RARBIS (r=0.40; p<0.001) and a weaker correlation between CIRAS and DAS28 (r=0.16; p=0.008).

Conclusion: The uniform increase in CIRAS and RARBIS values during the first year after index date may reflect initial spike of RA activity and initial extensive work up of RA disease. Subsequent decline in CIRAS scores is concordant with decreasing flare rates, and could be due to the gradual decrease in the need for comprehensive laboratory workup and decreased frequency of rheumatology visits in patients with established disease. CIRAS and RARBIS scores were found to be significantly correlated with DAS28 suggesting that these indices may be helpful measures of RA activity/ severity in healthcare database research.

Figure 1: Trends in CIRAS (solid line) RARBIS with medications (dashed line) and RARBIS without medications (dotted line) (upper panel) and flare rate (lower panel).

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Background/Purpose: Patient-reported outcome measures are important tools that assess the impact of disease on patients’ lives; in RA, patient-reported physical function is especially relevant. In contrast to legacy measures such as the Health Assessment Questionnaire (HAQ) or Short Form 36 Health Survey (SF-36), the Patient-Reported Outcome Measurement Information System (PROMIS) scales are brief and intended to address psychometric flaws in earlier measures such as ceiling effects. However, use of PROMIS in clinical practice has been limited. The current study evaluates the ceiling and floor effects of the PROMIS Physical Function short form 10a (PROMIS-PF10a) relative to the HAQ, and compares the construct validity of these measures to a commonly used measure of disease activity (Clinical Disease Activity Index, CDAI), among patients with RA in an ethnically diverse urban clinic.

Methods: We abstracted demographic and clinical data from the electronic health record (EHR) of patients from a university-based rheumatology clinic. Eligible patients had 2 ICD-9 codes for RA between February 2013 and March 2014, had completed PROMIS-PF10a and HAQ, and had CDAI scores recorded by a clinician. We characterized score distributions for PROMIS T-scores and HAQ, including percent of patients with minimum and maximum possible scores. Construct validity was evaluated by examining the matrix of correlation coefficients (Pearson’s r) among PROMIS-PF10a, HAQ and CDAI.

Results: Analyses included 78 patients. 78% were female, mean age was 57.0±14.4 years, 59% were Caucasian, 15% Hispanic/Latino, and 10% Asian. 82% were RF or CCP positive, 51% had erosive disease and mean disease duration was 12±11 years. The mean PROMIS-PF10a score was 44.3; the mean HAQ score was 0.82. The distribution of PROMIS-PF10a scores more closely approximated a normal distribution (Figure), and had a lower proportion of scores at the ceiling (Table). There was a statistically significant correlation between PROMIS-PF10a and HAQ scores of r = −0.61, and a modest significant correlation between PROMIS-PF10a and CDAI scores of r = −0.48. The relationship between HAQ and CDAI was not statistically significant (r = 0.19).

Conclusion: In this ethnically diverse RA clinic population, the shorter PROMIS-PF10a had a distribution closer to normal with less ceiling effect, which enables better discrimination at higher levels of functioning. PROMIS-PF10a also had a higher correlation with CDAI scores than HAQ. Further studies are needed to understand the relative responsiveness of changes in PROMIS physical function scores compared to legacy measures.

Table. Score Characteristics and Floor/Ceiling Effects for PROMIS-PF10a and HAQ.

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>N (%)</th>
<th>Ceiling (best function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS-PF10a</td>
<td>44.3 ± 9.3</td>
<td>41.4</td>
<td>27.1</td>
<td>61.7</td>
<td>0</td>
<td>10 (12.8%)</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.82 ± 0.66</td>
<td>0.88</td>
<td>0</td>
<td>2.25</td>
<td>0</td>
<td>15 (19.2%)</td>
</tr>
</tbody>
</table>

Higher PROMIS-PF10a scores reflect better function while higher HAQ reflects poorer function. Normalized PROMIS-PF10a scores can range from 14.1–61.7. A score of 50 represents average function in a healthy individual; each 10-point decrement represents one standard deviation from this norm. HAQ scores range from 0–3. A score of 0 represents no limitation in functioning.

Figure 2: Distribution of PROMIS-PF10a and HAQ scores among 78 patients with RA.
Correlation of RAPID3, DAS28 and CDAI in Disease Activity and Effects of Education Level and Co-Morbid Diseases on This Assessment in RA. Kubilay Sahin1, Yasar Karaslan2, Zeynep Ozbalik3, Ahmet Omm4 and Nesibe Yesil1. 1Ankara Numune Education and Research Hospital, Ankara, Turkey; 2Hitt University, Corum, Turkey.

Background/Purpose: RAPID3 is an activity index based on only the patient’s report in RA. It doesn’t require joint counts and it isn’t time consuming. Therefore this situation makes the index very attractive for physicians. It has been shown in clinical studies that RAPID3 gives correlated information with DAS28 and CDAI.

In this study, we aimed to determine the correlation of RAPID3, DAS28 and CDAI in the assessment of disease activity and effects of education level and co-morbid diseases on this assessment in RA patients who were followed in a tertiary rheumatology clinic of Turkey.

Methods: 246 RA patients (80.1% female, mean age: 53.2 ± 12.1 years) followed up for at least 3 months between January-June 2013 were included to the study. All patients were asked to fill out RAPID3 questionnaires. Uneducated patients completed the survey with the help of medical secretary. RAPID3, DAS28 and CDAI was calculated in all patients. Patients were subdivided according to disease severity as group A (remission-minimal disease activity) and group B (medium-severe disease activity) for all scoring systems. All data were analyzed using statistical software: SPSS (Statistical Package For Social Sciences) for Windows 20 (SPSS Inc, Chicago, IL). One way ANOVA, Kruskal Wallis analysis, kappa analysis and Spearman correlation were used for statistics. A level of p < 0.05 was considered significant.

Results: 77.2% of the patients were uneducated, the rest were educated graduating from 50.8% primary school, 16.6% secondary/high school and 5.3% university. Mean training period of the patients was 4.9 years. 47.6% of the patients had at least one comorbid disease (i.e. hypertension, diabetes, hyperhypertrophidrosis, coronary artery disease, lung disease or obesity). Correlation of RAPID3 with the DAS28 and CDAI score was statistically significant (p<0.001). Similarly, educational status and the presence of comorbidity disease didn’t effect this correlation (p<0.001). Kappa analysis showing compliance of RAPID3 with DAS28 and CDAI scores was also significant (p<0.001).

100% of the patients with severe disease activity according to DAS28 also had moderate/severe disease activity according to the RAPID3. 77% of patients who were in remission according to DAS28 have near remission-minimal disease activity according to RAPID3. Patients with high disease activity according to the CDAI also had severe disease activity (100%) according to RAPID3, while 97% of patients who were in remission according to the CDAI have near remission-minimal disease activity according to RAPID3.

Conclusion: Similar to previous studies, RAPID3 was significantly correlated with DAS28 and CDAI score. Even though RAPID3 could be affected by patients educational status, when we compared the patients as educated/uneducated, there was no significance. At the same time, presence of co-morbid diseases didn’t effect the correlation of RAPID3 with DAS28 and CDAI. RAPID3 can provide quantitative information in uneducated patients and with presence of comorbid diseases just like DAS28 and CDAI.

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Circulating Anti-Citrullinated Peptide Antibodies and Cytokines As Biomarkers of Response to Disease-Modifying Antirheumatic Drugs Therapy in Early Rheumatoid Arthritis. Mahmood MTM Ally1, Pieter Meyer2, Bridget Hodkinson3, Austausis Musenge3, Gregory Tintinger3, Mohammed Tikiy4 and Ronald Anderson3. 1University of Pretoria, Pretoria, South Africa; 2University of Witwatersrand, Johannesburg, South Africa, 3University of the Witwatersrand, Johannesburg, South Africa, 4University of Witwatersrand, Johannesburg, South Africa, 5 H Baragwanath Hospital, Johannesburg, South Africa.

Background/Purpose: Serial measurement of circulating anti-citrullinated peptide antibodies (ACPA) and cytokines is of potential importance in the management of patients with RA. However, the utility of this strategy in monitoring responses to traditional disease-modifying antirheumatic drugs (DMARDs) in early RA is largely untested.

Methods: A cohort of 140 predominantly (88.5%) black female South African patients with early RA median (IQR) symptom duration 9.7 (11.4)
months was treated with synthetic DMARDs, mostly methotrexate (MTX), either as monotherapy or combination DMARD therapy, mostly combined with low-dose oral corticosteroids (CS). The simple disease activity index (SDAI) was used to evaluate clinical response, while circulating ACPA and a panel of circulating cytokines/chemokines/growth factors were measured using immunofluorimetric and multiplex suspension bead array procedures respectively at baseline and after 6 months of therapy. Shared epitope genonomic analysis was done using PCR typing of the HLA-DRB1 allele.

**Results:** Following 6 months of therapy, the median SDAI declined from a baseline of 41.39 to 16 (p=0.0001) for the entire cohort. This decline in disease activity was paralleled by significant falls in median serum ACPA levels (516.6 vs. 255.65 units, p<0.00001) and several of the circulating cytokines (IL-4, IL-6, IL-7, IL-8, G-CSF, VEGF, CCL4; p<0.025 – p<0.0001) which were most evident in the subgroup of patients treated with a combination of MTX and CS. No significant correlations between these biomarkers and disease activity were observed. Baseline ACPA levels, but not SDAI or cytokines, were significantly higher in the subgroup of risk allele-positive patients (594.1 vs. 255.7 units, p<0.05), while no associations with ACPA and a smoking history were evident.

**Conclusion:** The use of synthetic DMARDs in early RA is associated with significant decreases in SDAI, paralleled by a decrease in ACPA and predominantly pro-inflammatory cytokines. However, the lack of correlation of ACPA and the other biomarkers with therapy-associated alterations in disease activity in the short term appears to preclude the utility of serial measurement of these biomarkers to monitor early responses to therapy, while the long-term, prognostic potential remains to be established.

**Disclosure:** M. M. Ally, None; P. Meyer, None; B. Hodgkinson, None; E. Munsen, None; G. Tintinger, None; M. Tikly, None; R. Anderson, None.

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**Background/Purpose:** To establish the importance of joint examination by ultrasound (US) in daily clinical practice of patients with rheumatoid arthritis (RA), we compared the US findings with the joint examination findings sorted by the presence of tenderness and/or swelling in the hand (proximal) interphalangeal (IP/PIP), metacarpophalangeal (MCP) and wrist joints.

**Methods:** A total of 208 RA patients (158 female, the mean age of 66 years, with a disease duration of 5 years) were recruited for this study. Joint assessment was performed at each visit. Spearman correlations were calculated between IPQ-R scales and CDAI. Adjusted regression models evaluated the effect of IPQ-R on patient global scores.

**Results:** 50 RA patients completing the survey were mostly female (n=58/3876) with a mean (SD) education of 15 (4) yrs, and median (IQR) of 15 (10). 36% (38/210) had a RA duration ≤ 1 year and 20 (40%) of 1–5 years. Most were seropositive for RF (61%) and anti-CCP (66%); 15% (36%) were on biologics. CDAI scores classified 13 (26%) in remission and 18 (36%), 13 (26%) and 6 (12%) with low, moderate and high disease activity levels, respectively.

**Conclusion:** Understanding patients’ beliefs about the cause of their RA, as well as expectations about controllability, may offer insight into patient behaviors (e.g., adherence to treatment) that impact long-term outcomes. Beliefs about causes of RA may also affect expectations of whether and how the disease can be controlled. Clinicians may find useful to directly explore patients’ expectations around treatment, and to provide hope, encouragement and ongoing support when expectations are low.

**Disclosure:** S. J. Bartlett, None; M. C. Bazan Bardales, None; J. Colmegna, None.

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Exploring the DAS: What Is the Level of Agreement in the Classification of Remission and Low Disease Activity (LDA) Among the Various Versions of the Disease Activity Score (DAS) and Their Correlation? An Analysis From a Prospective, Observational Registry. VFG Bensen, Edward Keystone, Philip Baer, Jude Rodrigues, J. Antonio Avina-Zubieta, Wojciech Olszynski, Deniz Choquette, Suniel Kapur, Manisha Mulgund, John S. Sampalis, Emmanuel Rampakakis, Francois Nantel, Allen J. Lehman, May Shawi and Susan Otawa. 1St Josephs Hospital and McMaster University, Hamilton, ON, 2Mount Sinai Hospital, University of Toronto, Toronto, ON, 3Private Practice, Scarborough, ON, 4Clinical Research and Arthritis Centre, Windsor, ON, 5Arthritis Research Centre of Canada, Richmond, BC, 6University of Saskatchewan, Saskatoon, SK, 7Institut de rhumatologie de Montréal (IRM), Montréal, QC, 8University of Ottawa, Ottawa, ON, 9JSS Medical Research, Montréal, QC, 10Janssen Inc., Toronto, ON.

**Conclusion:** Based on the US findings, physical joint examination of the IP/PIP and the wrist joints tends to overestimate and underestimate synovitis, respectively. Thus, clinical importance of US examination in daily clinical practice may differ among joint sites, probably due to the structural complexity in the wrists and the co-existing osteoarthritis in IP/PIP joints.

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**Background/Purpose:** Illness perceptions (IP) are the beliefs and expectations that an individual has about medical conditions. IP have been found to cluster around five coherent themes (identity; cause; time-line; consequences; and cure/control). Positive IPs have been associated with higher adherence, better disease outcomes and wellbeing in several chronic diseases. Relatively less is known about how illness perceptions impact patient perceptions of wellbeing and other disease outcomes in rheumatoid arthritis (RA).

**Methods:** Consecutive English speaking RA patients seen at an academic center between 2013–2014 were asked to complete the Illness Perception Questionnaire – Revised (IPQ-R). Clinical RA indicators were obtained at each visit. Spearman correlations were calculated between IPQ-R scales and CDAI. Adjusted regression models evaluated the effect of IPQ-R on patient global scores.

**Results:** 50 RA patients completing the survey were mostly female (n=38/76%) with a mean (SD) education of 15 (4) yrs, and median (IQR) of 15 (10). 36% (38/210) had a RA duration ≤ 1 year and 20 (40%) of 1–5 years. Most were seropositive for RF (61%) and anti-CCP (66%); 15% (36%) were on biologics. CDAI scores classified 13 (26%) in remission and 18 (36%), 13 (26%) and 6 (12%) with low, moderate and high disease activity levels, respectively.

**Timeline-Cyclic (rho = .32) and Personal Control (rho = .28) were significantly (p < .05) and directly associated with CDAI; Treatment Control (rho = -.40) was inversely related to CDAI in a dose response manner (mean difference 2.3 and 3.8 between remission, low, and mod-high levels). After controlling for disease activity, Treatment Control and Emotional Representations were independent additional predictors (p < .05) explaining 62% of the variance in patient global scores. Genetic risk factors (39%), altered immunity (26%) and psychological factors (24%) were viewed as the primary reason or an important contributing factor for developing RA. Patients who attributed their RA to psychological factors had significantly higher mean Cyclic Timeline scores (14.8 vs. 12.1; p = .004) reflecting attitudes of greater unpredictability and uncertainty around their disease.

**Conclusion:** Understanding patients’ beliefs about the cause of their RA, as well as expectations about controllability, may offer insight into patient behaviors (e.g., adherence to treatment) that impact long-term outcomes. Beliefs about causes of RA may also affect expectations of whether and how the disease can be controlled. Clinicians may find useful to directly explore patients’ expectations around treatment, and to provide hope, encouragement and ongoing support when expectations are low.

**Disclosure:** S. J. Bartlett, None; M. C. Bazan Bardales, None; J. Colmegna, None.
Background/Purpose: Two versions of DAS28 are available, DAS28-4 comprising 4 variables [tender and swollen joint counts, acute phase reactant (APR), and patient global assessment] and DAS28-3 where patient global has been omitted. Despite the difference between DAS28-4 and DAS28-3 thresholds for remission and low disease activity (LDA) are the same. Additionally, the APR used to calculate the DAS may be either ESR or CRP.

The aim of this analysis is to describe the agreement between these four possible indices, DAS28-4 ESR, DAS28-4 CRP, DAS28-3 ESR and DAS28-3 CRP and to compare them in terms of classifying remission and LDA in a real-world, routine clinical care setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab. In this analysis, data from RA patients who were treated with infliximab between 2002–2014 or with golimumab between 2010–2014 and had available information in all indices were used. The definitions for remission were as follows: DAS28-3/4 <2.6; LDA was defined as: DAS28-3/4 <3.2. Correlation between the different indices was assessed with the Pearson’s correlation coefficient (r) and classification agreement was assessed with Cronbach’s alpha (CA) and the kappa statistic.

Results: Eight hundred sixty nine RA patients who had 3,517 complete assessments were included in the analysis. Non-remission was classified by all indices in 61.4% of cases, while remission was achieved in two (10.3%), three (5.3%), or all four (17.2%) indices. Similarly, non-LDA assessments were included in the analysis. Non-remission was classified by the APR used to calculate the DAS may be either ESR or CRP.

Coalition (r): 0.905 for remission and 0.923 for LDA between all indices. When looking at the internal consistency in terms of individual inter-item correlations (Table 1), the agreement between indices was variable with the CA was 0.905 for remission and 0.923 for LDA suggesting an overall high internal consistency. However, when looking at the individual inter-item correlations (Table 1), the agreement between indices was variable with the DAS28-3 CRP and DAS28-4 CRP showing the highest correlation and DAS28-3 ESR and DAS28-4 CRP showing the lowest correlation. When comparing DAS28-4 ESR with DAS28-3 ESR, the latter categorized 16.5% of DAS28-4 ESR remission cases as non-remission and 3.0% of DAS28-4 ESR non-remission cases as remission. With respect to LDA, DAS28-3 ESR categorized 9.1% of DAS28-4 ESR LDA cases as non-LDA and 4.7% of DAS28-4 ESR non-LDA cases as LDA. Similar results were observed with DAS28-3 CRP.

Conclusion: The results of this analysis show that, despite being highly correlated, variability exists in the classification of remission and LDA by the various DAS indices. These results suggest that decision making based on disease state achieved may vary significantly based on the type of APR used in the DAS index.

Table 1 Inter-Item Correlation Matrix of DAS Remission / LDA Types

<table>
<thead>
<tr>
<th>Remission</th>
<th>DAS28-4 ESR</th>
<th>DAS28-4 CRP</th>
<th>DAS28-3 ESR</th>
<th>DAS28-3 CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-4 ESR</td>
<td>0.678</td>
<td>0.589</td>
<td>0.642</td>
<td>0.670</td>
</tr>
<tr>
<td>DAS28-4 CRP</td>
<td>0.678</td>
<td>0.589</td>
<td>0.642</td>
<td>0.670</td>
</tr>
<tr>
<td>DAS28-3 ESR</td>
<td>0.824</td>
<td>0.589</td>
<td>0.631</td>
<td>0.670</td>
</tr>
<tr>
<td>DAS28-3 CRP</td>
<td>0.670</td>
<td>0.846</td>
<td>0.631</td>
<td>0.670</td>
</tr>
<tr>
<td>LDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS28-4 ESR</td>
<td>0.728</td>
<td>0.864</td>
<td>0.702</td>
<td></td>
</tr>
<tr>
<td>DAS28-4 CRP</td>
<td>0.728</td>
<td>0.864</td>
<td>0.702</td>
<td></td>
</tr>
<tr>
<td>DAS28-3 ESR</td>
<td>0.864</td>
<td>0.670</td>
<td>0.696</td>
<td></td>
</tr>
<tr>
<td>DAS28-3 CRP</td>
<td>0.702</td>
<td>0.846</td>
<td>0.696</td>
<td></td>
</tr>
</tbody>
</table>


427 Multimedia Patient Education Tool for Patients with Rheumatoid Arthritis. Maria A. Lopez-Olivo1, Aparna Ingleshwar1, Robert Volk1, Andrea Barbo1, Maria Jibaja-Weiss1, Heather Lin1 and Maria E. Suarez-Almazor2.

1The University of Texas, TX; 2M.D. Anderson Cancer Center, Houston, TX; 3Baylor College of Medicine, Houston, TX.


Background/Purpose: Effective patient education provides individuals with essential information about their disease and treatment alternatives, and aids informed decision-making. The purpose of our study was to test the efficacy of a multimedia patient education tool (MM-PtET) including storylines and testimonials for patients with rheumatoid arthritis (RA).

Methods: Patients were recruited from 5 centers and through advertisement. Inclusion criteria were: (i) age ≥18 years (ii) diagnosis of RA by a rheumatologist (iii) disease duration ≥10 years (iv) adequate cognitive status and (v) ability to communicate in English or Spanish language. After completion of a baseline questionnaire, participants reviewed materials of the group to which they Patients were randomized to receive a MM-PtET or a written booklet, both with the same written information. They completed self-report questionnaires before and after viewing the assigned materials. Primary outcome measures included: a) Disease knowledge, and b) Decision conflict. Secondary outcomes included: a) Acceptability, and b) Educational tool evaluation. We compared differences between and within groups for outcomes of interest. Linear regression was performed to assess the influence of the intervention and patient characteristics on the knowledge score.

Results: 221 participants were randomized (111=MM-PtET, 110=written booklet). Mean age was 51±13 years, mean disease duration was 5±3 years, 85% were female 24% had inadequate health literacy levels and 41% were Spanish speaking. Post randomization, both, intervention and control groups, showed significantly higher knowledge scores (Intervention: 5.5±2.1 vs 7.6±1.5 and, Control: 5.5±2.1 vs 7.1±2.0; p<0.05 for both groups) and, significantly lower “Informed” and “Values clarity” scores (p<0.05 for both scales). No statistically significant differences was observed between the two groups for knowledge improvement and decisional conflict scales (p>0.1 for all measures). The majority of the participants in both groups gave a favorable response to all evaluation questions, with no significant differences in response options observed between the two groups (p>0.05).

Regarding acceptability, MM-PtET group participants were more likely to rate the presentation as “Excellent” for the following items: impact of RA, medication options, evidence about medications, benefits of medication, and self-care options (p<0.05 for all). Also, compared to the control group, more participants in the MM-PtET group found the length of the material presented as “just right” (Intervention vs Control: 92% vs 80%, p=0.03). Regression analysis indicated that, being in MM-PtET group, shorter disease duration and being Hispanic compared to White, was predictive of greater knowledge improvement (p<0.05, Adjusted R²=0.08).

Conclusion: Viewing of the MM-PtET was as effective and more acceptable than reading written materials in RA patients. Hispanics and patients with shorter disease duration may achieve the greatest benefit from multimedia tools incorporating narratives and stories.

Disclosure: M. A. Lopez-Olivo, None; A. Ingleshwar, None; R. Volk, None; A. Barbo, None; M. Jibaja-Weiss, None; H. Lin, None; M. E. Suarez-Almazor, None.
Investigation of MRI Bone Changes in Early-Stage RA Patients Achieved in Sustained Clinical Good Response: Sub-Analysis from Nagasaki University Early Arthritis Cohort. Mami Tama1, Kazuhiko Arima1, Yoshikazu Nakashima1, Masataka Umeda1, Shoichi Fukui2, Ayako Nishino1, Tomoki Origuchi1, Kiyoshi Aoyagi2 and Atsushi Kawakami1. 1Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, 2Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, 3Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, 4Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, 5Department of Radiological Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Given the improved detection of joint injury by MRI than by clinical examination, EULAR recommendations for the use of imaging of the joints in the clinical management of RA states that MRI may be useful in monitoring disease activity. However, few data have been established that specifically address how MRI should be applied to consider the outcome of RA. We have tried to examine whether MRI is useful to predict the development of radiographic progression in patients with early-stage RA from Nagasaki University Early Arthritis Cohort.

Methods: This is a sub-analysis from the 1-year observational study from seventy-six early-stage RA patients recruited consecutively from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrists and finger joints. All of the patients had been received DMARDs during 1 year after entry and we have selected 36 patients in which the favorable clinical response was obtained by DMARDs. The favorable clinical response was defined by decrement of DAS28 ≥ 1.2 at 3 months as well as achievement of DAS28 low disease activity or remission at 6 months. Synovitis, osteitis and bone erosion determined by Gd-enhanced MRI were scored by Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS). Plain radiographic progression was studied by Genant-modified Sharp score. The association of MRI findings with plain radiographic progression at 1 year was investigated.

Results: Median age, disease duration and Genant-modified Sharp score at entry from 36 patients were 55 y.o., 2.4 months and 0, respectively. Although all of the 36 patients showed the favorable clinical response, radiographic progression was found in 7 patients at 1 year. Although there were no significant differences between the patients with radiographic progression (N = 7) and those without radiographic progression (N = 29) in age, gender, disease duration, RF, ACPA, CRP, matrix metalloproteinase-3 and DAS28 at entry, the significant differences were found in the rate (100% vs 51.7%, p < 0.05) and RAMRIS score of osteitis (median score 5 vs 1, p = 0.0012) at baseline, the rate (100% vs 31.0%, p = 0.001) and RAMRIS score of bone erosion (median score 3 vs 0, p = 0.004) at baseline. In addition, initial therapy with MTX was significantly less in the patients with radiographic progression as compared those without radiographic progression (14.3% vs 69.0%, p = 0.013). Multivariate logistic regression analyses, the most appropriate model is selected on the basis of Akaikes information criteria in the SAS system, version 9.2, have shown that MRI osteitis at entry, MRI bone erosion at entry and initial MTX therapy tended to associate with plain radiographic progression. The presence of positive discordance was predictive of higher DAS28-CRP after 24 weeks of disease-modifying therapy (β coefficient = 1.58; p = 0.017) whereas negative discordance was not predictive (β coefficient = 0.65; p = 0.091), after adjusting for age, sex, disease duration, rheumatoid factor, anti-CCP antibodies, baseline tender joint count, baseline swollen joint count, baseline CRP, initial DMARD, prednisone use, and smoking status.

Conclusion: In conclusion, discordance in which patient’s assessment of disease activity is higher than the physician’s assessment is predictive of significantly higher DAS28-CRP after 24-weeks of disease-modifying therapy. Further research is necessary to explicate factors underlying patient-physician discordance and to develop strategies for managing these factors. This work is anticipated to improve treatment outcomes for patients with RA.

Disclosures: J. M. Davis III, None; C. S. Crowson, None; T. Bongartz, None; C. J. Michet, None; E. L. Matteson, None; S. E. Gabriel, None.

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Background/Purpose: Patient-reported outcomes (PROs) have been recognized as important in evaluating disease status of rheumatoid arthritis (RA). The minimal important difference (MID) for EQ-5D has been studied in RA for physical function, however, the MID for quality of life assessed by European Quality of Life-Five Dimensions (EQ-5D) has not yet been analyzed. Thus, we conducted this study to elucidate MID for EQ-5D.

Methods: Participants were patients with RA who enrolled in the IORRA study conducted in October 2011 and April 2012. The IORRA study was established as a large observational cohort of RA patients in October 2000 and the data collection was conducted biannually. The database includes the EQ-5D, the disease activity score in 28 joints (DAS28), and the Japanese version of the Health Assessment Questionnaire (J-HAQ) for physical disability. Patients self-rated their change in overall status in April 2012 as much better, somewhat better, the same, somewhat worse, or much worse compared to that in October 2011 using a 5-point Likert scale. In this study, the MID for EQ-5D in patients who rated themselves as somewhat better were analyzed. The MID is the means of each patient’s change in the EQ-5D, and the responsiveness to change was evaluated using effect size (ES) which of 0.2 to 0.5 is usually considered as relevant value for the MID.

Results: A total of 4,847 patients in this study had a mean (standard deviation [SD]) age of 60.4 (13.4) years, disease duration of 14.2 (10.0) years, DAS28 score of 2.9 (1.1), J-HAQ score of 0.64 (0.73), and EQ-5D of 0.800 (0.18), and 85.0% were women. Among them, 745 patients self-rated themselves somewhat better. The mean (SD) change in EQ-5D was 0.018 (0.17) with ES of 0.11 for patients who self-rated themselves somewhat better. When patients rated themselves somewhat better were stratified by baseline DAS28 into groups of remission, low, moderate and high disease activity, the mean (SD) changes in EQ-5D were −0.0002 (0.15), 0.017 (0.15), 0.032 (0.13) and 0.58 (0.12) with ES of 0.001, 0.11, 0.23 and 0.49, respectively. When stratified by baseline J-HAQ into groups of low (J-HAQ<0.5), moderate (0.5<J-HAQ≤1.5) and high (J-HAQ>1.5) physical disability, the mean (SD) changes in EQ-5D were 0.004 (0.13), 0.027 (0.12) and 0.032 (0.13) with ES of 0.03, 0.21 and 0.24, respectively. When stratified by baseline disease duration into groups of < 2 years, 2–5 years, 5–10 years and ≥10 years, the mean (SD) changes (EQ-5D) were 0.043 (0.12), 0.021 (0.16), 0.015 (0.16) and 0.014 (0.16) with ES of 0.33, 0.16, 0.09 and 0.08, respectively. Finally, the MID in EQ-5D in patients with baseline DAS28 >3.2, baseline J-HAQ >0.5 and disease duration <5 years was demonstrated as 0.036 with ES of 0.39.

Conclusion: This study demonstrated the MID in EQ-5D in RA patients from the IORRA cohort. The MID in EQ-5D varies in concordance with disease activity, physical disability and disease duration.

Disclosures: M. Tama, None; K. Arima, None; Y. Nakashima, None; M. Umeda, None; S. Fukui, None; A. Nishino, None; T. Suzuki, None; Y. Horai, None; A. Okada, None; T. Koga, None; S. Y. Kawashiri, None; N. Iwamoto, None; K. Ichinose, None; H. Nakamura, None; T. Origuchi, None; M. Uetani, None; K. Aoyagi, None; A. Kawakami, None.

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Joint Dermal Temperature Specifically Identifies the Individual RA Patient Most Likely to Develop Radiographic Change on Sharp Score; An Exam in Less Than a Minute Can Predict Who Specifically Needs Biologic Therapy. Maria Greenwald, Joann Ball and Harold Paulus.

Background/Purpose: Joint dermal temperature (temp) measured in less than a minute can identify specifically the individual RA patient most likely to develop radiographic change on Sharp Score in the next year. There is great debate regarding which patients should be treated with expensive therapies for rheumatoid arthritis (RA). Certain subsets of RA patients are more likely to cripple, such as sero-positive disease, those earlier in disease onset, and earlier age at onset, and higher inflammatory non-specific markers (like amyloid, fibrinogen). However, can we identify a specific patient at most risk for radiographic changes? We evaluated the power of touch to determine disease. It has long been noted in the literature that skin over a gout joint is “hot”, which we define as a temp equal to or above central temp. Elevated skin temps occur also over septic joints and RA. The hot joint will identify which individual is destined for new xray erosions.

Methods: A digital clinic dermal thermometer was used to record vital signs, both at skin on the forehead and over any painful joint, most often the wrist. The dermal temp can be measured accurately and in less than a minute (accuracy ±0.1 F). Sequentially 208 sero-positive RA patients on MTX (15–25 mg/week) and with baseline plus one year follow up hand/feet xrays were enrolled. No biologic therapy was permitted. Xrays were scored by a single reader (MG) with a modified van der Heijde total Sharp score (mTSS) without sequence order or identifiers. Medical history, WESR, CRP, baseline medications and xray were performed at screening. A small group of subjects without RA (n = 25) were used as controls to evaluate the usual range of joint temp.

Results: The dermal temp at a wrist of normal persons without RA is −12.0±4.6 F. The “hot” joint RA group had a joint temp in excess of central temp +1.06±0.69 (CI 0.23) and near a 4-fold higher individual risk of new erosions compared to those RA “cool” joints. Results were highly significant, p<0.001. Sensitivity for joint temp predicting erosions is 91.7% and specificity for joint temp predicting erosions 78%. Newer onset of RA, younger age, and WESR were mildly significant (P<0.05) but had poor specificity and sensitivity.

Conclusion: A simple dermal temperature taken with a standard digital thermometer can quickly and accurately identify RA patients who are at high risk for further destructive change on MTX alone. This can be submitted to insurers, national health registries, and provides objective data to what we have known for centuries, that the human hand can detect active disease.

Disclosure: M. Greenwald, None; J. Ball, None; H. Paulus, None.

Rheumatoid Arthritis-Associated Interstitial Lung Disease: Risk Factors for Disease Progression. Yashaar Chaichian, Imre Noth, Mary Strek, Tammy O. Utset and Rekha Vij. University of Chicago Medical Center, Chicago, IL.

Background/Purpose: Rheumatoid arthritis (RA) is the most common systemic connective tissue disease in the U.S. Interstitial lung disease (ILD) is a frequent extra-articular manifestation of RA that contributes significantly to morbidity and mortality. While risk factors for developing ILD have been identified, less is known about factors that predict progression. The objectives of this study were to identify factors associated with RA-ILD progression and determine how often RA-ILD pulmonary activity parallels joint disease activity.

Methods: We performed a retrospective analysis of adult patients with RA-ILD at the University of Chicago Medical Center. Demographic and clinical information were extracted from medical records. All patients met ACR 1987 classification criteria for RA. ILD diagnosis required interstitial abnormalities on high-resolution chest CT plus confirmation by a pulmonologist, with or without restrictive pattern on pulmonary function tests (PFTs) or compatible lung biopsy. Progressive RA-ILD was defined as decrease in forced vital capacity of ≥10% or diffusing capacity for carbon monoxide of ≥15% on serial PFTs ≥8 weeks apart. Progressive joint disease was defined as evidence of new erosion or persistent flare by rheumatologist on successive visits ≥8 weeks apart. Patients with parallel ILD and joint activity had worsening in PFTs and joint disease activity within 3 month overlapping period. Subgroups of patients were compared using Fisher’s exact tests for categorical variables and ANOVA for continuous variables.

Results: We identified 47 RA-ILD patients. Thirty six (77%) had progressive RA-ILD and 11 (23%) had stable RA-ILD. High-titer rheumatoid factor (RF), >3 times upper limit of normal, was associated with progressive RA-ILD (p=0.0394) while high-titer cyclic citrullinated peptide (CCP) antibody (p=0.0973) and smoking history (p=0.0933) trended towards association. Twenty eight patients had serial rheumatologic assessments coinciding with PFTs; 9 (32%) had parallel ILD and joint disease activity, and 19 (68%) had non-parallel disease activity. Usual interstitial pneumonia (UIP) was the most common radiographic pattern in patients with progressive and stable RA-ILD. There was a slight predominance of UIP as the radiographic pattern in patients with non-parallel ILD and joint disease activity. Radiographic patterns other than pure UIP were slightly more frequent in patients with parallel ILD and joint disease activity.

Conclusion: High-titer RF was associated with RA-ILD progression in this cohort. High-titer CCP antibody and smoking history trended towards...
association with progressive RA-ILD. Thus, we propose that RA-ILD patients with these risk factors merit closer monitoring for disease progression. For the majority of our RA-ILD cohort, IBD and joint disease activity did not parallel one another. This finding highlights the importance of monitoring joint and lung disease separately, as different factors may contribute to articular and pulmonary disease flares in RA-ILD patients. Furthermore, these results suggest that articular and pulmonary disease activity should be considered separately for therapeutic decision-making.

Disclosure: Y. Chaichian, None; I. Noth, None; M. Strek, None; T. O. Utset, None; R. Vij, None.

ACR Poster Session A
Rheumatoid Arthritis - Human Etiology and Pathogenesis

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Bronchiectasis: A Model for Chronic Bacterial Infection Inducing Autoimmunity in Rheumatoid Arthritis

Anne-Marie Quirke1, Elizabeth Perry2, Alison Cartwright3, Clive Kelly4, Anthony De Sozya5, Paul Eggett5, David Hutchinson6 and Patrick Venables7. 1University of Oxford, Oxford, United Kingdom, 2Royal Cornwall Hospital, Truro, United Kingdom, 3Queen Elizabeth Hospital, Gateshead, United Kingdom, 4The Freeman Hospital, Newcastle, United Kingdom, 5University of Exeter, Exeter, United Kingdom.

Background/Purpose: Anti-citrullinated peptide antibodies (ACPA) are associated with smoking in patients with rheumatoid arthritis (RA). Bronchiectasis (BR), which tends to occur in non-smokers, has been recognised as an uncommon, but potent risk factor for RA for 50 years. Here we examine the potential role for BR in ACPA in patients with BR alone and in patients with BR and RA (BRRA).

Methods: The multi-centre study included 122 patients with BR alone, 50 BRRA, 50 RA without lung disease, compared with 87 asthma and 79 healthy subjects as controls. All RA patients met the 2010 ACR criteria for RA. ACPA were measured using CCP2 and fine specificities to citrullinated α-enolase (CEP-1: 59VYAT-cit-SSAV-cit-L-cit-SSVP74), citrullinated vimentin (cVim: 4KIHA-cit-EIFDS-cit-GNPTVE21), citrullinated fibrinogen, β chain (cFib: 5NNEEGFFSA-cit-GHRPLDKK), with their arginine control peptides (REP-1, Vim, and Fib) by ELISA. The cut-off for positivity for CCP2 was 5 U/ml as per manufacturers instructions and for the remaining peptides was calculated using the 95th percentile of the healthy controls. The multi-centre study included 122 patients with BR alone, 50 BRRA, 50 RA without lung disease, compared with 87 asthma and 79 healthy subjects as controls. All RA patients met the 2010 ACR criteria for RA. ACPA were measured using CCP2 and fine specificities to citrullinated α-enolase (CEP-1: 59VYAT-cit-SSAV-cit-L-cit-SSVP74), citrullinated vimentin (cVim: 4KIHA-cit-EIFDS-cit-GNPTVE21), citrullinated fibrinogen, β chain (cFib: 5NNEEGFFSA-cit-GHRPLDKK), with their arginine control peptides (REP-1, Vim, and Fib) by ELISA. The cut-off for positivity for CCP2 was 5 U/ml as per manufacturers instructions and for the remaining peptides was calculated using the 95th percentile of the healthy controls. The Mann-Whitney U test was used to calculate p-values for differences between the results for each assay and Spearman non-parametric correlations between datasets were calculated.

Results: In the BR patients without RA, there was an increased antibody response to the uncitrullinated variants of the antigens tested in this study. Anti-CCP2 antibodies were positive in 5% of patients, significantly increased above the healthy (p<0.001) and asthma (p<0.01) controls. The anti-CCP2 arginine control test (anti-CPArg) was also significantly increased in 19%. Similarly, antibodies to the arginine control peptides from the specific citrullinated antigens were also increased: REP-1 19% (p<0.01), Vim 16% (p<0.01) and Fib 9% (p ns), compared to both healthy and asthma controls. There was a corresponding increase in antibodies to the citrullinated peptides which in each case strongly correlated with their uncitrullinated variants (Spearman ρ values =0.512–0.798), further supporting the findings of a citrulline-independent autoantibody response in BR.

In contrast to the BR patients, the BRRA patients had a highly citrulline specific ACPA response and the rate of seropositivity in BRRA vs RA was significantly reduced for each ACPA tested: anti-CCP, 88% vs 48%; anti-CEP-1, 60% vs 24%; anti-cVim, 56% vs 20% and anti-cFib 74% vs 40% (each p<0.001) despite a lower frequency of smoking (42% vs 58%; p=0.06). The citrulline specificity of the RA ACPA response was confirmed by the lack of correlation with response to the arginine-containing peptides (Spearman ρ values <0.298). Collectively, these data show that the citrulline specificity of ACPA in BRRA is increased compared to BR alone and its magnitude is increased compared to RA without any lung disease.

Conclusion: These findings provide further evidence linking BR to RA by indicating that BR may generate ACPA in two stages: firstly a citrulline independent B-cell response to host or bacterial antigens in the lungs with a subsequent evolution of citrulline specificity in the cases where BR evolves into BRRA.

Disclosure: A. M. Quirke, None; E. Perry, None; A. Cartwright, None; C. Kelly, None; A. De Sozya, None; P. Eggleton, None; D. Hutchinson, None; P. Venables, None.

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Characterization of Lung Inflammation in the Lungs of Early Rheumatoid Arthritis

Gudrun Reynisdottir1, Vijay Joshua2, Aase Haj Hensvold2, Lars Klareskog3 and Anca I. Catrina4. 1Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, 2Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, 3Rheumatology Unit, Karolinska University Hospital, Karolinska institutet, Stockholm, Sweden.

Background/Purpose: We have previously demonstrated that lung abnormalities are present already at disease onset in ACPA positive RA patients. We therefore aimed to further investigate lung changes in patients with rheumatoid arthritis (RA) in dynamic in a follow-up clinical study.

Methods: 105 RA patients (with patient-reported symptom duration less than 1 year and naive to DMARD treatment) were investigated by lung HRCT and functional pulmonary testing at disease onset and 6 months after. All patients were started on methotrexate. A smaller subgroup of these patients (n=24) were subjected to bronchoscopy and mucosal large bronchial biopsies and bronchoulecular lavage (BAL) samples were retrieved at disease onset (n=24) and after 6 months (n=21). Additional 16 large bronchial biopsies and 79 BAL samples from healthy volunteers were available. Histological analysis for identification of inducible bronchia associated lymphoid tissues (iBALT) and lymphocyte infiltration were performed. Further, immunohistochemical analysis was performed in RA biopsies to detect PAD enzymes, CD3, HLA-DR and to identify citrullinated targets.

Results: Both parenchymal and airway HRCT abnormalities were more frequent among RA patients than controls (54% as compared to 30%, OR 2.7, p<0.05 for parenchymal changes and 66% as compared 42%, OR 2.7, p<0.05 for airway changes). Fibrosis (12/105, 11%) was solely detected in RA patients. At follow up 4 out of these 12 patients show some progress signs while the remaining 8 were stable.

Bronchial lymphocyte infiltration and iBALT formation was observed at baseline in half of the ACPA+ RA patients but only 1 out of 6 ACPA- patients (17%) and 1 out of 9 healthy volunteers (10%). Signs of such infiltration were still present at 6 months. Higher expression of HLA-DR, HLA-DQ and citrullinated targets was observed in bronchial biopsies of ACPA+ as compared to ACPA- RA (p<0.05). CD3 expression also showed a tendency to higher expression in the ACPA+ as compared to ACPA- RA patients. HLA-DR expression showed a tendency to decrease at 6 months but no significant changes were observed.

ACPA+ RA patients had significantly higher proportions of BAL lymphocytes and neutrophils as compared to healthy controls (p<0.01). The increased relative numbers of BAL lymphocytes at disease onset was found reduced after 6 months of treatment (p<0.05). Markers of T cell activation (CD69 and CD103) were expressed by significantly more CD4+ BAL T cells in ACPA+ RA patients as compared to healthy controls, but no significant changes were observed at follow-up.

Conclusion: HRCT changes, signs of inflammation and accumulation of highly activated and differentiated BAL CD4+ T cells are present early in the lungs of ACPA+ RA patients and show relatively minimal changes during 6 months follow-up.

Disclosure: G. Reynisdottir, None; V. Joshua, None; A. H. Hensvold, None; L. Klareskog, None; A. I. Catrina, None.

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Smoking Functions As a Negative Regulator of IGF-1 Levels and Adipokine Network in Patients with Rheumatoid Arthritis

Maria Bokarewa1, Malin Erlandsson2, Sofia Töyrä Silfverswärd3, Andrea Ioan-Facsinay1 and Roberto Doria Medina1. 1University of Göteborg, Göteborg, Sweden, 2University of Gothenburg, Gothenburg, Sweden, 3University of Göteborg, Göteborg, Sweden, 4Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Smoking is an important player in the pathogenesis of rheumatoid arthritis (RA) being tightly connected to the genetic (carriage of HLA-DRB1 shared epitope) and serological (production of autoantibodies) risk factors for the development of RA. The molecular events connecting cigarette smoking to severe joint inflammation and low efficacy of
anti-rheumatic drugs, are poorly understood. Adipokines is a family of signalling molecules originating from adipose tissue and regulating carbohydrate metabolism and soft tissue regeneration. In RA, adipokines are connected to the disease activity and progressive radiological joint damage. Numerous effects of adipokines are mediated through insulin receptor/insulin-like growth factor-1 receptor (IGF-1R) complex.

Here we address a potential connections between cigarette smoking and changes in IGF-1 signalling and adipokine network function in patients with RA.

**Methods:** 543 patients from 2 independent RA cohorts (Göteborg, n=350 and Leiden, n=193) were included in this observational study. Patients were divided by their smoking habits defined as present smokers (n=126), ex smokers (n=177) and never smokers (n=240). Serum levels of total IGF-1 and adipokines (adiponectin, leptin, resistin and visfatin) were measured with sandwich ELISAs. The patient groups were compared by quantitative statistics and the association between smoking and serum parameters were evaluated by bivariate and multivariate correlation analysis.

**Results:** The two studied cohorts differed in disease duration, where the Leiden cohort consisted of early RA patients (DD md 0.4 years), higher disease activity (DAS28 md 5.1) and higher VAS-pain (md 46mm), while the Göteborg cohort consisted of patients with established RA (DD md 7.5 years), low DAS28 (md 3.0) and VAS-pain (md 27mm). In both cohorts the smokers were more often men (P<0.01).

Serum levels of IGF-1 were significantly lower in the present smokers followed by ex smokers. RA patients who never smoked had significantly higher serum levels of IGF-1 (P<0.001). Levels of adiponectin were also higher in never smokers (P=0.002). The correlation between leptin and resistin observed in the whole material was significantly weaker in the present smokers (rho=0.235) compared to the never smokers (rho=0.520). The present smokers had stronger correlations between IGF-1 and leptin (rho=0.233, P=0.009), resistin (rho=0.210, P=0.018). These correlations were not observed in the never smokers or the ex smokers.

The logistic regression analysis showed that low levels of IGF-1 were associated with low levels of leptin and visfatin and with current smoking. Neither age, gender, DAS28 nor BMI was contributing significantly in the regression model. Clinical impact of low leptin levels evaluated in a different logistic regression model showed an association with high DAS28, male gender and high BMI.

**Conclusion:** Smoking is associated with lower serum levels of IGF-1 in RA patients. The link between IGF-1 and the adipokines network is dependent on the smoking habit of the patient, and potentially supporting sustained disease activity and reducing regeneration processes in the damaged arthritic joints in RA patients.

**Disclosure:** M. Bokarewa, None; M. Erlandsson, None; S. Töyrä Silfverswärd, None; A. Ioan-Fasciuc, None; R. Doria Medina, None.

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**Anti-Citrusellated Heat Shock Protein 90 Antibodies Identified in Bronchialoveal Lavage Fluid Are a Marker of Lung-Specific Immune Responses.** Lisa Harlow1, Bernadette Gochuico1, Ivan Rosas2, Tracy Doyle1, Juan Osorio3, Timothy Travers4, Carlos Camacho2, Chester V. Odds2 and Dana Ascherman1, None.

**Background/Purpose:** Autoantibodies and other biomarkers of rheumatoid arthritis (RA) that may be detected years before disease onset in a subset of investigated individuals could be affected by exposures such as smoking. Changes in biomarker levels from the pre-clinical phase to early RA may reflect progression of joint damage in RA. The purpose was to investigate the relationship between COMP and smoking, as well as changes in COMP from the pre-clinical phase to early RA, and how these relate to early disease activity.

**Methods:** Between 1991 and 1996, 30 447 subjects from a defined catchment area were included in a health survey. From this population, individuals who developed RA after inclusion were identified by linking the health survey database to a community based RA register and local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 ACR criteria for RA. One control for each validated case, matched for sex, year of birth and year of screening, who was alive and free of RA when the index person was diagnosed with RA, was selected from the health survey database. Furthermore, the identified sample of incident cases of RA was linked to an inception cohort of early RA patients (symptom duration <12 months) from the same area. Serum COMP in pre-RA cases and controls, as well as in patients with early RA, was measured with a sandwich ELISA (AnaMar).

**Results:** Serum was available from 167 individuals (131 women, mean age at screening 63 years) who were diagnosed with RA after inclusion in the health survey (a median of 5 years later (range 1–13)). COMP levels were significantly lower among current smokers compared to non-smokers in pre-RA cases (mean 10.1 vs. 11.5 U/L, p=0.009) as well as in controls (mean 10.7 vs. 11.9 U/L, p=0.046). Fifty-seven cases (44 women) were also included in the early RA cohort after a median of 4.9 years (interquartile range 3.6–6.7). At inclusion, their mean age was 65 years, 56 % were anti-CCP positive and the mean DAS28 was 4.6 (SD 1.1). COMP levels increased significantly from the pre-RA sample to inclusion in the early RA cohort (mean change 1.6 U/L (SD 4.2); p=0.006). An increase in COMP tended to be associated with higher DAS28 at inclusion in the early RA cohort (β 0.09; 95 % confidence interval (CI) –0.01 to 0.18; adjusted for age, sex and baseline COMP). This association was observed in particular among smokers at baseline (n=22) (adjusted β 0.22; 95 % CI 0.04 to 0.39) and to a lesser extent in non-smokers (n=35) (adjusted β 0.06; 95 % CI –0.07 to 0.19).

**Conclusion:** COMP levels were lower in smokers among pre-RA cases as well as in controls who do not develop RA. Increasing COMP in the pre-clinical phase of RA appeared to be associated with a severe RA phenotype, in particular among smokers. The relation between early changes in cartilage turnover and long term outcomes in RA should be further studied.

**Disclosure:** C. Turesson, None; G. Book, None; U. Bergström, None; L. Jacobsson, None; T. Saxne, None.

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**Increased Cartilage Turnover in Smokers Developing Rheumatoid Arthritis Is Associated with High Disease Activity in Early Disease.** Carl Turesson1, Christina Book2, Ulf Bergström1, Lennart Jacobsson1 and Tore Saxne1.

**Background/Purpose:** Autoantibodies and other biomarkers of rheumatoid arthritis (RA) that may be detected years before disease onset in a subset of investigated individuals could be affected by exposures such as smoking. Changes in biomarker levels from the pre-clinical phase to early RA may reflect progression of joint damage in RA. Our purpose was to investigate the relationship between COMP and smoking, as well as changes in COMP from the pre-clinical phase to early RA, and how these relate to early disease activity.

**Methods:** Between 1991 and 1996, 30 447 subjects from a defined catchment area were included in a health survey. From this population, individuals who developed RA after inclusion were identified by linking the health survey database to a community based RA register and local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 ACR criteria for RA. One control for each validated case, matched for sex, year of birth and year of screening, who was alive and free of RA when the index person was diagnosed with RA, was selected from the health survey database. Furthermore, the identified sample of incident cases of RA was linked to an inception cohort of early RA patients (symptom duration <12 months) from the same area. Serum COMP in pre-RA cases and controls, as well as in patients with early RA, was measured with a sandwich ELISA (AnaMar).

**Results:** Serum was available from 167 individuals (131 women, mean age at screening 63 years) who were diagnosed with RA after inclusion in the health survey (a median of 5 years later (range 1–13)). COMP levels were significantly lower among current smokers compared to non-smokers in pre-RA cases (mean 10.1 vs. 11.5 U/L; p=0.009) as well as in controls (mean 10.7 vs. 11.9 U/L; p=0.046). Fifty-seven cases (44 women) were also included in the early RA cohort after a median of 4.9 years (interquartile range 3.6–6.7). At inclusion, their mean age was 65 years, 56 % were anti-CCP positive and the mean DAS28 was 4.6 (SD 1.1). COMP levels increased significantly from the pre-RA sample to inclusion in the early RA cohort (mean change 1.6 U/L (SD 4.2); p=0.006). An increase in COMP tended to be associated with higher DAS28 at inclusion in the early RA cohort (β 0.09; 95 % confidence interval (CI) –0.01 to 0.18; adjusted for age, sex and baseline COMP). This association was observed in particular among smokers at baseline (n=22) (adjusted β 0.22; 95 % CI 0.04 to 0.39) and to a lesser extent in non-smokers (n=35) (adjusted β 0.06; 95 % CI –0.07 to 0.19).

**Conclusion:** COMP levels were lower in smokers among pre-RA cases as well as in controls who do not develop RA. Increasing COMP in the pre-clinical phase of RA appeared to be associated with a severe RA phenotype, in particular among smokers. The relation between early changes in cartilage turnover and long term outcomes in RA should be further studied.

**Disclosure:** C. Turesson, None; G. Book, None; U. Bergström, None; L. Jacobsson, None; T. Saxne, None.
Distinct Profiles of Proinflammatory Macrophages in Rheumatoid Arthritis and Coronary Artery Disease. Tsuyoshi Shirai1, Eric L. Matteson2, David G. Harrison3, Barbara B. Wallis4, Themistocles L. Assimes5, Jorg J. Goronyz1 and Cornelia M. Weyand1. 1Stanford University School of Medicine, 2Mayo Clinic, Rochester, MN, 3Vanderbilt University School of Medicine, Nashville, TN, 4Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.

Background/Purpose: Patients with RA have an increased risk of developing coronary artery disease (CAD) compared to the general population. The underlying pathological process of CAD is atherosclerosis, which is a chronic inflammatory disease caused by maladaptive inflammatory responses. Macrophages are key players in the progression of atherosclerosis, contributing through proinflammatory effector functions, such as cytokine production. It is currently unknown whether accelerated CAD in RA results from similar or distinct pathomechanisms that underlie non-RA CAD. This study was designed to define and compare proinflammatory macrophages in patients with CAD and RA to clarify their potential contribution to the process of atherosclerosis.

Methods: Healthy controls, patients with RA who satisfied the ACR classification criteria, and patients with CAD who had a history of at least one myocardial infarction in the absence of co-existent autoimmune disease, were enrolled into this study. Monoctyes isolated from peripheral blood mononuclear cells were differentiated into macrophages with M-CSF for 5 days. Macrophages were further differentiated into M1 or M2 with IFN-γ and lipopolysaccharide or IL-4 and IL-13, respectively, for 2 days. RNA was purified from macrophages, and the expression of 55 genes were measured using quantitative PCR. Cytokine production was quantified by multi-parametric flow cytometry.

Results: The gene expression signatures of macrophages derived from healthy controls, RA and CAD were significantly different (p<0.01). CAD macrophages were characterized by high production of IL-6 and IL-1β (7.8 and 6.4-fold upregulation compared to controls, p=0.04 and p=0.03, respectively), a phenotype that RA macrophages did not share. CAD macrophages expressed high levels of chemokine receptors including CCR2, CCR5, and CCR7, while RA macrophages expressed similar levels of chemotactic receptors as healthy macrophages. The expression of the transcription factors Kruppel-like factor (KLF)-2 and KLF-4 also distinguished CAD and RA macrophages. KLF-2 and KLF-4 were distinctly low in CAD macrophages (p=0.04 and p=0.02, respectively), but well maintained in RA macrophages. A characteristic feature of RA macrophages was the high expression of CCL18, a CC chemokine attracting predominantly T lymphocytes. The signature of RA macrophages included the suppression of activation-induced IFN-β, indicating a down-regulation of type I IFN-dependent immunity.

Conclusion: CAD macrophages have a signature of super-inflammatory effector cells, characterized by the loss of negative regulators of inflammation (KLF-2; KLF-4) and the gain of cytokine production capability, releasing high amounts of IL-6 and IL-1β. Because of high expression of chemotactic receptors, they can efficiently navigate through the atherosclerotic plaque to enhance inflammation. In contrast, RA macrophages appear less mobile and are able to amplify inflammation through the CCL18-dependent recruitment of T cells. The data suggest that macrophage-dependent immune responses are fundamentally different in RA and CAD.

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The Anti-IL-6 Antibody Sirukumab Inhibits Vascular Inflammation in a Human Surrogate Model of Atherosclerosis. Ryan Feaver1, Soi Collado2, Stephen Hoang3, Erica Berzin4, Allison Armstrong5, Debbie Gardner5, Paul Fisher6, Hao Liu7, Aaron Mackey8, David Manka9, Brian Wambhoff2, David Shealy2, and Brett Blackman2. 1HemoShear, LLC, Charlottesville, VA; 2HemoShear, LLC, Charlottesville, VA, 3HemoShear, LLC, Charlottesville, VA; 4HemoShear, LLC, Charlottesville, VA, 5Janssen Research & Development, LLC, Spring House, PA; 6Janssen Research & Development, LLC, Spring House, PA; 7Immunology Research, Janssen Research and Development, LLC, Spring House, PA; 8Janssen Research & Development, LLC, Spring House, PA.

Background/Purpose: Rheumatoid arthritis (RA) and atherosclerosis are chronic inflammatory diseases that share many biological features. Prevalence of atherosclerosis is increased by approximately 2-fold in RA, with at least 2 prominent molecular links between the two: IL6 and TNFα signaling. Elevated circulating IL6 is an independent risk factor for cardiovascular disease and correlates with RA disease progression in patients. To test the hypothesis that compounds used for the treatment of RA decrease vascular inflammation under atherosclerotic conditions.

Methods: To elucidate the impact of RA treatments on vessel wall health, a novel in vitro human surrogate system that co-cultures human endothelial (EC) and smooth muscle cells (SMC) was used. Atheroprone flow conditions were applied, based upon human hemodynamic blood flow from the carotid bifurcation, a site prone to developing atherosclerosis. Atherogenic risk factors were added to the culture medium, including in vitro circulating concentrations of oxidized LDL (oxLDL) and TNFα. In addition, soluble IL-6 receptor (sIL6R) was added at a concentration typically seen in patient sera. RNA sequencing and multiplex protein assays were used to perform transcriptomic and biochemical pathway analyses of the response of the human surrogate system. We compared treatments that target pathogenic RA pathways including anti-IL6 and anti-IL6 receptor antibody (sirukumab or tocilizumab, respectively), anti-TNFα antibody (adalimumab) and a small molecule inhibitor of JAK (tofacitinib) at Cmax doses.

Results: Using this model, the combination of sIL6R, TNFα and oxLDL induced a robust transcriptional response of inflammatory genes under atheroprone hemodynamics compared to control conditions without sIL6R or TNFα and with non-oxidized LDL. The anti-IL6/IL6R treatments (sirku- numab, tocilizumab) significantly improved the vascular health phenotype relative to control IgG treatment. Both sirukumab and tocilizumab dramatically decreased adhesion molecule gene expression and NFκB-dependent genes while simultaneously increasing vasculoprotective responses such as eNOS and KLF2 expression, and promoting a contractile SMC phenotype. Adalimumab showed a weaker but similar trend compared to IL6 inhibition, while tofacitinib was not effective in suppressing inflammation or promoting vascular health. Sirukumab had a weaker but similar trend compared to TNFα signaling than adalimumab. Although broadly comparable, siru- kumab was more potent than tocilizumab in suppressing inflammation and promoting vascular health.

Conclusion: These data suggest that the IL6 pathway inhibitors (sirukumab and tocilizumab) potently suppress inflammation and promote vascular health in an in vitro model of RA-associated cardiovascular disease. In contrast the TNFα inhibitor, adalimumab, and JAK inhibitor, tofacitinib, were less effective in alleviating the disease phenotype. Collectively, the data suggest that IL6 inhibition may provide vascular protection in patients with RA.


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Comparison of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) with Estimated Glomerular Filtration Rate (eGFR) in Patients with Rheumatoid Arthritis (RA). Ilia Oksironomonopolu1 and John D. Carter2. 1University of South Florida Morsani College of Medicine, Tampa, FL; 2University of South Florida, Tampa, FL.

Background/Purpose: It has previously been demonstrated that the ESR and CRP correlate in patients with RA but with a high degree of variability. Reasons for this variability are not completely understood, but anemia, adiposity, and age can play a role. It has previously been suggested that ESR and CRP are inversely related to renal function in a non-RA population; it is felt that underlying inflammation is the explanation for the negative correlation with the CRP, specifically. The aim of this study is to see if the CRP and/or ESR inversely correlate with renal function in patients with RA.

Methods: This is a retrospective chart review of RA patients followed at USF Health. Subjects were identified by ICD-9 code (714.0) and they had to have a CRP, ESR, hemoglobin (Hgb) and eGFR performed on the same day. The most recent labs were utilized and no patient was included twice. Patients were excluded if they were <18 years of age or had a history of blood cancers known to affect inflammatory markers. The co-primary endpoints were the correlation between CRP and eGFR as well as ESR and eGFR. Secondary endpoints included correlation between CRP and ESR as well as both inflammatory markers with renal endpoints. The patient’s Spearman correlation coefficients (rho) were utilized to determine significance.

Results: 158 patients met the inclusion criteria: 136 (86%) were females with an mean age of 58.82 years (±/− 11.44 SD; range 26–84 years). 93/130 (71.5%) of these subjects were seropositive; status was unknown on 28
patients. The mean CRP and ESR in these subjects was 0.89mg/dL (+/− 1.37mg/dL SD) and 16.07mmHg (+/− 16.61mmHg SD), respectively; the mean eGFR and Hgb was 82.76 mL/min/1.73m² (+/− 20.92 mL/min/1.73m² SD) and 12.77g/dL (+/− 1.31g/dL SD), respectively. There was no correlation between the CRP and the eGFR (rho = 0.041; p = 0.60). There was also no correlation between the ESR and the eGFR (rho = −0.037; p = 0.64). There was a correlation between the CRP and ESR but with a high degree of variability (rho = 0.596; p < 0.0001). The ESR correlated weakly with Hgb and it did so in an inverse fashion (rho = −0.348; p<0.0001); the CRP did not appear to correlate with the Hgb (rho = −0.115; p = 0.15). There was no correlation with either CRP or ESR and age (rho = −0.075 and 0.006 respectively).

Conclusion: This retrospective chart review of 158 patients with RA suggests there is no correlation between CRP and/or ESR with renal function. Renal function does not appear to be an explanation for some of the variability that is documented between CRP and ESR in patients with RA.

Discussions: I. Oikonomopoulos, None; J. D. Carter, None.

Arthritis Associated Autoantibodies in Non-Rheumatoid Arthritis Patients with Mucosal Inflammation

Methods: The presence of anti-CAP, anti-CCP, and anti-CarP antibodies was assessed in 212 patients: 112 patients with active RA (10 patients with early RA and 102 with established RA), and 100 healthy controls. Anti-CCP2 Ab and total IgG were measured by ELISA. Female, sex (%)

Conclusion: Presence of anti-CCP2 and anti-CarP is slightly more prevalent in serum of non-RA patients with mucosal inflammation. The increased levels of anti-CAP indicate that at least part of the increased anti-CAP reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific.

Background/Purpose: Anti-CarP antibodies have been reported in both early and established RA patients. The aim was to assess the presence of anti-CarP antibodies in serum of patients with mucosal inflammation at different sites, namely in periodontitis, cystic fibrosis and bronchiectasis patients. Yes, healthy subjects without periodontitis (HC) and a cohort of established RA-patients were added (Table 1).

Results: Table 1: Characteristics of patients and healthy controls assessed for presence of autoantibodies.

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Anti-Carbamylation Protein Antibody Levels Are Elevated in Seropositive Rheumatoid Arthritis and Correlate with Anti-Sa/Citrullinated Vimentin Antibody Levels

Methods: The presence of anti-CarP antibodies was assessed in 212 patients: 112 patients with active RA (10 patients with early RA and 102 with established RA), and 100 healthy controls. Anti-CCP2 Ab and total IgG were measured by ELISA. Female, sex (%)

Conclusion: The presence of anti-CarP antibodies was clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presumed that at least part of the increased anti-CAP reactivity might not be citrulline specific.
level were determined by the clinical lab. A confirmatory analysis was performed using samples from early RA patients included in the Sherbrooke, QC (Canada) cohort. T-test, ANOVA and correlation analysis were utilized to evaluate relationships between variables. 63 healthy controls were also evaluated for levels of ACAP Ab.

**Results:** Among seropositive patients in the Dartmouth cohort (n=164), 46.6% exhibited elevated levels of ACAP Ab. ACAP Ab titers correlated with levels of ACPA (p=0.004) and IgM-RF (p=0.04). Seropositive patients in the early RA Sherbrooke cohort (n=173) displayed similar trends; 38.2% had elevated ACAP Ab levels, and ACAP Ab titer was highly associated with levels of ACPA (p=0.005) and weakly associated with IgM-RF (p=0.06). The relationship of ACAP Ab levels with baseline clinical parameters (age, DAS28-ERP, erosions, etc.) was either weak or absent in both cohorts. Intriguingly, we observed a highly significant correlation between anti-Sa status and ACAP Ab titer among seropositive patients in the Sherbrooke cohort (p<0.0002), with 47.9% of anti-Sa-positive patients harboring elevated levels of ACAP Ab versus 25.4% of anti-Sa-negative patients. This observation led us to test seropositive RA samples in the Dartmouth cohort for anti-Sa status; once again, a highly significant relationship was observed (p<0.000001): 62.6% of anti-Sa-positive patients showed elevated ACAP Ab levels versus 26.9% of anti-Sa-negative patients.

**Conclusion:** This is the first investigation of ACAP Ab levels in a population of established RA patients in the US, comparing it with an early RA Canadian cohort. A large proportion of each seropositive RA cohort exhibited elevated levels of ACAP Ab (38.2–46.6%). Most compellingly, we identified a strong relationship between levels of ACAP Ab and anti-Sa reactivity that raises the mechanistic question of how antibody responses to citrullinated and protein citrullinated vimentin (Sa) are linked in vivo.


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**Methods:** Twenty RA patients (80% female, mean age 62 years) and 15 age/gender matched healthy controls (81% female, mean age 58 years) participated in this study. Demographic and epidemiological data, including age, gender, disease duration and smoking habits, were collected. All the subjects underwent complete lung function tests, and provided induced sputum. The severity of the disease was evaluated in the RA patients by means of DAS score, and hand and feet X rays. Antibodies to Cit and Arg peptides in the sputum of the RA patients and healthy controls, as well as in the serum of the RA patients, were determined by ELISA.

**Results:** The RA patients suffered from long standing disease (mean disease duration of 12 years), displayed moderate disease activity (mean DAS 3.44), and showed a mean Sharp van der Heijde score of 57.5. Seventy % of the patients were on DMARDS and 65% on biologics, mainly TNF alpha blockers. Sixty % and 68 % of the RA and healthy controls, respectively, were defined as “ever smoker”. Eleven of the 20 RA patients showed in most cases high titers of ACPA in their sera. Six of the seropositive (55%) and none of the seronegative RA patients and none of the healthy controls showed detectable levels of ACPA in their sputum. The ratio between the reactivity with Cit and Arg peptides in the sputum was significantly higher in RA sputum than in control sputum (1.33 +/- 1.2 vs. 0.64 +/- 0.14, p=0.02). A positive correlation was found between sputum ACPA and age and serum ACPA in RA patients, as well as between sputum anti-Cit/Arg reactivity ratio and the proportion of neutrophils and lymphocytes in the sputum. No significant correlation was found between sputum ACPA and disease severity, smoking or lung function tests.

**Conclusion:** ACAP can be detected in the sputum of RA patients and are correlated with the presence in the serum. These findings further strengthen the hypothesized role of the lungs in RA pathogenesis.

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**Evidence for Citrullination of the Nuclear Transcription Factor Inhibitor of DNA Binding 1 (Id1) in Rheumatoid Arthritis.** Ray A. Ohara1, Gautam Edhuyan1, Christine M. Ha1, M. Asif Amin1, Ali S. Arbab2, Phillip L. Campbell3, David A. Fox4 and Jeffrey H. Ruth5. 1Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI; 2Georgia Regents University, Augusta, GA.

**Background/Purpose:** Citrullination is a post-translational modification mediated by peptidyl arginine deiminase (PAD) enzyme in which arginine is converted to citrulline. Inhibitor of DNA binding 1 (Id1) is known to be actively transcribed in endothelial progenitor cells (EPCs) and cells that exhibit hyperproliferative responses. Previously, we showed that Id1 is expressed in rheumatoid arthritis synovial tissues (RA STs) and upregulated in RA synovial fluids (SFs), suggesting that Id1 may be post-translationally modified in RA. A more detailed analysis of the structure of Id1 reveals a relatively small protein of approximately 16kDa, but containing 10 modificable arginines. We show that Id1 can be citrullinated, and that RA STs and SFs contain citrullinated Id1 (cit-Id1), suggesting that cit-Id1 may be pathogenic in the course of RA. We also show that by immunodepletion of Id1, we can reduce the angiogenic potency and overall amount of citrullinated protein in RA SF.

**Methods:** Id1 concentrations in RA SFs were measured by enzyme-linked immunosorbent assay (ELISA). To further explore the role of Id1 in RA SF, we immunodepleted Id1 with a neutralizing antibody or iso-specific IgG (“sham depleted”), and used this in the severe combined immunodeficient (SCID) mouse chimera. Mice grafted with human RA ST were injected i.v. with fluorescently dye-tagged EPCs while receiving simultaneous intragraft injections with the treated SFs. To examine Id1 citrullination, we modified recombinant human (rhu) Id1 by incubation with rabbit PAD enzyme. Cit-Id1 was measured for deamination by a cit-ELISA using an anti-citrullinated citrulline antibody. Citrullinated bovine serum albumin (BSA) was used as a relative standard. RA STs immunodepleted with either Id1 or sham depleted were also measured by cit-ELISA to determine the total amount of citrullinated protein contained in RA SFs before and after Id1 depletion. Finally, we homogenized RA ST and performed immunoprecipitation (IP) of Id1 to determine the presence of Id1 and cit-Id1 by Western blotting using anti-human Id1 and anti-modified citrulline antibodies.

**Results:** We found a 50% reduction in EPC recruitment to intragraft injections of RA SF immunodepleted of Id1 compared to sham depleted RA SF (p<0.05). We measured the amounts of total citrullinated protein in RA SF, and found that by removal of Id1, we could significantly reduce the total amount of citrullinated protein in RA SF (p<0.05). Western blot analysis of Id1 and cit-Id1 confirmed that we could discriminate cit-Id1 from non-cit-Id1, and that we could successfully modify Id1 in vitro. Similarly, Id1 isolated by IP from RA ST homogenates showed that we could detect both Id1 and cit-Id1 in RA ST homogenates, and that a significant portion of the total Id1 in RA ST was in modified form.

**Conclusion:** We identify Id1 as an angiogenic factor, capable of recruiting EPCs to RA ST. We also show for the first time that Id1 can be modified using rabbit PAD enzyme. The significant shift downward in total citrullination in RA SFs depleted of Id1 indicates that cit-Id1 is present and elevated in the RA SF. We also show that Id1 in the RA ST is also citrullinated. Taken together, we show that Id1 functions as an angiogenic mediator and is robustly modified in RA tissues.

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**Differing Specificities of Anticitrullinated Peptide-Protein Antibodies in Palindromic Rheumatism and Rheumatoid Arthritis: A Case-Control Study.** Sonia Cabrera-Villalba1, María José Gomara1, Julio Ramirez1, Georgina Salvador1, Virgina Ruiz-Esquide1, M. Victoria Hernández1, José Inciarte-Mundo1, Andrea Cuervo1, Celia Saura1, Juan D. Cañete2, Isabel Haro3 and Raimon Sammarti1. 1Hospital Clinic of Barcelona, Barcelona, Spain, 2IQAC-CSIC, Barcelona, Spain, 3Hospital Universitario Mutua Terrassa, Barcelona, Spain.

**Background/Purpose:** Palindromic rheumatism (PR) may evolve to rheumatoid arthritis (RA), particularly in patients with citrullinated peptide/protein antibodies (ACPA), although a significant number of patients do not progress to RA in the long term. Differences in ACPA specificities have been shown between patients with established and preclinical RA. It is unclear whether ACPA specificities differ between patients with longstanding PR and RA. To determine whether there are differences in the recognition of epitopes between patients with longstanding PR and established RA by analysis of different ACPA specificities.

**Methods:** Case-control study. Cases: patients with pure PR, with no evolution to RA or other rheumatic disease at study entry. Controls: patients with established RA (ACR-87) matched by sex, disease duration and ACPA positivity (commercial CCP2 test [Eurodiagnostica]; NV<50U). ACPA specificity in sera was determined by ELISA test using a synthetic citrullinated peptide of fibrinogen α chain as antigen: [Cit193-197]α-Fibrin (617–631)(p18), two peptides of vimentin ([Cit192] Vim (47–72)p48), [Cit69-71] Vim (47–72)p55) and one peptide of α-ensolase: [Cys42,22,Cit15] Enolase (5–21)cECP-1. The cut off for each ELISA test was established by ROC curves, with a specificity of 98% compared to a healthy population (blood donors, n=64). The presence and number of different ACPA specificities in the two groups was analyzed.

**Results:** We included 108 patients: 54 PR and 54 RA. 62.9% were female and 66.7% in both groups were CCP2 positive. No significant differences between groups in mean age (51.2 ± 11.3 vs 54.7 ± 11.8 years) and disease duration (11.6 ± 10.7 vs. 8.3 ± 6.1 years) were found. PR patients had a lower frequency of some ACPA specificities than RA, which was significant in the case of p48 vimentin (1.9% RP vs. 14.8% AR, p: 0.015) and, especially, p 55 vimentin (PR 24.1% vs. 59.3% AR, p: 0.001). The percentage of sera with no ACPA specificities was lower in PR than in RA patients (0.9 ± 0.9 PR vs. 1.4 ± 1.03 AR, p=0.008). The mean CCP2 level was 392.6 ± 527.6 (RA) vs. 487.4 ± 584.4 (PR) U/mL.

**Conclusion:** Patients with PR had a lower frequency of some antigenic specificities of ACPA in comparison with RA patients, especially in the case of citrullinated vimentin. PR patients also had a lower total number of specificities than RA patients. PR patients with fewer ACPA specificities and no recognition of citrullinated vimentin may have a better prognosis, without progression to RA.

**Table:** ACPA specificities in patients with PR and RA

<table>
<thead>
<tr>
<th>PR n = 54</th>
<th>RA n = 54</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCP2, n %</td>
<td>36 (66.7)</td>
<td>36 (66.7)</td>
</tr>
<tr>
<td>CCP2 levels</td>
<td>392.6 ± 527.6</td>
<td>487.4 ± 584.4</td>
</tr>
<tr>
<td>p18 α-fibrin n, %</td>
<td>19 (35.2)</td>
<td>26 (48.1)</td>
</tr>
<tr>
<td>CEP-1 enolase n, %</td>
<td>16 (29.6)</td>
<td>21 (38.9)</td>
</tr>
<tr>
<td>p48 vimentin n, %</td>
<td>1 (1.9)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>p55 vimentin n, %</td>
<td>13 (24.1)</td>
<td>32 (59.3)</td>
</tr>
<tr>
<td>Number of Vimentin specificities, mean</td>
<td>0.26 ± 0.4</td>
<td>0.74 ± 0.7</td>
</tr>
<tr>
<td>Total number of ACPA specificities (mmulti-max3)</td>
<td>0.91 ± 0.96</td>
<td>1.43 ± 1.03</td>
</tr>
</tbody>
</table>

**Disclosure:** S. Cabrera-Villalba, None; M. J. Gomara, None; J. Ramirez, None; G. Salvador, None; V. Ruiz-Esquide, None; M. V. Hernández, None; J. Inciarte-Mundo, None; A. Cuervo, None; C. Saura, None; J. D. Cañete, None; I. Haro, None; R. Sammarti, None.

**Immunoglobulin a Antibodies to Cyclic Citrullinated Protein Predominant in Individuals at-Risk for Future Rheumatoid Arthritis.** Gregory M. Ingolia1, M. Kristen Demoruelle2, Mark C. Parish3, Ryan W. Gan4, Jason R. Kolfenbach1, Michael H. Weisman5, Jane H. Buckner6, Peter K. Green7, Todd R. Mikuls8, James R. O’Dell9, Richard M. Keating10, Alvin Yee11, Michael Mahaler3, Jill M. Norris3, Kevin D. Deane3 and V. Michael Holers1. 1University of Colorado School of Medicine, Aurora, CO, 2Colorado School of Public Health, Aurora, CO, 3Cedars-Sinai Medical Center, Los Angeles, CA, 4Benaroya Research Institute at Virginia Mason, Seattle, WA, 5Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, 6University of Nebraska Medical Center, Omaha, NE, 7Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, 8Scripps Clinic, La Jolla, CA, 9INOVA Diagnostics, San Diego, CA.

**Background/Purpose:** Immunoglobulin A (IgA) autoantibodies (Abs) to citrullinated proteins (ACPAs) are present in the preclinical period of RA development, a finding that suggests a mucosal site of Ab generation (Kokkonen 2011). IgA ACPAs have also been found in subjects at-risk for future RA based on a family history of disease (Arlestig 2012; Barra 2013). In addition, we have identified apparent local mucosal generation of IgA RA-related Abs in at-risk subjects (Willis, Demoruelle 2013). Additional findings that serum IgA ACPAs predominate during the early natural history of RA would further support initial mucosal generation of RA-related autoimmunity.

Three groups from the Studies of the Etiology of RA (SEERA) project were evaluated: 77 AtRisk subjects who were first-degree relatives of patients with RA or subjects identified through health fair screening and all were serum positive for IgA-CCP (IgG, Axis-Shield), CCP3.1 (IgG/IgA, INOVA) and rheumatoid factor IgA/M/G (INOVA) without inflammatory arthritis, 53 subjects with seropositive RA (1987 criteria), and 71 blood donor controls. Each subject was tested for IgA ACPA/G/M using CCP3 antigen ELISAs (research use only; donated by INOVA), and by a technician blinded to group status. Positivity for CCP isotypes was mean levels +2 standard deviations in a separate set of 70 random blood donors. Shared epitope (SE) status was determined at AtRisk and RA subjects using published methods (Kolfenbach 2009).

**Results:** When comparing isotype proportions, IgA-CCP was positive in a higher number of AtRisk subjects than IgM (46.8% vs. 27.3%, p=0.03) (Table), and the prevalence was higher than IgG, although this was not statistically significant (46.8% vs. 39.0%; p=0.33). In contrast, in RA IgG-CCP was more common than IgA and IgM (86.8% vs. 69.8% and 47.2%, respectively; p’s<0.03). In Controls, IgA-ACP was also positive in a higher number of subjects than IgM or G (12.7% vs. 2.8% and 1.4%, respectively; p’s<0.03). In AtRisk, smoking was associated with positivity for CCP isotype; this was not seen in RA, however, RA subjects were more likely to be current smokers than AtRisk. In AtRisk and RA there was no association between CCP isotypes and the SE.

**Conclusion:** The high IgA ACPA positivity in AtRisk and high IgA ACPA in RA suggest that mucosal processes may be an early feature of RA-related autoimmunity that later transition to an IgG-dominant process. IgA ACPA positivity in controls also suggests that IgA-CCP is present in wider populations and perhaps related to non-disease-specific immune responses. These findings as well as the association of smoking with ACPA isotypes in AtRisk subjects and current smoking with RA status need exploration in larger studies that examine the genetic, environmental and mucosal factors that may be involved in the evolution of ACPA isotypes in transition from preclinical to clinically apparent RA.

**Table:**

<table>
<thead>
<tr>
<th>Controls</th>
<th>AtRisk</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>54.9 (12.5)</td>
<td>56.3 (14.5)</td>
</tr>
<tr>
<td>%Female*</td>
<td>79%</td>
<td>83%</td>
</tr>
<tr>
<td>%Non-Hispanic White*</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>Ever smoker*</td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td>Current smoker*</td>
<td>8%</td>
<td>45%</td>
</tr>
<tr>
<td>≥1 allele with the shared epitope (SE)*</td>
<td>56%</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Proportions of CCP positive subjects using commercial assays**

| CCP1 (Axis-Shield)** | 18.2% | 83.0% |
| CCP1 (INOVA)** | 0.0% | 51.9% | 64.9% |

**Proportions of CCP isotype positive subjects**

| IgA ACPA ** | 46.8% | 60.8% |
| IgM ACPA ** | 2.8% | 27.3% | 47.2% |
| IgG ACPA ** | 1.4% | 50.0% | 86.8% |
| ≥1 ACPA isotype | 16.9% | 75.3% | 88.7% |
smoking and any specific ACPA isotype. In AtRisk and RA, there was no association between any ACPA and RA, compared to controls. Within the AtRisk subjects, smoking was associated with positivity for all autoantibodies was significantly higher in RA than other groups, and higher in AtRisk when compared with controls (p < 0.01). Between the groups in sex or race. RA subjects were more likely to be current smokers and have differences in groups in sex or race. The mean age of AtRisk subjects was less than than RA (p < 0.01) although there were no significant differences in groups in sex or race. RA subjects were more likely to be current smokers and have RA, compared to controls.

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Rheumatoid Factor Isotypes in Relation to Antibodies Against Citrullinated Peptides in Individuals before Onset of Rheumatoid Arthritis. Mikael Brink1, Monika Hansson2, Linda Mathsson-alm1, Johan Rönnelid1, Lars Klaren2, Sorbitt Rantapää-Dahlqvist1. 1Umeå University, Umeå, Sweden, 2Karolinska Institute, Stockholm, Sweden, Uppsala University, Uppsala, Sweden, 3Institution of Public health and clinical medicine/Rheumatology, Umeå University, Umeå, Sweden.

Background/Purpose: The presence of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) has been shown to precede the development of rheumatoid arthritis (RA) by several years. The relationships between the separate antibody development of RF and ACPAs are unclear.

Methods: Three isotypes (IgA, IgG and IgM) of RF has been analyzed in samples from 333 pre-symptomatic individuals (contributing with 596 samples), who subsequently developed RA and 495 population controls, all donors to the Biobank of Northern Sweden. The pre-symptomatic samples were collected in median 6.1 (IQR 7.1) years before symptom onset. Cut-offs for RF isotypes were set at 95% specificity using ROC-curves. Data from the RF-isotypes were compared against ten ACPA specificities previously analyzed on a microarray based on the ImmunoCAP ISAC system (Phadia). RF isotypes were analyzed using the ELISA on the ImmunoCAP 2500 system (Phadia).

Results: The frequency of RF isotypes in pre-symptomatic individuals were 25.7% for IgA, 17.6% for IgG and 26.7% for IgM, significantly more prevalent compared with controls (p<0.0001). The concentrations for each isotype increased gradually the closer to onset of symptoms the sample was collected.

All three isotypes were associated with smoking (Odd’s ratio (OR) IgA= 2.9 (95% CI 1.3–3.6), IgG 2.1 (1.4–3.0) and IgM 2.8 (1.7–3.4), respectively) but not with HLA-SE or PTPN22 T-variant. The combinations of each of the RF isotypes with ACPA specificities (a-Enolase (CEP-1/Eno5–21), fibrinogen (Fib)β36–52, Fibrinolysis, fibrinogen (Fib)β36–52, Fibcorp91, fibrinogen (Fib)β36–52, CCAP-1/Fil307–324, vimentin (Vim) 60–75 or Vim2–17) were associated with significantly shorter time to onset of symptoms (p<0.01–0.05). The OR (95% CI) for disease development in IgA, IgG and IgM positive individuals were in combination with Fib36–52, CEP-1 or Fil307–324 further increased from 7.1 (4.5–11.2), 4.5 (2.8–7.3) and 7.4 (4.7–11.7), respectively to OR= 12.5–19.6 for IgA, 7.5–16.2 for IgG and 17.4–20.7 for IgM.

Conclusion: RF isotypes predicted development of RA and in particular using combinations of both ACPAs and RF isotypes the association with disease development was high and the predating time shorter.

Disclosure: M. Brink, None; M. Hansson, None; L. Mathsson-alm, None; J. Rönnelid, None; L. Klaren, None; S. Rantapää-Dahlqvist, None.

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Citrulline-Specific Autoimmunity Resides in Quiescent Circulating Memory B Cells in Rheumatoid Arthritis. Adam Pelzek, Caroline Grönwall, Jeffrey D. Greenberg and Gregg J. Silverman. New York University School of Medicine, New York, NY.

Background/Purpose: The detection of anti-citrullinated protein antibodies (ACPA) aids RA diagnosis, while B cell depletion by anti-CD20 can provide clinical benefits. We therefore undertook investigations of the phenotypic and functional properties of citrulline (Cit)-specific B cells in the bloodstream of RA patients.

Methods: RA met 2010 ACR/EULAR criteria. PBMC were cultured +/−CpG2006/IL-21/CD40L, and ELISpots performed. CD19+ B cell subsets were FACS sorted and cultured with CD40L-cell line/CpG2006/IL-21. Sera and supernatants were evaluated for total IgG, and for IgG1 and IgG4 subclasses by bead-based multiplex analysis, against 8 sets of paired cit/native cyclic self-peptides, plus CCP3, CQP3 (Cit to Q), Cit/native fibrinogen (Fib), tetanus toxoid (TT) and control ligands. We also surveyed 87 CCP3-seropositive and 30 seronegative RA serum samples, plus panels of disease specific control samples (SS, OA, PsA, SLE).

Results: ELISpots documented the presence of circulating anti-Cit B cells, as seropositive RA had 413.3+/−0.5 CCP3+ IgG (mean +/- SE) but only 1.9+/−0.6 CQP3+ spots/10^6 PBMC, while these were undetectable in seronegative RA and healthy adults. Anti-TT ISC were detected at 71.1+/−2.6 and 65.4+/−1.2 spots/10^6 PBMC in seropositive RA and controls, respectively. By multiplex assay, ACPA fine specificity reactivities in sera were compared with supernatant antibodies from stimulated PBMC. In 36 PBMC from seropositive RA, highly significant correlations by ACPA fine specificity were documented in comparisons with sera ACPA by Spearman correlations. From sorted B cells, we found ACPA-secreting B cells were enriched among CD19+IgD-CD27+ switched-memory (0.019–0.059% of CD19+CD27+IgD−), and included highly CCP3-reactive IgG. Yet, only rare weakly CCP3-reactive naïve B cells (IgG+CD27+) were detected, and none amongst pre-switched memory (IgD+/CD27−). From subclass-specific sera multiplex assays, amongst IgG1 ACPA-expressing seropositive RA, about half showed anti-CCP3 IgG1 only, while the remainder had both anti-CCP3 IgG1 and IgG4. Whereas reactivity levels were generally greater for IgG1 than IgG4, IgG1 responses usually displayed great Cit than native antigen-specific responses, while the IgG4 displayed greater reactivity with the native (non-Cit) form in 5/9 antigen sets.

Conclusion: In seropositive RA PBMC, IgG ACPA in vitro secretion was detected across all treatment groups tested (MTX, MTX+TNFi, MTX+abatacept), suggesting these cells persist despite therapeutic intervention. DAS28 score correlated with neither the level nor specificity of supernatant or sera ACPA. Pilot studies also suggest ACPA-secreting B cells predominantly reside within peripheral switched memory. Our data therefore suggest that seropositive RA patients have recirculating but quiescent memory B cells with repertoires akin to serum ACPA patterns. Furthermore, while IgG1 autoantibodies in RA are predominantly Cit-specific, with subclass switch to IgG4 there may be epitope spreading with progression to include recognition of determinants on the naive forms of the self-antigens. Our studies highlight defects in B cell tolerance in RA that may help guide development of better therapy.

Disclosure: A. Pelzek, None; C. Grönwall, None; J. D. Greenberg, None; G. J. Silverman, None.
with a neutralising antibody and found an increase in the magnitude of the IFN-g CitVim responses in the ACPA+ arthralgia, whereas in health there were no IFN-g responses (Fig. 2).

**Conclusion:** We demonstrate a sequential change from a regulatory (IL-10-predominant) to an inflammatory (IFN-g) CitVim-specific T-cell response as we move from health to ACPA+ arthralgia to RA. We have also shown that autoreactive IL-10 T-reg responses are actively inhibiting IFN-g responses in ACPA+ arthralgia individuals. It is plausible that such regulatory T-cell responses prevent progression to disease in health and in pre-clinical RA.

**Fig. 1.** IL-10 and IFN-g responses to CitVim peptide pools can be detected by ELISPOT. The percentage of individual with IL-10 and IFN-gamma cit-vim specific T-cell responses differed between RA, ACPA+ arthralgia and healthy volunteers ($\chi^2 = 28.4, p < 0.00001$).

**Fig. 2.** IL-10 mediated suppression of CitVim IFN-g T-cell responses. A. There was an increase in CitVim IFN-g T-cell responses after IL-10 blockade in ACPA+ arthralgia ($N=5, p=0.0051$). B. In healthy volunteers there was no increase ($N=5$).

**Disclosure:** A. Aslam, None; J. L. Nam, None; L. Hunt, None; C. Rakieh, None; A. W. Morgan, None; P. Emery, None.

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**The Mucosal Anti-Citrullinated Protein Antibody Response in Pre-Clinical Rheumatoid Arthritis.** Anneke van der Horst1, Ivy Y.K. Choi2, Dirkjan van Schaardenburg3, D.M Gerlag2, Paul Tak2, Dörte Hamann1 and Rogier M. Thurlings4. 1Sanquin Diagnostic Services, Amsterdam, Netherlands, 2Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 3Reade, Amsterdam, Netherlands.

**Background/Purpose:** Recent data suggest rheumatoid arthritis (RA) may originate from an autoimmune response in inflamed mucosa. RA is associated with gingival and airway inflammation and alterations in the microbiomol composition in the gut. Furthermore, anti-citrullinated (cit) protein antibodies (ACPA) of the IgA class, the main secreted mucosal antibody, precede arthritis by years in a proportion of RA patients. When aiming to prevent arthritis it is critical to understand the source and regulation of autoantibody production in preclinical RA.

**Objective** to determine whether ACPA are produced at mucosal sites in ACPA positive individuals at risk for RA and to compare the ACPA isotype and fine specificity in mucosal fluids to peripheral blood.

**Methods:** Saliva, sputum, faeces and peripheral blood were collected from 15 individuals with anti-cyclic cit protein (anti-CCP2) antibody positive arthralgia who are part of a cohort that is being prospectively followed for the possible development of arthritis. Saliva and sputum were collected during an early morning visit. Sputum was induced by inhalation of sodium chloride aerosols 4.5%. Mucus plugs were selected from sputum for extraction of supernatants. Faeces were collected at the same visit using stool collection kits and extracted using 6% BSA phosphate buffered saline. ACPA of IgA and IgG class were measured in mucosal fluids and blood using two cit fibrinogen peptides, one enolase peptide and one vimentin peptide and their respective arginine peptides as control.

**Results:** Thirteen of 15 individuals tested positive for the anti-CCP2 test and ACPA in their blood at the day of mucosal fluid collection. Two patients tested positive for anti-CCP2 but negative for ACPA. Two other patients had high reactivity against both cit peptides and arginin controls and were also considered ACPA negative. Anti-cit fibrinogen, enolase and vimentin antibodies were detected in respectively 11, 4 and 3 individuals. The saliva of 4 patients contained IgA ACPA with positive tests for anti-cit enolase and anti-cit fibrinogen. The saliva of another patient tested positive for IgG anti-cit enolase and anti-cit fibrinogen. Other saliva, sputum and faeces samples tested negative for ACPA. All 5 patients with ACPA in saliva tested positive for the same antibodies in blood. In addition, in 3 of 5 patients ACPA were detected in blood that were not detected in saliva, including anti-cit fibrinogen, anti-cit vimentin and anti-cit enolase antibodies.

**Conclusion:** Collection of saliva allows for the detection of ACPA in the saliva of a proportion of anti-CCP positive individuals at risk for RA. In these patients, IgG ACPA in blood are directed against more peptides compared to IgA ACPA in saliva. Future analyses should focus on further defining the precise source and regulation of mucosal ACPA compared to systemic ACPA.

**Acknowledgements:** The Dutch Reumafonds.

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**451**

**The Association of Fine Specificities of Anti-Citrullinated Protein Antibodies (ACPA) with disease Severity in African-Americans with RA.** Maria I. Danila1, Richard Reynolds4, Gordon Wu1, Hemant Tiwari1, William H. Robinson2, Jeremy Sokolove3, CLEAR Investigators3 and S. Louis Bridges Jr.1 University of Alabama at Birmingham, Birmingham, AL, 2VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, 3VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA.

**Background/Purpose:** RA is characterized by the presence of autoantibodies to citrullinated proteins (ACPA) and joint damage. The role of fine specificities of ACPA in radiographic severity has not been defined. The purpose of the current study was to evaluate whether fine specificities of ACPA are associated with radiographic severity of RA in African Americans.
Methods: Using a custom Bio-Plex™ bead-based autoantibody assay platform, we measured anti-CCP antibody and 19 autoantibodies targeting citrullinated proteins and peptides (vimentin, fibrinogen, histone 2A, histone 2B, and apolipoprotein E, clusterin, biglycan, enolase, fillagrin). We analyzed sera from 692 African-American patients with RA. A total antibody score was defined for each patient as the standardized sum of the log transformed autoantibodies. The total antibody score was used as predictor variable for radiographic severity. Radiographic severity defined as total Sharp/van der Heijde scores of hands/feet was the dependent variable. Zero-inflated negative binomial regression models were used to test the association of the autoantibody score with radiographic severity defined as total Sharp/van der Heijde scores of hands/feet given the covariates gender, BMI, smoking status and disease duration.

Results: High correlation coefficients among the autoantibodies were observed. Using zero-inflated negative binomial regression, the total sum of standardized antibodies had a statistically significant (p-value < 0.0002) effect among patients with a total RA radiographic severity (total score >0). For each unit increase in the total sum of standardized autoantibodies, the total radiographic score increases by 0.3 units. In addition, disease duration was found to be statistically significant (p-value < 0.0001).

Conclusion: Autoantibodies against citrullinated autoantigens are associated with joint damage in this cross sectional study of African Americans with RA. Future work will focus on longitudinal aspects of antibodies to specific peptides/proteins and their role in progression of radiographic damage.

Disclosure: M. I. Danila, None; R. Reynolds, None; G. Wu, None; H. Tiwari, None; W. H. Robinson, None; J. Sokolove, None; C. Investigators, None; S. L. Bridges Jr., None.

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In a Periodontal Disease Cohort without RA, Indeterminate or Low-Positive Anti-CCP-2 Antibodies Are Associated with Multiple Distinct ACPA.


1University of Minnesota, Minneapolis, MN, 2University of Minnesota School of Dentistry, Minneapolis, MN, 3Columbia Univ. Mailman School of Public Health, New York, NY, 4Benaroya Research Institute at Virginia Mason, Seattle, WA, 5University of Washington, Seattle, WA, 6Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Periodontal disease (PD) and RA share the risk factors HLA DR B1 shared epitope (SE) and tobacco exposure (TE). PD may represent a risk factor for subsequent RA. Individuals with multiple ACPA have increased risk of subsequent RA. We developed a prospective cohort with moderate to severe PD but no clinical features of RA, determining: i) the prevalence of HLA-DRB1 alleles; ii) seropositivity to CCP-2 antibodies (CCP-2) and ACPA; iii) whether HLA-DRB1 alleles were associated with CCP-2 or ACPA; and iv) if HLA-DRB1 alleles modified the association between CCP-2 and ACPA.

Methods: CCP-2 and IgM RF were performed by CLIA–certified assays. CCP-2 or RF+ individuals were offered clinical assessment to ensure they were free of RA by 2010 ACR/EULAR criteria. Sera were analyzed by multiplex assay for distinct ACPA. Positive cutoffs for ACPA were established by ROC analysis of prior studies. HLA DRB1 SE alleles were assayed using a high resolution genotyping platform. We measured anti-CCP antibody and 19 autoantibodies targeting citrullinated antigens identified as present in RA synovia. We have explored changes in fine specificity and levels of IgG- and IgA-ACPA following RTX.

Results: Median age was 60 years. Key findings:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th># (181 total)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>120</td>
<td>66.3</td>
</tr>
<tr>
<td>Ever used tobacco</td>
<td>131</td>
<td>72.3</td>
</tr>
<tr>
<td>Detectable CCP-2 (&gt; 0.5 u)</td>
<td>30</td>
<td>16.6</td>
</tr>
<tr>
<td>CCP-2 indeterminate or greater (&gt; 1.5 u)</td>
<td>11</td>
<td>6.1</td>
</tr>
<tr>
<td>RF positive (&gt; 10)</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>≥1 ACPA</td>
<td>62</td>
<td>34.3</td>
</tr>
<tr>
<td>≥3 ACPA</td>
<td>12</td>
<td>6.6</td>
</tr>
<tr>
<td>HLADRBl*0401</td>
<td>33</td>
<td>18.2</td>
</tr>
<tr>
<td>HLADRBl*0101</td>
<td>34</td>
<td>18.8</td>
</tr>
</tbody>
</table>

The most common ACPA was anti-citrullinated histone 2A; n=44(24%). all other ACPA occurred in < 7% of participants. There was a significant relationship between the presence of an indeterminate or low positive CCP-2 and the presence of ≥ 3 distinct ACPA (OR [95% CI] = 23.4[5.5, 100.1], p = 0.0001). The presence of DRBl*0401 was marginally associated with an indeterminate or low positive CCP-2 (OR = 3.2[0.8, 12.3], p = 0.09), and with the presence of ≥ 3 ACPA (OR = 15.1[1.6, 17.5], p = 0.01). RF was not associated with any specific ACPA, nor was it associated with indeterminate or low positive CCP-2. No relationships between tobacco exposure and any specific ACPA or RF were seen. Among DRBl*0401 negative individuals, prevalence estimates of ≥ 3 ACPA among those with an indeterminate or low positive CCP-2 were 17% vs. 4% This relationship was markedly stronger among DRBl*0401 positive individuals; prevalence estimates of ≥ 3 ACPA among those with an indeterminate or low positive CCP-2 were 100% vs. 7% (p for interaction = 0.06).

Conclusion: In this PD cohort, indeterminate or low positive CCP-2 is associated with the presence of ≥ 3 distinct ACPA. HLA DRBl*0401 alleles were free of RA by 2010 ACR/EULAR criteria. Sera were analyzed by multiplex assay for distinct ACPA. Positive cutoffs for ACPA were established by ROC analysis of prior studies. HLA DRB1 SE alleles were assayed using a high resolution genotyping platform.

Method: Using a custom Bio-Plex™ bead-based autoantibody assay platform, we measured anti-CCP antibody and 19 autoantibodies targeting citrullinated proteins and peptides (vimentin, fibrinogen, histone 2A, histone 2B, and apolipoprotein E, clusterin, biglycan, enolase, fillagrin). We analyzed sera from 692 African-American patients with RA. A total antibody score was defined for each patient as the standardized sum of the log transformed autoantibodies. The total antibody score was used as predictor variable for radiographic severity. Radiographic severity defined as total Sharp/van der Heijde scores of hands/feet was the dependent variable. Zero-inflated negative binomial regression models were used to test the association of the autoantibody score with radiographic severity defined as total Sharp/van der Heijde scores of hands/feet given the covariates gender, BMI, smoking status and disease duration.

Results: High correlation coefficients among the autoantibodies were observed. Using zero-inflated negative binomial regression, the total sum of standardized antibodies had a statistically significant (p-value < 0.0002) effect among patients with a total RA radiographic severity (total score >0). For each unit increase in the total sum of standardized autoantibodies, the total radiographic score increases by 0.3 units. In addition, disease duration was found to be statistically significant (p-value < 0.0001).

Conclusion: Autoantibodies against citrullinated autoantigens are associated with joint damage in this cross sectional study of African Americans with RA. Future work will focus on longitudinal aspects of antibodies to specific peptides/proteins and their role in progression of radiographic damage.

Disclosure: M. I. Danila, None; R. Reynolds, None; G. Wu, None; H. Tiwari, None; W. H. Robinson, None; J. Sokolove, None; C. Investigators, None; S. L. Bridges Jr., None.
were associated with an increased risk of $\geq 3$ ACPA, and with the presence of an indeterminate or higher CCP-2. These results have implications for the follow-up of individuals with RA risk factors and indeterminate or low positive CCP-2 findings, and for the design of RA prevention trials.

Disclosure: J. A. Molitor, None; B. S. Michalowicz, None; R. T. Demmer, None; J. H. Buckner, None; M. H. Wener, None; W. H. Robinson, Atreca, Inc., 5.

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Background/Purpose: Anti-carbamylated protein (anti-CarP) antibodies have been described in rheumatoid arthritis (RA) and arthralgia patients [1,2] and occur in subsets of the anti-CCP2 positive and negative patients [1,3]. In anti-CCP2 negative RA patients the presence of anti-CarP was associated with more severe joint destruction [1]. Here we investigated the sensitivity and specificity of anti-CarP antibodies for RA in a setting of early arthritis.

Methods: Anti-carbamylated fetal calf serum (anti-Ca-FCS), anti-CCP2 antibodies and rheumatoid factor (RF) IgM were measured by ELISA using serum samples available from a large inception cohort; the Leiden Early Arthritis Clinic cohort (EAC). For the anti-CarP antibodies we used as a cut-off for positivity the mean + 2 times the standard deviation of the healthy controls [1].

Results: In total 2086 sera of Leiden EAC patients suffering from early arthritis were analyzed for the presence of anti-Ca-FCS antibodies. Anti-CarP antibodies were present in 26% of the patients and in 2% of the controls. We observed that the sensitivity and specificity of anti-Ca-FCS in the EAC cohort for RA are 44% and 89%. As a reference the sensitivity and specificity of anti-CCP2 antibodies are 54% and 95% and for RF IgM are 59% and 90%. Analyzing the early arthritis patients that did not fulfill the EULAR/ACR 2010 criteria for RA that were anti-CarP positive (n=127) revealed that these patients were mainly diagnosed as undifferentiated arthritis (45%), reactive arthritis (9%), psoriatic arthritis (9%) or peripheral spondyloarthritis (8%).

Conclusion: Anti-CarP antibodies, as determined by the reactivity to carbamylated FCS, are predominantly present in RA but can also be detected in other forms of arthritis. The prognostic relevance of anti-CarP antibodies in these latter patients will have to be determined.


Disclosure: J. Shi, None; H. W. van Steenbergen, None; J. A. B. van Nies, None; E. W. N. Levarht, None; A. H. M. van der Helm- van Mil, None; T. W. J. Huizinga, None; R. E. M. Toes, None; L. A. Trouw, None.

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Clinical and Tissue Specificity of Antibodies Against Carbamylated Proteins in Patients with Rheumatoid Arthritis. Antonio Gonzalez1, Ariana Montes1, Eva Perez-Pampin1, Maria Dolores Boveda2 and Juan J. Gomez-Reino3. 1Instituto Investigacion Sanitaria- Hospital Clinico Universitario of Santiago, Santiago de Compostela, Spain, 2Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, 3University of Santiago de Compostela, Santiago de Compostela, Spain.

Background/Purpose: Antibodies against carbamylated proteins (CarP) are a new type of autoantibodies specific of patients with rheumatoid arthritis (RA) relative to healthy controls, but their specificity in relation with other rheumatic diseases has not been established. In addition, they have been analysed with CarP from Fetal Calf Serum (FCS) raising doubts about their protein specificity.

Methods: Anti-CarP FCS from 520 patients with RA was compared with reactivity in 208 healthy donors and 90 patients with each of the following diseases: osteoarthritis (OA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). In addition, anti-CarP-FCS from 97 patients with RA was correlated with reactivity against CarP from seven human tissues.

Results: Anti-CarP-FCS antibodies were found in 35.9 % of the patients with RA. These antibodies were also observed in 4.8 % of the healthy controls, 4 % of the OA patients, 6 % of the PsA patients and 24.4 % of the AS patients. Therefore, their specificity was high in relation with healthy controls and in relation with OA and PsA patients, but not in relation with patients with AS. These results reinforce the nature of anti-CarP as an independent autoantibody system that will be worth to study in AS patients.

Protein extracts from FCS and the 7 analysed tissues were car- bamylated with similar efficiency allowing for meaningful comparisons of the serum reactivities against them. There were at least some sera showing reactivity against each of the tissues analysed, but the frequencies and titers showed clear differences in function of the tissue used as source of CarP (Table 1).

In addition, the reactivities that best correlated with anti-CarP-FCS were against CarP from FLS and synovia. However, Western blot analysis showed a different pattern of binding of RA patient sera when the CarP were from synovia or from FCS in Western blots (Figure 1).

These results indicate the protein specificity of the anti-CarP antibodies present in RA sera.

Conclusion: The anti-CarP-FCS antibodies are moderately prevalent in patients with RA and highly specific of them in comparison with healthy controls, or patients with OA or PsA, but not with AS. Furthermore, analysis of reactivity against CarP from different tissues shows that the anti-CarP reactivity is dependent of specific CarP, which are different depending on the tissue. Fortunately, results with FCS, which has been used as source of CarP for testing RA sera, strongly correlate with synovia. This correlation contributes to confidence in the previously reported clinical and genetic associations of this new type of autoantibodies.

Disclosure: A. Gonzalez, None; A. Montes, None; E. Perez-Pampin, None; M. D. Boveda, None; J. J. Gomez-Reino, None.
AAA-Atpase p97 Regulates Autophagy-Associated Cell Death in Arthritis. Misaru Kato1, Kerstin Klein1, Caroline Ospeit2, Christoph Kolling3, Michihito Kono1, Shinsuke Yasuda1, Renate E. Gay4, Steffen Gay1 and Tatsuya Atsumi1. 1Hokkaido University Graduate School of Medicine, Sapporo, Japan, 2University Hospital Zurich, Zurich, Switzerland, 3Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, 4Schulthess Clinic, Zurich, Switzerland, 5Zurich University Hospital, Zurich, Switzerland.

Background/Purpose: Recently we described a hypersensitivity of rheumatoid arthritis synovial fibroblasts (RASF) compared to osteoarthrits synovial fibroblasts to autophagy under conditions of severe endoplasmic reticulum (ER) stress, leading to a massive cytoplasmic vacuolization, the formation of poly-ubiquitinated protein aggregates and non-apoptotic cell death. Valosin containing protein (p97/VCP) is an ATPase implicated in the degradation of ubiquitin-labelled proteins through the proteasome. We hypothesized that the inhibition of p97 further sensitizes RASF to autophagy-associated cell death due to impaired proaosomal degradation and subsequent overloaded autophagy.

Methods: RASF were transfected with siRNA targeting p97 or treated with the selective p97 inhibitor DBeQ (5 μM). To induce ER stress, RASF were treated with thapsigargin (TG, 5 nM-5 μM), 3-methyladenine (5 mM) was used as an autophagy inhibitor. The distribution of poly-ubiquitinated proteins was evaluated by immunofluorescence microscopy. Cell death was evaluated by flow cytometry using annexin V/propidium iodide staining. Collagen-induced arthritis (CIA) was induced in Lewis rats. Scrambled or p97 siRNA-atelocollagen complexes were injected into ankle joints of rats. Three, seven and eleven days after the injection, CIA was scored from 0 to 4 according to paw thickness and ankle diameter.

Results: Both siRNA-mediated knockdown and inhibition of p97 in RASF boosted a cytoplasmic vacuolization, the formation of poly-ubiquitinated protein aggregates and cell death under 5 μM TG treatment, and this cell death was inhibited by 3-methyladenine. Smaller amounts of TG (50 or 500 nM) induced a cytoplasmic vacuolization and the formation of poly-ubiquitinated protein aggregates in p97-inhibited RASF but not in control RASF. Intra-articular injection of p97 siRNA significantly suppressed CIA (Day 3, p = 0.002; Day 7, p = 0.002; Day 11, p = 0.04; n = 6) in rats.

Conclusion: Our data indicate that the inhibition of p97 promotes autophagy-associated cell death in RASF and suppresses CIA in vivo. p97 may be a new potential target in the treatment of arthritis.

Disclosure: M. Kato, None; K. Klein, None; C. Ospeit, None; C. Kolling, None; M. Kono, None; S. Yasuda, None; R. E. Gay, None; S. Gay, None; T. Atsumi, None.

ACR Poster Session A
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy: Safety of Biologics and Small Molecules in Rheumatoid Arthritis
Sunday, November 16, 2014, 8:30 AM–4:00 PM

First Confirmation Data of Long Term Safety for Tocilizumab in Real-World Setting: 3 Year Follow-Up Postmarketing Surveillance of 5573 Patients with Rheumatoid Arthritis in Japan. Kazuhiro Yamamoto1, Hajime Goto2, Kenzo Hiroa3, Atsuo Nakajima4, Hideki Oriiga5, Nobuhiro Takagi6, Minako Tomobe6 and Kyoichi Totusuka1. 1Univ Tokyo Gr School of Med, Tokyo, Japan, 2Fukuijuji Hospital, Tokyo, Japan, 3Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan, 4Tokyo Metropolitan Police Hospital, Tokyo, Japan, 5University of Toyama School of Medicine, Toyama, Toyama, Japan, 6Chugai Pharmaceutical, Tokyo, Japan, 7Kitaatami Hospital, Tokyo, Japan.

Background/Purpose: To evaluate the long-term safety of tocilizumab (TCZ) for the treatment of rheumatoid arthritis (RA) in a real-world clinical setting in Japan.

Methods: In this long-term extension of the single-arm, observational postmarketing surveillance study of TCZ, patients who received at least 1 dose of intravenous TCZ (8 mg/kg) between April 2008 and August 2010 were observed for 3 years. Patient characteristics and the incidences of mortality, serious infection, malignancy, GI perforation and serious cardiac dysfunction were evaluated during observation period. The analyses included the adverse events (AEs) after discontinuation of TCZ. Data were summarized as the proportion (95% CI) of patients experiencing each event or as incidence rates presented as the number of patients per 100 patient-years (PY).

Results: In total, 5573 patients were enrolled, with a total observation of 15,106 PY. Excluding patients who died, transferred hospitals, or were lost to follow-up, a total of 5327 patients (95.59%) completed 1 year, 4850 (87.03%) completed 2 years, and 4527 (81.23%) completed 3 years of observation. The median and median treatment duration was 2.1 and 2.9 years, respectively. The overall mortality rate during the observation period was 2.58% (144/5573 patients). The most common cause of death was infection (28.47%), followed by respiratory disease (15.97%), malignancy (14.58%), and cardiac dysfunction (9.03%). The standardized mortality ratio (SMR) in comparison with the general Japanese population was 1.27 (95% CI, 1.08–1.50), which is comparable to the SMR reported in a large observational cohort of Japanese patients with RA (all-cause mortality between 1.46 [95% CI, 1.32–1.60] and 1.90 [95% CI, 1.75–2.07]). The incidence rate of malignancy during the observation period was 2.24% (0.83/100 PY), and the standardized incidence ratio (SIR) was 0.79 (95% CI, 0.66–0.95), which was stable over time. Only malignant lymphoma had a significantly higher incidence compared to the general Japanese population, with a SIR of 3.13 (95% CI, 1.82–5.39) which is comparable to that of all RA patients compared with the general population (SIR, 6.07; 95% CI, 3.71–9.37)2. There was no increase in rate of any AEs with prolonged observation period, GI perforation and serious cardiac dysfunction decreased over time. (Table).

Conclusion: The safety profile of TCZ was consistent over time with respect to mortality, serious infections, malignancy, gastrointestinal perforation, and serious cardiac dysfunction. These data confirm the long-term safety of TCZ use in patients with RA in a real-world clinical setting in Japan.


Table. Changes in the incidence of fatal events, serious infections malignancy GI perforation and serious cardiac dysfunction during observation period

<table>
<thead>
<tr>
<th>Incidence rate [95%CI]</th>
<th>0–52 wk (n=5573)</th>
<th>53–104 wk (n=5168)</th>
<th>105–156 wk (n=4721)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.18 [0.92–1.50]</td>
<td>0.85 [0.62–1.14]</td>
<td>0.47 [0.29–0.70]</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.68 [0.48–0.93]</td>
<td>0.81 [0.59–1.10]</td>
<td>0.66 [0.45–0.93]</td>
</tr>
<tr>
<td>Serious infections</td>
<td>5.67 [5.08–6.31]</td>
<td>3.25 [2.78–3.77]</td>
<td>2.16 [1.77–2.62]</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>0.36 [0.22–0.55]</td>
<td>0.15 [0.07–0.30]</td>
<td>0.15 [0.06–0.31]</td>
</tr>
<tr>
<td>Serious cardiac dysfunction</td>
<td>0.61 [0.42–0.85]</td>
<td>0.41 [0.25–0.62]</td>
<td>0.11 [0.03–0.25]</td>
</tr>
</tbody>
</table>

Disclosure: K. Yamamoto, AbbVie, Astellas, BMS, Daiichi-Sankyo, Mitsubishi-Tanabe, Pfizer, Sanofi, Takeda and Teijin., 2 AbbVie, Astellas, BMS, Boehringer Ingelheim, Chugai, Eisai, Oox, Pfizer, Sater, Taiho Toyama and UCB., 3 AbbVie, Astellas, BMS, Boehringer Ingelheim, Chugai, Eisai, Oox, Pfizer, Sater, Taiho Toyama and UCB., 4 Ono, Pfizer, Santen and Takeda, 5; K. Hira, BIOTRONIK, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Japan LifeLine and MSD., 2 BIOTRONIK, Boehringer-Ingelheim and Chugai, 5; Japanese Heart Rhythm Society., 6 Bayer, BIOTRONIK, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Japan LifeLine and MSD., 3; A. Nakajima, AbbVie, Astellas, Chugai, Mitsubishi-Tanabe, Oox, Pfizer, Sater and Takeda., 5; H. Oigasa, Chugai and UCB., 6; T. Nakagi, Chugai, 3; M. Tomobe, Chugai, 3; K. Totuka, Bayer, Chugai, Eiken Chemical, Kyorin and Toyota Chemical., 5.

Meta-Analysis of Serious Infections with Tofacitinib and Biological Treatment in Rheumatoid Arthritis Clinical Trials. Y. Strand1, Ş. Ahadiş2, J. French1, J. Geier1, S. Krishnaswami2, S. Menon1, T. Checchio3, R. Riese1 and J. Gomez-Reino1. 1Biopharmaceutical Consultant, Portola Valley, CA, 2Pharmacometrics, Pfizer Inc, Groton, CT, 3Metrum Research Group, Tariffville, CT, 4Pfizer Inc, New York, NY, 5Clinical Pharmacology, Pfizer Inc, Groton, CT, 6Pfizer Inc, Groton, CT, 7Hospital Clinic, Universi- tario de Santiago, Santiago, Spain.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Serious infection events (SIEs) have been reported in the tofacitinib RA trials. Limited head-to-head comparator data are available within the tofacitinib RA development program to directly compare rates of events relative to approved biologic therapies. Here we present a meta-analysis of published randomized controlled trials (RCTs) and corresponding long-term extension (LTE) studies to contextualize the risk of SIEs for tofacitinib relative to biologics approved for treatment of moderate to severe RA.
Methods: A systematic literature search (Medline, Embase, PubMed, and regulatory submission documents for approved therapies) was conducted through October 2013. A total of 66 RCTs and 22 LTE trials met the inclusion criteria for the meta-analysis. Incidence rates (per 100 patient-years) of SIs for each therapy across trials were estimated based on RCT and LTE data using a random effects model. Relative and absolute risk comparisons to placebo were made using RCT data only, based on Mantel-Haenszel methods. Placebo-controlled data ranging between 3–12 months for biologics and 3 months for tocilizumab were assessed. Statistical heterogeneity was assessed using I² statistic.

Results: Incidence rate (per 100 patient-years [95% CI]) estimates from the meta-analysis were 3.04 (2.49, 3.72) for abatacept, 3.27 (2.99, 4.62) for rituximab, 5.45 (4.26, 6.96) for tocilizumab, and 4.90 (4.41, 5.44) across TNFi therapy (TNFi) therapies. The tofacitinib incidence rates from the five Phase (P) 3 trials only were 3.02 (2.25, 4.05) and 3.00 (2.44, 4.02) for 5 mg twice daily (BID) and 10 mg BID, respectively. The incidence rates in the ongoing LTE studies (as of August 2015) were 2.50 (2.05, 3.04) for 5 mg BID and 3.19 (2.74, 3.72) for 10 mg BID. The risk ratio (RR; [95% CI]) for TNFi relative to placebo in methotrexate inadequate responder (MTX-IR) trials (n=24) was 1.50 (1.00, 2.25). The tofacitinib RRs, relative to placebo, in P3 were 2.21 (0.60, 8.14) for 5 mg BID and 2.02 (0.56, 7.28) for 10 mg BID. Risk differences (expressed as difference in incidence percent; RD; [95% CI]) relative to placebo were 0.94% (0.25%, 1.63%) for TNFi therapies, 0.38% (0.24%, 0.99%) for tofacitinib 5 mg BID, and 0.40% (0.23%, 1.02%) for tofacitinib 10 mg BID. Separate analyses of MTX-naïve studies (n=10) showed a RR of 1.24 (0.87, 1.77) for TNFi relative to MTX. RRs from the tofacitinib ORAL Start (A3921069) study vs. MTX were similar to the TNFi estimates for both tofacitinib doses (i.e. 1.10 [0.39, 3.11] for 5 mg BID and 0.75 [0.25, 2.26] for 10 mg BID).

Conclusion: This meta-analysis provided an indirect quantitative assessment of the SIs for biological therapies to contextualize data from the tofacitinib RA clinical development program. Comparisons of incidence rates, RRs and RDS suggest that risk of SIs with tofacitinib is comparable to published rates for biological therapies in the treatment of moderate to severe RA.

Disclosure: V. Strand, AbbVie, Afferent, Angen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celtrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, SKK, Takeda, UCB, Vertex, 5; S. Ahadieh, Pfizer Inc, 5, Pfizer Inc, 8; J. French, Pfizer Inc, 5, Pfizer Inc, 3; S. Menon, Pfizer Inc, 1, Pfizer Inc, 3; S. Krishnaswami, Pfizer Inc, 1, Pfizer Inc, 3; S. S. Krishnaswami, Pfizer Inc, 1, Pfizer Inc, 3; T. Checchio, Pfizer Inc, 1, Pfizer Inc, 3; R. Riese, Pfizer Inc, 1, Pfizer Inc, 3; J. Gomez-Reino, Pfizer Inc, 5, Pfizer Inc, 8.

Table: Renal endpoints (ANCOVA) in Full Analysis Set (observed case)

<table>
<thead>
<tr>
<th>Period</th>
<th>Treatment Sequence</th>
<th>N</th>
<th>Baseline to Baseline</th>
<th>Adjusted Geometric Mean Fold Change (90% CI)</th>
<th>Ratio of Adjusted Geometric Mean Fold Change (Tofacitinib vs PBO) (PBO vs PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Tofacitinib vs PBO</td>
<td>91</td>
<td>0.91 (0.88, 0.95)</td>
<td>0.92 (0.86, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Period 1</td>
<td>PBO vs PBO</td>
<td>46</td>
<td>0.99 (0.94, 1.04)</td>
<td>0.92 (0.86, 0.98)</td>
<td></td>
</tr>
<tr>
<td>End Period 1 to End Period 2</td>
<td>Tofacitinib vs PBO</td>
<td>86</td>
<td>1.03 (0.99, 1.07)</td>
<td>1.09 (1.02, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Baseline to Baseline</td>
<td>PBO vs PBO</td>
<td>86</td>
<td>0.96 (0.92, 1.00)</td>
<td>1.04 (0.97, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Baseline to Baseline</td>
<td>Tofacitinib vs PBO</td>
<td>92</td>
<td>0.96 (0.95, 0.98)</td>
<td>0.95 (0.92, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Baseline to Baseline</td>
<td>PBO vs PBO</td>
<td>44</td>
<td>1.00 (0.97, 1.02)</td>
<td>0.99 (0.97, 1.02)</td>
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<tr>
<td>Baseline to Baseline</td>
<td>Tofacitinib vs PBO</td>
<td>87</td>
<td>1.03 (1.01, 1.05)</td>
<td>1.04 (1.01, 1.07)</td>
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<tr>
<td>Period 1</td>
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<td>1.00 (0.97, 1.02)</td>
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<tr>
<td>Period 1</td>
<td>Tofacitinib vs PBO</td>
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<td>1.04 (1.02, 1.06)</td>
<td>1.05 (1.02, 1.08)</td>
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</tr>
<tr>
<td>Baseline to Baseline</td>
<td>PBO vs PBO</td>
<td>44</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.97 (0.94, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Baseline to Baseline</td>
<td>Tofacitinib vs PBO</td>
<td>87</td>
<td>0.97 (0.95, 0.99)</td>
<td>0.97 (0.94, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Baseline to Baseline</td>
<td>PBO vs PBO</td>
<td>44</td>
<td>1.00 (0.98, 1.03)</td>
<td>1.01 (0.98, 1.04)</td>
<td></td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>Baseline to Baseline</td>
<td>Tofacitinib vs PBO</td>
<td>92</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.05 (1.02, 1.08)</td>
</tr>
<tr>
<td>Period 1</td>
<td>PBO vs PBO</td>
<td>44</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.97 (0.94, 1.00)</td>
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<tr>
<td>End Period 1 to End Period 2</td>
<td>Tofacitinib vs PBO</td>
<td>87</td>
<td>1.00 (0.98, 1.03)</td>
<td>1.01 (0.98, 1.04)</td>
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<tr>
<td>Baseline to Baseline</td>
<td>PBO vs PBO</td>
<td>44</td>
<td>1.00 (0.97, 1.02)</td>
<td>1.00 (0.97, 1.02)</td>
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<td>1.00 (0.97, 1.02)</td>
<td>1.00 (0.97, 1.02)</td>
<td></td>
</tr>
</tbody>
</table>
| ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; mGFR, measured glomerular filtration rate; OC, observed cases; RAS (OC) include available data from all randomized patients who took at least one dose of study medication (treatment group vs placebo); Data collected after patients (one in Period 1 and two in Period 2, all in tofacitinib) took a wrong treatment bottle were excluded. Missing data were not imputed.

Conclusions: Small mean increases in SCr and mean decreases in eGFR in pts with RA treated with tofacitinib may occur in parallel with small mean decreases in mGFR, and that changes in these parameters with short-term tofacitinib treatment appear reversible after discontinuation. Safety monitoring will continue in ongoing and future clinical trials and routine pharmacovigilance. 

Disclosure: J. Kremer, Pfizer Inc, 2, Pfizer Inc, 5; A. J. Kivitz, Pfizer Inc, 2, Pfizer Inc, 5; J. A. Simon Gough, None; E. L. Nasonova, None; H. Tony, None; B. Vlahos, Pfizer Inc, 1, Pfizer Inc, 3; C. Hammond, Pfizer Inc, 1, Pfizer Inc, 3; J. Bukowski, Pfizer Inc, 1, Pfizer Inc, 3; H. Li, Pfizer Inc, 1, Pfizer Inc, 3; S. Schulman, Pfizer Inc, 1, Pfizer Inc, 3; S. Raber, Pfizer Inc, 1, Pfizer Inc, 3; A. Zuckerman, Pfizer Inc, 1, Pfizer Inc, 3; J. Isaacs, Pfizer Inc, 2, Pfizer Inc, 5.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The incidence of non-melanoma skin cancer (NMSC) in the tofacitinib RA program was evaluated using data from randomized Phase (P) 1, 2, 3, and open-label long-term extension (LTE) studies (P1P2P3LTE studies).

Methods: NMSC data (cut-off date: August 30, 2013) were pooled from two P1, eight P2, six P3, and three LTE studies; LTE data collection and analyses are ongoing; study databases have not yet been locked. Patients in P1, P2, P3, and LTE studies were treated with tofacitinib 5 mg or 10 mg twice daily (BID) either as monotherapy or with background disease-modifying antirheumatic drugs (DMARDs). LTE patients rolled over from qualifying P1, P2, and P3 studies; patients from P2 studies were treated with tofacitinib 1 to 30 mg BID or 20 mg once daily. Incidence rates per 100 patient-years (py) of exposure (IRs) for first new NMSC were calculated for combined doses (all doses) of tofacitinib in the P1P2P3LTE patient population. The overall NMSC IR was analyzed as well as IRs for subgroup analyses according to the following conditions: dose of tofacitinib (5 mg vs 10 mg); prior treatment with tumor necrosis factor inhibitors (TNFi); age of patients (65 years old); history of RA vs DMARD-IR; previous treatment with DMARDs; previous history of malignancy (NMSC); previous history of skin cancer (NMSC) in the tofacitinib RA program was evaluated using data from original Phase (P) 1 and 2 studies and ORAL SOLO (placebo control), ORAL SYNC (etanercept plus placebo control); ORAL STANDARD (MTX plus placebo control); ORAL STEP (etanercept plus MTX plus placebo control); all ran for 52 weeks.

Results: A total of 6,092 tofacitinib-treated patients (representing 15,103 py of exposure) received tofacitinib (all doses) in the P1P2P3LTE studies. One or more events of NMSC occurred in 83 patients receiving tofacitinib (all doses). Of these 83, squamous cell carcinomas (SCC) occurred in 39 patients, and basal cell carcinomas (BCC) occurred in 52 patients. A total of five patients had a history of NMSC prior to tofacitinib exposure compared with 78 patients who did not. In the whole P1P2P3LTE patient population, the IR for SCC overall was 0.55 (95% confidence interval [CI] 0.45, 0.69); the IRs for SCC and BCC were 0.26 (0.19, 0.35) and 0.35 (0.26, 0.45), respectively. The IRs for patients from the P1/2/3 and LTE cohorts receiving tofacitinib 5 mg BID were 0.61 (0.34, 1.10) and 0.41 (0.26, 0.66), respectively; for patients receiving tofacitinib 10 mg BID, the IRs were 0.47 (0.24, 0.90) and 0.79 (0.60, 1.05), respectively. Patients on background DMARDs had a numerically higher IR (0.64, 95% CI 0.49, 0.84) than patients on tofacitinib monotherapy (0.43, 95% CI 0.30, 0.64). There was a higher rate of NMSC in patients previously treated with TNFi (IR 1.01, 95% CI 0.67, 1.51) vs TNFi-naive patients (IR 0.47, 95% CI 0.37, 0.61). Patients ≥65 years old had a higher rate of NMSC (IR 1.67, 95% CI 1.19, 2.35) vs patients <65 years old (IR 0.38, 95% CI 0.29, 0.51). Patients of White ethnicity had the highest IR of NMSC vs patients of Asian, Black, or Other ethnicity (0.86 vs 0.03, 0.10, or 0.14). The IRs for NMSC, analyzed in 6-month intervals (through ≥42 months), were stable over time.

Conclusion: The overall IR for NMSC in the tofacitinib clinical development program remained stable over time. The NMSC IRs appear to be consistent with published estimates in patients with RA treated with TNFi (IR 0.22–0.66).

Disclosure: J. R. Curtis, Pfizer Inc; 2, E. B. Lee, Pfizer Inc; 5, G. Martin, Abbvie; 6, Galderma, 6, Pfizer, 5, X. Mariette, Pfizer Inc; 2, K. K. Terry, Pfizer Inc; 3, Pfizer Inc; 1; Y. Chen, Pfizer Inc; 1, P. Jenner, Pfizer Inc; 3, Pfizer Inc; 1; J. Andrews, Pfizer Inc; 3, Pfizer Inc; 3, M. Kaur, Pfizer Inc; 1, K. Kwok, Pfizer Inc; 3, Pfizer Inc; 1; C. Nduma, Pfizer Inc; 1, Pfizer Inc; 3.

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Comprehensive Summary of the Efficacy and Safety of Tofacitinib 5mg Twice Daily in Patients with Rheumatoid Arthritis and an Inadequate Response to Disease-Modifying Antirheumatic Drugs

Methods: Week 12 efficacy and safety data for tofacitinib 5 mg BID and placebo (PBO) were compiled from five Phase 3 studies (NCT00814307, ORAL Solo; NCT00856544, ORAL Sync; NCT00853385, ORAL Standard; NCT00847613, ORAL Scan; and NCT00960440, ORAL Step). Pts with RA received tofacitinib as monotherapy (ORAL Solo) or with background DMARDs (ORAL Sync, ORAL Standard, ORAL Scan, ORAL Step). All pts in ORAL Standard and ORAL Scan had an IR to MTX, those in ORAL Step had an IR to TNFi, those in ORAL Solo were biologic or nonbiologic DMARD-IR, and those in ORAL Sync were nonbiologic DMARD-IR.Endpoints evaluated included ACR20, ACR50, ACR70 response rates, DAS remission (DAS28<4), change in Health Assessment Questionnaire-Disability Index (HAQ-DI), adverse events (AEs), discontinuations due to AEs, serious adverse events (SAEs), and serious infection events (SIEs). For binary variables, such as ACR20/P50/70 and DAS28<4/ESR<2.6, non-responder imputation (NRI) was used.

Results: Baseline demographics and disease characteristics were generally similar within and between studies, except TNFi-IR pts having a longer history of RA than DMARD-IR. ACR20 rates were significantly improved with tofacitinib vs PBO either as monotherapy or with background DMARDs; ACR50 and ACR70 rates demonstrated similar patterns (Table 1). After only 12 weeks of treatment, significantly more pts receiving tofacitinib 5 mg BID than PBO achieved DAS28<4/ESR<2.6, apart from those in ORAL Solo (Table 1). Significant changes from baseline in HAQ-DI were also observed with tofacitinib vs PBO, both as a monotherapy or with background DMARDs (Table 1).

Frequency of AEs and SAEs were similar between tofacitinib and PBO across all studies (Table 1). Discontinuations due to AEs, by pts receiving tofacitinib, were ≤7% in all groups. Pooled and long-term analyses of Phase 3 and long-term extension studies have further described the AE profile associated with tofacitinib therapy.

Conclusion: This comprehensive summary demonstrates that, regardless of prior therapy, short-term treatment with tofacitinib 5 mg BID significantly reduced signs and symptoms of RA, as measured by ACR20/P50/70, DAS28<4/ESR<2.6, and HAQ-DI. There were no unexpected safety findings at the US-recommended dose.


Table 1. Efficacy and safety of 5mg tofacitinib treatment vs placebo at Week 12

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
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<tbody>
<tr>
<td>ORAL Solo</td>
<td>60%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>ORAL Sync</td>
<td>60%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>ORAL Standard</td>
<td>60%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>ORAL Scan</td>
<td>60%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>ORAL Step</td>
<td>60%</td>
<td>48%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Table 1. Efficacy and safety of 5mg tofacitinib treatment vs placebo at Week 12**

**Table 2. AEs and SAEs of tofacitinib treatment vs placebo at Week 12**

<table>
<thead>
<tr>
<th>AEs</th>
<th>SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>60%</td>
<td>48%</td>
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<tr>
<td>60%</td>
<td>48%</td>
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<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>60%</td>
<td>48%</td>
</tr>
</tbody>
</table>

VA Boston Healthcare System, Boston, MA, 2VA Boston HealthCare System, Boston, MA, 3University of Toronto, Toronto, ON, 4Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, 5Veteran Affairs Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: TNF inhibitors and combinations of conventional disease-modifying antirheumatic drugs are commonly added to treat methotrexate non-responsive rheumatoid arthritis patients. In the 48-week double blind, RACAT trial (NEJM 2013;369:307–18), 353 methotrexate suboptimal responders were randomized to two treatment strategies, either first adding sulfasalazine and hydroxychloroquine, triple therapy (T) or etanercept (E, N=178), or etanercept (E, N=175) to methotrexate. Participants without significant improvement in DAS28 at 24 weeks switched treatment while maintaining the blind. We examined differences between T and E in the most common adverse events reported in the trial, gastrointestinal (GI) toxicity and infections, taking into account possible confounding factors.

Methods: All adverse events during the trial were recorded and coded by blinded reviewers. Serious (SAE) or non-serious (NAE) infections and GI events reported during the intervention period and for 4 weeks after completing the intervention were included in the analysis. The trial design posed challenges for analysis for 13 switcher patients who had infection (N=8) or GI (N=5) events before both before and after switching treatment (either T to E or E to T). For these switchers we included in the analysis only the infections that occurred when patients were currently on T and GI events that occurred when patients were currently on E. This is a conservative approach because infections were the most common side effect for E and GI events were few. We calculated the rate of event, total number of events, and the mean duration in the treatment when events occurred. Logistic and linear regression models were used for treatment comparison with and without controlling for participant characteristics (age, sex, race, BMI, smoking) and comorbidities.

Results: Participants who were on E were more likely to have infection NAEs (OR=1.68, p=0.02) and had a higher total number of events (mean of 0.7 vs. 0.4, p=0.004) than participants who were on T. Participants who were on T had a higher number of GI NAEs than those on E (mean 0.55 vs. 0.34, p=0.02). Furthermore, the amount of time on the treatment when the GI events occurred was shorter for T (mean duration 10.0 vs. 17.7 weeks, p=0.001). The same conclusions remain after using regression models to control for patient characteristics and comorbidities. Serious infections and GI events were rare for both treatments. However, there were a greater number of SAE infections that occurred when receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T). When receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T). When receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T). When receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T). When receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T).

Conclusion: In RACAT, infectious NAEs were significantly increased in participants receiving E compared with T even after controlling for participant demographics and comorbidities. GI NAEs were significantly more frequent in T as compared with E. Though numbers of SAE were small, there was a trend toward greater number of infectious SAEs when receiving E, which were predominately pneumonias. Our study findings might help clinicians when prescribing medications by considering patients’ tolerance of each treatment’s more common adverse events.


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Golimumab 5-Year Safety: an Analysis of Pooled Data from the Long Term Extensions of Randomized, Double-Blind, Placebo-Controlled Studies in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis. Jonathan Kay1, Roy Fleischmann2, Edward C. Keystone3, Elizabeth C. Hsia4, Neil Goldstein4, Benjamin Hsu5, Jürgen Braun6 and Arthur Kavanaugh7, 1UMass Memorial Medical Center, Worcester, MA, 2Metropolis Clinical Research Center, University of Texas, Dallas, TX, 3Mount Sinai Hospital, Toronto, ON, 4Janssen Research & Development, LLC., Spring House, PA, 5Rheumazentrum Ruhrgebiet, Heme, Germany, 6University of California San Diego, La Jolla, CA.

Background/Purpose: To present an analysis of pooled data through approx 5yrs of follow-up from 5 completed golimumab/GLM) Ph3 SC trials across rheumatological indications.

Methods: SC placebo (PBO) or GLM (50mg or100mg) was administered q4wks in Ph3 trials. After wk24/52, pts in the Ph3 studies entered LTE and received GLM50mg or 100mg q4wks in an unblinded fashion. Dose adjustment from 50mg to 100mg and 100mg to 50mg was allowed once. Concomitant meds included DAMARDS (mostly MTX). AE’s were analyzed based on treatment received by a pt during the course of the study; PBO, GLM50mg only, only 100mg only, or 50mg and 100mg. Pts could cross-over from PBO to GLM, a pt may appear in both PBO and GLM columns. Due to the short duration of the PBO-controlled portion, comparisons between GLM and PBO grps are limited.

Results: In Ph3 trials, 639pts received PBO, 671 GLM50mg, 765 GLM50mg and GLM100mg, and 792 GLM100mg through 5yrs. In Ph3, 5.2%, 15.4%, 9.5% and 19.9% of PBO, GLM50 only, GLM50 plus GLM100mg, and GLM100mg only pts, respectively, discontinued due to AE through 5yrs. The incidences per 100PY of deaths, serious infections (including TB, opportunistic infections [OI]), demyelination, and malignancies are presented. Injection site reactions were low; most were mild, and 2 cases led to discontinuation. No GLM SC-treated pt developed anaphylaxis/ serum sickness-like reaction. Malignancies occurring during the 5 Ph3 trials included skin cancers, solid tumors, and lymphoma. In comparison to SEER, overall incidence of malignancies in GLM and PBO-treated pts was similar to that expected in the general US population. Incidence of lymphomas per 100 pt-years of follow-up was greater in the GLM100mg dose grp through 5yrs and higher than that expected in the general US population.

Conclusion: The safety of continued GL SC GXM exposure demonstrates that GLM SC treatment was generally well-tolerated with overall low rates of discontinuation due to AEs. Safety profiles were generally similar between GLM dose with exception of higher rates of serious infections, including TB and opportunistic infections, and lymphoma in the GLM100mg grp. Results are confounded by LTE design in which pts could receive GLM100mg after being exposed to GLM50mg with higher GLM dose used for pts with more refractory disease and by limited exposure to PBO making the comparisons between PBO and treatment grps of less value.

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Analysis of Pooled Data from Two Randomized Controlled Trials and Their Open-Label Extensions: Long-Term Safety in Rheumatoid Arthritis before and after Certolizumab Pegol Dose Increase/Decrease.

Boulos Harauyi1, Vivian P. Bykerk2, Ronald van Vollenhoven3, Marc de Hida1, Janssen Research and Development, LLC., 3; N. Goldstein, Janssen Research & Development, LLC., 3; Y. Zhou, Janssen Research & Development, LLC., 3; J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB, 2, A. Kavanaugh, AbbVie, 2, Amgen, Roche, Pharmaceuticals, 2, Pfizer Inc, Janssen Pharmaceuticals Product, L.P., UCB, 2, BMS, 2, Asselas, 2.

Background/Purpose: Certolizumab pegol (CZP) is approved for adult patients (pts) with rheumatoid diseases (RA, PsA and AS) at a maintenance dose of 200mg every 2 wks (Q2W) or 400mg every 4 wks (Q4W). In RAPID1 1 (52 wks) and RAPID2 2 (24 wks) randomized clinical trials (RCTs; NCT00152386 and NCT00160641), CZP was administered at a loading dose of 400mg at Wks 0, 2, and 4, followed by CZP 200mg Q2W, or at CZP 400mg Q2W in pts with active RA. All pts entering open-label extensions (OLEs; NCT00175877 and NCT00185552) received CZP 400mg Q2W for 6 months. The dose was subsequently reduced to CZP 200mg Q2W for all pts, 3,4 as feeder studies revealed that the null hypothesis of no difference between doses could generally not be rejected. We present safety data evaluating the potential effect of CZP dose change over 12 wks prior to and post dose-escalation or dose-reduction, in line with treat-to-target.

Methods: Post-hoc analysis was performed on pooled RAPID1 and RAPID2 CZP data to: 1) dose-escalation from CZP 200mg Q2W to CZP 400mg Q2W, 2) dose-reduction from CZP 400mg Q2W to CZP 200mg Q2W (Figure). Results: 557 pts randomized to CZP 200mg Q2W in the RCTs entered the OLEs, with dose escalation to 400mg Q2W. Of these, 210 pts (37.7%) experienced an adverse event (AE) in the 12 wks prior to dose-escalation versus 203 pts (36.4%) in the 12 wks post dose-escalation (Table). 94.4% of AEs were mild-moderate: 65 and 71 pts, respectively, experienced AEs considered to be drug-related. Serious AEs are reported in the table. The incidence of infections increased post dose-escalation. Malignancies were reported in 3 pts during 12 wks prior to (1 testis, 2 basal cell carcinoma [BCC]) and post (testis, lung, and stomach). The dose was subsequently reduced to CZP 200mg Q2W for all pts, 3,4 as feeder studies revealed that the null hypothesis of no difference between doses could generally not be rejected.

Conclusion: Overall, the number of AEs leading to withdrawals was low and no deaths were reported during the dose-escalation and dose-reduction study periods evaluated.

References

Table: SAEs reported in n=3 pts by SOC during 12-wk periods prior to and post CZP dose increase/decrease

<table>
<thead>
<tr>
<th>Event Type</th>
<th>SOC</th>
<th>Incidence (n=3)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection and Infestation</td>
<td></td>
<td>405</td>
<td>13.5</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>405</td>
<td>13.5</td>
</tr>
<tr>
<td>Neoplasm Events</td>
<td></td>
<td>405</td>
<td>13.5</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
<td>405</td>
<td>13.5</td>
</tr>
<tr>
<td>All Other AEs</td>
<td></td>
<td>405</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Overall, despite a modest infection rate increase after dose-escalation, no new safety concerns emerged during dose-escalation or dose-reduction, and AE rates were generally similar between periods. However, the natural trend of a decreasing rate of AEs was observed over time, as is usual in RA clinical trials.
first/second/third 6-month interval, respectively. The most commonly reported SI events (n \( \geq 10 \)) include pneumonia (33), urinary tract infection (26), sepsis (15), diverticulitis (11), and herpes zoster (HZ) infections (10). A small number of opportunistic infections (OI) were reported including reactivation of tuberculosis (2), disseminated HZ (1), histoplasmosis (1), Cryptococcal gastritis/oesophagitis (1), and unspecified OI (1). The reporting rate of serious neoplasm events across the first/second/third intervals was 0.14, 1.02, and 0.54 per 100 PYs, respectively. The commonly-reported serious neoplasm events (n \( \geq 2 \)) include lymphoma (6), bladder cancer (3), brain neoplasm (3), lung neoplasm malignant (2), basal cell carcinoma (2), and unspecified neoplasm malignant (2). Most of the case reports did not have sufficient information for a causality assessment. In the reports where time to onset was provided, eight events were diagnosed before or within 2 months of the initiation of tofacitinib. Across the reporting period, no significant change in reporting rate was noted for GI and hepatobiliary disorders. Of the 91 reported serious GI events, the most common reported events (n \( \geq 5 \)) include diarrhoea (11), nausea (6), vomiting (6), GI hemorrhage (5), and hematoch缕ia (5).

Conclusion: Review of AEs from PMS reports did not reveal any new safety signal compared with the safety profile identified from tofacitinib RA clinical studies during its development program. SAEs including SIs and safety signal compared with the safety profile identified from tofacitinib RA.

Across the reporting period, no significant change in reporting rate was noted for GI and hepatobiliary disorders. Of the 91 reported serious GI events, the most common reported events (n \( \geq 5 \)) include diarrhoea (11), nausea (6), vomiting (6), GI hemorrhage (5), and hematoch缕ia (5).

Conclusion: Review of AEs from PMS reports did not reveal any new safety signal compared with the safety profile identified from tofacitinib RA clinical studies during its development program. SAEs including SIs and malignancy have been reported in the post-marketing setting and the safety profile of tofacitinib will continuously be monitored via pharmacovigilance. Limitations of PMS reports (such as under-reporting and reporting bias) and estimated reporting rate due to lack of denominators should be considered when interpreting these results.

Disclosure: S. Cohen, Pfizer Inc; 5. J. R. Curtis, Pfizer Inc; 2. T. Barnetche, Arnaud Constantin and Alain G. Cantagrel; 2. Hospital Purpan, Toulouse, France; 3. CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France; 4. Rheumatology Department, Bordeaux University Hospital, Bordeaux, France.

Background/Purpose: Anti-TNFs have greatly contributed to improve RA prognosis. Hence, the needs for orthopedic surgery have considerably decreased in the past years. However, surgery, whether programmed or not, whether orthopedic or not, is sometimes necessary in patients treated with TNF inhibitors. Current recommendations are to discontinue biologic DMARDs to reduce the risk of surgical site infection. The guidelines for perioperative cessation periods of biologic DMARDs differ among countries but generally a stop of the biotetherapy 2 to 6 weeks before programmed surgery is recommended. Anti-TNF can be resumed after wound healing.

The purpose of this current study was to ask:
1. Whether patients treated with anti-TNF are really at risk for infection upon surgery.
2. Whether stopping anti-TNF treatment increases the risk of infection upon surgery.

Methods: We have conducted a systematic review of the literature indexed in Pubmed, Embase, and Cochrane using the following keywords: “Rheumatoid arthritis AND surgery AND infection AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab)”. This search was conducted up to February 2014 and was limited to papers in English and French languages. Reviews and case reports were excluded.

We selected studies reporting numbers of infections observed post-surgery by:
- i) comparing patients using anti-TNF with patients using DMARDS without biologics and
- ii) comparing patients keeping up with anti-TNF with patients who interrupted anti-TNF before surgery.

Results: Fourteen studies reported the frequency of post-surgery infections of RA patients undergoing orthopedic surgery, most often joint replacement.

Eleven studies were pooled in order to evaluate the infection risk in patients treated with anti-TNF compared with patients treated with DMARD without biologics. There were 4,925 surgeries and 121 infections in patients using anti-TNF and 60,678 surgeries and 711 infections in patients with DMARDs alone. Thus, patients treated with anti-TNF are at higher risk of post-surgery infection (OR = 1.95 [1.34–2.85]). Some joints such as foot, ankle and elbow seem to be at higher risk.

Six studies were pooled for meta-analysis evaluating the benefits of stopping anti-TNF as post-infection risk is concerned. Two studies were not informative, as no infection was reported in any of them. Stopping the anti-TNF treatment did not modify the infection risk: OR = 0.70 [0.39–1.25].

Conclusion: This meta-analysis shows that patients treated with anti-TNF are more exposed to risks of infection after orthopedic surgery. The increased rate of infection in those patients was not ameliorated by stopping anti-TNF before surgery. This could lead clinicians, at least in surgeries with lower risks of infection, to reconsider stopping anti-TNF before surgery since this may expose patients to a flare-up.

Acknowledgement: We wish to thank AbbVie who provided logistic support.

Disclosure: C. Mahille, None; A. Ryussen Witrand, None; T. Barnetche, None; A. Constantine, None; A. G. Cantagrel, None.

467 Evaluation of the Rabbit Risk Score for Serious Infections in a UK Anti-TNF Treatment Cohort. Lucia Silva-Fernandez1, Mark Lunt1, Kath D. Watson1, BSRBR Control Centre Consortium2, Deborah P. Symmons3, Kimmy Hyrich3 and On behalf of the BSRBR. 1Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom; 2British Society for Rheumatology, London, United Kingdom.

Background/Prognosis: Serious infections (SI) are a major concern in patients treated with tumour necrosis factor inhibitors (TNFi). The RABBIT Risk Score (RRS) (1) allows a calculation of the expected number of SI over a one year period of TNFi treatment according to patient characteristics. This score was developed in a cohort of German patients with rheumatoid arthritis (RA) enrolled in the RABBIT biologics register and then validated in a second cohort from the same register. The aim of the present study is to assess the reliability of the RRS in two cohorts of patients with RA treated with TNFi from the British Society for Rheumatology Biologics Register (BSRBR-RA).

Methods: The BSRBR-RA is an ongoing national prospective cohort study of subjects with RA starting biologic therapy. Patients were recruited to a first TNFi cohort (old) between 2001 and 2008 and to a second TNFi cohort (new) from 2010 to date. Risk factors included in the RRS include age, Health Assessment Questionnaire (HAQ) score, chronic lung disease, chronic renal disease, previous serious infection, number of treatment failures, mean daily glucocorticoid dose and treatment with TNFi. As the BSRBR-RA does not capture the dose of oral steroids or intramuscular injections (common in the UK), we applied a modified version of the score to both cohorts assuming that all patients receiving steroids would take between 7.5–14 mg of prednisolone per day. We calculated the area under the ROC curve (AUC).

Results: 13,121 patients were recruited to the old cohort and 1,475 patients were recruited to the new cohort. There were significant differences between cohorts (Table). Patients from the old cohort had a longer disease duration, higher DAS28 and HAQ score, and more likely to be receiving steroids compared to newer patients. The crude incidence rate of SI was lower between cohorts (29.3 new vs 62.3 old/1000 patient-years) as was the expected incidence number of SIs in the new cohort (29.3 new vs 62.3 old/1000 patient-years) as was the expected number of patients with \( \geq 1 \) SI during the first year of therapy and compared to the observed numbers in each cohort. To evaluate the predictive performance of the RRS we calculated the area under the curve (AUC).

Conclusion: The RRS was better for the new cohort (AUC=0.82) than for the old cohort (AUC=0.62).

<table>
<thead>
<tr>
<th></th>
<th>Old cohort (n=13,121)</th>
<th>New cohort (n=1,475)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>56.1 (12.3)</td>
<td>56.5 (12.6)</td>
</tr>
<tr>
<td>Gender: n (%) female</td>
<td>10,010 (76.3)</td>
<td>1,112 (75.7)</td>
</tr>
<tr>
<td>RA disease duration (years), Median (IQR)</td>
<td>11.6 (8–19)</td>
<td>6.2 (4–14)</td>
</tr>
<tr>
<td>HAQ score, mean (SD)</td>
<td>6.4 (1.0)</td>
<td>6.2 (1.0)</td>
</tr>
<tr>
<td>RA disease activity score (DAS28), mean (SD)</td>
<td>4.0 (3.3)</td>
<td>4.1 (3.5)</td>
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<tr>
<td>Smoking</td>
<td>5,867 (44.7)</td>
<td>3,366 (23.4)</td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>2,661 (20.2)</td>
<td>279 (20.2)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>4,002 (30.7)</td>
<td>505 (36.5)</td>
</tr>
<tr>
<td>Never smoked, n (%)</td>
<td>5,238 (40.2)</td>
<td>600 (43.4)</td>
</tr>
<tr>
<td>More than 5 previous DMARDs, n (%)</td>
<td>325 (2.5)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>750 (5.8)</td>
<td>119 (9.0)</td>
</tr>
</tbody>
</table>
Conclusion: TNFi are being used earlier in RA patients with lesser disease activity, steroid use and disability. These patients are also experiencing lower SI rates. Among these cohorts of UK patients, the RRS underestimated the total number of SI, although some misclassification of steroid dose and differential access to TNFi resulting in other unmeasured patient differences may have contributed. The predictive power improved in a more recent cohort which strengthens the utility of this score in current routine clinical practice.

Reference:

Disclosure: L. Silva-Fernandez, None; M. Lunt, None; K. D. Watson, None; BSRBR Control Centre Consortium, None; D. P. Symmons, None; K. Hyrich, Pfizer, Abbvie, 8. On behalf of the BSRBR, Pfizer Inc, Abbvie, UCB, Merck, Roche, 2.


Background/Purpose: Despite efficacy of anti-tumor necrosis factors (anti-TNFs) in treating chronic immune conditions, some patients (pts) report serious adverse events (SAEs) highlighting a need to identify at risk pts before starting treatment.1,2 We examine safety data for rheumatoid arthritis (RA) pts treated with the anti-TNF, certolizumab pegol (CZP), in the RAPID1 and RAPID2 randomized clinical trials (RCTs; NCT00152386/NCT00160602) and their open-label extensions (OLEs) to identify baseline (BL) risk factors for specific SAEs, with the goal of risk stratifying pts for adverse outcomes to provide more personalized estimates of expected risks and benefits of therapy.

Methods: Post-hoc analysis was performed on CZP safety data pooled across RCTs (RCT CZP data) and RCT+OLE periods (All CZP data). Pts with prior anti-TNF/biologicals use (4.1%) were excluded from analyses due to limited pt numbers in this group. 3 non-sequential stepwise multivariate Cox proportional hazards models were used to estimate relative risk (Hazard Ratio [HR]; entry p<0.2, stay p<0.05) of BL covariates to the first serious infectious event (SIE), major cardiovascular event (MACE), or all-cause death. Any event between first CZP dose and 84 days after the last study dose was considered drug-related: 2 infusion reactions, 2 cases of leukopenia and 15 cases of grade 3/4 infections (7 respiratory tract, 5 urinary tract, 1 soft tissue infection, 1 case of pneumonia, 1 case of bacteremia and 1 septic shock), and 4 of which were considered serious according to medical criteria, although no patient discontinued RTX for those reasons. No opportunistic infection or malignancy was reported. Patients with low Ig levels did not have a greater number of infections than those with normal Ig levels.

Conclusion: After prolonged exposure to RTX, serious adverse events, including infections, were stable over time and multiple treatment courses, and showed a good safety profile, even in patients with reduced Ig levels.
Safety Profile of Biologic Agents for Rheumatoid Arthritis Treatment after the Complication with Methotrexate-Related Lymphoproliferative Disorder: A Retrospective Study of 28 Patients

Background/Purpose: Lymphoproliferative disorder (LPD) is a rare complication in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX). Although not a few patients experience exacerbation of RA disease activity after withdrawal of MTX, there have been very few reports referring how the LPD complication in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX) is related to outcomes of RA treatment.

Methods: We retrospectively studied all 32 RA patients regarded as being complicated with MTX-LPD from 2007 to 2013 in our institution. The patients were classified into 2 groups: patients treated with biologic agents after MTX withdrawal (Biologics group) and patients treated with conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) other than MTX or prednisolone (PSL) (non-biologics group). The rates of LPD recurrence after these RA treatments were compared. The recurrence rates were analyzed by Kaplan-Meier curves and compared by log-rank test.

Results: Four patients were excluded because three died before the restart of RA treatment and one needed no treatment, so twenty eight patients were analyzed in this study. Baseline characteristics of 28 patients were as follows: age, 65; Female, 89%; duration of MTX administration, 7.5 years; RA disease duration, 14 years; disease activity score (DAS) 28, 2.95. Of 28 patients, 22 patients were pathologically diagnosed as LPD, and 10 were highly suspected of LPD with imaging tests. Seven patients were treated of LPD with chemotherapy (Biologics group) and patients treated with conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) other than MTX or prednisolone (PSL) (non-biologics group). The rates of LPD recurrence after these RA treatments were compared. The recurrence rates were analyzed by Kaplan-Meier curves and compared by log-rank test.

Conclusion: Biologics agents did not increase LPD recurrence compared to csDMARD, and could be the choice of RA treatment in post-MTX-LPD.

Recurrence free RA treatment period (months)

Recurrence free RA treatment period [months]

Incidence of AEs caused discontinuation of 1^st biologics

Disclosure: A. Cuervo, None; M. V. Hernández, None; S. Cabrera, None; J. Inierite-Mundo, None; J. Ramirez, None; V. Ruiz-Esquide, None; J. D. Calleve, None; R. Sammarti, None.

470 Improving of Safety in Treatment with Biologics during First Seven-Years Experiences; Long-Term Results from Observational Cohort Study of Clinical Practice Using Multicenter Registry in Japan.

Background/Purpose: Many evidences including clinical trials of biologics lead us earlier and more aggressive treatment strategy for patients with rheumatoid arthritis (RA). It is stated as "treat-to-target", that is remission. It is critical issue in clinical practice how to evaluate risks and to balance between safety and efficacy of treatment, which could be related to experience.

The aims of this study are to explore the learning curve of treatment with biologics during the first 7 years in Japan (2003–2010) based on safety results associated with the changes in baseline characteristics according to treat-to-target strategy in RA patients treated with biologics using multicenter registry; Tsunumai Biologics Communication Registry (TBCR).

Methods: We analyzed changes in baseline characteristics by initiation year of 1^st biologics and the incidence rate of adverse event (AE) caused discontinuation of 1^st biologics in patients who were registered in TBCR from 2003 to 2008 and followed up to 2010. Predictive factors at baseline for incidence of adverse event were determined using multivariable Cox’s proportional-Hazards regression model.

Results: A total of 874 cases (2052 person-years) were observed. Patients with younger age (<53 years) had significantly shorter disease duration (<2 years), less dysfunction, joint damage, and disease activity (DAS28-CRP) at 2005 while the impact disappeared up to 2 years observation. The impact of year of initiation had significant impacts on incidence of AEs up to 6 months (OR 0.3–0.7) had significant impacts on incidence of the AEs. Interestingly, worse physical function (OR 2.1, 95%CI (1.4–3.1)), MTX use (OR 0.4, 95%CI (0.3–0.7)), and etanercept use (vs infliximab use) (OR 0.4, 95%CI (0.3–0.7)) had significant impacts on incidence of the AEs. Interestingly, initiation year had significant impacts on incidence of AEs up to 6 months [initiation at 2008; OR 0.3, 95%CI (0.1–0.7), compared to initiation 2003–2005] and while the impact disappeared up to 2 years observation. The impact of vs infliximab use was not detected up to 6 months observation.

Incidence rate of AEs decreased with year of initiation, especially in older age group and that the differences was remarkable up to 6 months. Actually, multivaliable analysis showed that, during 2 years observation, older age [OR 1.8, 95%CI (1.1–3.0)], worse physical function [OR 2.1, 95%CI (1.4–3.1)], MTX use [OR 0.4, 95%CI (0.3–0.7)], and etanercept use (vs infliximab use) [OR 0.4, 95%CI (0.3–0.7)] had significant impacts on incidence of the AEs. Interestingly, initiation year had significant impacts on incidence of AEs up to 6 months [initiation at 2008; OR 0.3, 95%CI (0.1–0.7), compared to initiation 2003–2005] and while the impact disappeared up to 2 years observation. The impact of vs infliximab use was not detected up to 6 months observation.

Incidence rate of AEs in patients with older age who were initiated biologics at 2008 was comparable to patients with younger age. These results suggested that, during first 3 years (2003–2005), we could not evaluate risk factors properly, especially in respiratory system, with inadequate experience.

Conclusion: We clearly demonstrated improving of safety of 1^st biologics with first 7-years experiences in real clinical practice using multicenter registry of biologics in Japan.
Disclosures: T. Kojima, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation, 2; Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; N. Takahashi, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; K. Funahashi, None; S. Asai, None; T. Takenoto, None; N. Ishiguro, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda, 8; A. Kameko, Janssen Pharmaceutica Product, L.P., 8; Astellas Pharma, 8; Mitsubishi-Tanabe Pharma, 8; Chugai, 8; Eisai, 8; Abbott Immunology Pharmaceuticals, 8; Bristol-Myers Squibb, 8; Y. Hirano, AbbVie Inc.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Takeda Pharma Corporation; Pfizer Co. Ltd.; Chugai Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co. Ltd., 8; Y. Yabe, Abbott Immunology Pharmaceuticals, 8; Mitsubishi-Tanabe Pharma, 8; Eisai, 8; Chugai, 8; Bristol-Myers Squibb, 8; Pfizer Inc., 8; Y. Kanayama, Astellas Pharma, 8; Eisai, 8; Mitsubishi Tanabe Pharma Corporation, 8; AbbVie Inc. 8; Chugai, 8.

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Abatacept Can be Used Safely for RA Patients with Interstitial Lung Disease. Shinni Motojima1, Tarnao Nakashita2, Akira Jibatake3 and Katsutoshi Ando4, 1Kameda Medical Center, Kamogawa City, Japan, 2Kamed Medical Center, Kamogawa-city, Japan, 3Kameda Medical Center, Kamogawa city, Japan, 4Juntendo university, tokyo, Japan.

Background/Purpose: Interstitial lung disease (ILD) associated with RA is a big concern particularly in Japanese patients evidenced by the reports that the cause of death in approximately 10% of patients with RA is ILD compared with only few percent in western countries. We have reported that ILD exacerbated in 24% (14/58) of RA patients associated with ILD when TNF-inhibitors were administrated and 2 of 14 died of ILD, although the degree of exacerbation was minimal in half of the patients (ACR 2012). Here we retrospectively analyzed the effects of abatacept (ABT), a CTLA4-Ig fusion protein, on RA associated with ILD.

Methods: Subjects were 16 patients with RA (male/female = 6/10, mean age 71 years-old) associated with ILD who were administrated with ABT for longer than 52 weeks and analysis was done for the changes between 0 to 52 weeks, because the exacerbation of ILD developed between 4 to 52 weeks of administration of TNF-inhibitors with the mean of 24 weeks in our previous study. Chest CT scan was done before and 52 weeks after administration of ABT. Chest X-ray film (CXR) was taken at least every 3 months. When newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done. The severity of ILD was graded into 4, grades 0 to grade 3, according to the extent of ILD on chest CT by the method of Gochniuc et al. (Arch Intern Med 2008). Chest CT images were graded by 2 independent radiologists.

Results: All the patients completed 52 weeks administration and none abandoned ABT due to the exacerbation of ILD. The grades of ILD (grade 0/1/2/3) before and at 52 weeks were 0/9/4/3 and 2/7/4/3, respectively. In 2 patients with grade 1, the grade decreased to 0, suggesting the improvement of ILD. We further attempted to analyze more in detail the CT images according to the method by Kondoh et al. (Respirology 2013), and obtained what % of lung fields have findings of ILD. All the abnormalities suggestive of ILD before and at 52 weeks were 12.9 +/- 12.7 (mean +/- SD) and 2/7/4/3, respectively, and no significant differences were found. Mean DAS28-ESR and SDAI decreased from 4.47 +/- 1.44 to 2.84 +/- 0.85, and from 16.9 +/- 11.7 to 8.1 +/- 4.2, respectively, and the differences were statistically significant. The mean dose of PSL decreased from 6.6 mg/day to 5.6 mg/day significantly (n = 15); KL-6, a biomarker of ILD, did not change significantly.

Conclusion: ABT can be used safely for RA patients with ILD. ABT even may improve ILD and is an appropriate treatment option for such patients.

Authors do not have any COI.

Disclosure: S. Motojima, None; T. Nakashita, None; A. Jibatake, None; K. Ando, None.

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Complications of Varicella Zona Virus Infections Are More Frequent in Patients Treated with Biologic Drugs When Combined with Steroids. Jacques Morel1, Florence Tubach2, Yannick Allanore3, Daniel Wendling3, Celine Cozig2, Emmanuelle Dermis Labous4, Eric Leganagneux5, Thao Pham5, Sophie Odoit6, Isabelle Roita7, Isabelle Koné-Pault1, Pierre Quartier1, Jean Sibilia3 and Severine Guillaume Czitrom4, 1Hospital Lapeyronie, Montpellier, France, 2Universite Paris Diderot, Paris, France, 3Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, 4CHU J Minjoz, Besancon, France, 5CHD la Roche sur Yon, La Roche Sur Yon, France, 6CHU Biétre, Le Kremlin Biétre, France, 7Centre Hospitalier Public du Cotentin, 50100, France, 8Saint Marguerite Hospital, Marseille, France, 9CHU de la Réunion, Saint Denis, France, 10Hopital De Perpignan, Perpignan, France, 11CHU Bicêtre, Le Kremlin Bicêtre, France, 12IMAGINE Institute, Hopital Necker-Enfants Malades, ABBVIE Hôpitaux de Paris, Université Paris-Descartes, Paris, France, 13University Hospital of Strasbourg, Strasbourg, France, 14CH De Bicetre, Le Kremlin Bicetre Cedex, France.

Background/Purpose: To assess varicella zona virus (VZV) infection features under biological drugs.

Methods: A call for observations was sent from April 2013 to April 2014 by email through the Club Rheumatisme et Inflammation website to collect varicella zona virus (VZV) infections in adults and children under biologic DMARDs (bDMARDs). Cases collected between first 1st 2004 and January 31th 2007, by the french observational study RATIO were added. Khi-two or Fisher tests were used for qualitative variables when appropriate.

Results: 103 VZV infections were collected in 76 adults and 27 children receiving anti-TNF (71), anti-IL-1 (10), tocitizumab (10), colitizumab (6) and other (46), for rheumatoid arthritis (47), spondylarthritides (13) and juvenile idiopathic arthritis excluding Still’s diseases (11), Still’s disease (11), Crohn’s disease (8), psoriasis or psoriatic arthritic (3), connective digestive tissue disease (2) and other chronic inflammatory diseases (6). Adult patients were mainly women (72.4%), 56% aged 19–60 years old and the others were over 60. At the time of infection, associated to bDMARDs were NSAIDs in 5 patients were on NSAID, steroids in 43 on steroids, conventional synthetic (cs) DMARDs in 54 on conventional synthetic drugs and 9 VZV infections occurred late after drug onset (> 6 months for 97.2% of patients with steroids, 70.2% for bDMARDs and after 3 years for cs DMARDs for 70.4%. 27 children aged less than 18, mainly girls (74.1%) were treated with methotrexate (15) or immunosuppressive drugs (2) combined with NSAIDs for 10 patients in addition to bDMARDs. Most children were on steroids (11), or bDMARDs (16) for at least 6 months when VZV infections occurred. None of the patients had been vaccinated against VZV. Zoster was more frequently observed in adults (68/76 adults), whereas varicella was most often reported in children (18/27). For varicella, 4 complications were reported in adults (2 skin and 2 disseminated) and 2 in children (1 ophthalmic and 1 disseminated). Complications were more frequent for zoster: 40 in adults (28 skin, 6 neurological, 6 ophthalmic) and 2 in children (1 neurological and 1 ophthalmic). Complications were significantly higher in patients on steroids (p = 0.02 vs non abactept 4) and tend to be more elevated in anti-TNF group (p = 0.055 vs non TNF inhibitor bDMARDs). None received IV immunoglobulin. 90 patients (71 adults and 19 children) were treated with an anti-herpes virus (HSV) drug usually prescribed oral for 1 to 2 weeks and intravenously in 28 patients. NSAIDs were used in 11% of the children and 83% of the adults. bDMARDs were at least transiently interrupted in 63 patients (62%) and csDMARDs were stopped for 17 patients. Outcome was favourable for 98 patients with no death.

Conclusion: In this retrospective study, VZV infections were mainly varicella in children and zoster in adults. Outcome was favourable in most cases even when bDMARDs or NSAIDs were pursued and remarkably, even when no specific treatment of VZV infection was applied. Under bDMARDs, complications of VZV infections occurred more frequently in patients treated with steroids.

Disclosure: J. Morel, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Bristol-Myers Squibb, 5, Union Chimique Beige, 5, Merck Pharmaceuticals, 5, Abbott Laboratories, 5; F. Tubach, None; Y. Allanore, None; D. Wendling, None; C. Cozic, None; E. Dermis Labous, None; E. Leganagneux, None; T. Pham, None; S. Odoit, None; I. Roigt, None; I. Koné-Pault, None; P. Quartier, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 2, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum, 5; J. Sibilia, None; Guillaume Czitrom, None.

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Assessment of 12-Month Efficacy and Safety of 168 Certolizumab-pegol Rheumatoid Arthritis Treated Patients from a Multicenter Retrospective National Study in Spain. Vicente Torrente-Segarra1, Ana Urruticoechea2, Héctor Corominas3, Amalia Sánchez4, Juan

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Sunday, November 16

On clinical practice, CZP showed benefit in 71% of RA after 12-m, even in Response/SDAI we saw some predictors of response (p

differences in BT-naive / monotherapy prior DMARD / BT; higher CRP, ESR, TJC, SJC, DAS28, SDAI. No DMARD / H11006
disease time 7.5 (mean number (nr) prior DMARD: 1.4 (±1.2). Prior BT (54.2% none, 28.6% 1, 17.2% ≥2); etanercept 23.8%, adalimumab 19.0%, infliximab 16.1%, rituximab 6.5%, tocilizumab 5.4%, abatacept 4.2%, golimumab 3.0%. Mean nr prior BT 0.8 (±1.1). Mean time on CZP 9.8 m (±3.4), 93.5% induction dose. Concomitant treatment: 11.9% oral steroids, 24.4% DMARD, 50.0% DMARD + steroids (69.6% 1 DMARD, 4.8% 2 DMARDs).

Results: 168 patients: 79.2% women, mean age 54.5 (±13.2), mean disease time 7.5 (±7.3), prior DMARD: 25.6% none: 32.1% 1, 42.3% ≥2; MTX 55.4%, leflunomide 36.9%, gold 25.6%, SSZ 11.3%, HCOQ 10.7%. Mean number (nr) prior DMARD: 1.4 (±1.2). Prior BT (54.2% none, 28.6% 1, 17.2% ≥2); etanercept 23.8%, adalimumab 19.0%, infliximab 16.1%, rituximab 6.5%, tocilizumab 5.4%, abatacept 4.2%, golimumab 3.0%. Mean nr prior BT 0.8 (±1.1). Mean time on CZP 9.8 m (±3.4), 93.5% induction dose. Concomitant treatment: 11.9% oral steroids, 24.4% DMARD, 50.0% DMARD + steroids (69.6% 1 DMARD, 4.8% 2 DMARDs).

Table 1: Basal, 3-m, 6-m, 12-m clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>3-m</th>
<th>6-m</th>
<th>12-m</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>70.8%</td>
<td>(mean RF: 132.4 ± 183.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Cyclic citrullinated Protein (CCP)</td>
<td>59.8%</td>
<td>(mean CCP: 275.1 ± 454.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>9.0 (±2.7)</td>
<td>5.7 (±3.7)</td>
<td>4.7 (±2.9)</td>
<td>4.6 (±2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR</td>
<td>32.3 (±23.5)</td>
<td>25.7 (±21.2)</td>
<td>25.7 (±21.9)</td>
<td>23.5 (±19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TJC</td>
<td>8.0 (±5.2)</td>
<td>4.7 (±5.3)</td>
<td>3.6 (±5.0)</td>
<td>3.3 (±5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SJC</td>
<td>6.6 (±4.5)</td>
<td>3.1 (±4.2)</td>
<td>2.1 (±3.7)</td>
<td>2.2 (±3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease Activity Score (DAS28)</td>
<td>5.1 (±1.3)</td>
<td>4.0 (±1.6)</td>
<td>3.5 (±1.7)</td>
<td>3.4 (±1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EULAR</td>
<td>19.6%</td>
<td>19.9%</td>
<td>24.3%</td>
<td>29.8%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Moderate/Good Response SDAI</td>
<td>35.6 (±18.1)</td>
<td>22.1 (±20.7)</td>
<td>17.8 (±19.3)</td>
<td>17.1 (±19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroids (mg)</td>
<td>8.6 (±6.9)</td>
<td>6.6 (±5.7)</td>
<td>5.7 (±5.7)</td>
<td>4.8 (±5.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
respiratory adverse events were documented in 4579 participants. Six cases of placebo comparators, met our inclusion criteria. Seven hundred and eight intervals.

Results: Among the 396 articles initially identified, 22 were finally selected. These articles included 6682 patients in the anti-TNF-a group (Adalimumab: 2507, Golimumab: 575, Certolizumab: 1512, Infliximab: 1087 and Etanercept: 1001) and 3607 in the placebo group. The duration of patient follow-up ranged from 24 to 78 weeks.

There was no excess of risk of serious adverse event (death or severe infection) in the TNF-a inhibitors compared to placebo (Odds Ratio OR: 1.14, 95% Confidence Interval CI: 0.91–1.44). Nevertheless, we noticed an increased risk of serious event under Certolizumab (OR: 2.06, CI: 1.52–3.15).

There was no increased risk of death in the TNF-a inhibitor group compared to the placebo group (OR: 1.27). We referenced 36 deaths among 6208 patients under TNF alpha inhibitors (0.58%) and 10/3282 deaths under placebo (0.30%). However, increased risk of severe infections in the TNF alpha inhibitor group was observed compared to the placebo group (OR: 1.66) with 192 serious infections among 5889 patients under TNF alpha inhibitors (3.26%) versus 63 serious infections among 3398 patients under placebo (1.85%). Sensibility analysis revealed that adalimumab had an increased risk of severe infection (OR: 2.10).

Conclusion: This meta-analysis has been performed on a large number of patients and included the five TNF-a inhibitors currently available. It allowed an indirect comparison between the different molecules according to their medium-term safety. We did not find an increased risk of serious adverse events or deaths in patients treated with TNF-a inhibitors. However, we observed an increased risk of severe infections. Further studies aiming at the evaluation of the long-term safety are now needed to confirm these results.

Disclosure: L. Poiroux, None; Y. Allanoire, None; A. Kahan, None; J. Avouac, None.

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Leflunomide Use Is Not Associated with an Increased Risk of Lung Disease in Rheumatoid Arthritis: A Meta-Analysis of Randomised Controlled Trials. Richard Conway1, Candice Low2, Robert J. Coughlan1, Martin O’Donnell3 and John J. Carey1. 1Galway University Hospitals, Galway, Ireland, 2St. James Hospital, Dublin, Ireland.

Background/Purpose: Leflunomide is an effective treatment for rheumatoid arthritis. An association between pulmonary adverse events, in particular interstitial lung disease, and leflunomide use has been reported. Incident respiratory events may result in cessation of leflunomide treatment. Clarification of its potential role in pulmonary disease is therefore of clinical importance.

Methods: We performed a systematic literature search of Pubmed and Cochrane databases with no date limits for double-blind randomised controlled trials of leflunomide versus placebo or active comparator agents in adults with rheumatoid arthritis. We evaluated the association between leflunomide use and pulmonary adverse events by performing a meta-analysis of the results. Studies with less than 50 subjects, of less than 12 weeks duration, or with no reporting of respiratory adverse events were excluded. Random effects meta-analysis using the Mantel-Haenszel method was used to assess total respiratory adverse events, infectious respiratory adverse events, non-infectious respiratory adverse events, pneumonitis, and death.

Results: Our literature search returned 884 results. A total of 8 studies, 4 with placebo comparators, met our inclusion criteria. Seven hundred and eight respiratory adverse events were documented in 4579 participants. Six cases of pneumonitis occurred, all in the comparator group. Four pulmonary deaths were reported, none in the leflunomide group. Leflunomide was not associated with an increased risk of total adverse respiratory events, RR 0.95 (95% CI 0.56–1.78), or infectious respiratory adverse events, RR 1.02 (95% CI 0.58–1.82). Leflunomide was associated with a decreased risk of non-infectious respiratory adverse events, RR 0.64 (95% CI 0.41–0.97).

Conclusion: Our study found no evidence of increased respiratory adverse events with leflunomide treatment.

Figure 1: Forest Plot of Total Adverse Respiratory Events

Disclosure: R. Conway, None; C. Low, None; R. J. Coughlan, None; M. O’Donnell, None; J. J. Carey, None.

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Adverse Events and Infections in Patients with Rheumatoid Arthritis Treated with Conventional Drugs or Biologic Agents: A Real World Study. Christos E. Lampropoulos1, Philippos Orfanos2, Vasiliki-Kalliopi Bournia1, Theofilos P. Karatsourakis3, Clio P. Mavragani1, Dimitrios Pikazis1, Menelaos N. Manoussakis1, Athanasios G. Tzioufas2, Haralampos M. Moutsopoulos1 and Panayiotis G. Vlachoyiannopoulos1. 1School of Medicine, National University of Athens, Athens, Greece, 2Department of Epidemiology, Occupational and Environmental Medicine, Medical School, National University of Athens, Athens, Greece, 3School of Medicine, National University of Athens, Athens, Greece, 4School of Medicine, National University of Athens, Athens, Greece, 5School of Medicine, National University of Athens, Athens, Greece, 6School of Medicine, National University of Athens, Athens, Greece.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease with joint destruction and permanent disability. Biologic agents (BAs) offer a better outcome when disease is not adequately controlled by DMARDs. Nevertheless, many doubts still exist about the safety of BAs compared to classical treatment. Purpose of the study was to test the hypothesis that adverse events (AEs), including infections, are rather common in patients receiving BAs than in those with DMARDs.

Methods: Analysis of the medical records of patients with RA followed in a single outpatient clinic was performed. In total, 1403 adults (295 men, 1108 women) were included in the analysis (969 treated with DMARDs only, 434 with biologics). All AEs and infections were recorded and their severity was graded according to international criteria. Cox proportional-hazards models were performed to examine the association of treatment groups and other confounding factors with the risk of first AE or infection. Incident rates were calculated as number of events/100 person-years.

Results: The risk of first AE or infection, mild or serious, was significantly increased in patients with biologics compared to classical treated patients. Purpose of the study was to test the hypothesis that adverse events (AEs), including infections, are rather common in patients receiving BAs than in those with DMARDs.

Methods: Analysis of the medical records of patients with RA followed in a single outpatient clinic was performed. In total, 1403 adults (295 men, 1108 women) were included in the analysis (969 treated with DMARDs only, 434 with biologics). All AEs and infections were recorded and their severity was graded according to international criteria. Cox proportional-hazards models were performed to examine the association of treatment groups and other confounding factors with the risk of first AE or infection. Incident rates were calculated as number of events/100 person-years.

Results: The risk of first AE or infection, mild or serious, was significantly increased in patients with biologics (Figure 1, p<0.001). Hazard ratios ranged from 1.93 (95% CI: 1.59 to 2.34) for any AE to 5.92 (95% CI: 2.55 to 13.75) for serious infection (Table 1). Age, ESR >40mm/h and total steroid dose >500mg were significant detrimental risk factors. The risk for infection was equal across biologic agents, but infliximab and adalimumab were marginally significantly associated with AEs in general (Figure 2, p<0.05).

There were 519 AEs in the biologic group with an IR of 35.5 events/100 PY (IRR=2.24 95% CI: 1.96 to 2.55), as compared with 407 and 15.9 events/100 PY with DMARDs only. When only the follow-up time up until the first AE or infection in both treatment groups was counted in, the IRR for the biologic group was 2.14 for any first AE (95% CI: 1.78 to 2.58), 4.43 for first serious AE (95% CI: 2.83 to 7.08), 5.27 for any first infection (95% CI: 3.62 to 7.8) and 7.93 for first serious infection (95% CI: 3.60 to 19.83).

Conclusion: Biologic agents are associated with a higher frequency and severity of AEs and infections compared to conventional DMARDs.

Disclosure: C. E. Lampropoulos, None; P. Orfanos, None; Y. K. Bournia, None; T. P. Karatsourakis, None; C. P. Mavragani, None; D. Pikazis, None; M. N. Manoussakis, None; A. G. Tzioufas, None; H. M. Moutsopoulos, None; P. G. Vlachoyiannopoulos, None.
**Long Term Safety of Intravenous Golimumab and Comparison with Subcutaneous Golimumab in Rheumatoid Arthritis: Results through 2 Years.** Rene Westhovens, Edward C. Keystone, Clifton O. Bingham III, Elizabeth C. Hsia, Lilianne Kim, Yiying Zhou, Alan M. Mendelsohn and Michael E. Weinblatt. 1 University Hospital KU Leuven, Leuven, Belgium, 2 Mount Sinai Hospital, University of Toronto, Toronto, ON, 3 Johns Hopkins University, Baltimore, MD, 4 Janssen Research & Development, LLC, Spring House, PA, 5 Brigham and Women’s Hospital, Boston, MA.

**Long Term Safety of Intravenous Golimumab in Rheumatoid Arthritis: Results through 2 Years**

**Background/Purpose:** To describe the safety profile of IV GLM in RA (MTX nonresponders) from the phase 3 GO-FURTHER trial. AE rates of interest are indirectly compared to those observed in the SC GLM GO-FORWARD trial in a similar pt population.

**Methods:** In GO-FURTHER, pts with active RA despite MTX were randomized to MTX + IV PBO or GLM 2mg/kg at wks 0, 4, and q8wks. In GO-FORWARD, pts with active RA despite MTX were randomized to SC PBO+MTX or SC GLM 100mg+PBO, GLM 50 mg+MTX, or GLM 100 mg+MTX administered q4wks. Observed safety findings through wk 112 for GO-FURTHER and wk 104 in GO-FORWARD are reported; incidence rates/100 pt-yrs are reported for AEs of interest from data through the August 15, 2012 cut-off (120-day safety update) in GO-FURTHER and from the wk160 CSR in GO-FORWARD. Comparison of targeted safety events between IV and SC GLM are reported. Pts who received ≥1administration were included.

**Results:** Baseline demographic and disease characteristics were similar in GO-FURTHER and GO-FORWARD. 584 pts received IV GLM, with a mean follow-up of 95.9 wks. 434 pts received SC GLM, with a mean follow-up of 89.9 wks. Overall AEs observed in GO-FURTHER and GO-FORWARD are summarized (Table). Similar proportions of pts in GO-FURTHER (wk 112) and GO-FORWARD (wk 104) had an AE (79.1% and 89.4%, respectively), an SAE (18.2% and 22.6%, respectively), or discontinued due to an AE (7.0% and 9.4%, respectively). Infections/ infestations were the most common type of AE in both trials. Rates of selected SAEs per 100 pt-years through the August 15, 2012 cut-off in GO-FURTHER and wk 160 in GO-FORWARD showed no difference in AE rates or significant SAEs between GLM IV and SC RA pts previously treated with MTX with the exception of patients with ALT abnormalities (>1 - <3 x ULN). Similar differences were noted through all ALT tertiles (≥3 - <5 x ULN; ≥5 x ULN). (Table). Incidence of nonserious infusion reactions (median 30 minute infusions) remained low regardless of infusion length, and no serious infusion reactions, requiring study discontinuation, were reported. NMSC (incidence/100 pt-yrs of f/u: 0.10 [95% CI: 0.00, 0.58]) vs. 0.81 [95%CI: 0.37,1.54] for GLM IV vs GLM SC and lymphoma rates were numerically lower in GO-FURTHER vs. GO-FORWARD.

**Conclusion:** Overall safety profile of IV GLM in pts with RA despite MTX observed through wk 112 in GO-FURTHER was similar to that for SC GLM in a similar pt population (GO-FORWARD). Rates 100 pt-yrs (through August 15, 2012 in GO-FURTHER and wk 160 in GO-FORWARD) for events of interest such as malignancies and serious infections in GO-FURTHER were comparable to or lower than rates in GO-FORWARD.

<table>
<thead>
<tr>
<th>Overall AE summary: GLM-treated patients in GO-FURTHER (IV through wk 112) and in GO-FORWARD (SC; through week 104)</th>
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<tr>
<td><strong>GO-FURTHER</strong></td>
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<td><strong>IV GLM 2 mg/kg + MTX</strong></td>
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<td><strong>Pts treated/Mean duration of f/u (wks)</strong></td>
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<td><strong>AE/Serious AE/Dis due to MTX</strong></td>
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<td><strong>Overall infection/Serious infection</strong></td>
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<td><strong>Infusion or reaction reactions</strong></td>
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<td><strong>All of interest in pts receiving IV SC GLM: Incidence per 100 pt-years of follow-up (95% CI)</strong></td>
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<tr>
<td><strong>Total pts of follow-up</strong></td>
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<td><strong>Deaths</strong></td>
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<td><strong>Tuberculosis</strong></td>
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<td><strong>Opportunistic infections</strong></td>
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<tr>
<td><strong>Cellulitis</strong></td>
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<tr>
<td><strong>Pneumocystis ALT ↑ (&gt;2 to &lt;5 x ULN)</strong></td>
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<tr>
<td><strong>Pneumocystis ALT ↑ (≥5 x ULN)</strong></td>
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<tr>
<td><strong>Pneumocystis ALT ↑ (≥5 x ULN)</strong></td>
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</tbody>
</table>


**480**

**Serious Infection Risk by Treatments and Types in Patients with RA.** Kaleb Michaud, Sophie Pedro, Andre Kaliel, Ted R. Mikulski and Frederick Wolfe. 1 National Data Bank for Rheumatic Diseases, Wichita, KS, 2 University of Nebraska Medical Center, Omaha, NE.

**Background/Purpose:** Recent studies provide conflicting results on the impact of DMARDs on the risk of serious infections for patients with RA. We examined these infection risks by type, site, and treatment in a real world setting.

**Methods:** Participants were followed biannually from 1998 through 2013 in a large US longitudinal observational study. Serious infections were defined as those requiring hospitalization or intravenous antibiotics, or led to death within a year after the patient’s last observation. Infections were validated from hospitalization, physician, and death records. Infections were categorized as opportunistic, by cause and by syndrome. Survival analysis methods (Cox regression, time to first infection using time-varying covariates and Andersen-Gill multiple failures model) were applied, both in a univariate and multivariate manner. Confounders included demographics, clinical status, disease severity and medications. DMARDs and biologics were grouped using different categorizations: methotrexate (MTX), non-MTX DMARDs (NMTX), anti-TNF (TNF), and no DMARD/biologic (nDB). Individual drugs included abatacept (ABA), adalimumab (ADA), etanercept (ETA), infliximab (INF), rituximab (RT), and leflunomide (LEF). An at-risk window of 3 months was considered for all drugs (except RIT with 12 months).

**Results:** We had 21,727 RA patients participate, with 21% male, a mean (SD) age of 59.0 (13.7) yrs, and 1.7 (1.5) comorbidities. During 92,138 patient-year follow-up, the treatment exposures included: prednisone (53%), MTX (61%, median 2.4 yrs), NMTX (53%, 1.9 yrs), TNF (50%, 1.5 yrs), and NTNF (5%, 1.4 yrs). There were 2530 serious infections of any type (69 opportunistic, 881 bacterial, 114 viral, 43 fungal and 1048 unable to classify). The most frequent by syndrome were pneumonia (1017), skin (424), and sepsis (367). From the univariate and multivariate analyses, no differences between treatments were found when compared to MTX monotherapy in any group of infections considered. Some exceptions were found: patients who were on INF seemed to be at a higher risk of any infection (HR: 1.29 (1.10–1.50)) and opportunistic infections (2.96 (1.38–6.33)). Patients who took ETA or INF were also at higher risk for skin infections (1.38 (1.04–1.38) and 1.32 (1.00–1.76), respectively) (Figure 1). When decomposing DMARDs into 5 classes, the results also didn’t change but patients on LFE seemed to be at higher risk for bacterial infections (1.4 (1.12–1.75), bone/joint (2.01 (1.37–2.94)) and skin (1.48 (1.11–1.95)). HEC was protective for pneumonia (0.82 (0.61–1.14)).

**Conclusion:** Our preliminary results indicated little differences between treatments in risk of serious infections in RA. Next steps will include propensity scores to adjust for possible channeling and to adjust for previous infections and geographical region.

Background/Purpose: With the expanding use of Biological Agents (BA), in particular TNF inhibitors, opportunistic infections (OI) are a major concern in Rheumatology. Our purposes were to describe the incidence of OI global and by periods in Rheumatoid Arthritis (RA), and comparing the risk of OI by BA.

Methods: We performed a retrospective longitudinal observational study from 2000 to 2013. We included subjects followed in our outpatient clinic, diagnosed with RA according to ACR criteria 87, whom started treatment with a BA [etanercept (ETN), golimumab (GOLI), certolizumab (CTZ), infliximab (IFX), adalimumab (ADA), rituximab (RTX), abatacept (ABA), or tocilizumab (TCZ)]. Our primary endpoint was OI that involved the suspension of the BA. We consider OI when there was a positive culture (for Virus, Fungus, and bacterial) or compatible symptoms that responded to specific treatment. We also collected secondary variables: sociodemographic (age, sex); clinical (disease duration, type of BA, hospital admission, previous BA). We used survival techniques to estimate the incidence of OI, expressed per 1000 patient-year [CI 95%]. The exposure time was defined from the start date of each BA to its suspension, loss of follow up or end of study (2/3/11/2013). We performed Cox regression models (adjusted by age, duration of RA, sex, calendar time and prior BA) to compare the risk of OI between each BA.

Results: 453 RA patients were included in the study; they started 853 different courses of BA treatment. Of these, 81% were women with a mean age at diagnosis of 52.4 ± 14 years. The median time from onset of BA until onset of OI was 1.7 years [0.48–2.8]. Except for one all patients with OI took steroids. The most frequently used drug was ADA (33%), followed by ETN (25%), IFX (19%) and RTX (14%). There were 33 OI (22 Virus [18 Herpes Zoster, 2 virus B reactivation, 1 Avian flu], 10 Fungus [Candida, 2 Aspergilus], and 1 Bacterian [Legionella]), 36% required hospitalization and 4 died (2 fungus infection, 1 Legionella and 1 virus B reactivation with a myelodysplasic syndrome). The global incidence of OI was 17.7 [12.5–24.8], TZC had 1 OI, with a incidence of 68.1 [9.6–483.5], followed by RTX, with 4 OI. Incidence 22.2 [8.3 to 59]: ADA, with 14 OI. Incidence: 19.9 [11.8–33.6]; IFX with 9 OI. Incidence: 19.4 [10.1–37.3], and ETN with 5 OI. Incidence: 11.6 [4.8–27.9]. We did not find statistical differences in the rate of OI between BA. Age was found a predictor of OI in the multivariate analysis.

Conclusion: The incidence of OI and its evolution over time in real life conditions is described. Incidence found was near 18 cases per 1000 patients -year. Four of them resulted in death. Incidence of opportunistic infections showed no variance during the years. We did not find statistical differences in the rate of OI between BA. Doctors using Biological Agents should be concerned about this problem and be aware for the detection and management of OI.

Disclosure: A. Gomez-Gomez, None; Z. Rosales, None; L. Leon, None; J. A. Jover, None; L. Rodriguez-Rodriguez, None; L. Abasolo, None.
HBcAb+) and treated with ABA or TCZ, have been retrospectively analyzed for the risk of ‘viral re-activation’ (rise in viral load>1 log10 IU/mL, compared with baseline values, or detection of previously undetected serum HBV-DNA) and/or ‘viral hepatitis B’ (increase in LFT and serum HBV-DNA, necroinflammation and/or fibrosis in liver biopsy) by regularly detecting HBsAg, HBV-DNA, LFT throughout follow-up.

**Results:** Out of a total of 125 RA patients, 17 (13.6%) were HBcAb+: 16 occult carriers (8 treated with ABA+b treated with TCZ), and 1 chronic inactive carrier treated with ABA. Patients have been followed for a median time (IQR) of 1.2 (0.7–1.5) years. They were previously treated with a median (IQR) number of 2 (1–3) synthetic DMARDs (sDMARDs) and 0 (0–1) bDMARDs. The mean age (sd) was 54.7 (13.8) years, the median disease duration was 5.8 (1.8–7.6) years. Most patients were treated with concomitant methotrexate (8/9 in the ABA group, 5/6 in the TCZ group) and corticosteroids. In the ABA group, 1 patient with chronic HCV co-infection (HCV-RNA+) started lamivudine, due to LFT elevation (>2-fold ULN) occurring 2 months after ABA initiation; amelioration of LFT along with undetectable viral load occurred throughout 12 months of follow-up. 2 patients (1 occult carrier and 1 chronic inactive carrier) underwent lamivudine before ABA with no HBV-related adverse events; among the other 6 ABA patients not receiving lamivudine only 1 experienced a temporary positive detection of viral load (85 UI/mL) without LFT elevation at 12 months of follow-up; spontaneous negativization of viral load was registered at 18 months. In the TCZ group, no patient received lamivudine with no HBV reactivation.

**Conclusion:** Despite limited to few patients and short follow-up, the use of ABA and TCZ in RA patients with past history of HBV infection seems relatively safe. However, periodic monitoring of liver function tests and viral load is mandatory. According to scientific literature, viral prophylaxis might be considered mainly in patients undergoing ABA. Further data are needed to clarify long-term safety issues.

**References:**


### Table 1. Characteristics of patients with RA and past HBV infection treated with ABA and TCZ.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ABA group</th>
<th>TCZ group</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>8</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2/6</td>
<td>2/7</td>
<td>4/7</td>
</tr>
<tr>
<td>Age (sd)</td>
<td>49.5 (13.8)</td>
<td>50.2 (16.3)</td>
<td>49.7 (13.8)</td>
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<tr>
<td>Disease duration, median (IQR) (yrs)</td>
<td>4.7 (1.7–7.5)</td>
<td>5.8 (2.7–9.9)</td>
<td>5.8 (4.7–7.6)</td>
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<tr>
<td>Duration of follow-up, median (IQR) (yrs)</td>
<td>1.2 (0.7–1.5)</td>
<td>1.2 (0.7–1.5)</td>
<td>1.2 (0.7–1.5)</td>
</tr>
<tr>
<td>Number of previous sDMARDs, median (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
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<tr>
<td>Number of previous bDMARDs, median (IQR)</td>
<td>1 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>Co-treatment: steroids</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Co-treatment: methotrexate</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Chronic inactive infection</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Occult carrier</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Antiviral prophylaxis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Disclosure:** F. De Nard, None; V. Grosso, None; M. Todoerti, None; C. Montecucco, None; R. Caporali, None.

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**Incidence of Clinical and Serological Lupus-like Disease during Anti-TNF-Treatment – a Two-Year Prospective Study in an Interdisciplinary Patient Cohort.**

Simon Julius Winkelmann,1 Raimald A. Zeuner,1 Dörte Schuldt,1 Johannes Bethge,2 Ulrich Mrowietz,2 Matthias Lauedes,1 Stefan Schreiber1 and Johann Schroeder1. 1University of Kiel, Kiel, Germany, 2Univ Schleswig-Holstein, Kiel, Germany.

**Background/Procedure:** TNFα-Inhibitors are the most widely used biological agents in rheumatic conditions or other chronic inflammatory diseases. Over the last ten years, the occurrence of lupus-like disease and the induction of antinuclear antibodies have been observed in more than 800 individuals receiving anti-TNFα-treatment worldwide. However, the exact incidence of serological changes and the frequency of associated clinical manifestations are unknown.

**Methods:** We conducted a single center, interdisciplinary prospective study on patients with RA, spondyloarthropathies and inflammatory bowel diseases who were elected for anti-TNFα-therapy as their first biological treatment. Clinical and serological parameters were collected before the first application and thereafter at six-monthly intervals. The evaluation included a clinical questionnaire and serological testing for ANA, dsDNA-antibodies and ANCA. We calculated the incidence rates based upon duration of drug exposure. The odds ratios within the subgroups were adjusted to the diagnosis or the compound with the lowest event rate, respectively.

**Results:** Between January 2011 and February 2014, 223 patients entered the study. The underlying diseases of these patients were RA (68), spondyloarthropathies (67), inflammatory bowel disease (84) and JIA (4). During the follow-up, 318 serum samples were collected, 117 of these were allotted to ABA and 201 to TCZ. Clinical and serological parameters before the first application and thereafter at six-monthly intervals. The evaluation included a clinical questionnaire and serological testing for ANA, dsDNA-antibodies and ANCA. We calculated the incidence rates based upon duration of drug exposure. The odds ratios within the subgroups were adjusted to the diagnosis or the compound with the lowest event rate, respectively.

**Conclusion:** Study indicates the risk of HBV reactivation during anti-TNF therapy. Careful management is mandatory for patients who planned to be treated with TNF inhibitors.

**Disclosure:** S. M. Jung, None; H. K. Min, None; J. H. Koh, None; J. Y. Kang, None; J. Lee, None; S. K. Kwok, None; J. H. Ju, None; H. J. Ko, None; K. S. Park, None; H. Y. Kim, None; S. H. Park, None.
Tofacitinib Improves Arterial Stiffness Despite up-Regulating Serum Cholesterol with Chronic Cardiovascular Disease in Methotrexate-Resistant Active Rheumatoid Arthritis Patients. A Cohort Study. Ken- suke Kume1, Kanzo Amano2, Susumu Yamada3, Toshikatsu Kanazawa4, Hiroshi Komori5, Kazuhiko Hatta4, Kuniki Amano6 and Noriko Kowabaa.

Background/ Purpose: Patients with rheumatoid arthritis (RA) have an increased cardiovascular (CV) risk. We should have strategies for primary cardiovascular prevention in RA. Tofacitinib (Tofa) could possibly play a role in up-regulating levels of serum cholesterol. But there is no evidence of CV risk management about Tofa. To examine the effect of Tofa plus methotrexate (MTX) on arterial stiffness with CV disease in MTX resistant RA patients in a cohort study design.

Methods: 18 RA patients with moderate to severe active disease despite MTX treatment (disease activity score; DAS28 >3.2) were received Tofa plus MTX. All patients have previous history of CV. Arterial stiffness was assessed by pulse wave velocity (PWV), and CAVI measures arterial wall stiffness independent of blood pressure and it is superior to brachial ankle PWV as an index of arterial stiffness. No new all treatments (statin, low lipids drug, etc.) were allowed.

Results: Treatment with Tofa attenuated the CAVI significantly from baseline to 24 weeks follow up (p=0.016). Treatment with Tofa attenuated the Aix@75 significantly from baseline to 24 weeks follow up (p=0.01). On the other hand, fasting serum total cholesterol TC was significantly increased from baseline to follow-up at 24 weeks (195±21.2mg/dL, 211±24.2mg/dL, p=0.03). No patients suffered from new CV disease.

Conclusion: These findings suggest that combination therapy, Tofa with MTX not only reduced RA disease activity but also limited vascular damage despite up-regulating serum cholesterol with CV disease in patients MTX resistant active RA.

References:

Disclosure: K. Kume, None; K. Amano, None; S. Yamada, None; T. Kanazawa, None; H. Komori, None; K. Hatta, None; K. Amano, None; N. Kowaba, None.

Assessment of Lipid Changes in Patients with Early Rheumatoid Arthritis Treated with Tofacitinib or Methotrexate over 24 Months. C. Charles-Schoeman1, A. Dikranian2, J. Taylor3, B. Wilkinson4, T. Jones5, K. Kwok6 and C. Nduaka4. 1University of California, Los Angeles, CA, 2San Diego Arthritis Medical Clinic, San Diego, CA, 3Anderson Arthritis and Rheumatology Center, Meridian, MS, 4Pfizer Inc, Groton, CT, 5Pfizer Inc, Collegeville, PA, 6Pfizer Inc, New York, NY.

Background/ Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Post-baseline (BL) increases in mean low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed in Phase 3 (Ph 3) studies of tofacitinib (mostly with background DMARDs). In the Ph 3, 24-month (mo) ORAL Start study (NCT01039688), methotrexate (MTX)-naïve patients (pts) treated with tofacitinib monotherapy had significant and clinically meaningful improvements in RA signs and symptoms, physical function, and inhibition of radiographic progression vs MTX-treated pts. Here, the lipid profile during tofacitinib monotherapy treatment over 24 mos was investigated in these MTX-naïve pts with RA.

Methods: Pts were randomized 2:2:1 to receive tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or MTX (mean dose by Mo 3, 18.5 mg/week). LDL-C, HDL-C, and triglyceride (TG) levels were measured at BL and Mos 3, 6, 9, 12, 18, and 24, and descriptive statistics provided. Categorical changes (defined by National Cholesterol Education Program Adult Treatment Panel III) in LDL-C, HDL-C, and TG levels from BL to maximum on-treatment values through Mos 6 were compared using shift analyses.

Results: 956 pts were treated: tofacitinib 5 mg BID, n=373; tofacitinib 10 mg BID, n=397; and MTX, n=186. With both tofacitinib doses, median increases in LDL-C, HDL-C, and TG levels were observed at Mos 3 (first time point for analysis) but generally stabilized thereafter (Fig 1). Median increases and decreases in LDL-C, HDL-C, and TG levels were observed with MTX treatment (Fig 1). The total cholesterol (TC)/HDL-C ratio remained unchanged from BL through Mos 24 in all treatment groups. Categorical increases in lipid profile (ie shifts from a lower to higher lipid category) from BL through Mos 6 in pts receiving tofacitinib 5 mg BID, tofacitinib 10 mg BID, or MTX, respectively, were reported in: 52.2%, 57.3%, and 27.7% of pts for LDL-C; 5.7%, 10.2%, and 1.1% of pts for HDL-C; and 24.0%, 21.6%, and 14.7% of pts for TG levels. A similar percent of pts in each treatment group had LDL-C >130 mg/dL (tofacitinib 5 mg BID: n=251/362 [69.3%]; tofacitinib 10 mg BID: n=277/391 [70.8%]; MTX: n=132/184 [71.7%]). A minority of these pts had maximum on-treatment LDL-C >160 mg/dL by Mos 6 (tofacitinib 5 mg BID: n=32/251 [12.7%]; tofacitinib 10 mg BID: n=38/277 [13.7%]; MTX: n=4/132 [3.0%]).

Conclusion: Tofacitinib monotherapy was associated with increases in LDL-C, HDL-C, and TG levels by Mos 3 (first time point measured) which generally stabilized thereafter. TC/HDL-C ratios were unchanged across all treatment groups. These changes were consistent with changes observed in the tofacitinib Ph 3 program. Most pts had LDL-C <130 mg/dL at BL and a minority of these had maximum on-treatment LDL-C >160 mg/dL by Mos 6.

Fig 1. Median change (mg/dL) from BL in LDL-C (A), HDL-C (B), and TG (C) at Mos 3, 9, 18, and 24 by treatment group.

Increases in Serum Cholesterol with Baricitinib Treatment Are Associated with Favorable Changes in Apolipoprotein Content and with Improvement in DAS28-CRP in Patients with Rheumatoid Arthritis. Joel M. Kremer1, Mark C Genovese1, Edward C. Keystone2, Peter C. Taylor3, Steven H. Zuckerman4, Douglas E. Schlichting5, Eric P. Nantz6, Scott D. Beattie6 and William L. Macias6.1 Albany Medical College and the Center for Rheumatology, Albany, NY; 2 Stanford University Medical Center, Palo Alto, CA; 3 University of Toronto, Toronto, ON; 4 University of Oxford, United Kingdom; 5 Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Treatment with baricitinib (bari), an oral inhibitor of JAK1/JAK2, demonstrated improvements in signs and symptoms of RA through 52 wks in a Phase 2b study.1 Bari treatment also resulted in dose- and time-dependent changes in serum lipids detectable by Wk 2 and persisting through Wk 24 and was associated with increases in LDL particle size and HDL and VLDL particle numbers. Increases in HDL, but not LDL cholesterol, correlated with decreases in CRP at Wk 12. Changes from baseline in serum cholesterol through 52 wks of bari treatment as well as changes in the apolipoprotein content of LDL, VLDL, and HDL particles with bari treatment at Wks 4 and 12 were evaluated. The relationship between cholesterol changes and measures of clinical efficacy was also explored.

Methods: Patients (pts) with RA were randomized to QD doses of placebo (PBO) (n=38) or bari 1 mg (n=49), 2 mg (n=52), 4 mg (n=52), or 8 mg (n=52) for 12 wks. Pts assigned to 2-, 4-, or 8-mg bari continued blinded treatment for an additional 12 wks. Pts who completed the 24-wk study could enter a 2-yr, open-label extension. Serum samples were collected through 52 wks for conventional lipid determinations (total cholesterol, LDL, HDL, and triglycerides). Apolipoprotein content was assessed at Wks 4 and 12 for PBO, 4-, and 8-mg bari groups. Pearson correlations and partial correlations, adjusted for assigned treatments, between changes in cholesterol and efficacy measures were evaluated at 12 wks.

Results: Pts treated with bari through 52 wks maintained a stable cholesterol and triglyceride profile with no further changes beyond Wks 12 and 24. Increases in apolipoprotein A-I, apolipoprotein B, and total apolipoprotein CIII were observed with 4- and 8-mg bari with no increase in LDL-associated apolipoprotein CIII. Bari treatment also demonstrated a significant reduction in HDL-associated SAA at the 4- and 8-mg doses compared to PBO while a significant reduction in Lp(a) was observed only in the 8-mg bari group (all p<0.05). These changes in apolipoproteins coincided with the increases in serum lipids apparent by Wk 4. In pts treated across all doses of bari, a significant correlation was observed between change in HDL cholesterol and absolute DAS28-CRP score at Wk 12 (r=0.33, p<0.001) as well as the change from baseline to Wk 12 in the DAS28-CRP (r=-0.29, p<0.001). Specifically, pts achieving DAS28-CRP <2.6 and larger decreases in DAS28-CRP demonstrated larger increases in HDL cholesterol. No significant correlations were observed between HDL and disease activity measures and no significant correlations were observed between disease activity and total cholesterol or LDL levels in the bari arms.

Conclusion: In addition to increases in serum cholesterol and lipoprotein number (HDL and VLDL) and size (LDL), there were changes in apolipoprotein content of these particles in pts treated with bari. The increase in HDL cholesterol with bari treatment correlated with an improvement in DAS28-CRP. Further studies are necessary to determine if these changes influence long-term cardiovascular outcomes.


Legends: Fig 1: AIX: augmentation index, PWV: pulse wave velocity

Rosuvastatin Improves Arterial Stiffness in Patients with Inflammatory Joint Diseases. Eirik Ikdahl1, Silvia Rollefstad2, Jonny Hisdal1, Inge C. Olsen1, Ingar Holme2, Terje R. Pedersen3, Tore Kvien1 and Anne Grete Semb1. 1 Diakonhjemmet Hospital, Oslo, Norway; 2 Oslo University Hospital Aker, Oslo, Norway; 3 Oslo University Hospital, Oslo, Norway; 4 University of Oslo, Oslo, Norway.

Background/Purpose: Arterial stiffness, as pulse wave velocity (PWV) and augmentation index (AIX) has emerged as early risk markers of cardiovascular disease (CVD) in patients with inflammatory joint diseases (IJD). In IJD patients, statin treatment has demonstrated a significant improvement in arterial stiffness. Furthermore, we have shown that statin treatment induced carotid plaque (CP) regression in IJD patients. However, the effect of statins on arterial stiffness in IJD patients with established atherosclerosis is still not elucidated. The aim of the present study was therefore to evaluate the effect of rosuvastatin on arterial stiffness in patients with IJD who had CP. We also evaluated the association between the change in arterial stiffness and change in inflammation markers, disease activity, low-density lipoprotein cholesterol (LDL-c), blood pressure (BP), CP height and intima-media thickness (IMT) after 18 months of rosuvastatin treatment.

Methods: The study population included 89 statin naïve patients with IJD (55 with rheumatoid arthritis, 23 with ankylosing spondylitis and 11 with psoriatic arthritis). All patients had B-mode ultrasound verified CP and received rosuvastatin therapy over 18 months to obtain LDL-c goals (<1.8mmol/L). The arterial stiffness variables PWV and AIX were measured prior to, and at the end of the study, using the Sphygmocor device. We used paired-samples t-tests to assess change from baseline, and regression analysis to assess the association between change in arterial stiffness and other outcome measures.

Results: Study population demographics are presented in table 1. After 18 months rosuvastatin therapy, a significant reduction in AIX was observed, from mean (SD) 27.9 (7.7) % to 26.2 (8.2) % (p<0.026). Furthermore, PWV decreased from 8.1 (1.6) m/s² to 7.8 (1.5) m/s² (p=0.031). In a logistic regression model where change in arterial stiffness was the dependent variable (defined as either increasing or decreasing related to baseline value), change in and exposure of PWV and AIX significantly increased the odds ratio (95% CI): 1.06 (1.02, 1.09)(p=0.005) and 0.97 (0.94; 1.00)(p=0.035). Change in CP height and rosuvastatin dose predicted change in AIX 5.72 significantly: odds ratio (95% CI): 1.25, 26.25(p=0.025) and 1.22 (1.05, 1.41) (p=0.009).

Conclusion: This is the first clinical trial showing that rosuvastatin treatment improves arterial stiffness in IJD patients with atherosclerosis.
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*Do Patients with Congestive Heart Failure Treated with Biologics for RA Have a Lower Risk of Fatal Outcome of Serious Infections?*

*Anja Strangfeld*, Adrian Richter*, Yvette Meissner*, Matthias Schneider*, Michael Zaenker†, Wolfgang Ochs‡, Thomas Klopsch†, Angela Zink‡ and Joachim Listing†

1. German Rheumatism Research Center, Berlin, Germany, 2. Heinrich-Heine-University, Düsseldorf, Germany, 3. Immanuel Klinikum Bernau, Rheumatology Center Northern Brandenburg, Bernau, Germany, 4. Rheumatologist in private practice, Bayreuth, Germany, 5. Rheumatologist in private practice, Neubrandenburg, Germany, 6. German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany.

**Background/Purpose:** Patients with multimorbid conditions are at high risk of developing serious infections (SI) and of premature mortality. TNF inhibitors increase the infection risk (1) in patients with rheumatoid arthritis (RA). However, they are likely to decrease all-cause mortality (2). We aimed to examine a) the infection risk and b) the outcome of SI in a group of patients at high mortality risk: RA patients with congestive heart failure (CHF). We used data from the German biologics registry RABBIT with 10,671 RA patients included at start of a synthetic or biologic DMARD (bDMARD) at least one DMARD failure. In 242 patients, CHF was reported as comorbid condition at enrollment (NYHA grade III: 16%, NYHA IV: none). We investigated the incidence of SI in CHF patients compared to a matched control sample and the rest of the cohort. Age, sex and morbidity (chronic lung disease, chronic kidney disease, hypertension) were used as matching criteria for the nested case control study. For 238 CHF patients exactly matching controls without CHF were found. Multiple logistic regression was applied to investigate the risk of fatal outcome of the first SI in CHF patients.

**Results:** Compared to the rest of the cohort (n=10,429), CHF patients were older (mean age 68 vs. 56), more frequently males (34% vs. 23%), at baseline they had a higher level of disease activity (DAS28: 5.9 vs. 5.2), considerably more comorbidities (e.g. chronic lung disease: 7% vs. 3%, kidney disease: 24% vs. 3%) and lower functional capacity (FFh (mean %) 1.2 vs. 1.07). These patient characteristics predispose CHF patients to develop SI. Compared to the rest of the cohort, we observed a nearly five times higher incidence per 100 patient-years (PY) (16 [95%CI: 13, 19] vs. 3.4 [3.2, 3.6]). In addition we found a higher risk of fatal outcome of SI in CHF patients.

In the sample of 238 CHF patients with exact matched controls, the difference in incidence rates of SI in CHF patients vs. controls was considerably smaller: 13.0 [10.7,15.8] vs. 10.3 [8.2,13.0] per 100 PY.

In patients of the matched sample who developed SI we observed a nearly five times higher incidence per 100 patient-years (PY) (16 [95%CI: 13, 19] vs. 3.4 [3.2, 3.6]). In addition we found a higher risk of fatal outcome of SI in CHF patients.

**Conclusion:** Patients with CHF are at increased risk of SI with a high lethality risk. Our data suggest that SI occurring in RA patients on biologic therapy tend to have a lower risk of fatal outcome.


**Disclosure:** S. Oakley, Abbvie, 2, UCB, 9, Roche Pharmaceuticals, 9, Janssen Pharmaceuticals Product, L.P., 9, Pfizer Inc, 9, N. Esmaili, Abbvie Laboratories, 2; G. Major, Abbvie, 2, Abbvie, 2; D. Mathers, Abbvie, 2, Pfizer Inc, 9, BMS, 9, Abbvie, 9, UCB, 9, Janssen Pharmaceuticals Product, L.P., 9, S. van der Kallen, Abbvie, 2; J. van der Kallen, Abbvie, 2, Novartis, 8; M. Collins, 2; A. Semb, 2, BMS, 9, Roche Pharmaceuticals, 9, Abbvie, 9; M. Toth, Abbvie, 2; J. Glass, Abbvie, 2.
Patient-Reported Outcomes from a Canadian Study of Patients Taking Methotrexate and Etanercept. J. Carter Thorne,1 Edward C. Keystone,2 Janet E. Pope,3 Melanie Poulin-Costello,4 Krystene Phan-Chronis5 and Boulous Harauoui.6 Southlake Regional Health Centre, Newmarket, ON, University of Toronto, Toronto, ON, St Joseph Health Care, London, ON, 7Amgen Canada Inc., Mississauga, ON, 8Institut de rhumatologie de Montréal (IRM), Montréal, QC.

Background/Purpose: The Canadian Methotrexate and Etanercept Outcome Study (CAMEO) evaluated etanercept (ETN) monotherapy vs ETN plus methotrexate (MTX) in biologic-naive patients with rheumatoid arthritis (RA) who had an inadequate response to MTX.

Methods: This phase 4, randomized, open-label, noninferiority study enrolled patients who had an inadequate response to MTX. All patients received ETN+MTX for 6 months; they were then randomized at month 6 to ETN monotherapy or remained on ETN+MTX for an additional 18 months. Patient-reported outcomes (PROs) were assessed at baseline and at 6, 12, 18, and 24 months and included the Short Form-36 (SF-36) Health Survey questionnaire (higher scores represent better health); Health Assessment Questionnaire Disability Index (HAQ-DI; 0=no disability to 3=severe disability), and pain based on visual analog scale (VAS; 0=no pain to 100=severe pain). The minimal clinically important difference (MCID) for the SF-36 physical and mental component scores is a change ≥0.22, for the HAQ-DI a change ≥0.22, and for the pain VAS is a change ≥10mm.

Results: Of 258 patients enrolled, 205 were randomized at month 6 to ETN (n=98) or ETN+MTX (n=107); 53 were not randomized. These PROs through month 24 are shown (Table). As expected, on average, PROs demonstrated improvements at 6 months, when all patients had been on ETN+MTX. From month 6 (randomization) to month 24, mean improvements were maintained in both treatment arms.

Table 1. Efficacy responses at Month 3 (pooled Ph 2 and Ph 3 studies) within each treatment group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tofacitinib 5mg BID</th>
<th>Tofacitinib 10mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR50 (%)</td>
<td>36.7</td>
<td>39.9</td>
<td>21.2</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>19.9</td>
<td>25.1</td>
<td>7.5</td>
</tr>
<tr>
<td>DAS28&lt;2.6%</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
</tr>
<tr>
<td>SDAI&lt;3.3%</td>
<td>34.5</td>
<td>41.2</td>
<td>28.8</td>
</tr>
<tr>
<td>CDAI&lt;10%</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
</tr>
<tr>
<td>HAQ-DI (0-10)</td>
<td>34.5</td>
<td>41.2</td>
<td>28.8</td>
</tr>
</tbody>
</table>

Conclusion: Clinically meaningful improvements in PROs were demonstrated from baseline to month 6. In general, patients who discontinued MTX at month 6 and those who remained on ETN+MTX, maintained improvements to month 24.

Disclosure: J. C. Thorne, Abbvie, 2; Amgen, C. Engelge, 2; Centocor, Inc., 2; Novartis Pharmaceutical Corporation, 2; Pfizer Inc. Abbvie, 2; Amgen, 5; Kelgine, 5; Centocor, Inc., 5; Genzyme Corporation, 5; Janssen Pharmaceutica Products, 5; Pfizer Inc. 5; E. C. Keystone, 1; J. E. Pope, Amgen, 2; Amgen Inc., 5; M. Poulin-Costello, Amgen Inc., 1; Amgen Inc., 3; K. Phan-Chronis, Amgen Inc., 1; Amgen Inc., 3; B. Harauoui, Abbvie, 2; Abbvie, 5; Amgen, 2; Amgen, 5; Bristol-Myers Squibb, 2; Bristol-Myers Squibb, 2; Janssen Pharmaceutica Product, L.P., 2; Janssen Pharmaceutica Product, L.P. 2; Pfizer Inc, 5; Pfizer Inc, 5; Roche Pharmaceuticals, 2; Roche Pharmaceuticals, 5; UCB, 2; UCB, 5.

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Efficacy and Safety of Tofacitinib Following Inadequate Response to Nonbiologic DMARD or Biologic DMARD. C. Charles-Schoeman1, Gerd Burmester2, P. Nash3, C.A.F. Zerbini4, S. Anway5, K. Kwok6, T. Hendriks2, E. Bananis3 and Roy Fleischmann7. University of California, Los Angeles, CA, 2Charité – University Medicine Berlin, Berlin, Germany, 3Rheumatology Research Unit, Nambour Hospital, Sunshine Coast and Department of Medicine, University of Queensland, Queensland, Australia, 4Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, 5Pfizer Inc. Groton, CT, 6Pfizer Inc, New York, NY, 7Pfizer BV, Capelle aan den IJssel, Netherlands, 8Pfizer Inc, Collegeville, PA, 9Metropolis Clinical Research Center, University of Texas Southwestern Medical Center, Department of Medicine, Dallas, TX.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we compare the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily (BID) vs placebo (PBO) in patients (pts) who had an inadequate response (IR) to nonbiologic/conventional synthetic DMARDs only (csDMARDs; biologic-naïve) and pts with an IR to previous anti-TNF drugs or other biologic DMARDs (biologic-IR pts).

Methods: Efficacy comparisons were performed on pooled data from 4 Phase (Ph) 2 and 5 Ph 3 randomized, controlled studies of tofacitinib in RA pts. Pts received tofacitinib 5 mg or 10 mg BID or PBO as monotherapy, or with background MTX or other csDMARDs. In this analysis, efficacy in biologic-naive and biologic-IR subpopulations was assessed by American College of Rheumatology (ACR) 20/50/70, disease activity score (DAS28-4(ESR [erythrocyte sedimentation rate]), Health Assessment Questionnaire-Diability Index (HAQ-DI), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Safety was assessed in pooled Ph 3 pts from 5 studies.

Results: A total of 1071, 1090 and 651 biologic-naïve pts were randomized to tofacitinib 5 mg BID, 10 mg BID PBO, respectively. For biologic-IR pts, 259, 253, and 193 were randomized to tofacitinib 5mg BID, 10 mg BID and PBO, respectively. Baseline demographics and disease characteristics were similar between tofacitinib and PBO groups within subpopulations. Biologic-IR pts were heavier, with a higher proportion of white pts, had longer disease duration and had slightly greater disease activity at baseline compared with biologic-naïve pts. In both biologic-naive and biologic-IR pts in the pooled Ph 2 and 3 studies, clinical response was significantly greater for tofacitinib 5 and 10 mg BID vs PBO: significantly more pts achieved low disease activity and remission with both tofacitinib doses vs PBO by DAS28-4(ESR), SDAI or CDAI (Table 1). Clinical response appeared numerically greater with biologic-naive vs biologic-IR pts. Rates of safety events of special interest in pooled Ph 3 studies were generally similar between tofacitinib doses and subpopulations (Table 2). Confidence intervals (CI) for safety events were wide and overlapping for all events and treatment groups due to the limited sample size in PBO and biologic-IR groups.

Conclusion: Tofacitinib reduced signs and symptoms of RA in pts who were biologic-naive and biologic-IR. Tofacitinib had a numerically greater clinical response in the biologic-naïve population compared with the biologic-IR population. The safety profile appeared similar between the Ph subpopulations in Ph 3 studies.

Table 1. Efficacy responses at Month 3 (pooled Ph 2 and Ph 3 studies) within each subpopulation. All measures were significantly improved with tofacitinib 5 mg or 10 mg BID vs PBO (p<0.05)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tofacitinib 5mg BID</th>
<th>Tofacitinib 10mg BID</th>
<th>Placebo</th>
<th>Tofacitinib 5mg BID</th>
<th>Tofacitinib 10mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>36.3</td>
<td>39.9</td>
<td>21.2</td>
<td>36.3</td>
<td>39.9</td>
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<tr>
<td>ACR50 (%)</td>
<td>19.9</td>
<td>25.1</td>
<td>7.5</td>
<td>19.9</td>
<td>25.1</td>
<td>7.5</td>
</tr>
<tr>
<td>CDAI&lt;28%</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
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<tr>
<td>SDAI&lt;3.3%</td>
<td>34.5</td>
<td>41.2</td>
<td>28.8</td>
<td>34.5</td>
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<td>28.8</td>
</tr>
<tr>
<td>DAS28&lt;2.6%</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
<td>32.4</td>
<td>40.4</td>
<td>22.9</td>
</tr>
</tbody>
</table>

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Patients who did not fail any of the six algorithm criteria; biologic dose escalation, body mass index (BMI) were conducted. Divided by the percentage of patients categorized as effectively treated. The cost per effectively treated patient was calculated using annual medication and administration cost (DMARDs) and cost per effectively treated patient.

In lieu of clinical measures was validated using data from the Veteran’s patients with positive rheumatoid factor, positive anti-cyclic citrullinated peptide antibodies (aCCP), and BMI ≥30, but the differences were not statistically significant.

Conclusion: In US veterans, the percentage of patients categorized as effectively treated using the algorithm was highest for ADA (33%) and ETN (32%) and the cost per effectively treated patient was lowest for ETN ($39.4k) and ADA ($41.5k). Male gender was associated with higher annual drug cost but lower cost per effectively treated patient.

Table 2. Incidence rates (95% CI) of safety events in Ph 3 studies

<table>
<thead>
<tr>
<th>Safety Event</th>
<th>Tofacitinib</th>
<th>PBO (100 mg BI D)</th>
<th>PBO (40 mg BI D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>2.4  (2.2–2.6)</td>
<td>1.6  (1.4–1.9)</td>
<td>1.0  (0.8–1.2)</td>
</tr>
<tr>
<td>PBO (100 mg BI D)</td>
<td>1.5  (1.3–1.7)</td>
<td>0.8  (0.6–1.0)</td>
<td>0.5  (0.4–0.7)</td>
</tr>
<tr>
<td>PBO (40 mg BI D)</td>
<td>0.9  (0.7–1.2)</td>
<td>0.5  (0.4–0.7)</td>
<td>0.3  (0.3–0.6)</td>
</tr>
</tbody>
</table>

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Estimation of Cost per Effectively Treated Patients with Biologic Disease Modifying Anti-Rheumatic Drugs in US Veterans with Rheumatoid Arthritis, Grant W. Cannon, Chia-Chen Teng 1, Tao He 2, Jianwei Leng 3, Chao-Chin Lu 1, Derek Tang 1, Neel Shah 1, David J. Harrison 1 and Brian Sauer 1. Salt Lake City VA and University of Utah, Salt Lake City, UT. 2. Salt Lake City VA and University of Utah, Salt Lake City, UT, 3. Amgen Inc., Thousand Oaks, CA.

**Background:** An algorithm based on administrative claims data (in lieu of clinical measures) was validated using data from the Veteran’s Affairs (VA) Rheumatoid Arthritis (RA) Registry (VARA). It can be used to evaluate effectiveness of biologic disease modifying anti-rheumatic drugs (DMARDs) and cost per effectively treated patient.

**Methods:** National VA pharmacy and administrative claims for US veterans initiating biologics (abatacept (ABA) (intravenously [IV]), adalimumab (ADA), etanercept (ETN), infliximab (INF), or rituximab (RIT)) from Jan 1, 2008 to Jan 1, 2011 were evaluated. Patients were included if they newly initiated biologic treatment ≥365 days after VA enrollment and were followed for 1 year. Only biologics with ≥100 patients were evaluated.

Clinical effectiveness was estimated using an algorithm based on claims data. Patients who did not fail any of the six algorithm criteria: biologic dose escalation, switching biologics, adding a new non-biologic DMARD, receiving >1 intra-articular glucocorticoid injection, increasing glucocorticoid dose, or low treatment compliance (<80%) were categorized as effectively treated. Cost per effectively treated patient was calculated using annual medication and administration cost divided by the percentage of patients categorized as effectively treated.

Subgroup analyses stratified by age, smoking status, serologic status, and body mass index (BMI) were conducted.

**Results:** A total of 4,696 patients (mean age 61 years, 87% male) met all inclusion and exclusion criteria. Demographic characteristics were similar across groups. The percentage of patients categorized as effectively treated ranged from 25% to 33% and was higher for self-injected than IV biologics. Annual cost was higher for INF and RIT compared to ABA, ADA, and ETN.

Outcomes were similar across all subgroups other than gender. Men had higher drug cost, but a higher percentage were categorized as effectively treated and the cost per effectively treated patient was lower, ($40.7k vs. $57.5k). Cost per effectively treated patient was lower for current non-smokers, patients with positive rheumatoid factor, positive anti-cyclic citrullinated peptide antibodies (aCCP), and BMI ≥30, but the differences were not statistically significant.

**Conclusion:** In US veterans, the percentage of patients categorized as effectively treated using the algorithm was highest for ADA (33%) and ETN (32%) and the cost per effectively treated patient was lowest for ETN ($39.4k) and ADA ($41.5k). Male gender was associated with higher annual drug cost but lower cost per effectively treated patient.

**Disclosure:** G. W. Cannon, Amgen Inc., 2; C. C. Teng, Amgen Inc., 2; T. He, Amgen Inc., 1; L. Leng, Amgen Inc., 2; C. C. Lu, Amgen Inc., 2, D. Tang, Amgen, 3, Angen, 1; N. Shah, Amgen, 3, Amgen, 1; D. J. Harrison, Amgen, 3, Amgen, 1; B. Sauer, Amgen Inc., 2.

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Discontinuation of Biologics in Patients with Rheumatoid Arthritis after Achieving Low-Activity Disease Status. Moeko Ochiai, Eri Sato, Eichi Tanaka, Etsuke Inoue, Ayako Nakajima, Shigeki Morohara, Atsuo
Background/Purpose: Several clinical trials have reported bio-free remission or discontinuation of biologic DMARDs; however, these findings have not been confirmed in a real-world setting. The aim of this study is to evaluate the discontinuation of biologics after achieving low -activity disease status among patients with rheumatoid arthritis (RA) undergoing treatment in daily practice.

Methods: Among 1,775 patients (infliximab [IFX], 418 patients; etanercept [ETN], 690 patients; adalimumab [ADA], 267 patients; tocilizumab [TCZ], 318 patients; and abatacept [ABT], 82 patients) who had been treated with biologics in our clinic between 2003 and 2012, we extracted data on 43 patients with RA (IFX, 26 patients; ETN, 9 patients; ADA, 4 patients; TCZ, 2 patients; and ABT, 2 patients) who discontinued biologics since their disease activity was well controlled. In these patients, DAS28 scores were < 3.2 at the time of biologics discontinuation. Those 43 patients were divided into two groups (bio-free or bio-reuse) on the basis of biologic usage 1 year after discontinuation. Those 43 patients were also divided into bio-free success and bio-free failure groups on the basis of disease activity (DAS28 ≤ 3.2 or DAS28 ≥ 3.2, respectively) 1 year after discontinuation. The clinical features of the patients at the time of initiation and discontinuation of biologics were compared between the bio-free and bio-reuse groups and between the bio-free success and bio-free failure groups.

Results: The percentages of patients who discontinued biologics due to well-controlled disease activity and in the bio-free success group among biologics users in our clinic were 2.4% (43/1775) and 1.5% (25/1775), respectively. Of patients in the bio-free success group, 92.9% achieved low disease activity at the 48th week, which was a significantly higher rate than that for those in the MTX-monotherapy and MTX-LD-TAC add-on groups (65.4% and 66.7%, respectively; p < 0.01). The achievement rates for good response according to the DAS28-based European League of Associations for Rheumatology response and Boolean-based remission criteria were also significantly higher in the bio-free success group as compared to those in the MTX-monotherapy group. Furthermore, the prednisone dose was significantly lower in the simultaneous combination group than in the bio-free success group at the 48th week. No significant difference in the incidence of adverse events was observed between the groups. No serious adverse event was observed during the study period.

Conclusion: This study demonstrates the efficacy and safety of induction therapy with simultaneous administration of MTX and LD-TAC for RA. Large-scale prospective cohort studies are required for a more precise understanding of the treatment.

Disclosure: T. Nakamishi, None; H. Horikoshi, None; K. Takaishi, None; K. Tongu, None; J. Nishioka, None; F. Kimura, None; Y. Nishioka, None; K. Itoh, None.

Efficacy and Safety Study of a Sequential Therapy of Tocilizumab and, If Inadequately Responded to Tocilizumab, Followed By Rituximab in Patients with Rheumatoid Arthritis and Inadequate Response to Traditional Disease Modifying Anti-Rheumatic Drugs

Background/Purpose: The MIRAI study evaluated a sequential exposure to 2 defined biologics under rigorous study conditions within a homogeneous population of biological naïve patients (pts) with moderate/severe active RA who inadequately responded to traditional DMARDs. This study investigated the early response to the IL-6 inhibitor tocilizumab (TCZ); non-responders to TCZ subsequently received 1 cycle of rituximab (RTX; anti-CD20 therapy).

Methods: We report the results of the final analysis (first-pat-in: MAR-2011; last-pat-out: FEB-2014) of MIRAI (NCT01332994), a German, multicenter, two-arm, open-label, phase-III study. All pts received 4 TCZ infusions (8 mg/kg, q4w; 1st treatment period) until week 16. Primary responders (ΔDAS28 >1.2 or DAS28 ≥2.6 and ≤3.2) received further 4 TCZ infusions (8 mg/kg, q4w); non-responders (ΔDAS28 ≥1.2 and DAS28 >3.2) received subsequent RTX treatment (1g each at weeks 16 and 18). All pts with a 2nd treatment period (TCZ or RTX) completed study at week 32. Primary endpoint: pts in remission (DAS28 ≤2.6) at week 16 (expected 45%); secondary endpoints: DAS28<3.2 response at week 32, patient-reported outcomes, B-cells, adverse events (AE).

Results: 519 pts (ITT-Main/Safety; mean age: 56 years, females 67.8%) received TCZ in the 1st treatment period. 504 pts received concomitant DMARDs (mosty MTX, 365 pts). At week 8, a clinically relevant DAS28

Traditional Disease Modifying Anti-Rheumatic Drugs

Efficacy and Safety Study of a Sequential Therapy of Tocilizumab and, If Inadequately Responded to Tocilizumab, Followed By Rituximab in Patients with Rheumatoid Arthritis and Inadequate Response to Traditional Disease Modifying Anti-Rheumatic Drugs

Background/Purpose: The MIRAI study evaluated a sequential exposure to 2 defined biologics under rigorous study conditions within a homogeneous population of biological naïve patients (pts) with moderate/severe active RA who inadequately responded to traditional DMARDs. This study investigated the early response to the IL-6 inhibitor tocilizumab (TCZ); non-responders to TCZ subsequently received 1 cycle of rituximab (RTX; anti-CD20 therapy).

Methods: We report the results of the final analysis (first-pat-in: MAR-2011; last-pat-out: FEB-2014) of MIRAI (NCT01332994), a German, multicenter, two-arm, open-label, phase-III study. All pts received 4 TCZ infusions (8 mg/kg, q4w; 1st treatment period) until week 16. Primary responders (ΔDAS28 >1.2 or DAS28 ≥2.6 and ≤3.2) received further 4 TCZ infusions (8 mg/kg, q4w); non-responders (ΔDAS28 ≥1.2 and DAS28 >3.2) received subsequent RTX treatment (1g each at weeks 16 and 18). All pts with a 2nd treatment period (TCZ or RTX) completed study at week 32. Primary endpoint: pts in remission (DAS28 ≤2.6) at week 16 (expected 45%); secondary endpoints: DAS28<3.2 response at week 32, patient-reported outcomes, B-cells, adverse events (AE).

Results: 519 pts (ITT-Main/Safety; mean age: 56 years, females 67.8%) received TCZ in the 1st treatment period. 504 pts received concomitant DMARDs (mostly MTX, 365 pts). At week 8, a clinically relevant DAS28

Sunday, November 16
**Disclosure:** T. Dörner, Roche Pharmaceuticals, Chugai, 5, Roche Pharmaceuticals, Chugai, H. P. Tony, Roche Pharmaceuticals, 5; G. Burmester, Roche Pharmaceuticals, Abbott, Pfizer, UCB, Merck Sharp and Dohme, Bristol-Myers Squibb, 2, Roche Pharmaceuticals, Chugai, Pfizer, UCB, Bristol-Myers Squibb, 5, Roche Pharmaceuticals, Pfizer, Merck Sharp and Dohme, Abbott, Bristol-Myers Squibb, 8; H. Schulze-Koops, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8; J. Kaufmann, None; P. Kästner, None; H. Kellner, None; R. Kurthen, None; S. Wagner, None, M. A. Peters, Roche Pharmaceuticals, 3; C. Ibing-Konert, Roche Pharmaceuticals, Chugai Pharma, 5.

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**Patient Experience with Initiation of SQ and Oral MTX.** Jeffrey R. Davis,1 David Mackey,1 Noam Gerber,2 Aseem Bharat,3 Lang Chen,4 Fenglong Xie4, Ben Nowell2, Kenneth G. Saag5 and Seth Ginsberg6.

1University of Alabama at Birmingham, Birmingham, AL, 2CreakyJoints/Global Healthy Living Foundation, Upper Myrtle, NY, 3The University of Alabama at Birmingham, Birmingham, AL.

**Background/Purpose:** Methotrexate is the anchor drug used for the treatment of rheumatoid arthritis (RA). Despite its prominent position in RA therapeutics, its real-world effectiveness may be influenced by a relative lack of tolerability or other side effects that physicians may not be aware of that are bothersome to patients.

**Methods:** We conducted a prospective, compensated ($25), online survey among RA patients who were members of CreakyJoints, a large arthritis patient community. Eligible participants must have recently initiated a new biological, SQ-MTX, or oral MTX in the last 12 months and were uniquely assigned to one of these 3 exposure cohorts. Patients eligible for more than 1 cohort were assigned in the hierarchy above. Results were stratified by exposure cohort: SQ-MTX, oral MTX, and biologic. Descriptive statistics were used to compare patient-reported side effects and tolerability related to MTX use, comparing SQ vs. oral formulations and referent to biologic initiation. Recruitment is still ongoing to an expected sample size of 350 pts and results are reported through June 5th, 2014.

**Results:** A total of 783 patients were screened for the survey, and 346 were eligible. Of these, 287 (83.0%) completed the survey, distributed to the biologic (n=175, including 85 initiating SQ biologics), SQ-MTX (n=33), and oral MTX (n=79). Demographics were similar across treatment arms; overall, mean (SD) age was 47.91 (13.01) years, 90.2% women. Commonly-reported side effects were included in the table and showed differences between exposure groups in diarrhea, nausea, fatigue, and other adverse events. Pain initiating SQ biologics compared to SQ MTX reported greater pain, particularly with SQ etanercept and adalimumab compared to SQ MTX. The mean pain score (0–10 scale) for patients on SQ MTX was 2.18, lower than mean score for etanercept (4.21, p=0.002) and adalimumab (4.43, p=0.0001). Patients reported a monthly co-payment of $0 with the following monthly co-payments between $0 and $25: oral MTX – 61%, SQ MTX - 9%, and biologics (n=175, including 85 initiating SQ biologics), SQ MTX (n=33), and oral MTX (n=79). Demographics were similar across treatment arms; overall, mean (SD) age was 47.91 (13.01) years, 90.2% women. Commonly-reported side effects were included in the table and showed differences between exposure groups in diarrhea, nausea, fatigue, and other adverse events. Pain initiating SQ biologics compared to SQ MTX reported greater pain, particularly with SQ etanercept and adalimumab compared to SQ MTX. The mean pain score (0–10 scale) for patients on SQ MTX was 2.18, lower than mean score for etanercept (4.21, p=0.002) and adalimumab (4.43, p=0.0001). Patients reported a monthly co-payment of $0 with the following frequencies: oral MTX – 13%, SQ MTX – 0%, and biologic users - 23%; and monthly co-payments between $0 and $25: oral MTX – 61%, SQ MTX – 44%, and biologics - 30%.

**Conclusion:** Results: from this real-world RA patient cohort suggest that oral MTX is accompanied by many patient-reported side effects and tolerability problems that may be under-recognized by physicians. These may impact both treatment satisfaction and medication adherence that adding or switching to biologics or SQ MTX may attenuate.

**Table:** Patient Reported Side Effects and Tolerability Associated with use of Biologics and MTX
Background/Purpose: Adherence and persistence to treatment are a cornerstone of treatment success in chronic diseases such as rheumatoid arthritis (RA). The purpose of this study was to describe biologic treatment discontinuation and assess the predictors of discontinuation in RA patients followed at a Canadian clinic.

Methods: In this prospective cohort study, adult patients included in the RHUMADATA computerized database with a diagnosis of RA and treated with at least one biologic agent since 2003 were selected. The RHUMADATA database includes clinical, laboratory and socioeconomic information of patients with rheumatic diseases followed at the Institut de Rhumatologie de Montréal, a rheumatology clinic in Montreal (Quebec, Canada). Patients were followed for three years after therapy initiation or until treatment discontinuation. Biologic therapies considered include abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and anakinra. Treatment discontinuation was measured using pharmacy records. Time to discontinuation and predictors of treatment discontinuation were explored using Cox proportional hazards models.

Results: A total of 623 eligible patients were treated with at least one biologic. The average age was 53.2 years (SD = 12.4), 77% were women and patients had been diagnosed for an average of 7.7 years. The average time on treatment for the first biologic agent was 1.7 years (SD = 2.1). In all, 233 (37%), 326 (52%), 405 (65%), and 438 (70%) patients had stopped their first biologic treatment after 6, 12, 24, and 36 months, respectively. In time-to-event analyses (Cox proportional hazard models), type of work [part time vs. full time; hazard ratio (HR): 1.57; 95% confidence interval (CI): 1.05–2.34] and income [$20,000 to $40,000 vs. less than $20,000 (HR: 1.35; 1.01–1.80) and $80,000 to $100,000 vs. less than $20,000 (HR: 2.16; 1.23–3.80)] were significantly associated with biologic discontinuation over the complete treatment duration. The number of disease-modifying antirheumatic drugs (DMARDs) used (HR: 0.89; 0.80–0.99) and the use of methotrexate (yes vs. no; HR: 0.80; 0.64–0.99) were associated with a reduced risk of biologic discontinuation.

Conclusion: In this real-life Canadian study, high biologic discontinuation rates were observed over three years. This study also suggests that many clinical and socioeconomic variables are predictors of biologic therapy discontinuation in RA patients. These results may help design interventions aiming at improving treatment adherence in RA, a chronic and progressive disease.

Disclosure: D. Choquette, Notre-Dame Hospital, Quebec, Canada, 3, AbbVie, 5, Amgen, 5, Celgene, 5, BMS Canada, 5, Janssen Pharmaceuticals, Product, L.P., 5, Pfizer Inc, 5; L. Coupal, None; M. C. Laliberte, AbbVie, 3, AbbVie, 1; O. Desjardins, AbbVie, 3, AbbVie, 1, BMS, 1.

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Prediction of Successful Dose Reduction or Discontinuation of Adalimumab or Etanercept Using Serum Drug Levels and Antidrug Antibody Measurement. Noortje van Herwaarden1, Chantal Bouman1, Aakje van der Maas2, Ronald F. van Vollenhoven3, Johannes W.J. Bijlsma4, Frank HJ, van den Hoogen5, Allons A. den Broed6 and Bart van den Bemt7. 1Institut de rhumatologie de Montréal (IRM), Montréal, QC; 2AbBvie, St. Laurent, QC.

Background/Purpose: Dose reduction and discontinuation of TNF inhibitors (TNFi) is feasible in many rheumatoid arthritis (RA) patients, but leads to (temporary) worsening of disease activity in some patients. We evaluated the predictive value of baseline adalimumab and etanercept serum levels and antidrug antibodies for successful dose reduction or discontinuation in patients with RA and low disease activity.

Methods: Patients with RA and a stable low disease activity, included in the intervention arm of an 18 months randomised controlled trial (DRESS study) assessing non-inferiority of a dose reduction strategy of adalimumab or etanercept compared to usual care were analysed. Dose was reduced by stepwise increasing the interval between injections every 3 months until flare or discontinuation of the TNFi. Serum levels of adalimumab or etanercept and antidrug antibodies were measured before start of dose reduction. Receiver-operator-curves (ROC) and optimal cut-off drug serum levels were calculated. A sensitivity analyses was done for timing of serum sampling (days after last injection), per tertile. Sensitivity/specificity of anti-drug antibodies were calculated for successful discontinuation and for successful dose reduction separately.

Results: Data was available for 118 of 121 included patients. Mean DAS28-CRP baseline was 2.2 (SD 0.6). At 18 months follow up TNFi could be stopped in 19% (95%CI 12–27) of patients, the interval increased in 44% (95%CI 35–53) and in 37% (95%CI 29–47) of patients no dose reduction was possible. Mean drug levels and anti-drug antibodies were not different per subgroup (table 1). ROC analyses showed no predictive value of drug levels for successful dose reduction or discontinuation (figure 1). Sensitivity analyses showed no influence of serum sample timing, with the exception of adalimumab trough level (last tertile) predicting successful dose reduction (AUC 0.86, 95% CI 0.58–1.00, optimal cut-off 7.8 µg/ml).

Anti-adalimumab antibodies were detected in 4 patients (10%), and were not predictive for successful discontinuation. No anti-etanercept antibodies were detected.

Conclusion: Adalimumab and etanercept serum levels and antidrug antibodies have no predictive value for successful dose reduction or discontinuation in RA patients with low disease activity, with a possible exception of adalimumab trough levels for predicting successful dose reduction.

References:

Figure 1. Serum level predicting successful discontinuation or dose reduction

Table 1 Mean drug levels and anti-drug antibodies at baseline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome at 18 months</th>
<th>Mean drug level at baseline µg/ml (SD)</th>
<th>Anti-drug antibodies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: adalimumab</td>
<td>Stopped (n = 11)</td>
<td>8.5 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dose reduced (n = 15)</td>
<td>8.1 (5.2)</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>No dose reduction possible (n = 16)</td>
<td>6.8 (4.1)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>B: etanercept</td>
<td>Stopped (n = 11)</td>
<td>2.7 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dose reduced (n = 37)</td>
<td>2.0 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No dose reduction possible (n = 28)</td>
<td>2.4 (1.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Disclosure: N. van Herwaarden, None; C. Bouman, None; A. van der Maas, Roche, MSD, 9; R. F. van Vollenhoven, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 5; J. W. J. Bijlsma, AbbVie, Roche, Pfizer, MSD, UCB, BMS, 2, AbbVie, Roche, Pfizer, MSD, UCB, BMS, Jansen, 5; F. H. J. van den Hoogen, None; A. A. den Broed, None; B. van den Bemt, Roche Pharmaceuticals, Pfizer, 2, Roche, Pfizer, MSD Abbvie, 5.
Bio-naïve Patients with Rheumatoid Arthritis Benefit More from Abatacept Treatment Compared to Those Who Are Inadequate Responders to Other Biologics – Results from the National Swedish Rheumatology Quality Register. 

Background/Purpose: Abatacept is a biological anti-rheumatic drug used in Rheumatoid Arthritis (RA). Data on patient characteristics, diagnosis, previous treatment and outcome of abatacept have been collected within the Swedish Rheumatology Quality register (SRQ) which comprises the Swedish Biologics Register (ARTIS; Arthritis Treatment In Sweden), since the drug was first available in 2006. The objective of this study was to evaluate drug survival probability and short term outcome of abatacept in clinical practice for patients with RA, using a national register.

Methods: Observational data from the SRQ were collected for the period from April 1st, 2006 to May 20, 2014. Analyses were stratified by previous exposure to biologics, regardless of the cause of discontinuation. Kaplan-Meier survival analysis with right censoring and log-rank test of equality across strata were performed and Šidák multiple-comparison adjustments applied. EULAR good or moderate response rates at 6 and 12 months were calculated, and corrected for survival on drug using the Lundex method (proportion still on drug x proportion responding(1)).

Results: A total of 1291 patients with RA (1023 females, 79.2%) started abatacept treatment between April 2006 and May 2014. The mean age at start of abatacept was 59.2 years, and the median duration of RA was 11.2 years. Abatacept was prescribed as the first biologic treatment in 200 cases (15.5 %), after inadequate response (IR) to one other biologic in 349 cases (27.0 %) and after IR to ≥ 2 other biologics in 742 cases (57.5 %). The baseline disease activity was slightly lower in bio-naïve patients starting abatacept compared to those who had received one or ≥2 previous biologics (mean DAS28 5.01, 5.16 and 6.17 respectively). The bio-naïve group treated with abatacept were older at baseline (mean 62.0 vs 60.6 and 57.8 years, respectively), and less likely to be female (71 % vs. 80 % and 81 %). Survival on drug was significantly longer in patients treated with abatacept as the first biological compared to those previously exposed to 1 biological (p=0.002) or ≥ 2 biologics (p=0.002). The corresponding estimated survival rates were 91%/77%/78% at 6 months and 75%/60%/62% at 12 months. There was no significant difference in drug survival between those with IR to one or vs two biologics (p=0.84). At 12 months, among those still on treatment, a EULAR good or moderate response was achieved in 74 % of patients in the bio-naïve subset compared to 62 % among those with previous IR to one biological, and 57 % among those exposed to ≥ 2 biologics. The Lundex corrected EULAR good/moderate responses were 67%/48%/45% at 6 months and 47%/41%/37% at 12 months.

Conclusion: In this observational study of RA patients treated with abatacept in clinical practice, a greater proportion of bio-naïve patients had a significant clinical response and remained on treatment compared to those with a previous IR to other biologic drugs. These results are compatible with reports from clinical trials, and indicate that a substantial number of RA patients treated with abatacept as their first biological in clinical practice have a favorable outcome.

Background/Purpose: Tocilizumab, as an intra-venous agent, has been approved for rheumatoid arthritis (RA) in Canada in April 30th, 2010. It was the sixth approved agent after adalimumab, etanercept, abatacept, infliximab and rituximab. It has been demonstrated effective in the treatment of RA either in monotherapy or combo therapy after non-biologic or biologic DMARDS [1–3]. The goal of this analysis is to describe its effectiveness in patients with RA failing a first anti-TNF DMARDS and to compare its retention rate versus adalimumab, etanercept and infliximab in the same clinical situation.

Methods: All patients with RA having failed a first anti-TNF agents and subsequently exposed to tocilizumab after the 1st of January 2005 were extracted from the Rhumadata® database. 4 cohorts were created according to the time tocilizumab or the subsequent anti-TNF agents was introduced: One cohort of patients starting tocilizumab and 3 other cohorts starting either adalimumab, Etanercept or infliximab. Demographics and baseline characteristics including age, gender, disease duration, Rheumatoid factor and anti-CCP antibodies, CRP and ESR, previous failed treatment number, DAS 28 ESR and CDAI, HAQ-DI were included for each cohorts.

Results: The data from 259 patients prescribed either tocilizumab (53=20%), adalimumab (97=37%), etanercept (82=33%) or infliximab (27=10%) as a second biologic agent were extracted from the Rhumadata® registry and clinical database. Mosts subjects were female (75%) and the average age of cohort subjects was 58.2 (SD=14.3). Mean CRP and ESR were respectively 17.0 (SD=29.5) mg per L and 26.6 (SD=24.1) mm per hour. No clinically significant differences at baseline were observed between groups. The four year retention rates of tocilizumab, adalimumab, etanercept and infliximab as second line biologic agents were 44.3%, 27.2%, 37.1% and 34.0% respectively. Kaplan-Meier survival analysis revealed significant differences in the drug retention rates (logrank p=0.0249).

Conclusion: In RA patient having failed their first anti-TNF agent, tocilizumab, an II-6 inhibitor, could be a more valuable alternative than cycling to a second anti-TNF agent.

References:

503 Does a Higher Dose of Folic Acid Reduce Adverse Effects of Methotrexate in Rheumatoid Arthritis? a Randomized Controlled Trial. Varun Dhir1, Amit Sandhu1, Jasbinder Kaur2, Nidhi Gupta1, Prabhdeep Kaur1, Ankita Sood1, Aman Sharma1 and Shefali Sharma1.

Background/Purpose: There is good evidence that folic acid 5–10mg per week leads to reduction in methotrexate (MTX) toxicity in rheumatoid arthritis (RA). However, this data comes from old studies using a lower dose of MTX. There is limited data of folic acid doses with contemporary usage of MTX, i.e., when MTX is started at a high dose and rapidly escalated. We wondered whether a higher dose of folic acid i.e. 30mg per week (approx. 1:1 MTX) would be better, in this context, in reducing toxicity than 10 mg per week.

Methods: This was a single-center double-blind randomized controlled trial of 24 weeks duration. Included patients 18–75 years of age, who fulfilled 1987 ACR criteria for RA and had active disease (DAS28(3)>3.2). MTX was started at 15mg/week and escalated by 8 weeks to 25 mg/week. At 16 weeks, a new DMARD could be added on the physician’s discretion. Folic acid was given at a dose of 10 mg (FA-10) or 30 mg per week (FA-30), as 6 identical tablets for every day of the week except the day of taking MTX. Patients were seen every 8 weeks. Co-primary endpoints were incidence of toxicity and change in disease activity by 24 weeks. Toxicity included undesirable symptoms (evaluated by questionnaire) and laboratory abnormalities (cytopenias: WBC<4000 or platelet<100x10^9/l or transaminis:

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Abatacept after Rituximab in Rheumatoid Arthritis, a Pan-European Collaboration of RA Registries. Axel Finkh1, David Neto2, M. Victoria Hernández1, Florencia Iannone4, Elisabeth Lie5, Helena Canhao6, K. Pavelka7, Carla Turesson8, Xavier Mariette9, Merete Lund Hetland10 and Jacques Gottenberg11. 1Geneva University Hospital, Geneva, Switzerland, 2University of Geneva, Geneva, Switzerland, 3Hospital Clinic of Barcelona, Barcelona, Spain, 4Reumatologa Università di Policlinico di Bari, Bari, Italy, 5Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 6Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, 7Institute of Rheumatology, Prague, Czech Republic, 8Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, 9Université Paris-Sud, Le Kremlin Bicêtre, France, 10DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, 11Strasbourg University Hospital, Strasbourg, France.

Background/Purpose: Some observations have suggested that the effectiveness of abatacept (ABA) may be decreased in rheumatoid arthritis (RA) patients (pts) who previously failed rituximab (RTX). (1) The objective of this study was to compare the effectiveness of ABA started after prior inadequate response (IR) to RTX (RTX-IR) versus prior IR to anti-TNF agents only (aTNF-IR) in routine care.

Methods: This is a pooled observational database analysis of 9 prospective registries of RA pts (Czech Republic, Denmark, France, Italy, Norway, Portugal, Spain, Sweden, Switzerland). We included all RA pts treated with ABA with information on prior use of specific bDMARDs and who experienced either a RTX-IR or a aTNF-IR. The primary outcome was drug retention of ABA, defined as the time between first and last administration plus one dispensation interval, and analyzed using a Cox proportional hazards model. A secondary endpoint was EULAR good or moderate response rate at one year, estimated by longitudinal interpolation and corrected for drug retention (Lundex2). All analyses were adjusted for potential confounders, such as calendar year, demographics, country, number of prior bDMARDs and other disease characteristics.

Results: We identified 1994 pts initiating ABA with 3105 pt-years of follow-up. Of these, 486 pts (24%) received ABA after failing RTX and 1508 pts (76%) after failing > 1aTNFs, but never RTX. RTX-IR pts had significantly higher disease activity at baseline, longer disease duration, more functional disability, more prior bDMARDs and used more concomitant glucocorticoids than had aTNF-IR pts. (Table)

Table 1: Frequency of MTX related toxicity in patients who had at least one follow up visit

<table>
<thead>
<tr>
<th>ABA (N=486)</th>
<th>aTNF-IR (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics*</td>
<td></td>
</tr>
<tr>
<td>Age, (yrs)</td>
<td>57</td>
</tr>
<tr>
<td>Female, (%)</td>
<td>84</td>
</tr>
<tr>
<td>DSAS8</td>
<td>5.2</td>
</tr>
<tr>
<td>Dis. Duration (yrs)</td>
<td>13.9</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.4</td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>24.8</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>34</td>
</tr>
<tr>
<td>RF (%)</td>
<td>70</td>
</tr>
<tr>
<td>N° prior bDMARDs, med (IQR)</td>
<td>3(2–4)</td>
</tr>
<tr>
<td>Oral Glucocorticoid use, (%)</td>
<td>74</td>
</tr>
</tbody>
</table>

* Values are the means, unless stated otherwise.

Disclosure: V. Dhir, None; A. Sandhu, None; J. Kaur, None; N. Gupta, None; P. Kaur, None; A. Sood, None; A. Sharma, None; S. Sharma, None.

The crude median retention time of ABA after RTX-IR was 1.65 y (IQR: 1.42–2.13) compared to 2.05 y (IQR: 1.87–2.27) after aTNF-IR (p = 0.11). After adjustment for potential confounders no difference between ABA retention rates was found (Hazard Ratio (HR) RTX-IR vs aTNF-IR: 1.00 (95%CI: 0.83 – 1.21)). Similar results were found when examining only ABA treatment discontinuations due to ineffectiveness (HR: 1.04 (95%CI: 0.84 – 1.29)). However, response rates at one year were slightly lower in pts with RTX-IR compared to pts with aTNF-IR (73% EULAR good or moderate response versus 83% in aTNF-IR (p=0.001); Lundex-adjusted EULAR good or moderate response 45% versus 56% in aTNF-IR, p=0.003, respectively).

Conclusion: The results of this large pooled RA population of inadequate responders to bDMARDs suggest that the slightly decreased effectiveness of ABA in patients having experienced a RTX-IR may be largely driven by a selection of pts with more treatment refractory disease.

References:

Disclosure: A. Finkh, BMS, 2. Roche Pharmaceuticals, 8, Abbvie, 8, Pfizer Inc, 8, MSD, 5; D. Neto, BMS, 5; M. V. Hernández, None; F. Iannone, None; E. Lie, Abbvie, 5, UCB, 5, Bristol-Myers Squibb, 5, Hospina, 5, Pfizer Inc, 5, Abbvie, 8, UCB, 8, M. Canhao, None; K. Pavelka, MSD, Abbvie, Pfizer, UCB, Roche, Aemgen, Merck, BMS, 5; C. Turesson, Unrestricted research grants from Abbvie, Pfizer and Roche, 2, Advisory Boards: Bristol-Myers Squibb, MSD, Pfizer, Roche, 5, X. Mariette, None; M. L. Hetland, None; J. Gottenberg, None.

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A Structured Approach for Comparative Benefit-Risk Assessment of Rituximab for the Treatment of Rheumatoid Arthritis. A. John1, George Quartery1, Patricia B. Lelancgo2, Nicole Mairesse2, Michael Schulze1, Ashwinini Shewade1, Carol Chung3 and Dominic Borisie1. 1Genentech, Inc, South San Francisco, CA, 2Roche Products Ltd, Welwyn Garden City, United Kingdom, 3Hoffmann-La Roche Ltd, Basel, Switzerland.

Background/Purpose: Rituximab in combination with methotrexate (MTX) is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have an inadequate response to tumor necrosis factor therapies (TNF-IR). A structured systematic assessment of a drug’s benefit-risk profile is useful to inform decisions at each developmental milestone, and could meaningfully inform multiple stakeholders, physicians, patients, payors and researchers on the trade-offs between benefits and risks during the lifecycle of a drug product. The objective of this post-hoc analysis...
was to apply a structured descriptive approach to compare the benefit-risk profile of rituximab from the REFLEX 24-week placebo (PBO)-controlled trial and to produce a graphical representation of this profile in TNF-IR patients with RA.¹

Methods: Presentations of data were based on the Benefit Risk Assessment Tool Framework developed for pharmaceutical benefit-risk decision-making in drug development and post-approval settings.²,³ Key benefits and risks of rituximab were identified and organized in a hierarchical manner to construct a ‘value tree’ as a basis for potential treatment benefits and risks. Absolute differences in efficacy outcome measures and safety event rates between (rituximab + MTX) and (PBO + MTX) treated patients were calculated to summarize key benefit-risk metrics and then presented graphically in a descriptive manner.

Results: Key benefits of rituximab treatment in TNF-IR patients identified included measures of clinical response (ACR and EULAR response and DAS28-ESR) and patient-oriented outcomes (Health Assessment Questionnaire Disability Index [HAQ-DI]). Safety assessments included rates of overall adverse events (AEs), serious AEs, all infections and serious infections. Mean (95% CI) efficacy differences and adverse event rate differences between the rituximab and PBO arms of the 24-week trial were calculated and displayed in the Figure. Overall, patients receiving rituximab treatment demonstrated meaningful clinical and statistically significant improvement compared with PBO in ACR20/50/70 response rates, EULAR response rates, DAS28-ESR and HAQ-DI, with no meaningful differences in safety events including serious AEs and infections.¹

Conclusion: A graphical representation of key benefits and risks was generated to present the positive benefit-risk profile of rituximab in TNF-IR patients with RA. Future applications of this structured approach could include interpretation of the benefit-risk profile of longer term outcomes and of subpopulations of patients with RA receiving rituximab or a similar structured assessment of other drugs in a consistent manner.

References:

506
Trial of Six Weeks Interval of Tocilizumab Infusion in Patients with Rheumatoid Arthritis. Osamu Saiki, Hiroshi Uda and Koji Shigematsu. Higashiosaka City General Hospital, Higashiosaka, Japan.

Background/Purpose: For active rheumatoid arthritis (RA) patients with inadequate response to synthetic DMARDs, biologic agents, such as TNF inhibitor and IL-6 receptor inhibitor, are indicated. However, all biologics are very expensive, and therefore all patients with high disease activities always can not receive biologics. Indeed, the interval of administration is fixed in most of biologics, but the interval is flexible in some biologics such as etanercept and infliximab. Tocilizumab (TCZ) is one of useful biologics, and the interval of TCZ infusion is fixed for 4 weeks. In the course of treating active RA patients by TCZ with 4 weeks interval, sometimes we experienced that longer interval was also effective. In preliminary study, we found that six weeks interval was effective in these patients. The present study is carried out to clarify the efficacy of six weeks interval of TCZ infusion in the patients with active RA.

Methods: The patients who showed inadequate response to DMARDs and the patients who showed inadequate response to biologics other than TCZ and who agreed with TCZ therapy of six weeks interval were enrolled in the present study. In addition to oral medicines, the patients were infused 8mg/kg of tocilizumab in every six weeks (SIWETO study). The clinical assessments and blood tests were also carried out in every 6 weeks. To the patients who did not achieve clinical remission by 6 weeks interval of TCZ, prednisolone (PSL) and/or methotrexate were added with increasing the dose. The patients who achieved clinical remission in 12 months were estimated as responder and others were as non-responders. We followed up the patients at least for 3 years.

Results: Total of 74 patients was enrolled in the present study. Male and female were 18 and 56 respectively. Forty-four patients achieved clinical remission with 6w interval, and the rest of the patients were non-responder. To the patients who did not achieve clinical remission with 6w interval, TCZ infusion with 5w or 4w interval was carried out. Nineteen patients achieved clinical remission by 5w interval and four patients by 4w interval, respectively. The rest of 7 patients could not achieve clinical remission by TCZ infusion. In 44 patients who achieved clinical remission with 6w interval of TCZ infusion, 10 patients were treated by TCZ alone without any oral medicines for rheumatoid arthritis and kept the condition throughout the observation and the rest of patients received either or both PSL (1 to 7.5 mg) and MTX (2 to 8mg). It is generally accepted in Japanese rheumatologist that the effective dose of MTX in Japanese is lower than that in Caucasian. Severe adverse events including tuberculosis and death were not found. The frequency of other adverse events of 6w interval of TCZ was less than those of regular use (4w interval).

Conclusion: The SIWETO study provides evidence that 6w interval of TCZ infusion is also effective in active rheumatoid arthritis patients. The finding of SIWETO study is quite useful for taking care of active rheumatoid arthritis patients, especially in financial aspects. The cost of 6 weeks interval of TCZ became two thirds of that of 4 weeks regular use.

Disclosure: A. John, Genentech, Inc, 3; G. Quayle, Genentech, Inc, 3; P. B. Lehane, Roche Products Ltd, 3; N. Maieron, F. Hoffmann-La Roche Ltd, 3; M. Schulte, F. Hoffmann-La Roche Ltd, 3; A. Shewade, Genentech, Inc, 3; C. Chung, Genentech, Inc, 3; D. Bori, Genentech, Inc, 3.

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HIGH RATE OF IMPROVEMENT IN SERUM MATRIX METALLOPROTEINASE-3 LEVELS AT 4 WEEKS PREDICT REMISSION AT 52 WEEKS IN RA PATIENTS WITH ADALIMUMAB THERAPY

Background/Purpose: Serum Matrix metalloproteinase-3 (MMP-3) is a specific inflammatory marker of the synovium in patients with rheumatoid arthritis (RA). Our aim in this study is to investigate whether serum MMP-3 is the predictor for remission in treatment for RA patients with biologics.
Methods: All RA patients (n=269) who underwent Adalimumab (ADA) treatment in the multicenter study group (Tsurumai Biologies Communication Registry; TBCR) were enrolled in this study. We analyzed 114 patients in continuation with ADA therapy for 52 weeks. We divided into 2 groups based on the improvement of serum level of MMP-3 and CRP: high rate of improvement (MMP-HR group) and low rate of improvement (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: high rate of improvement (CRP-HR group) and low rate of improvement (CRP-LR group) in serum CRP levels at 4 weeks (Table1). We also divided into 2 groups based on the serum level of MMP-3 and CRP: high value (MMP-H group) and low value (MMP-L group) in serum MMP-3 levels at 4 weeks, and: high value (CRP-H group) and low value (CRP-L group) in serum CRP levels at 4 weeks (Table2). We evaluated the rate of remission at 24, and 52 weeks in 2 groups.

Results: In patients continuing at 52 weeks, the rate of remission at 24 and 52 weeks in MMP-HR group is 56% and 60%, and MMP-LR group is 32% and 37%. The rate of remission at 24 and 52 weeks in MMP-HR group is significantly higher than in MMP-LR group (Fig.1). However, the rate of remission at 24 and 52 weeks had no significance in CRP-HR group and CRP-LR group (Fig.2). The rate of remission at 24 and 52 weeks in MMP-H group is 35% and 44%, and MMP-L group is 55% and 53%. The rate of remission at 24 weeks in MMP-L group is significantly higher than in MMP-H group (Fig.3). However, the rate of remission at 24 and 52 weeks had no significance in CRP-H group and CRP-L group (Fig.4). Moreover, the rate of remission at 24 and 52 weeks in MMP-L (L and HR) group is very high (Fig.5). In patients continuing at 52 weeks, the best cut-off rate of improvement in MMP-3 at 4 weeks for determining remission at 52 weeks was 40% (Fig.5). The estimated median decrease for 5 mg BID at Week 24 was ~35%. Cross-sectional analyses in different groups of pts showed similar median NK cell count in the LTE (141 cells/µL) compared to pre-treatment baseline (135 cells/µL). No clear association between baseline or nadir NK cell counts (predominantly collected within first 6 months of treatment) and the incidence of SIE, HZ or malignancy (Figure 2) was seen over the period of observation (median duration 1.9 years).

Conclusion: Tofacitinib treatment is associated with a dose-dependent decrease in NK cell counts. No association between baseline or nadir NK cell counts and the incidence of SIE, HZ or malignancy was observed. Long-term lymphocyte subset data are being collected in the ongoing LTE study to confirm these relationships.

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Relationship Between NK Cell Count and Important Safety Events in Rheumatoid Arthritis Patients Treated with Tofacitinib. R. van Vollenhoven1, Y. Tanaka2, R. Riese2, M. Lamba3, T. Kawabata4, T. Hirose5, S. Toyoizumi6, A. Hazra7 and S. Krishnaswami7 1The Karolinska Institute, Stockholm, Sweden, 2University of Occupational and Environmental Health, Kitakyushu, Japan, 3Pfizer Inc, Groton, CT, 4Pfizer Inc, Tokyo, Japan.

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Cytokines (e.g. interleukin [IL]-2, -4, -7, -15, -21) involved in lymphocyte development, function and homeostasis are known to signal through JAK. Objectives were to characterize changes in natural killer (NK) cell counts following tofacitinib treatment and evaluate the relationship between NK counts and rates of infection and malignancy.

Methods: Lymphocyte subset data, enumerated by flow cytometric analyses, were pooled from 3 double-blind, placebo-controlled, Phase 2 (P2) studies (two monotherapy and one background methotrexate [MTX]) in MTX inadequate responders, and from a sub-study of an ongoing long-term extension (LTE) study (study is ongoing; database not locked). RA patients (pts) received tofacitinib (1 to 30 mg twice-daily [BID]) or placebo for 6 to 24 weeks in P2 and tofacitinib 5 or 10 mg BID for 22 months (median) in LTE. 928 and 161 pts contributed NK cell data in P2 and LTE, respectively. Correlations between baseline or nadir NK cell count and serious infections (SIE), any infection that requires hospitalization for treatment or parenteral antimicrobial therapy, herpes zoster (HZ) and malignancy (excluding non-melanoma skin cancer) were assessed by sub-dividing NK cell data into deciles and calculating incidence rate (events/100 pt years) of adverse events for each decile.

Results: Following tofacitinib administration, NK cell counts decreased in a dose-dependent manner by Week 2 (Figure 1). Median NK cell counts returned to baseline 2 to 6 weeks after treatment discontinuation (dc). At the 5 mg BID dose, pts with the largest (>90th percentile) decrease in NK cell counts recovered from ~70% below baseline to ~18% by 6 weeks after treatment dc (n=4). The estimated median decrease for 5 mg BID at Week 24 was ~35%. Cross-sectional analyses in different groups of pts showed similar median NK cell count in the LTE (141 cells/µL) compared to pre-treatment baseline (135 cells/µL). No clear association between baseline or nadir NK cell counts (predominantly collected within first 6 months of treatment) and the incidence of SIE, HZ or malignancy (Figure 2) was seen over the period of observation (median duration 1.9 years).

Conclusion: Tofacitinib treatment is associated with a dose-dependent decrease in NK cell counts. No association between baseline or nadir NK cell counts and the incidence of SIE, HZ or malignancy was observed. Long-term lymphocyte subset data are being collected in the ongoing LTE study to confirm these relationships.

Disclosure: Y. Hattori. None.
Sule Apras Bilgen1 and Ihsan Ertenli1, 1Hacettepe University Faculty of Medicine, Ankara, Turkey, 2Hacettepe University, Faculty of Medicine, Ankara, Turkey, 3Hacettepe Univ.Tıp Fakultesi-Romatoloji Servis, Ankara, Turkey.

Etanercept have better drug survival than monoclonal antibodies in Rheumatoid Arthritis: Results of single center HÜR-BYO registry

Background/Purpose: In routine practice, observational registries may show retention rates of TNFi drugs in rheumatoid arthritis (RA). The objective of this study was to compare TNF inhibitors regarding the drug survival rate in RA patients.

Methods: HÜR-BYO (Hacettepe University Rheumatology Biologic Registry) is a single center biological registry since 2005. Data collected includes demographic data, switch ratio, baseline and follow-up disease activity parameters (if available). Patients with regularly follow-up status were recorded systematically. Patients with lost of follow-up searched regarding to parameters (if available). Patients with regularly follow-up status were found in 246 (37.3%) patients. Patients were divided as regularly follow-up (either first biological drugs or another biological drugs) 487 (73.9%), lost of follow-up 114 (17.3%), drug cessation 35 (5.3%), exitus 15 (2.3%) and not for the two routes of administration of abatacept. This supports clinical trials that have demonstrated similar efficacy and safety for the two lines of treatment, motives for treatment introduction, motives for treatment introduction and motives for treatment introduction. Yet, available data regarding treatment after rituximab, abatacept and tocilizumab failure is weak. The objective of this study was to compare continuation rates of second line non-anti-TNF-α treatments after a first non-anti-TNF-α failure. Methods: This retrospective multicentre study included patients treated for RA with rituximab, abatacept or tocilizumab after having received in a previous line abatacept, tocilizumab or rituximab from 2002 to 2013. Data were collected from patients’ file including baseline and final DAS28-ESR and DAS28-CRP for both lines of treatment, motives for treatment introduction and discontinuation. Follow-up of the second line of treatment was one year. The primary endpoint was the continuation rate at the end of the first year of treatment.
Results: A total of 100 patients were included. Patients had previously received an average of 2.6 (±/− 0.9) biological DMARDs. Patients were aged 55.4 (±/− 11.5) years and disease duration was 14.3 (±/− 9.4) years. In first line, 29 patients were treated with tocilizumab, 26 with abatacept, and 45 received rituximab. In second line of treatment, 49 patients were treated with abatacept, 26 with tocilizumab, and 36 received rituximab. Methotrexate was associated in 36% of cases. The first line of treatment was continued for 15.6 (±/− 14.4) months. At baseline, DAS28-ESR was 5.57 (±/− 1.19) and DAS28-CRP was 5.25 (±/− 1.15) for the first line and DAS28-ESR was 5.00 (±/− 1.41) and DAS28-CRP was 4.84 (±/− 1.22) for the second line of treatment. Treatment continuation rates at the end of the first year was 45.9% in first line and 58.6% in second line of treatment (p=0.10). In patients without Methotrexate, continuation rates at the end of the first year was 37.5% for the first line of treatment and 64.3% in the second line (p=0.009). In the first line of treatment, 66.6% of patients that interrupted their treatment for a reason of intolerance in the first year of treatment versus 15.5% in the second line of treatment.

Conclusion: After a first non-anti-TNF-α biological DMARD failure, continuation rates at one year are similar in the second line of non-anti-TNF-α treatment. Association to Methotrexate does not seem to bring any benefits in the second line of treatment.

Disclosure: T. Pascart, None; R. M. Flipo, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5; X. Deprez, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5; E. Houvenagel, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5.

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Effect and Safety of Concomitant Methotrexate and Tacrolimus on Clinical Response of Abatacept in Rheumatoid Arthritis Patients with Prior Use of Biological Dmards. Nobunori Takahashi1, Toshishia Koijima1, Yuji Hirano2, Yasuhide Kanayama2, Koji Funahashi3, and Naoki Ishiguro1.

Background/Purpose: Abatacept (ABT) is a new class of biologic agents for the treatment of rheumatoid arthritis (RA) that inhibits T cell activation by binding to CD80/86. It has been reported that ABT was less effective in the patients with previous biological DMARDs and concomitant MTX had only little enhancing effect on ABT efficacy. Tacrolimus (TAC) was approved in Japan for the treatment of RA (oral dosage of ≤ 3 mg/day). It down-regulates the synthesis of inflammatory cytokines activated by T cells mainly via inhibition of a calcineurin. In this study, we investigated whether concomitant TAC had enhancing effect on ABT efficacy in the patients with previous biological DMARDs, using data from a Japanese multicenter registry system (TBCR).

Methods: The present study included all patients who had previous biological DMARDs and were initiated intravenous ABT and prospectively observed for longer than 52 weeks at TBCR-affiliated institutes (n = 121). Demographic data and the following parameters of disease activity were collected: tender joint count (TJC) and swollen joint count (SJC), patient global assessment (VAS), ESR, and serum CRP at baseline, 4, 12, 24, and 52 weeks. We compared these clinical data between the patients treated without concomitant MTX or TAC (ABT-mono, n=42), those treated with concomitant MTX (ABT-MTX, n=56), and those treated with concomitant TAC (ABT-TAC, n=18). The last observation carried forward (LOCF) method was used in each analysis.

Results: In the baseline characteristic data, the ABT-mono group had higher pulmonary comorbidity rate (23.8%, p = 0.030) compared to the ABT-MTX (5.4%) and ABT-TAC (16.7%) group while no other clinical parameters showed significant difference including all disease activity indices such as DAS28-ESR (5.10, 5.30, and 5.30, p = 0.949). The ABT-TAC group demonstrated significantly lower 24% of DAS28 score compared to the ABT-mono group while no difference between the ABT-mono and ABT-MTX group (Left panel). The patients taking 3 mg/day dosage of TAC demonstrated apparently lower 24% of DAS28 score compared to those taking < 3 mg/day (Middle panel). Kaplan-Meier analysis demonstrated that the ABT-MTX group showed significantly higher discontinuation rate due to adverse events compared to the ABT-mono group while no difference between the ABT-TAC and ABT-mono group (Right panel).

Conclusion: We clearly demonstrated that concomitant TAC treatment had dose-dependent enhancing effect on the ABT efficacy, while there seemed to be little combinational effect of ABT and MTX. Since both ABT and TAC are the agents targeting T cells, there is concern regarding safety issue when used in combination. However, in our results, the ABT-TAC group did not show increased discontinuation due to adverse events. We would suggest that combination of ABT and TAC treatment should be helpful when we treat the patients with previous biological DMARDs history.

Disclosure: N. Takahashi, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; T. Koijima, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; Y. Hirano, Abbott Immunology Pharmaceuticals,
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Analysis of Shoulder Joint Destruction in Rheumatoid Arthritis Patients Treated with Biologics. Yukio Yonemoto, Koichi Okamura, Tetsuya Kaneko, Chisa Okura and Kenji Takagishi. Gunma University Graduate School of Medicine, Maebashi, Japan.

Background/Purpose: The assessment of joint destruction in rheumatoid arthritis (RA) patients being treated with biologics is normally mainly carried out for small joints. There are a few reports that have so far assessed joint destruction of large joints, and no reports that assess joint destruction of the shoulder joint. The aim of this study was therefore to assess the risk factors for shoulder joint destruction in RA patients being treated with biologics based on the findings of both the magnetic resonance imaging (MRI) and 18F-fluorodeoxy glucose positron emission tomography (PET).

Methods: Twenty-nine shoulders (5 male shoulders, 25 female shoulders; 16 right shoulders, 14 left shoulders) in 30 patients with RA were assessed using PET and MRI before starting biologics and then again six months later. The mean age (range) was 54 (18–72) years and the mean disease duration using PET and MRI before starting biologics and then again six months later. The mean age (range) was 54 (18–72) years and the mean disease duration was 7 (0.8–30) years. The XP findings were assessed before starting biologics and then again three years later. The CRP, ESR and MMP-3 levels, and the DAS28-ESR, DAS28-CRP, CDAI and SDAI scores were also assessed. We compared these parameters between the progression of joint destruction group (P group) and the no progression group (N group).

Results: The SUV max, the rates of synovitis and the rates of rotator cuff tear on MRI before biologics treatment were significantly higher in the P group than in the N group. The SUV max and synovitis detected by MRI after six months of MTX (±methyprednisolone) therapy remission or low disease activity (DAS28ESR<3.2) was achieved in 76%. BMI, fasting plasma glucose, insulin, triglyceride, cholesterol or urate levels remained unaltered. Conversely, HbA1c (%) decreased in a time-dependent manner from the baseline value of 5.80±0.29% to 5.55±0.31% (n=26, P=0.017) at 6 months. HbA1c (%) was reduced in 17 out of 26 patients. The decrease in HbA1c (%) was especially pronounced in patients without insulin resistance at inclusion (5.82±0.35% vs. 5.42±0.32%, P=0.013, 12 out of 14 patients). Overall, the number of patients with prediabetes was reduced from 18 to 8. HOMA-IR, HOMA-B and QUICKI remained unaltered in patients receiving MTX or MTX and methyprednisolone, indicating co-thrapy with methyprednisolone did not impair insulin sensitivity.

Conclusion: MTX reduces serum HbA1c in non-diabetic RA or PsA patients during the initial 6 months of treatment. As assessed by HbA1c, MTX also reduces the prevalence of prediabetes, consistent with the notion that MTX protects against the development of DM. According to recent data HbA1c (%) is not only an established predictor of CV risk in diabetic patients, but also an independent CV risk predictor in non-diabetics. Taken together, our findings support a possible role of MTX in reducing DM and CV risk in RA as well as PsA patients.

Disclosure: K. Perdan-Pirkmajer. None; S. Pirkmajer. None; A. Hocevar. None; Rotar. None; N. Gaspersic. None; S. Praprotnik. None; M. Tomšič. None; A. Ambrozic. None.

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Dosing of Intravenous Tocilizumab in a Real-World Setting—Analyses from a US RA Registry. Dimitrios A. Pappas1, Ani John2, Jeffrey R. Curtis3, 4, George W. Reed5, Chitra Karki6, Robert Magner6, Joel M. Kremer7, Ashwini Shewade2 and Jeffrey D. Greenberg6, 7. 1Columbia University, New York, NY, 2Genentech, Inc, South San Francisco, CA, 3University of Alabama at Birmingham, Birmingham, AL, 4Corrona, LLC, Southborough, MA, 5University of Massachusetts Medical School, Worcester, MA, 6AbbVie Inc, Chicago, IL, 7Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: In the US, the recommended starting dose of intravenous tocilizumab (TCZ) in combination with DMARDs or as mono-therapy is 4 mg/kg every 4 weeks and increased to 8 mg/kg based on clinical response for patients with moderate to severe rheumatoid arthritis (RA)1. However, on actual dosing, data on actual dosing and escalation is limited to 3-month follow-up data. The primary objective of this analysis was to evaluate how intravenous TCZ is dosed in a real-world setting using data from the Corrona registry.

Methods: All patients enrolled in the comparative effectiveness substudy (CERTAIN) nested within Corrona who initiated TCZ and had 3- and 6-month follow-up data available were eligible for inclusion in this analysis. Data were collected from patients who remained on their initial TCZ dose of 4 mg/kg at 3 months (Group 1) and patients who had their TCZ dose escalated to 8 mg/kg by or at 3 months (Group 2). Unadjusted efficacy response data were provided for patients at 3 and 6 months, including Disease Activity Score in 28 joints using C-reactive protein (DAS28-ESR), Clinical Disease Activity Index (CDAI), CRP, modified Health Assessment Questionnaire, patient pain, patient fatigue and EULAR response. Reponses at 3 months were mostly

Results: Of the 196 patients included in this analysis, 56.1% (95% CI, 48.9% to 63.2%) escalated their TCZ dose by or at 3 months (Group 1) and patients who had their TCZ dose escalated to 8 mg/kg by or at 3 months (Group 2). Unadjusted efficacy response data were provided for patients at 3 and 6 months, including Disease Activity Score in 28 joints using C-reactive protein (DAS28-ESR), Clinical Disease Activity Index (CDAI), CRP, modified Health Assessment Questionnaire, patient pain, patient fatigue and EULAR response. Reponses at 3 months were mostly
similar between the 2 groups, except median (IQR) decrease from baseline in CRP was significantly greater in Group 2 vs Group 1 (−1.4 [−12.8, −0.8] mg/L vs −1.0 [−5.0, 1.0] mg/L; P = 0.001). At 6 months, efficacy outcomes remained similar between the 2 groups (Table); however, a numerically higher proportion of patients in Group 2 achieved EULAR good responses, CDAI low disease activity and DAS28-CRP low disease activity and remission vs Group 1, and median decrease from baseline to 6 months in CRP was significantly greater in Group 2 vs Group 1.

Conclusion: Real-world data show that physicians escalate the dose of TCZ at varying frequencies, slightly more than one half of TCZ initiators in this refractory to therapy population, the TCZ dose was escalated by 3 months. The majority of patients in both groups achieved moderate or good EULAR response.

Reference:

Table. Summary of Efficacy at 6 Months by Dosing Pattern

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1 - No Dose Escalation (n = 86)</th>
<th>Group 2 - Dose Escalated (n = 110)</th>
<th>P-Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI remission, n (%)</td>
<td>8 (9.30)</td>
<td>8 (7.55)</td>
<td>0.79</td>
</tr>
<tr>
<td>CDAI LDA, n (%)</td>
<td>29 (33.72)</td>
<td>37 (34.91)</td>
<td>0.88</td>
</tr>
<tr>
<td>CDAI MCIDc, n (%)</td>
<td>55 (67.90)</td>
<td>68 (67.33)</td>
<td>1.00</td>
</tr>
<tr>
<td>DAS28 remission, n (%)</td>
<td>14 (17.95)</td>
<td>28 (27.18)</td>
<td>0.16</td>
</tr>
<tr>
<td>DAS28 LDA, n (%)</td>
<td>21 (26.22)</td>
<td>41 (39.81)</td>
<td>0.08</td>
</tr>
<tr>
<td>EULAR response, n (%)</td>
<td>16 (22.54)</td>
<td>33 (35.87)</td>
<td>0.13</td>
</tr>
<tr>
<td>Good</td>
<td>16 (22.54)</td>
<td>33 (35.87)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30 (42.25)</td>
<td>28 (30.43)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>25 (35.21)</td>
<td>31 (33.70)</td>
<td></td>
</tr>
</tbody>
</table>

Median change from baseline to 6 months, median (IQR)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>−14.0</td>
<td>−13.0</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>−3.1</td>
<td>−3.3</td>
</tr>
<tr>
<td>mHAQ</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Patient pain</td>
<td>−9.0</td>
<td>−10.0</td>
</tr>
<tr>
<td>Patient fatigue</td>
<td>−10.0</td>
<td>−5.0</td>
</tr>
<tr>
<td></td>
<td>(−23.6, −5.5)</td>
<td>(−24.0, −9.7)</td>
</tr>
<tr>
<td></td>
<td>(−7.9, 0.3)</td>
<td>(−15.7, −0.8)</td>
</tr>
<tr>
<td></td>
<td>(−0.4, 0.0)</td>
<td>(−0.3, 1.0)</td>
</tr>
<tr>
<td></td>
<td>(−30.5, 0.0)</td>
<td>(−35.0, 0.0)</td>
</tr>
<tr>
<td></td>
<td>(−25.0, 3.0)</td>
<td>(−30.0, 5.0)</td>
</tr>
</tbody>
</table>

a Of the 86 patients in Group 1, 45 patients remained on TCZ 4 mg/kg throughout the 6-month period and 41 patients escalated their dose to 8 mg/kg by or at 6 months.

b P-values between groups were calculated using Fisher’s exact test for categorical outcomes and the Wilcoxon Rank-Sum test for continuous outcomes.

c MCID is defined as a decrease in CDAI of 2 in patients with baseline CDAI < 10 (low disease), as a decrease in CDAI of 6 in patients with baseline CDAI between 10 and 22 (moderate disease) and as a decrease in CDAI of 11 in patients with baseline CDAI > 22 (high disease).

The Safety and Treatment Efficacy of Abatacept in Rheumatoid Arthritis Patients with Pulmonary Complications: From the Tsuru-most Biologics Communication Registry (TSURU-BRC) Multicenter Study.

Disclosure: D. A. Pappas, Corrorna, LLC, 3; Novartis, 9; A. John, Genentech, Inc, 3; J. R. Curtis, AbbVie, Amgen, BMS, Corrorna, LLC, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, 5, AbbVie, Amgen, BMS, Corrorna, LLC, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, 9; G. W. Reed, Corrorna, LLC, 3; C. Karki, Corrorna, LLC, 3; R. Magner, University of Massachusetts Medical School, 3; J. M. Kremer, Corrorna, LLC, 3; Genentech, Inc, 5, Genentech, Inc, 2; A. Shewade, Genentech, Inc, 3; J. D. Greenberg, Corrorna, LLC, 3; Corrorna, LLC, 1; AstraZeneca, Celgene, Novartis and Pfizer, 5.

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Background/Purpose: Roughly 10–30% of rheumatoid arthritis (RA) patients reportedly develop pulmonary complications. These patients are at increased risk of MTX or biologics-induced damage, which often becomes problematic for RA treatment. Abatacept (ABT) has been reported to have relatively few adverse events, and is often used in clinical settings in patients with pulmonary complications. Given the paucity of studies on the safety of ABT, however, accumulation of safety data under actual clinical settings is warranted. In the present study, we examined the persistence rates and treatment effects of ABT in patients with pulmonary complications.

Methods: We divided 250 RA patients registered in the Tsurumi Biosciences Communication Registry who used ABT for ≥52 weeks according to whether they had pulmonary complications (L group: n = 32) or not (N group: n = 218). We then compared the persistence rates, incidence of adverse events, and disease activity between the two groups.

Results: No significant differences were found between groups with regard to mean age (L group, 67.7 ± 6.9; N group, 64.0 ± 12.8), disease duration (L group, 12.6 ± 9.8; N group, 11.8 ± 8.8), concomitant use rates of steroid (L group, 62.5%; N group, 60.5%), CRP (L group, 2.6 ± 2.9; N group, 2.1 ± 2.8), DAS28-28 (L group, 4.7 ± 1.5; N group, 4.4 ± 1.3), or SDAI (L group, 28.8 ± 16.5; N group, 24.5 ± 14.0) at the time ABT was initiated, but significant differences were found in the percentage of women (L group, 65.6%; N group, 83.5%) and concomitant use rates of MTX (L group, 25%; N group, 53.2%). The persistence rates for 52 weeks were 73.1% and 74.3% in the L and N groups, respectively (Figure 1a). Adverse events occurred in 1 (3.13%) and 7 (3.83%) patients in the L and N groups, respectively. No pulmonary complications occurred after ABT administration in the L group, but 2 patients in the N group had interstitial pneumonia. Treatment was discontinued due to insufficient response in 6 (18.8%) and 29 (15.9%) patients in the L and N groups, respectively. None of these were significantly different by group. Mean DAS28-CRP significantly improved in both groups (Figure 1b), from 4.7 at ABT initiation to 3.2 at 52 weeks in the L group (P < 0.01), and from 4.4 to 3.1 in the N group (P = 0.034). Achievement of those with low disease activity also increased, from 9.4% at ABT initiation to 53.3% at 52 weeks in the L group, and from 8.3% to 47.7% in the N group.

Conclusion: The safety, treatment effects, and persistence rates of ABT were similar among RA patients with and without pulmonary complications. Use of ABT is beneficial even in patients with pulmonary complications, under close consideration of the risks involved.

Real-World Use of Tocilizumab in Rheumatoid Arthritis Patients in Canada: Interim Results. Boulou Haraoui1,2, Shahin Jama1,2, Vandana Ahluwalia1,3, Tarang Manchanda3,4 and Majed Khraishi2. 1Centre Hospitalier de l’Université de Montréal, Montréal, QC, 2University of British Columbia, Vancouver, BC, 3William Osler Health Center, Brampton, ON, 4Pharmaceutica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, 3, USP, 4, Hoffmann-La Roche Canada, Mississauga, ON, 5; 2ABRM, 3MCRC, 4AEC, 5Actelion, 7NimbleGen, 8Astellas Pharma, 8, Eisai, 8, Mitsubishi Tanabe Pharma Corporation, 8, AbbVie Inc., 8, Genentech, Inc., 8, Bayer, 8, Pfizer Inc, 8, Janssen Pharmaceutica Product, L.P., 8, Janssen Research & Development, L.L.C., 8, Abbvie, 8, GlaxoSmithKline, 8, Janssen Pharmaceuticals, Inc., 8, Chugai Pharmaceutical Co. Ltd; Chugai Pharmaceutical Co. Ltd; Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8, AbbVie Inc., 8, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8, AbbVie Inc., 8, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, Abrome, 5, SanoPharma Services, 5, SanoPharma Services, 5, AbbVie, 5, Genentech, Inc., 5, Hoffmann-La Roche, 5, Hoffman-La Roche, 5, Hoffmann-La Roche Canada, Mississauga, ON, 5; 6New Clinical Research, 6; 7St John’s, NF.

Background/Purpose: Tocilizumab (TCZ) has been approved for the treatment of adults with rheumatoid arthritis (RA) either as monotherapy or as combination with disease-modifying antirheumatic drugs (DMARDs). However, to date, data on its real-world utilization and durability are limited. The aim of this analysis is to describe the pattern of TCZ use at baseline (BL) and after 6 months (mos) of treatment in Canadian patients enrolled in ACT-UP, a multi-national observational study in moderate-to-severe RA patients treated with TCZ. ACT-UP is an ongoing, multi-national, observational study with TCZ. As of June 2014, 1,375 patients have been enrolled from 14 countries. In this analysis, data from the 200 Canadian patients participating in ACT-UP were used. Descriptive statistics were produced and between-group comparisons were performed with the independent samples t-test (continuous variables) and the chi-square test (categorical variables).

Results: Among the 200 patients included, 67 (33.5%) started TCZ as monotherapy and 133 (66.5%) in combination with DMARD(s) (mean methotrexate dose: 19.9 mg/week). BL age (55.2 vs 55.6 years, respectively), gender (79.1% vs 80.5% females) and disease duration (13.8 vs 12.0 years) were similar in the two groups. No difference in the initial TCZ dose was observed between groups with 91.0% in each receiving 8 mg/kg and the remaining receiving <8 mg/kg. Similarly, concomitant use at BL of a corticosteroid (38.8% vs 36.1%; mean prednisone dose: 10.7 vs 9.2 mg/day) and prior exposure to a biologic (80.6% vs 82.0% in monotherapy vs combination therapy) were also comparable in TCZ monotherapy vs combination therapy. Lack of efficacy (70.4% vs 68.2%) and intolerance (12.2% vs 10.9%) were the most common reasons for stopping a previous biologic in both treatment groups. However, a significantly higher proportion of patients in the monotherapy group had been previously treated with <1 traditional DMARD (90.8% vs 66.9%; P < 0.001). Overall, BL disease parameters were statistically comparable between treatment groups with the exception of patient global assessment which was significantly higher in the TCZ monotherapy group (68.1 vs 60.6 mm; P = 0.017).

Upon 6 mos of treatment, 86.6% of patients in the monotherapy group and 85.0% in the combination therapy group were still on TCZ. Over that period no change in TCZ dose was reported in 80.6% patients (76.9% vs 82.5% in mono- vs combination therapy), while the TCZ dose was down-titrated in 14.7% patients (18.5% vs 12.7%, respectively). Seven of 67 (10.4%) patients in the TCZ monotherapy group added a concomitant DMARD to TCZ within 6 mos. Regardless of treatment group significant improvements were observed over 6 mos in all disease parameters examined (BL vs 6 mos DAS28: 5.3 vs 3.4; P < 0.001).

Conclusion: In this real-world observational study, TCZ was used as monotherapy in 33.5% of patients. Despite the fact that 81.5% of patients had been previously treated with a biologic, more than 85% of patients remained on TCZ treatment after 6 mos of treatment. TCZ treatment alone or in combination with DMARD(s) over 6 mos was effective in inducing significant improvements in all disease parameters studied.
Patterns of Tocilizumab Use and Safety in Patients with Rheumatoid Arthritis: Interim Results from a Multinational Observational Study. Boulos Haraoui1, Gustavo Casado2, Elke Theander3, Laszlo Czirják4, Andrew Taylor5, Peter Button6, Lykke Hinsch Gylvin7 and Roberto Caporali8.

Background/Purpose: Tocilizumab (TCZ) is indicated for the treatment of patients with RA who have had inadequate responses to DMARDs either as monotherapy (Mono) or in combination with DMARDs (Combo). ACT-UP is an umbrella project with data pooled from several international, observational, postmarketing studies investigating intravenous TCZ use in patients with RA in routine care. Interim observations of patterns of TCZ use, adherence to label recommendations, and safety are reported.

Methods: Adult patients with moderate to severe RA who started TCZ within 8 wk of enrollment were observed in clinical practice for 6 mo. There were no specified dosing regimens (concomitant RA treatments were permitted) and no interventional procedures, clinic visits, or laboratory analyses outside routine practice.

Results: Of 961 patients who received their first TCZ dose by June 30, 2013, 352 (37%) started Mono and 609 (63%) started Combo; 94% and 95% of Mono and Combo patients, respectively, started TCZ at 8 mg/kg, and 93% and 94% of patients, respectively, who received TCZ at 6 mo received 8 mg/kg. TCZ dose changes were reported for 34 (10%) Mono patients (7 increased, 11 decreased, 16 both increased and decreased) and 68 (11%) Combo patients (13 increased, 20 decreased, 35 both increased and decreased). Reasons for dose changes were AEs for 4% of Mono and 5% of Combo patients and lack of efficacy for 2% of Mono and 1% of Combo patients. Median MTX dose for Combo patients was 15.0 mg/wk. Sixty-three patients changed MTX dose during the study at a median dose change of 5.0 mg/wk. Twenty-eight (8%) patients who started TCZ Mono added a DMARD during the study. Corticosteroids were used by 57% of Mono and 70% of Combo patients (median prednisone-equivalent dose of 7.5 and 5 mg/d, respectively, at baseline). At 6 mo, 72% of Mono and 84% of Combo patients were still receiving TCZ. Overall, 100 (10%) patients discontinued TCZ in the first 3 mo and another 54 (10%) discontinued in the next 3 mo. Reasons for discontinuations included lack of efficacy (11% Mono; 27% Combo), adverse events (AEs; 27% Mono, 29% Combo), and other (62% Mono, 44% Combo). Regarding safety, AEs occurred in 53% of patients in each group. AEs classified as infections were less common in Mono than in Combo patients (Table). No gastrointestinal perforations were reported in either group. Among patients for whom an AE required TCZ dose modification or discontinuation, manual lab test result follow-up was reported by 35% of patients. The investigator reported that local label/protocol recommendations were followed for 98% of Mono and 95% of Combo patients.

Conclusion: In this multinational observational study, 37% of patients started TCZ as monotherapy in clinical practice. Most patients continued TCZ treatment 6 mo after initiation whether they started it as monotherapy or in combination with DMARDs. TCZ was well tolerated in both groups, and adherence to local label recommendations was high.

Table. Safety

<table>
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<tr>
<th>Event</th>
<th>TCZ Mono n = 352</th>
<th>TCZ Combo n = 609</th>
<th>All Patients n = 961</th>
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<tr>
<td>AEs, n (%)</td>
<td>185 (52.6) [193]</td>
<td>230 (53.2) [205]</td>
<td>515 (53.5) [521]</td>
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<tr>
<td>AEs by SOC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>56 (15.9)</td>
<td>51 (8.8)</td>
<td>107 (11.1)</td>
</tr>
<tr>
<td>Investigations</td>
<td>38 (10.8)</td>
<td>71 (11.7)</td>
<td>109 (11.3)</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>33 (9.4)</td>
<td>52 (8.5)</td>
<td>85 (8.9)</td>
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<td>Gastrointestinal disorders</td>
<td>29 (8.3)</td>
<td>49 (8.0)</td>
<td>78 (8.1)</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>28 (8.0)</td>
<td>44 (7.2)</td>
<td>72 (7.5)</td>
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<td>General disorders and administration site conditions</td>
<td>22 (6.3)</td>
<td>34 (5.6)</td>
<td>56 (5.8)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>20 (5.7)</td>
<td>44 (7.2)</td>
<td>64 (6.7)</td>
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<td>Neuronal system disorders</td>
<td>18 (5.1)</td>
<td>32 (5.3)</td>
<td>50 (5.2)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>18 (5.1)</td>
<td>23 (3.8)</td>
<td>41 (4.3)</td>
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<tr>
<td>SAEs, n (%)</td>
<td>34 (9.7) [37]</td>
<td>40 (6.9) [44]</td>
<td>74 (7.7) [81]</td>
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<tr>
<td>Infection SAEs</td>
<td>15 (4.3)</td>
<td>22 (3.6)</td>
<td>37 (3.9)</td>
</tr>
<tr>
<td>Total AEs leading to withdrawal, n (%)</td>
<td>32 (9.1) [37]</td>
<td>42 (6.9) [44]</td>
<td>74 (7.7) [81]</td>
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</tbody>
</table>

520 Genetic Variant and High Levels of CCL11 in Serum Are Associated with the Occurrence of Lymphoma and Disease Activity in Primary Sjögren’s Syndrome Patients (pSS). Gaetane Nocturne1, Olivier Fogel2, Joanne Nititham3, Kimberly E. Taylor4, Philippe Dieude5, Jean Jacques Dubost6, Anne-Laure Fauchais7, Vincent Goeb8, Eric Hachulla9, Claire Larroche10, Véronique Le Guern11, Jacques Morel12, Aleth Perdriger13, Xavier Puech11, Stephanie Rist Bouillon11, Alain Sarraz16, Damien Sène16, Olivier Testaquet17, Lindsey A. Byrwal18, Corinne Moret-Richard11, Jacques Gottenberg19 and Xavier Mariette20. 1Paris sud university, Le Kremlin Bicetere, France, 2Paris sud university, Le Kremlin Bicetere, France, 3374 Parmaus Avenue, San Francisco, CA, 4University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, 5Hopital Claude Bernard, Paris, France, 6CHU G-Montpeyri, Clermont-Ferrand, France, 7Department of Internal Medicine A, Dupuytren Hospital, Limoges University Hospital, Limoges, France, 8Amiens University Hospital, Amiens, France, 9Université Lille Nord de France, Faculté de Médecine Henri Warenbourg, Lille, Lille, France, 10Assistance Publique des Hôpitaux de Paris, Bobigny, France, 11National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, 12Hôpital Lapeyronie, Montpellier, France, 13Rhumatologie, Rennes, France, 14Hopital La Source, La Source, France, 15CHU Brest and EA 2216, UBO, Brest, France, 16Hopital Lariboisière, service de Médecine Interne, Paris, France, 17Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, 18Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France, 19Strasbourg University Hospital, Strasbourg, France, 20Université Paris-Sud, Le Kremlin Bicêtre, France.

Background/Purpose: Development of non-Hodgkin lymphoma (NHL) is one of the most severe complicati of pSS. It occurs in 5–10% of the patients. A more accurate detection of the high risk patients is mandatory to enable a more individualized approach. Presence of ectopic germinal center (GC) in salivary glands biopsy has been shown to be a predictor of NHL occurrence in pSS patients[1]. Interestingly, 2 single nucleotide polymorphisms (SNPs) located within CCL11 (Eotaxin) gene are associated with GC structures in pSS patients[2]. CCL11 is a chemokine that plays a role in chemotaxis of eosinophils and in allergy. In this study, we decided to assess the role of CCL11 both at the genetic and proteic level in the occurrence of pSS-associated NHL.

Methods: Genotyping of the 2 SNPs (rs3091328 and rs1860184, located on chromosome 17) known to be associated with GC structures was performed in 562 pSS cases (ASSESS cohort and Paris-Sud teaching hospital cohort) and 435 healthy controls, both of them of European ancestry as assessed by 47 ancestry informative markers. Among patients, 25 had a history of NHL. CCL11 serum levels at inclusion in the ASSESS cohort were evaluated in 385 pSS patients by multiplex assay. Among them, 21 patients had a NHL (history or future). Case-only associations (i.e., pSS patients vs. without lymphoma) were tested with logistic regression adjusting for the top two Immunochip principal components. Association between CCL11 levels and genotype was assessed with the Kruskal-Wallis test. Levels of

<table>
<thead>
<tr>
<th>PV</th>
<th>patient-years</th>
<th>SAEs</th>
<th>serious AEs</th>
<th>SOC</th>
<th>system organ class</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days</td>
<td>50.5</td>
<td>285</td>
<td>50.5</td>
<td>28 days</td>
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</tr>
</tbody>
</table>
CXCL1 were compared in the different subsets of patients with a Mann-Whitney test.

Results: The 2 CXCL1 SNPs were not significantly associated with risk of pSS. However, we found a significant association between the rs1860184A located within the first intron of CXCL1 and pSS complicated by NHL: OR 1.87 CI95% [1.07–2.72], p = 0.03 compared to pSS patients without NHL and OR 1.84 CI95% [1.02–3.31], p = 0.04 compared to healthy controls. The median [range] serum level of CXCL1 was 106.5 [13.2–238.5] pg/ml in the 385 pSS patients in the ASSESS cohort. We did not find any association between the CXCL1 serum levels and the r1860184 genotype (p=0.36). We found a trend for an association between CXCL1 levels and the occurrence of NHL: (median [range]): 105 [13.2–238.5] in patients without NHL vs 141.3 [46.76–211] in patients with NHL (p=0.05). Interestingly we found a significant increased serum level of CXCL1 in patients with an active disease defined by an ESSDAI ≥ 5 vs patients with inactive disease (112.2 pg/ml [13.23 – 238.5] vs 103.1 pg/ml [14.13 – 281.5] respectively; p=0.01). Last, we found significant correlation between CXCL1 serum levels and B cells biomarkers (RF titer: p=0.01; free light chain kappa/lambda ratio: p=0.02 and B2-microglobulin level: p=0.0003).

Conclusion: This study highlights the potential implication of CXCL1 in the occurrence of NHL in pSS patients. We show that the rs1840186 SNP is associated with NHL occurrence. An increased serum level of CXCL1 tends to be associated with NHL occurrence and is associated with increased disease activity and B cells bio-markers. Further studies will be mandatory to determine the functional role of CXCL1 in this phenomenon.


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CXCL13 Serum Levels Is Associated with Lymphoma, High B Cells Markers and Disease activity in Primary Sjögren’s Syndrome Patients.

Gaetane Nocturne1, Olivier Fogel2, Philippe Puechal3, Veronique Le Guern4, Jacques Morel5, Aleth Perdriger6, Xavier Puechal7, Gaetane Nocturne1, Olivier Fogel2, Philippe Puechal3, Veronique Le Guern4, Jacques Morel5, Aleth Perdriger6, Xavier Puechal7, Veronique Le Guern4, Jacques Morel5, Aleth Perdriger6, Xavier Puechal7

Background/Purpose: The role of CXCL13 in the lymphomagenesis in pSS patients remain poorly understood. The aim of this project is to identify a miRNA signature for PSS-related lymphoma.

Methods: We profiled the expression of miRNAs in whole blood from 339 pSS patients and controls from the UK Primary Sjögren’s Syndrome Registry (UKPSSR) (12 PSS patients with lymphoma, 12 PSS patients without lymphoma, 12 healthy controls) using Taqman Low Density Arrays (TLDAs). We developed an approach which we considered most appropriate for analysing microRNAs with the highest fold-changes between the two groups. Indeed, the 2 miRNAs that are differentially expressed in patients with lymphoma and those without lymphoma were identified using cluster analysis followed by validation with a second independent cohort of 36 patients and controls.

Results: The initial miRNA array profiling revealed a clear clustering of the 3 subject groups. Between the High Function and Lymphoma patient groups, 44 miRNAs were found to be differentially expressed. The differential expressions of these miRNA were validated by RT-PCR in 3 out of 9 miRNAs with the highest fold-changes between the two groups. Indeed, based on the expression levels of these 3 miRNAs were sufficient to distinguish PSS patients with lymphoma from those without. Two out of these 3 miRNAs were also differentially expressed between the same two groups in the validation cohort.

Conclusion: We have identified 2 miRNAs that are differentially expressed in peripheral blood between PSS patients with lymphoma and those without lymphoma. Identifying the miRNA targets of these miRNAs in PSS may improve our understanding of the pathogenesis of PSS-related lymphoma. Furthermore, miRNAs may be useful biomarkers for PSS-related lymphoma.
Disclosures: J. Tarn, None; S. Cockell, None; C. Gillespie, None; S. Al-Ali, None; K. James, None; J. Locke, None; S. Bowman, None; B. Griffiths, None; D. Young, None; W. F. Ng, None.

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Serum CXCL4 Is Increased in Patients with Primary Sjögren’s Syndrome and Is Associated with Parameters of Microvascular Involvement. Rosaria Irace1, Antonella Riccardi1, Daniela Iacono1, Luciana Pellecchia1, Lucia Vicedomini1, Gabriele Valentini2 and Serena Vettori1. 1Second University of Naples, Naples, Italy, 2Second University of Naples, Napoli, Italy.

Background/Purpose: CXCL4 is a pleiotropic antiangiogenic and immunomodulatory chemokine. We aimed to investigate CXCL4 serum levels in primary Sjögren’s syndrome (pSS) and looked for associations with disease features, with a focus on parameters of microvascular involvement.

Methods: Thirty-nine consecutive pSS patients meeting the 2012 classification criteria for the disease were enrolled and underwent clinical assessment, nailfold videocapillaroscopy (NVC), and autoantibody profiling. Additional serum to measure levels of CXCL4 and soluble E-selectin (sE-selectin) was available from 36 pSS patients and 30 healthy controls (HC). At NVC, enlargement, density, and tortuosity of capillaries, and microhemorrhages were scored on a 0 to 3 scale (0 = normal, 3 = high grade). Plexus visualization and neoangiogenesis were also considered as present/absent.

Autoantibodies were assayed by ELISA, while CXCL4 and sE-selectin were measured by multiplex suspension immunosassay.

Results: Serum levels of CXCL4 were increased in pSS patients (median 1.79 ng/ml [0.2–11.18] vs 1.02 ng/ml [0.02–14.45] in HC, p = 0.05), the highest found in anti-La/SSB autoantibody-negative patients (2.89 ng/ml [101–11.18] vs 1.69 [0.2–2.72] ng/ml, p < 0.05), and correlating with a longer disease duration (r = 0.35, p < 0.05). Most interestingly, we found a higher prevalence of CXCL4 levels above the 95th percentile of the HC group (10.91 ng/ml) in pSS patients with Raynaud’s phenomenon (RP) (11/14 vs 3/25, p < 0.001). This prompted us to look for associations of serum CXCL4 with microvascular abnormalities at NVC and/or correlations with serum levels of s-E-selectin, a marker of endothelial activation. Indeed CXCL4 positively correlated with s-E-selectin (r = 0.45, p < 0.01), but was not associated with any NVC finding. However, a reduced capillary density and high grade enlarged capillaries were more prevalent in patients with RP (14/15 vs 6/21 and 16/16 vs 8/23, respectively; both p < 0.0001). An NVC “scleroderma pattern” was observed only in 3 patients (megacapillaries), and neoangiogenesis in 2 (both p > 0.05).

Conclusion: Here we show for the first time that pSS patients have increased serum CXCL4 levels, which correlate with disease duration and serum s-E-selectin levels, and are associated with the presence of RP. These data suggest that CXCL4 might be implicated in microvascular/endothelial impairment in pSS. Actually, our pSS patients with RP had microvascular damage, as a reduced capillary density and high grade enlarged capillaries showed. Lastly, we detected higher CXCL4 levels in anti-La/SB autoantibody-negative patients. This negative association might be related to the role played by pSS specific autoantibodies in promoting pathological angiogenesis in human salivary glands. Taken together this data provide preliminary evidence of a role for circulating CXCL4 as a marker of microvascular damage in pSS on larger cohorts of patients.

Disclosure: R. Irace, None; A. Riccardi, None; D. Iacono, None; L. Pellecchia, None; L. Vicedomini, None; G. Valentini, None; S. Vettori, None.

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Distinct Patterns of DNA Methylation in Labial Salivary Gland Tissue Based on Sjögren’s Syndrome Disease Status. Michael Cole1, Xiaorong Shao1, Diana Quach1, Hong L. Quach1, Lisa F. Barcellou1 and Lindsey A. Criswell2. 1University of California, Berkeley, Berkeley, CA, 2University of California, San Francisco, Rosalind Russell / Ephraim P. Engelmann Rheumatology Research Center, San Francisco, CA.

Background/Purpose: Sjögren’s Syndrome (SS, OMIM #270150) is a chronic, multi-system autoimmune disease characterized by progressive destruction of the exocrine glands, with subsequent mucosal and conjunctival dryness. A growing body of evidence indicates that epigenetic changes contribute to the development of this complex disease. In particular, altered patterns of DNA methylation may modulate both risk and severity.

Methods: We report an expanded case-control study of DNA methylation differences within labial salivary gland tissues, using biopsies sampled from 12 primary SS cases, 2 secondary SS cases, and 14 controls in the Sjögren’s International Collaborative Clinical Alliance (SICCA; http://sicca.ucsf.edu/; HHSN268201300057C) collection. These subjects are part of a larger, 36-subject study group for which blood, gland tissue, and cell-sorted blood samples have been methylotyped (110 samples total). We generated genome-wide DNA methylation profiles using Illumina HumanMethylation450 Bead-Chips and further characterized full genome SNP profiles using the Illumina HumanOmni2.5-Quad platform. All methylation results were background corrected via out-of-band normal-exponential convolution (NOOB) and normalized via all sample mean normalization (ASMN) and beta-mixture quantile normalization (BMQ).

Results: Multidimensional Scaling (MDS) applied to the 360,546 CpG sites passing strict QC criteria visibly separates primary SS cases from controls within the first 2–3 components, and this clustering changes substantially with the inclusion of a subset of 9 symptomatic SICCA control subjects (control status based on SICCA’s extensive clinical and serologic data). We demonstrate significant gene-centered NVC differences across IL10 and IRF5 in SS cases (False Discovery Rate ≤0.05). Mean methylation levels within 15 other putative SS-associated genes were similar between cases and controls. We report median methylation levels in specific BLK and KHLH24 CpGs that are 15–25% hypermethylated in primary SS cases versus controls; other sites in IRF5 and BLK display 10–20% hypomethylation. Single-site methylation differences across 7 of the 17 genes retain significance after multiple-testing correction, with 6 of the 7 genes exhibiting hypomethylation at a majority of sites.

Conclusion: Our results emphasize the utility of DNA methylation as a potential biomarker of disease status. Additional research, including studies of pathway-specific gene expression will be required to fully define the role of DNA methylation in SS-aFFECTED salivary glands.

Disclosure: M. Cole, None; X. Shao, None; D. Quach, None; H. L. Quach, None; L. F. Barcellou, None; L. A. Criswell, None.

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The Genetic Basis of Sjögren’s Syndrome (SS) Clinical Manifestations from Genome-Wide Association Analysis of Subphenotype Extrinsics in an International Cohort. Lindsey A. Criswell1, Kimberly E. Taylor2, Quinn Wong3, David M. Levine4, Caitlin McHugh5, Cathy Laurie2, Kimberly Dobbs6, Mi Y. Lapa7, Alan N. Bier8, Stephen Challacombe9, Yi Dong8, Hector Lanfranchi9, Morten Schiold4, S. Mirsivas10, Susumu Sugai1, Hisanori Umehara1, Frederick B. Vivino12, Zhao Yan13, Stephen Shiboski1, Troy Daniels4, John S. Greenspan4, Caroline H. Shiboski1 and Sjögren’s Syndrome Collaborative Clinical Alliance (SICCA)4. 1University of California, San Francisco, Rosalind Russell / Ephraim P. Engelmann Rheumatology Research Center, San Francisco, CA, 2University of Washington, Biostatistics, Seattle, WA, 3Center for Inherited Disease Research, Baltimore, MD, 4University of California San Francisco, San Francisco, CA, 5Johns Hopkins University School of Medicine, Baltimore, MD, 6Kings College London, London, United Kingdom, 7Peking Univ Med Coll Hospital, East City Beijing, China, 8University of Buenos Aires, Buenos Aires, Argentina, 9Rigshospitalet, Copenhagen, Denmark, 10Aravind Eye Hospital, Madurai, India, 11Peking University Medical University, Chikaka, Japan, 12Permanente Med Ctr, Philadelphia, PA, 13Peking Union Medical College Hospital, Beijing, China.

Background/Purpose: Our goal is to define the contribution of genetic factors to two hallmark manifestations of SS, keratoconjunctivitis sicca (KCS) and focal lymphocytic sialadenitis (FLS), in an international cohort.

Methods: We studied 3,334 participants in the Sjögren’s International Collaborative Clinical Alliance (SICCA; contract # HHSN268201300057C) registry who were characterized for the Illumina HumanOmni 2.5-Quad marker set. SICCA participants were enrolled according to standardized protocols at 9 international sites, including Argentina (n=428), China (n=304), Denmark (n=831), India (n=127), Japan (n=367), the UK (n=296) and the US (total n=1229 from 3 sites). QC measures included filters based on SNP and sample missingness (≥2%), unexpected relatedness, non-Mendelian inheritance, and chromosomal regions of anomaly (≥10Mb). SICCA participants were assessed for presence and severity of FLS defined by focus score (FS, positive ≥1) on minor salivary gland biopsies and degree of KCS based on ocular staining pattern measured by ocular staining score (OSS, positive ≥3). In order to investigate the genetic basis of these manifestations, we compared patients with high values (OSS ≥7, FS ≥2.5) to patients with normal values (OSS < 3, FS < 1) via logistic regression. Principal components analysis (PCA) was used to characterize each participant for genetic ancestry, and PC’s 1 – 5 were included as covariates in all.

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association analyses. We analyzed the entire group and also the two largest strata by ethnicity (European and Asian, with outliers removed outside of PCA clusters).

Results: Out of 3284 unrelated subjects with post-QC genotypes and sufficient clinical data, patients were categorized for analysis as follows: high FS (n=636), normal FS (n=1968), high OSS (n=1333), normal OSS (n=857). A total of 1,550,200 SNPs with MAF ≥ 1% passed all QC filters and were genotyped successfully. Not surprisingly, the MHC was the most significantly associated with both traits in the full dataset (FS p=3e-22, OSS p=6e-12) and in Europeans (FS 375 SNPs p<5e-8, lowest 3e-17; OSS 60 SNPs p<3e-8, lowest p=4e-11). However, in Asians the MHC appears to have much less importance. There was only one suggestive MHC SNP (p=8e-6) for FS; the most associated FS gene in Asians was PTTRD, with 12 SNPs p<5e-6 (lowest p=1.8e-7). Outside of the MHC, some genes appear to influence both phenotypes while others are trait-specific. For example, IRF5 is the highest-associated region for FS (p=2e-7) but not suggestive for OSS. The XYL11 region is the highest-associated region for OSS (p=1e-6) but is not implicated in FS. On the other hand, STRAT7 is among the most-associated regions for both FS (p=1e-6) and OSS (p=3e-6).

Conclusion: These results demonstrate that the ocular (OSS) and oral (FS) manifestations of SS are influenced by both shared and trait-specific genetic factors. Furthermore the genetic profile appears to be quite different for both diseases, in particular when comparing European and Asian SS patients. Additional work including imputed genetic data and more extensive ancestry analysis will provide more power for extending these findings and fully characterizing the genetic contribution to SS.

Disclosure: L. A. Criswell None; K. E. Taylor None; Q. Wong None; D. M. Levine None; C. McHugh None; C. Laurie None; K. Dohney None; M. Y. Lam None; A. N. Baer None; S. Challacombe None; Y. Dong None; H. Lawrench None; M. Schiold None; M. Srinivasan None; S. Sugai None; H. Umemura None; F. B. Vivino None; Z. Yan None; S. Shiboski None; T. Daniels None; J. S. Greenspan None; C. H. Shiboski None; S. S. C. C. A. (SCCA) None.

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A Descriptive and Comparative Study of the Transcriptome from Salivary Exosomes of Sjögren’s Syndrome Patients Using RNA-Seq. Alessia Gallo1, Mayank Tandon2, Shyh-Ing Jang3, Ana Paola Cotrim1 and Ilias Alevizos1. 1Rheumatology Unit, Pisa, Italy, 2NIH, Bethesda, MD, 3Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Saliva is a biofluid secreted by the salivary glands (SCGs) that is critical for the health of the oral cavity. In Sjögren’s Syndrome (SS), changes in salivary biomarkers are not only useful for diagnosis, but may also reflect the mechanisms underlying SG dysfunction. The RNA content of saliva has been shown to be useful for monitoring the health of oral tissue and the oral microbiome. Next-Generation Sequencing (NGS) offers a high-throughput method for comparing the salivary transcriptomes of SS patients and healthy volunteers (HV). We have previously shown that RNA is protected within exosomes and we focus this study in using salivary exosomes, isolated from the parotid. Porcine saliva has the advantage of being pure without the contamination generated from all type of cells found in the whole saliva.

Methods: Total RNA was extracted from exosomes isolated from porcine saliva from 4 healthy volunteers and 4 primary SS patients. The amount and the quality of the RNA were assessed using Nanodrop, Qubit and Bioanalyzer. The Ion Torrent Proton sequencer was used sequencer according to manufacturer protocols. Reconstructed reads were aligned using the TMAP (Torrent Mapper) algorithm sequentially to miRBase 19, hg19, viral, and bacterial genomes, i.e. reads left unmapped were used as input for each subsequent step. The bacterial reference included 14,549 contigs representing bacterial genomes, i.e. reads left unmapped were used as input for each analysis. The bacterial reference included 14,549 contigs representing bacterial genomes, i.e. reads left unmapped were used as input for each analysis. The most associated region with both traits in the full dataset (FS p=3e-22, OSS p=6e-12) and in Europeans (FS 375 SNPs p<5e-8, lowest 3e-17; OSS 60 SNPs p<3e-8, lowest p=4e-11). However, in Asians the MHC appears to have much less importance. There was only one suggestive MHC SNP (p=8e-6) for FS; the most associated FS gene in Asians was PTTRD, with 12 SNPs p<5e-6 (lowest p=1.8e-7). Outside of the MHC, some genes appear to influence both phenotypes while others are trait-specific. For example, IRF5 is the highest-associated region for FS (p=2e-7) but not suggestive for OSS. The XYL11 region is the highest-associated region for OSS (p=1e-6) but is not implicated in FS. On the other hand, STRAT7 is among the most-associated regions for both FS (p=1e-6) and OSS (p=3e-6).

Conclusion: These results demonstrate that the ocular (OSS) and oral (FS) manifestations of SS are influenced by both shared and trait-specific genetic factors. Furthermore the genetic profile appears to be quite different for both diseases, in particular when comparing European and Asian SS patients. Additional work including imputed genetic data and more extensive ancestry analysis will provide more power for extending these findings and fully characterizing the genetic contribution to SS.

Disclosure: L. A. Criswell None; K. E. Taylor None; Q. Wong None; D. M. Levine None; C. McHugh None; C. Laurie None; K. Dohney None; M. Y. Lam None; A. N. Baer None; S. Challacombe None; Y. Dong None; H. Lawrench None; M. Schiold None; M. Srinivasan None; S. Sugai None; H. Umemura None; F. B. Vivino None; Z. Yan None; S. Shiboski None; T. Daniels None; J. S. Greenspan None; C. H. Shiboski None; S. S. C. C. A. (SCCA) None.

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Salivary Expression of S100A7/Psoriasin and Oral Damage in Primary Sjögren’s Syndrome and Overlapping Disorders. Francesca Sernissi1, Chiara Baldini1, Daniela Martini1, Leonardo Lorenzini1, Laura Bazzichi1, Antonietta Raffaella Maria Sbabutini1, Giada Marchi2, Camillo Giacomei3, Marta Mosca4 and Stefano Bombardieri5. 1Rheumatology Unit, Pisa, Italy, 2Rheumatology Unit, University of Pisa, Pisa, Italy, 3Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: S100A7/pS100A7, a 11.4kDa protein belonging to the S100 family of Ca2+-binding proteins, is known to exhibit an antimicrobial activity at skin level, but has also been implicated in the regulation of cell proliferation, differentiation, invasion and metastasis. By using a proteomic approach, S100A7/pS100A7 has been recently identified in the whole saliva of patients with Systemic Sclerosis as a potential disease biomarker. The aims of the present study were (1) to compare the expression of salivary S100A7/pS100A7 in patients with Sjögren’s Syndrome associated to anti-centromere antibodies (ACA) positive Systemic Sclerosis (SS-SSc), versus patients with primary Sjögren’s Syndrome (pSS), and (2) to explore any correlation between salivary S100A7/pS100A7 and oral damage.

Methods: Unselected pSS and SS-SSc patients (AECG 2002) were consecutively recruited in the study. Unstimulated salivary flow (USF) rate was measured according to the sialometry protocol, and saliva samples were collected on ice, centrifuged and stored at -80°C. S100A7/pS100A7 levels were determined by CircuLex S100A7/pS100A7 ELISA kit (MBL International Corporation), according to manufacturer’s instructions. All subjects had a standardized evaluation for pSS which included oral and ophthalmologic examinations, laboratory testing and a rheumatologic evaluation.

Results: Eighteen SS-SSc and 33 pSS female patients were included in the study. SS-SSc patients had a mean age (± standard deviation) of 56.5 ± 11.3, which did not differ from that of pSS (59.8 ± 11.3). S100A7/pS100A7 levels were significantly higher in SS-SSc subjects (p=0.02). S100A7/pS100A7 salivary levels negatively correlated with the USF rate (r=-0.27, p<0.05), particularly in pSS subjects (r=-0.508, p=0.003), and were significantly higher in patients with a USF <1.5 ml/15 minutes (p=0.006). Regarding the relationship between S100A7/pS100A7 and patients’ oral damage, we found that the salivary expression of the protein was significantly associated with the Sjögren’s Syndrome disease damage index (SSDDI) (p<0.05) and specifically with the complete loss of teeth (p=0.02).

Conclusion: Salivary S100A7/pS100A7 might be useful in differentiating pSS from SS-SSc and seems to be able to reflect oral damage in both pSS and SS overlapping disorders. The potentially predictive value of this biomarker for oral damage accrual in SS-SSc cells for further studies.

Disclosure: F. Sernissi None; C. Baldini None; D. Martini None; L. Lorenzini None; L. Bazzichi None; A. R. M. Sbabutini None; G. Marchi None; C. Giacomei None; M. Mosca None; S. Bombardieri None.

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Calcium-Calmodulin-NFAT Signaling Pathway Regulates AQP5 Expression in Primary Salivary Gland Acellar Cells. Shyh-Ing Jang1, Hwei-Chen Ong1, Indu Ambudkar2 and Ilias Alevizos3. 1NIH, Bethesda, MD, 2NIH, Bethesda, MD, 3NIH, Bethesda, MD.

Background/Purpose: Aquaporin (AQP) 5 belongs to a family of small integral membrane proteins which function as a water channels in cells. AQP5...
plays a critical role in mediating the secretion of fluid in salivary gland. Decrease or no saliva flow is one of the key symptoms in Sjögren’s syndrome patients. Towards understanding the molecular basis of the loss of salivary secretion, here we have studied the regulation of AQP5 expression in primary human salivary gland epithelial cells (phSG).

Methods: cell culture, Western blot, qPCR, siRNAs, site-directed mutagenesis, chromatin immunoprecipitation.

Results: We observed that the phenotype of the cells depended largely on the calcium levels in the culture conditions. AQP5 transcript showed more than 3-fold increase in phSG cells grown in high calcium (0.8 mM) medium compared to that in low calcium (0.05 mM) condition. This was confirmed by both immunofluorescence staining and Western blot studies. Evaluation of expression transcripts of calcium signaling proteins in phSG cells revealed that NFAT1 expression was dependent on calcium in a dose-response manner. Furthermore, when cells were switched to a high calcium medium pGFP-NFAT1 was translocated from the cytoplasm into the nucleus. Expression of AQP5 was also reduced when phSG cells were treated with cyclosporine A confirming the involvement of calcineurin-NFAT1 signaling pathway in regulation of AQP5 expression. Since NFAT activation has been linked to calcium influx, we examined the role of the calcium entry regulatory proteins STIM1 and STIM2 as well as the channel protein Orai1. Knockdown of NFAT1 and STIM1, but not STIM2 or Orai1, resulted in 70% decrease of AQP5 expression. Further analysis revealed that several NFAT binding motifs were identified in the AQP5 promoter and these were validated using AQP5-promoter-luciferase assays. Mutagenesis of putative NFAT-binding motifs in the AQP5 promoter and these were validated using AQP5-promoter-luciferase assays. Mutagenesis of putative NFAT-binding regions as well as chromatin immunoprecipitation analyses revealed the presence of functional NFAT binding sites within the proximal AQP5 promoter. These alterations in calcium signaling could lead to alterations in AQP5 expression and function in pSS. Further studies are being directed towards determining the status of calcium signaling in pSS salivary glands.

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IP3R3 Deficit Underlies the Loss of Fluid Secretion in Salivary Glands from Sjögren’s Syndrome Patients.

Leyla Y Teos1, Bill Swaim2, Margaret Grissius1, Ana Paula Cotrim1, Shy-Ing Jang2, Lolita Bebris1, David Yule4, Gabor G. Illi5, Indu Ambudkar1 and Ilias Alevizos6, None.

Background/Purpose: Sjögren’s syndrome (SS) is an exocrinopathy, which is mainly characterized by salivary glands (SG) hypofunction. SGs from SS patients present dilated lumen in acini and loss of microvilli in the acinar cell SG. Previously, we reported that these changes correlate with an aberrant localization of the acinar cells and an overexpression of ezrin. Ezrin is a cytoplasmic peripheral membrane protein that regulates the microvilli organization and secretion of exocrine cells. The mechanism of gene expression and specific function of ezrin in SS is unknown. We also proved that microRNA hsa-miR-183 is downregulated in SG from SS patients and it can modify the expression of SG cell culture in 3D. Here we are further confirming the function of hsa-miR-183 in vivo, its implication in salivary secretion and exploring a mechanism by which ezrin mislocalization produces saliva hyposecretion.

Methods: LNA-antimiR-183 was transfected into mice parotid SG. The effect of the blockage of hsa-miR-183 was assessed evaluating the volume of saliva secretion after stimulation with isoproterenol and ezrin protein expression. Proximity ligation assay was performed to determine the interaction of ezrin with three possible targets: Sodium-hydrogen antiporter 3-regulator1 (SLC9A3R1), Anotacmin1 (ANO1) and Rab27A.

Results: The in vivo transfection of the LNA-antimiR produced an increase in protein levels of ezrin and a decrease in the saliva secretion. ANO1 did not appear to form complex with ezrin in human SG. The complex ezrin/SLC9A3R1 was decreased in apical pole acinar cells of SS patient. A similar change was observed for ezrin/Rab27.

Conclusion: These experiments suggest that in SG of SS patients the overexpression of ezrin is produced by the down regulation hsa-miR-183 and propose a role of ezrin in the mechanism of SG hyposecretion. In this mechanism the mislocalization of ezrin affect the localization of the sodium-hydrogen antiporter 3-regulator1, altering the activation of the SLC9A3R1 and the electrolyte balance to regulate water secretion. Additionally, the change in the interaction of ezrin- Rab27A would affect the fusion of the secretory granules with apical plasma membrane.

Disclosure: P. Perez Rivers1, None; M. Tandon, None; S. Kazmi, None; A. Gallo, None; G. G. Illi, None; I. Alevizos, None.

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Expression of Indoleamine 2,3 Dioxygenase-1 and -2 in Focal Sialoadenitis of Patients with Sjögren’s Syndrome.

Claudio Vitali1, Antonina Przfioriti2, Domenico Sambataro2, Andrea Di Bernardo3, Elisabetta Admiraglio3, Saba Nayar3, Francesca Barone4 and Nicoletta Del Papa5. 1Istituto San Giuseppe, Como, Italy, 2Istituto G.Pini, Milan, Italy, 3University of Birmingham, Birmingham, United Kingdom.
Background/Purpose: The role of indoleamine 2,3 dioxygenase 1 and 2 (IDO1, IDO2) enzymes in modulating the immune response has not been so far completely clarified. IDO1 may induce immune-tolerance by suppressing antigen-specific T-cell response, directly or by activating T-reg cells, as shown in some cancer cells and in the placental tissue. IDO1 and IDO2 function in autoimmune diseases is controversial. In collagen-induced arthritis of DBA/1 mice, IDO1 limits the arthritis phenotype, as suggested by arthritis worsening after IDO1 inhibition. Conversely, IDO2 is critical for arthritis development in K/BxN transgenic mice, since IDO2-null mice display less aggressive joint inflammation.

This study was aimed at investigating whether IDO1/IDO2 are expressed in focal sialoadenitis of Sjögren’s syndrome (SS), and possibly at identifying the inflammatory cells where these enzymes are active.

Methods: Minor salivary gland biopsies from 22 patients (21 F with SS (according to the AECG classification criteria) were examined for IDO1 and IDO2 expression by using monoclonal antibodies, and immuno- histochemical (IH) and immuno-fluorescence (IF) methods. In IH-stained sections the prevalence (or number) of CD3+ T-cells, CD20+ B-cells, CD123+ dendritic cells (DC), IDO+ cells and of the other inflammatory cells was investigated by IF methods.

Results: IH studies showed that IDO1 was notably expressed within the focal infiltrates. Correlations were found between the amount of IDO1+ cells and the focus score (R = 0.52, p < 0.005), the prevalence of B-cells (R = 0.79, p < 0.0005), and the number of DCs (R = 0.64, p < 0.005). IDO2 was expressed in the vessel walls and ductal cells surrounded by infiltrates, but not in the CD3+ T-cell area.

In germinal centre-like foci, IF studies showed that IDO1+ cells were noticed around the B-cell area, at the boundaries of the T-cell zone. IDO2 was expressed only in a part of samples within the B-cell area, and in both CD3+ plasma cells and CD68+ macrophages.

Conclusion: In focal infiltrates of patients with SS, different areas and different cells may express IDO1 and IDO2 enzymes, thus suggesting that activity and function of these molecules in this context could be different.

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Adipose Tissue Is Prominent in Salivary Glands of Sjögren’s Syndrome Patients and Appears to Influence the Autoimmune Microenvironment in These Organs. Kathrine Skarstein1, Lara Adnan Agrawi1, Roland Jonsson1 and Janice Cecille Liaaen Jensen2, 1University of Bergen, Bergen, Norway, 2University of Oslo, Oslo, Norway.

Background/Purpose: A positive salivary gland (SG) biopsy with a focus score of ≥ 1 is the only widely accepted pathological finding confirming the salivary gland component of Sjögren’s syndrome (SS). SG biopsies can yield important information about the autoimmune activity and severity of the disease process including identification of germinal centers that may be possible predictors of lymphoma development. Moreover, adipocytes can occupy a large percentage of the gland area, and at present, little is known about their significance in SS lesions. The aim of the present study was to characterize adipose tissue infiltration in labial SG biopsies of patients under evaluation for SS.

Methods: 3–5 SGs were excised from the lower lip following a standard procedure. Evaluation of the glands was performed by one oral pathologist and included area assessment and counting of foci (dense aggregates of 50 or more mononuclear cells), as well as evaluation of acinar atrophy, fatty replacement, interstitial fibrosis, nonspecific chronic inflammation, and scattered or focal infiltrates of mononuclear cells adjacent to tissue not appearing normal. Patients were classified according to the AECG classification criteria and included 28 SS patients and 28 subjects evaluated for SS but not fulfilling the criteria (non-SS controls). IL-6 (rabbit polyclonal, Abcam-ab6672) expression was assessed by immunohistochemical staining of paraffin embedded salivary gland biopsies from SS patients and non-SS controls.

Results: Fatty replacement was evident in all SS patients possessing autoantibodies (RoSS-A and/or LaSS-B) as well as a positive SG biopsy (focus score ≥ 1), whereas 62% of the SS patients having autoantibodies but a negative biopsy showed fatty infiltration. Less than one third of the non-SS controls demonstrated fatty replacement. Overall, the SS group (mean age 53.0 years) had a significantly higher degree (p-value 0.0003) of fatty infiltration than the non-SS controls (mean age 54.8 years). Interestingly, adipocytes were located in IL-6 rich areas, and scattered IL-6 positive adipocytes were detected.

Conclusion: Our observations indicate that although fatty infiltration may occur in the repair process of glandular epithelium, fat deposition seems to be more extensive in salivary glands affected by SS. The important finding of IL-6 positive adipocytes supports the notion that adipocytes have the potential to secrete IL-6, thus being active contributors to immune reactions. Further analysis to delineate possible roles of adipocytes in the autoimmune salivary gland microenvironment is needed. Moreover, assessing the adipose tissue replacement may be helpful for diagnostic accuracy in SS.

Disclosure: K. Skarstein, None; L. A. Agrawi, None; R. Jonsson, None; J. C. Liaaen Jensen, None.

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Predictive Significance of CCL21 and CXCL13 Levels in the Minor Salivary Glands of Patients with Sjögren’s Syndrome. Kyung-Eun Lee, Dong-Jin Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea.

Background/Purpose: Chemokines, which control inflammatory cell migration, have been shown to play important roles in the inflammatory processes associated with Sjögren’s Syndrome (SS). CCL21 and CXCL13 within the lymphocytic infiltrate characteristic of the condition have been reported to contribute to ectopic lymphoepoiesis. In the current study, we investigated whether the laboratory and clinical manifestations of SS patients were associated with CCL21 and CXCL13 expression levels in the minor salivary gland.

Methods: We obtained sociodemographic data on a total of 106 SS patients, documented glandular and extraglandular manifestations of the disease, performed minor salivary gland biopsies, and analyzed laboratory findings, EULAR index values of SS disease activity (ESSDAI values) at the time of biopsy, and SS disease damage index (SSDDI) values, were also noted. An immunohistochemical approach was used to (semiquantitatively) measure the expression levels of CCL21 and CXCL13 in the minor salivary glands.

Results: The minor salivary glands of SS patients stained positively for CCL21 and CXCL13 in 46.2% (49/106) and 70.7% (75/106) of all cases, respectively. Higher-level expression of CCL21 was associated with an elevated ESR, an increased IgG level, elevated anti-SS-A and -SS-B titers, a higher focus score, and a greater ESSDAI value at the time of biopsy. Higher-level expression of CXCL13 was associated with an elevated ESR, an increased IgG level, elevated anti-SS-A and -SS-B titers, a rise in the level of rheumatoid factor, a higher focus score, and a greater ESSDAI value at the time of biopsy. In patients with extraglandular manifestations of SS, the prevalence of lymphadenopathy tended to rise with an increase in the level of CCL21.

Conclusion: The expression levels of CCL21 and CXCL13 within the lymphocytic infiltrates of SS patients were associated with several laboratory features of the disease, lymphadenopathy, and the extent of clinical disease activity. CCL21 and CXCL13 levels should serve as useful markers predicting SS disease activity and prognosis.

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Serum Biomarkers of Inflammation and Fibrosis in Advancing Diagnosis, Prognosis and Treatment of Anti-Ro Associated Congenital Heart Block. Amit Saxena, Peter M. Izmirly, Sung Won Han, Andrew Markham, Robert M. Clancy and Jill P. Buyon. New York University School of Medicine, New York, NY.

Background/Purpose: Women with Sjögren’s Syndrome (SS) and anti-Ro antibodies face the risk of a pregnancy complicated by fetal congenital heart block (CHB). Identification of maternal and fetal biomarkers which associate with development and morbidity of CHB should provide clues to pathogenesis with translational implications for management. Several candidates were chosen based on potential roles in cardiac disease, inflammation and fibrosis: 1) C-reactive Protein (CRP), elevated in fetal sepsis and hypoxia 2) NT-proBNP, elevated in neonates with congenital heart disease 3) Matrix Metalloproteinase-2 (MMP2), a proinflammatory/profibrotic factor associated with heart failure in adults 4) Urokinase plasminogen activator, its receptor and plasminogen (UPA, UPAR, PGN), proteins in a cascade induced by anti-Ro binding to apoptotic cardiocytes, resulting in TGFβ activation 5) Vitamin D, negative regulator in TGFβ signaling and fibrosis.

Methods: Sera from anti-Ro positive mothers and cord blood from their CHB and unaffected children in the Research Registry for Neonatal Lupus...
were analyzed. Cord CRP and NT-proBNP were assessed on Luminex and MMAP2, UPA, UPAR and PG in ELISA. Maternal vitamin D 25-OH was analyzed by LC-MS. Logistic regression was applied to identify predictors of CHB, fetal echo endocardial fibroelastosis (EFE) and hydrops, need for and age at pacemaker (PM) placement, and requirement of B-Blocker, digoxin, and/or ACE-I on long term follow up. Confounders were added stepwise, including maternal steroid, HCQ and IVIg use, race, maternal SS/lnusps, child's gender, gestational week (GW) of delivery, and GW of greatest disease vulnerability during winter. Skewed data were log transformed for normalization.

Results: Log transformed levels of cord CRP positively associated with CHB and hydrops in 50 affected and 62 unaffacted cases (adjusted OR 1.65, p = 0.02, OR 3.7, p = 0.02). Log cord NT-proBNP positively associated with CHB and hydrops in 57 affected and 65 unaffected (OR 2.24, p = 0.01, OR 2.46, p = 0.02). Log cord MMP2 positively associated with CHB in 36 affected and 28 unaffected (OR 20.23, p = 0.01). Cord UPA (OR 45.42, p = 0.001), UPAR (OR 1.29, p = 0.03) and log PGN (OR 38.28, p < 0.001) were positively associated with CHB in 27 affected and 22 unaffected. UPA and log PGN (OR 1.22, p = 0.02, OR 1.27, p = 0.03) were positively associated with cardiac meds (mean age at follow-up 7.34 ± 4.93 y) in 18 affected cases. Other cord biomarkers did not associate with PM, timing of PM or cardiac meds. Although maternal vitamin D at GW 20 of CHB and healthy pregnancies were equivalent (34.3 ± 11.3 and 34.1 ± 14.5 mg/dl in 81 unaffected), levels were negatively associated with fetal EFE (OR 0.89, p = 0.03), and positively associated with later age at PM (p = 0.01) in CHB cases.

Conclusion: Elevated inflammatory markers in neonates with CHB and extranodal disease support close follow up to identify worsening heart function. The association of NT-proBNP supports consideration of this maker as a diagnostic during amniocentesis. Elevations of MMP2, UPA, UPAR and PGN in CHB children suggest therapies aimed at decreasing fibrosis. Optimizing maternal vitamin D levels could become routine in the management of all anti-Ro positive pregnancies.

Disclosure: A. Saxena, None; P. M. Izmirly, None; S. W. Han, None; A. Markham, None; R. M. Clancy, None; J. P. Buyon, None.

535 WITHDRAWN

ACR Poster Session A
Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
Sunday, November 16, 2014, 8:30 AM–4:00 PM

536 Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a Phase 3, Randomized, Placebo-Controlled Trial with Subcutaneous Loading and Maintenance Dosing. Joachim Sieper1, Jürgen Braun2, Xenofon Bartaliokos3, Dominique L. Baeten4, Maxime Dougas5, Paul Emery6, Atul A. Deodhar7, Brian Porter7, Mats Andersson8, Shephard Mpofu8 and Hanno Richards8. 1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Rheumazentrum Ruhrgebiet, Herne, Germany, 3Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, 4INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France, Paris, France, 5University of Leeds, Leeds, United Kingdom, 6Oregon Health and Sciences University, Portland, OR, 7Novartis Pharmaceuticals Corporation, East Hanover, NJ, 8Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Previous data indicate that interleukin (IL)-17, a key pro-inflammatory cytokine, might play a role in the pathogenesis of ankylosing spondylitis (AS). We assessed the efficacy and safety of two different doses of secukinumab, a fully human anti-IL-17A monoclonal antibody, in a randomized, multicenter, double-blind, placebo (PBO)-controlled, phase 3 trial in patients with AS (MEASURE 2; NCT01649375).

Methods: Adults with active AS fulfilling modified New York Criteria and a BASDAI ≥ 4, despite adequate NSAID therapy, were randomized to receive weekly subcutaneous (s.c.) secukinumab 75 mg, 150 mg or PBO for 4 weeks followed by dosing every 4 weeks. Subjects naïve to anti-TNF agents (61.6%) and subjects with prior intolerance or inadequate response to anti-TNF agents (TNF-IR; 38.4%) were included. The primary endpoint was the proportion of subjects achieving an ASAS20 response at Week 16. Secondary endpoints included ASAS40, hsCRP, BASDAI ASAS 5/6, SF-36, ASQoL, and ASAS partial remission. Statistical analyses used non-responder imputation and followed a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity.

Results: 219 subjects were randomized. Demographics and baseline disease characteristics were comparable between study arms: mean age 43.3 years, mean time since diagnosis 6.2 years and mean BASDAI 6.65. The primary endpoint was met with secukinumab 150 mg at Week 16: ASAS20 response rate was 61.1% vs. 27.0% with PBO (P < 0.001; Figure), with significant improvements seen as early as Week 1. Secukinumab 150 mg also significantly improved hsCRP, ASAS40, ASAS 5/6, BASDAI SF-36 PCS and ASQoL compared with PBO. Efficacy of secukinumab 150 mg vs. PBO was observed in both TNF-naïve and TNF-IR subjects for ASAS20 (68.9% vs. 31.1% and 48.1% vs. 20.7%, respectively; both P < 0.05) and ASAS40 (44.4% vs. 17.8% and 22.2% vs. 0%, respectively; both P < 0.05). Secukinumab 75 mg provided numerically greater responses than PBO at Week 16, but these did not reach statistical significance for any of the pre-specified primary or secondary endpoints based on hierarchical testing. Similar adverse event (AE) rates were reported up to Week 16 for secukinumab 75 mg (57.5%), 150 mg (62.5%), and PBO (63.5%). Serious AEs were reported in 5.6% of subjects in the secukinumab 75 mg group, compared with 5.6% in the secukinumab 150 mg group and 4.1% in the PBO group.

Conclusion: Secukinumab 150 mg s.c. was effective at rapidly reducing the signs and symptoms of disease and improving health-related quality of life in subjects with active AS, regardless of prior anti-TNF exposure. Secukinumab was well tolerated, with no unexpected safety findings.

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Secukinumab, a Human Anti–Interleukin-17A Monoclonal Antibody, Significantly Reduces Psoriasis Burden in Patients with Psoriatic Arthritis: Results from a Phase 3 Randomized Controlled Trial. Alice B. Gottlieb1, Philip Mease2, Iain B. McInnes3, Bruce Kirkham4, Arthur Karvonen5, Jan P. van der Heijde6, Peter Nash7, Lumin L. Tulkens8, Jiacheng Yuan9, Hanno Richards10, and Shephard Mpofo11.

1Tufts Medical Center, Boston, MA, 2Swedish Medical Center and University of Washington, Seattle, WA, 3University of Glasgow, Glasgow, United Kingdom, 4Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom, 5UCSD School of Medicine, La Jolla, CA, 6Memorial University of Newfoundland, St. John’s, NF, 7University of Queensland, Brisbane, Australia, 8Novartis Pharmaceuticals Corporation, East Hanover, NJ, 9Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Reducing the burden of skin manifestations of psoriatic arthritis (PsA) is an important aspect of disease management. Secukinumab, a human anti–IL–17A monoclonal antibody, has demonstrated rapid and sustained efficacy in the treatment of psoriasis in phase 3 trials, including in the subset of patients (pts) with PsA. Here we present the effect of secukinumab on dermatological parameters in pts enrolled in FUTURE 1 (NCT0197226), the first phase 3 trial to evaluate the efficacy of IL–17A inhibition in pts with PsA.

Methods: Adults with moderate to severe PsA according to the Classification Criteria of Psoriatic Arthritis criteria were randomized to a secukinumab 10 mg/kg intravenous (i.v.) loading dose at baseline (BL), Week (Wk) 2, and Wk 4, then either 75 mg subcutaneously (s.c.; 10 IV → 75 SC) or 150 mg s.c. (10 IV → 150 SC) every 4 wks from Wk 4, or placebo (PBO) on the same i.v. and s.c. schedule. Pts with psoriasis skin involvement included 75% and 90% improvement in Psoriasis Area and Severity Index and Physician’s Global Assessment, respectively (mPsA52 and mPsA90), and the Dermatology Life Quality Index (DLQI) value ≤ 8. A random subset of patients (3%) of body surface area at BL (psoriasis subset), 510 pts, were included for analysis of psoriatic arthritis outcomes. The improvements in dermatological parameters observed with secukinumab at Wk 24 were analyzed by sensitivity analyses (SA) using the full analysis set (FAS) and in the per-protocol (PP) population.

Results: From the full analysis set (FAS) of 606 pts, 325 (53.6%) had psoriasis affecting > 3% of body surface area at BL (psoriasis subset), 510 pts, and 435 (71.8%) had nail involvement (nail subset). Improvements in dermatology parameters with secukinumab vs. PBO at Wk 24 are presented in the table. In the psoriasis subset, 10 IV → 75 SC and 10 IV → 150 SC significantly improved the proportion of PASI 75, PASI 90, and IGA 0/1 responders vs. PBO at Wk 24, and provided clinically meaningful improvement (≥ 4-point change from BL) in DLQI, with most pts having a decline in DLQI score from > 10 (severe) at BL to < 4 at Wk 24. Pts in the TLS subset experienced a rapid (from Wk 1) and significant improvement in TLS with secukinumab vs. PBO at Wk 24, while mPsA52 was significantly improved with secukinumab in the nail subset. hsCRP values were significantly lower with secukinumab vs. PBO from Wk 1 through Wk 24 (FAS). The improvements in dermatological parameters observed with secukinumab at Wk 24 were sustained through Wk 52.

Table. Effect of treatment on skin and involvement at Week 24

<table>
<thead>
<tr>
<th>BL and Wk 24 Data</th>
<th>Secukinumab10 mg/kg IV → 75 mg SC</th>
<th>Secukinumab10 mg/kg IV → 150 mg SC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75% / % responders</td>
<td>64.8*/49.1*</td>
<td>61.1*/45.4*</td>
<td>83.7/3.7</td>
</tr>
<tr>
<td>PASI 90% / % responders</td>
<td>54.6*/49.1*</td>
<td>60.0</td>
<td>6.1</td>
</tr>
<tr>
<td>IGA 0/1 / % responders</td>
<td>5.5</td>
<td>-4.4*</td>
<td>-3.1</td>
</tr>
<tr>
<td>LS</td>
<td>18.6</td>
<td>18.7</td>
<td>17.5</td>
</tr>
<tr>
<td>BL</td>
<td>-12.3*</td>
<td>-10.9*</td>
<td>-4.1</td>
</tr>
<tr>
<td>Mean change from BL</td>
<td>11.2</td>
<td>12.6</td>
<td>12.5</td>
</tr>
<tr>
<td>BL</td>
<td>-7.87*</td>
<td>-8.80*</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Conclusion: This is the first phase 3 trial in pts with active PsA to demonstrate that selective IL–17A inhibition with secukinumab significantly reduces the severity of plaque and nail psoriasis and improves quality of life in those pts with a significant concomitant psoriasis burden in addition to their joint disease.

Disclosure: A. B. Gottlieb, Consulting fees from Amgen Inc., Astellas, Akros, Centocor (Janssen), Inc. Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (AbbVie), DUSA, TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermispor Ltd., Incyte, Pfizer; C. K. Kirkham, Lilly, 5, Advisory Board Agreements: Amgen Inc., Astellas, Akros, Centocor (Janssen), Inc. Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (AbbVie), DUSA, TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermispor Ltd., Incyte, Pfizer, Cantile, 9, Research/Educational Grants (paid to Tufts Medical Center); Centocor (Janssen), Amgen, Abbott (AbbVie), Novartis, Celgene, Pfizer, Lilly, Corronado, Levia, Merck, 2, P. Mease, Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UC; and, Vertex, 2, Consulting fees from: AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UC, and, Speaker’s bureau: Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, and, UC; 8, L. B. McInnes, Consulting fees from Novartis, Amgen, Janssen, BMS, Pfizer, UC, Abbvie, Celgene and Lilly; 5, B. Kirkham, Research grants from AbbVie and UC2, 2, Consulting fees from Novartis, AbbVie, BMS, Lilly, and, MSD, 5, Speaker’s bureau BMS, MSD, and UC; 8, A. Kavanaugh, Consulting fees from Novartis, 5, P. Rahman, Consulting fees from Abbott, AbbVie, Amgen, BMS, Celgene, Janssen, Novartis, Pfizer and Roche; 5, P. Nash, from Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene, 2, Honoraria for lectures and advice from Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene, 9, L. Priop, Employee of Novartis, 3, N. Yuan, Employee of Novartis, 3, H. Richards, Employee of Novartis, 3, S. Mpofo, Novartis stock, 1, Employee of Novartis, 3.

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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Physical Function and Quality of Life in Subjects with Active Ankylosing Spondylitis: Results of a Phase 3 Randomized, Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Atul A. Deodhar, Dominique L. Baeten, Jürgen Braun, Xenofon Baraliakos, Joachim Sieper, Maxime Dougdas, Paul Emery, Brian Potter, Ruvie Martin, Shephard Mpofo, Hanno Richards, Antwerp Rheumatology and Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, Rheumazentrum Ruhrgebiet, Herne, Germany, Charité Universitätsmedizin Berlin, Berlin, Germany, Descartes University, Cochin Hospital, Paris, France, University of Leeds, Leeds, United Kingdom, Novartis Pharmaceuticals Corporation, East Hanover, NJ, Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Ankylosing spondylitis (AS) can have a profound negative effect on an individual’s physical functioning, health status and quality of life (QoL), affecting the ability to work (Sieper J et al. Ann Rheum Dis. 2002). Since interleukin (IL)–17A is implicated in the pathogenesis of AS (Douagos M. Baeten, D. L. Baeten, M. L. Baeten, 2011), improvement of cytokine with secukinumab, a fully human anti–IL–17A monoclonal antibody, may help reduce the burden of disease. Here we present the impact of high-dose intravenous (i.v.) loading with secukinumab followed by subcutaneous (s.c.) maintenance dosing on patient-reported outcomes (PROs) in a phase 3 trial (MB2–4; NCT01358175) over 52 weeks.

Methods: 371 adults with active AS fulfilling modified New York Criteria and Bath Ankylosing Spondylitis Disease Activity Index ≥ 4 were randomized to receive i.v. secukinumab 10 mg/kg (Week 0, Week 2, Week 4) followed by s.c. secukinumab 75 mg every 4 weeks (10 IV → 75 SC); i.v. secukinumab 10 mg/kg (Week 0, Week 2, Week 4) followed by s.c. secukinumab 150 mg every 4 weeks (10 IV → 150 SC); or i.v. placebo (Week 0, Week 2, Week 4) followed by s.c. placebo every 4 weeks (placebo group; PBO). PBO subjects were re-randomized to either 75 mg or 150 mg s.c. secukinumab based on ASAS20 response at Week 16, with non-responders switched to secukinumab at Week 16 and responders at Week 24. PROs were measured every 4 weeks using the following questionnaires: short form 36 (SF-36), EuroQol (EQ-5D), ASC QoL (ASQoL), Functional Assessment of Chronic Illness Therapy — Fatigue (FACT-Fatigue) and Work Productivity and Activity Impairment — General Health (WPAI-GH). PROs to Week 16 are reported using a mixed-effect model repeated measures (MMRM) analysis, except WPAI-GH domains which are observed data.

Results: Demographics and disease severity were comparable among the three groups with subjects experiencing moderate to severe levels of fatigue and impaired health-related QoL at baseline. Secukinumab groups 75 SC and 150 IV → 150 SC significantly improved scores on the SF-36 physical and mental component summaries, ASQoL, EQ-5D and FACT-Fatigue vs. PBO at Week 16 (Table), with significant differences in these parameters seen with both doses in all assessments starting at Week 4. Mean changes from baseline at Week 16 were greater than the minimum clinically important difference (MCID) for SF-36.
Efficacy and Safety of Ustekinumab in Psoriatic Arthritis Patients with Spondylitis and Peripheral Joint Involvement: Results from a Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study. Arthur Kavanaugh1, Lluis Puig Sanz2, Alice B. Gottlieb3, Christopher T. Ritchlin4, Yin You5, Yuhua Wang5, Alan M. Mendelssohn6, Michael Song7, Proton Raham8 and Ian B. McNeile9. 1University of California San Diego, La Jolla, CA, 2Universitat Autonoma de Barcelona, Barcelona, Spain, 3Tulane University Medical Center, Boston, MA, 4University of Rochester Medical Center, Rochester, NY, 5Janssen Research & Development, LLC, Spring House, PA, 6Memorial University of Newfoundland, St. John's, NF, 7University of Glasgow, Glasgow, United Kingdom.

Methods: Adult PsA patients (n=615) with active disease (≥5 SJC and ≥5 TJC) were randomized to UST45mg or Placebo at wks 0, 4, and q12wks. Pts receiving prior anti-TNF agents were excluded. Stable concomitant MTX was permitted but not mandated. At wk16, pts with <5% improvement in TJC & SJC entered blinded early escape (PBO—UST45mg; UST45mg—90mg; 90mg—90mg). PBO pts subsequently crossed over to UST45mg at wk24. Pts received q12w dosing to wk88, with final efficacy evaluation at wk100 and safety assessment at wk108. Pts with spondylitis and peripheral joint involvement as their primary arthritis presentation of PsA also had BASDAI assessments at wks12 and 24.

Results: 186 randomized pts (70 PBO, 116 UST combined) had spondylitis with peripheral joint involvement at baseline (30% of overall population); mean baseline characteristics were similar to the overall population (age 45.6yrs, weight 82.8kg, PsA duration 6.3yrs). At Wk14, 91.1%/83.0%/94.0% of UST45mg/90mg/Placebo pts had dactylitis or peripheral joint involvement. Clinical improvements were generally maintained through wk100. A significantly higher proportion of UST-treated pts achieved BASDAI20/50/70 responses vs. PBO at wk24 (54.1%/27.9%/14.4% vs. 26.2%/13.1%/0.0%). Peripheral structural damage assessed by total xHS-S scores also showed improvement in the UST groups vs PBO at wk24. Of the 135 patients with ≥3% BSA involvement and spondylitis with peripheral arthritis at baseline, PASI75 responses were also maintained through wk100. During the PBO-controlled period, the proportion of pts with AEs were comparable between the PBO and combined UST-treated groups (AEs 32.9% vs. 24.1%; SAs 14.0% vs. 9.0%; discontinuations due to AEs 2.9% vs. 0.9%; serious infections 14.3% vs. 7.8%). Through 2yrs, safety observations were consistent with the overall PsA population.

Conclusion: In this post-hoc subgroup analysis, UST significantly improved signs and symptoms, and demonstrated improvements in BASDAI and peripheral radiographic progression compared with PBO through wk24; efficacy was maintained through wk100. UST was well-tolerated and demonstrated a safety profile similar to that observed in the overall PsA study population.
Background/Purpose: According to the ASAS axial spondyloarthritis (SpA) criteria, patients suffering from inflammatory back pain (IBP) can be recognized as suffering from axial SpA even in the absence of structural damage of the sacroiliac joints (SIJ) but the natural history of these patients is not well known. The objective of this study was to evaluate 1) the rate of SIJ structural progression over a 2 years period and 2) the influence of baseline objective signs of inflammation on this progression rate in patients suffering from recent onset inflammatory back pain suggestive of SpA.

Methods: Patients: IBP < 3 years duration suggestive of axial SpA according to the treating rheumatologist (DESIR cohort)
Outcome measures: Pelvic X-rays collected both at baseline and at the 2 year follow up visit and MRI of the SIJ collected at baseline were stored after anonymizing and blinding for the visit. Radiographic structural damage was defined as the fulfillment of the modified New-York (mNY) criteria and inflammation on MRI ("positive MRI") was defined according to the ASAS criteria. The radiographs and MRIs were read centrally by two pairs of well calibrated central readers blinded for clinical, laboratory and other imaging data. In case of disagreement, images were adjudicated by an experienced radiologist.

CRP at baseline was defined as abnormal if >6 mg/l.

Results: Of the 708 enrolled patients, 449 had a complete radiological data set (34 + 9 years old, 53 % females, HLA B27 positive: 61%). At baseline, 123 of 449 (27%) fulfilled the mNY criteria. Of the remaining 326 patients, 16 (4.9%) progressed (fulfilling the mNY criteria at the 2 year visit). Among these 326 patients, baseline MRI, CRP and both MRI and CRP were available in 307, 314 and 303 patients respectively. The table summarizes the main findings of this study. MRI positivity, CRP abnormality and either MRI positivity or CRP abnormality was observed in 14/15 (93%) versus 67/292 (23%), 7/15 (46%) versus 61/299 (20%) and 14/15 (93%) versus 11/288 (39%) of the patients with versus without a radiographic progression after the 2 year follow up visit. A normal MRI and CRP at baseline almost excluded the development of sacroilitis according to the mNY criteria after two years.

Table: SIJ structural progression among the 326 patients not fulfilling SIJ mNY criteria at baseline

<table>
<thead>
<tr>
<th>SIJ structural progression</th>
<th>Baseline Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>mNY positive at year 2</td>
<td>Sex (% male)</td>
</tr>
<tr>
<td>positive</td>
<td>14*</td>
</tr>
<tr>
<td>negative</td>
<td>67</td>
</tr>
<tr>
<td>OR: 47.0 (6.1–364.1)</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>PPV: 0.17</td>
</tr>
<tr>
<td>negative</td>
<td>1</td>
</tr>
<tr>
<td>abnormal</td>
<td>225</td>
</tr>
<tr>
<td>OR: 0.0004</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>PV: 0.010</td>
</tr>
<tr>
<td>normal</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>OR: 3.1 (1.2–9.8)</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>PPV: 0.10</td>
</tr>
<tr>
<td>presence</td>
<td>8</td>
</tr>
<tr>
<td>238</td>
<td></td>
</tr>
<tr>
<td>OR: 0.033</td>
<td></td>
</tr>
<tr>
<td>Infarction**</td>
<td>PV: 0.011</td>
</tr>
<tr>
<td>absence</td>
<td>14</td>
</tr>
<tr>
<td>117</td>
<td></td>
</tr>
<tr>
<td>OR: 0.006</td>
<td></td>
</tr>
</tbody>
</table>

*values given are the number of patients and OR [1]; Odds ratio [95% confidence interval]; PPV: positive predictive value; NPV: negative predictive value.
**baseline inflammation: either MRI positive or abnormal CRP.

Conclusion: These data suggest that 1) SIJ structural progression to fulfillment of mNY criteria in this cohort was low after a two years follow-up period 2) the presence of objective signs of inflammation are a predisposing factor of structural progression keeping in mind that the majority of patients with baseline signs of inflammation did not progress.

Disclosure: M. Dougdas, Pfizer Inc; 2, C. Demattei, None; R. van den Berg, None; V. Vo Hong, None; F. Thivenin, None; M. Reijnierse, None; D. Loeuille, None; A. Feydy, None; P. Claudepierre, None; D. van de Heijde, None.

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Collagen II Neo-Epitopes in Spondyloarthritis. Heidi Lausten Munk1, Natasja Staelr Gudmann2, Anne Friesgaard Christensen3, Leif Ejstrup4, Grith Lykke Sørensen2, Anne Gite Loft3, Anne C. Bay-Jensen2, Anne Sofie Siebuth2 and Peter Junker1, 1Department of Rheumatology, Odense University Hospital, Odense, Denmark, 2Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, 3Department of Rheumatology, Vejle Hospital, Vejle, Denmark, 4Department of Rheumatology, Esbjerg Hospital, Esbjerg, Denmark, 5Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark.

Background/Purpose: Spondyloarthritides (SpA) is characterized by aspecific inflammation of the axial skeleton which may ultimately lead to irreversible deformities due to bony ankylosis. Occasionally, peripheral joints and extraskeletals sites are also involved. The etiology is unknown, but there is a well-established association with HLA-B27. Intervertebral discs and diarthrodial joints of the spine are targeted by the disease, and studies on cartilage have indicated increased turnover of several extracellular matrix components, mainly collagen, in active ankylosing spondylitis (AS). Thus, C2M, a matrix metalloproteinase derived collagen type II fragment has been found to be increased in AS. Procollagen II, an alternatively spliced collagen II variant, is preferentially expressed during embryogenic skeletal patterning where it is supposed to participate in the regulation of chondro- and osteogenesis. In adults PIIANP is present in damaged cartilage and osteophytes.

The aims of this investigation were to assess collagen II turnover in SpA by studying C2M and PIIANP concomitantly in patients treated with or without TNF inhibitors (TNFi).

Methods: One hundred and ten patients (age 18–63 years) with SpA according to the ASAS criteria were recruited from two secondary and one tertiary center. Demographic and clinical disease measures were recorded. Ninety six volunteer blood donors served as healthy controls. C2M and PIIANP were quantified in serum by ELISA. Mann–Whitney U test for intergroup comparisons and Spearman’s rank test for correlations were applied. The discriminative power of the serum markers between healthy and diseased was calculated by receiver-operator characteristics (ROC) and expressed by the area under the curve (AUC).

Results: The serum level of C2M was higher in SpA patients compared to healthy controls (p<0.01)(table). The PIIANP level did not differ between SpA patients and controls. There was no correlation between C2M and PIIANP. C2M correlated negatively with smoking (r = −0.22;p =0.02) and positively with disease duration (r = 0.31;p =0.001). C2M AUC was estimated to 0.67.

These findings indicate that active SpA is associated with enhanced cartilage turnover as reflected by increased collagen II degradation and repair. Conversely, this sero-marker profile was normal during TNFi treatment. In addition, C2M discriminates well between healthy subjects and SpA.

Disclosure: H. L. Munk, None; N. S. Gudmann, Nordic Bioscience Diagnostic, 3; A. F. Christensen, None; L. Ejstrup, None; G. L. Sørensen, None; A. G. Loft, None; A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 3; A. S. Siebuth, Nordic Bioscience Diagnostic, 3; P. Junker, None.
Predictors for Cardiovascular Events in Patients with Psoriatic Arthritis – a Cohort Study. Lili Eder1, Arane Thavaneswaran1, Vinod Chandran1, Hua Shen2, Richard J. Cook2 and Dafna D. Gladman1. 1University of Toronto, Toronto Western Hospital, Toronto, ON, 2University of Waterloo, Waterloo, ON.

Background/Purpose: The prevalence of cardiovascular (CV) morbidity is increased in patients with psoriatic arthritis (PsA). CV risk is only partially explained by traditional CV risk factors. We aimed to identify predictors for CV events in a cohort of patients with PsA.

Methods: A retrospective cohort analysis was conducted in patients attending a large PsA clinic from 1978 to 2013. Patients were assessed at 6–12 month intervals according to a standard protocol. The collected information included demographics, lifestyle habits, medical history and disease-related outcomes. The following factors were assessed as candidate predictors of CV events: traditional CV risk factors, measures of PsA disease activity and laboratory biomarkers of inflammation. The primary outcome was the time to the first major CV event that comprised myocardial infarction (MI), ischemic stroke, re-vascularization or CV death. The secondary outcome was the time to any first CV event that included major CV events, angina, transient ischemic accident (TIA) and congestive heart failure (CHF). Each event was confirmed by reviewing hospital records and death certificates. Cox proportional hazard model, with time-dependent explanatory variables and date of birth as the time of origin, was used to compute the multivariate relative risk (RR) for incident CV events adjusting for sex and duration of PsA.

Results: The analysis included 1103 patients with PsA for a combined follow-up time of 10,751 person-years, during which 104 cardiovascular events occurred (57 MI, 9 stroke, 19 re-vascularization, 2 CV death, 10 angina, 1 TIA and 6 CHF). The mean follow-up period was 9.8±8.5 years. The mean age at the first visit was 44±12.9 years and 56.3% of the patients were males. The incidence rate of CV events did not change significantly across the three decades from 1978 to 2013 (p = 0.65). The following variables were associated with a higher incidence rate of major CV events: diabetes (RR 2.7, p = 0.002), hypertension (RR 1.93, p = 0.003), high triglycerides (RR 1.95, p = 0.005), high cholesterol (RR 1.58, p = 0.05), erythrocyte sedimentation rate (ESR) (RR 1.36, p = 0.009), leukocyte count (RR 2.19, p = 0.007) and tender joint count (RR 1.34, p = 0.01). The variables that were associated with a higher incidence rate of any CV event were: diabetes (RR 2.68, p = 0.0007), hypertension (RR 1.99, p = 0.0008), high triglycerides (RR 1.71, p = 0.02), ESR (RR 1.30, p = 0.02) and tender joint count (RR 1.34, p = 0.01). Achieving a minimal disease activity state was associated with a lower incidence rate of major CV events (RR 0.56, p = 0.009) and any CV event (RR 0.62, p = 0.02). No association was found between the use of non-steroidal anti-inflammatory drugs, disease modifying anti-rheumatic agents or TNF-α blockers and CV events.

Conclusion: Cardiovascular morbidity in patients with PsA is explained by the presence of elevated inflammatory burden and traditional CV risk factors. The achievement of a minimal disease activity state may decrease CV risk in patients with PsA.

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543 Disease Activity and Clinical Response Early in the Course of Treatment Predict Long-Term Outcomes in Axial Spondyloarthritis Patients Treated with Certolizumab Pegol. Désirée M. van der Heijde1, Atul A. Deodhar2, Owen Davies3, Tommi Nurminen4 and Martin Rudwaleit5. 1Leiden University Medical Center, Leiden, Netherlands, 2Oregon Health and Science University, Portland, OR, 3UCB Pharma, Slough, United Kingdom, 4UCB Pharma, Monheim, Germany, 5Endokrinologikum, Berlin, Germany.

Background/Purpose: Early response to anti-TNF therapy has been shown to be a strong predictor of good long-term outcomes in ankylosing spondylitis (AS). However, early identification of patients (pts) unlikely to achieve good long-term disease control by anti-TNF therapy has been less well characterized, although identifying such pts may help avoid unnecessary exposure, increase cost-effectiveness and improve the chance of achieving long-term treatment goals. Here we aim to assess the association between disease activity (DA) during the first 12 weeks (wks) of treatment, and attainment/lack of attainment of treatment targets at Wk48 in axial spondyloarthritis (axSpA) pts, including AS and non-radiographic (nr-) axSpA pts, receiving certolizumab pegol (CZP).

Methods: The relationship between DA during the first 12 wks of treatment and achievement of the Wk48 treatment targets: ASDAS Inactive Disease (ID) or BASDAI <2 with or without CRP levels equal to or below the upper limit of normal (ULN = 7.9mg/L), was assessed post hoc using CZP data from the RAPID-axSpA trial (NCT01087762). DA state was defined for AS as: ID, moderate (MD), high (HD) or very high DA (vHD), and for BASDAI as Low (<2), Moderate (2 to <4), High (≥4 to ≥6) or Very High (≥7). BASDAI thresholds have not been validated. Analyses are based on all pts randomized to CZP (200mg Q2W or 400mg Q4W) in the overall axSpA population and also the AS and nr-axSpA subpopulations. Predictability analyses for a given wk are based on all pts continuing treatment at that wk. For these pts, LOCF was applied for withdrawals before, or missing evaluation at, Wk48.

Results: ASDAS ID state at Wk2 was associated with likelihood of achieving ID at Wk48, with 71% (22/31) of pts with ID at Wk2 achieving ID at Wk48, compared with 0% (0/27) of pts with vHD at Wk2 achieving ID at Wk48. A similar trend was observed at Wk12, although fewer pts had HD and vHD, and more pts had ID at this time point (Table A). BASDAI Very High DA also successfully predicted the lack of attainment of the treatment target BASDAI <2 + CRP ≤ULN (Tables B and C), and results were not altered if only BASDAI <2 (and not CRP level) was the target. Lack of clinical response (CR) to CZP was also an effective negative predictor of Week 48 DA (Table C), with 3/45 (6.7%) pts with Wk12 BASDAI improvement <1 achieving Wk48 DA of BASDAI <2, and 12/65 (18.5%) pts with Wk12 BASDAI improvement less than clinically important improvement (=<CII) achieving Wk48 ASDAS ID. Similar trends were observed in the AS and nr-axSpA subpopulations (Table D).

Conclusion: Using ASDAS or BASDAI state or CR during the first 12 wks of CZP treatment, it was possible to identify a subset of pts who are unlikely to achieve long-term treatment goals. This approach may enable physicians adopting a treat-to-target strategy to determine early on when to change therapy in pts not responding to CZP.

Disclosure: D. M. van der Heijde, AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanoft-Aventis, Schering-Plough, UCB, Vertex, 5; Imaging Rheumatology bv, 9; A. A. Deodhar, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 5; O. Davies, UCB Pharma, 3, UCB Pharma, 1; T. Nurminen, UCB Pharma, 3; M. Rudwaleit, Abbott, BMS, MSD, Pfizer, Roche, UCB Pharma, 5.
Observed Incidence Rates of Uveitis over 96 Weeks of Certolizumab Pegol Treatment in Patients with Axial Spondyloarthritis. James T. Rosenbaum,1 Martin Rudwaleit,2 Robert B. M. Landewe,3 Helena Marzo-Ortega4, Joachim Sieper,5 Désirée M. van der Heijde,5 Owen Davies,6 Christian Stach,3 Tommi Nurminen2 and Atul A. Deodhar.1,3,4 OHSU, Portland, OR, 5Endokrinologikum, Berlin, Germany, 3Amsterdam Rheumatology Center, Amsterdam, Amsterdam, Netherlands, 7University of Leids and NIH Research Unit, Leids, United Kingdom, 8University Hospital Charité, Berlin, Germany, 4Leiden University Medical Center, Leiden, Netherlands, 7UCB Pharma, Slough, United Kingdom, 8UCB Pharma, Monheim, Germany, 9Oregon Health and Sciences University, Portland, OR, 9Portland, OR.

Background/Purpose: Axial spondyloarthritis (axSpA) is characterized by inflammation in the spine and sacroiliac joints, but can also manifest as inflammation at extra-spinal sites, most commonly inflammation of the uvea (uveitis).1 Here we aim to estimate the incidence of uveitis flares in patients (pts) with axSpA following certolizumab pegol (CZP) treatment in the RAPID-axSpA trial.

Methods: RAPID-axSpA (NCT01087762) was double-blind and placebo-controlled (PBO)-controlled to Week (Wk) 24, dose-blind to Wk48 and open-label to Wk204. Pts fulfilled ASAS criteria and had active axSpA, including a history of uveitis (defined using standard medical history, ASAS classification criteria screening assessment and baseline extra-articular assessment). At Wk24, combined CZP dosing regimens were compared with PBO; for Wk96 analyses all pts exposed to CZP were considered. Incidence rates (IR) are reported per 100 pt-yrs (PY) with censoring at time of event. No analyses of statistical significance were carried out on these data.

Results: At baseline, 38/218 (17.4%) CZP-randomized pts had a history of uveitis, as did 31/107 (29.0%) PBO-randomized pts. The proportion of pts with history of uveitis was similar in AS (20.8%) and nr-axSpA (21.1%) subpopulations. During the 24-wk double-blind phase, overall IR of uveitis flares (regardless of previous history) was lower in CZP pts (IR = 2.0/100 PY) than PBO pts (IR = 10.6/100 PY). There were no de novo cases of uveitis flares observed to Wk24 – ie. all cases were observed in pts with history of uveitis. Events were analyzed in pts with or without a history of uveitis (defined using standard medical history, ASAS classification criteria screening assessment and baseline extra-articular assessment).

Conclusion: The IR of uveitis flares was lower for axSpA pts treated with CZP than with PBO during the randomized controlled phase, and was comparable to the rate reported for AS pts receiving anti-TNF therapy.

References:

Table A: Incidence of uveitis flares in axSpA patients treated with CZP or placebo to Week 24

<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients (n = 218)</th>
<th>PBO (n = 63)</th>
<th>Placebo (n = 54)</th>
<th>CZP (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR per 100 pt-yrs</td>
<td>2.0 (1.9–2.2)</td>
<td>0.0 (0.0–0.0)</td>
<td>4.0 (3.7–4.2)</td>
<td>2.0 (1.9–2.2)</td>
</tr>
<tr>
<td>Pts (Exposure, pt-yrs)</td>
<td>3824 (1752)</td>
<td>862 (205)</td>
<td>393 (97)</td>
<td>2960 (1353)</td>
</tr>
</tbody>
</table>

Table B: Incidence of uveitis flares in axSpA patients treated with CZP to Week 96

<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients (n = 218)</th>
<th>History of Uveitis (n = 315)</th>
<th>No History of Uveitis (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR per 100 pt-yrs</td>
<td>4.0 (3.1–4.9)</td>
<td>16.3 (13.4–19.1)</td>
<td>1.3 (0.9–1.7)</td>
</tr>
</tbody>
</table>
Psoriatic Arthritis Mutilans: Characteristics and Radiographic Progression.

Deepak R. Jadon1, Gavin Shaddick2, William Tillett3, Graham Robinson3, Charlotte Cavill3, Nicola Waldron3, Eleanor Korendowych3 and Neil A. McHugh4. 1Oregon Health and Sciences University, Portland, OR, 2Oregon Health & Science University, Portland, OR, 3OHSU, Portland, OR, 4Oregon Health and Science University, Portland, OR.

Background/Purpose: Psoriatic arthritis mutilans (PAM) is a rare extreme subtype of psoriatic arthritis (PsA). Our objectives were to: (1) compare clinical characteristics of PsA patients with PAM and without PAM (non-PAM); (2) determine the rate of PAM radiographic progression.

Methods: A retrospective cohort study was conducted of all PsA patients attending a teaching hospital. Clinical characteristics were recorded. Most recent radiographs of hands and feet were evaluated for PAM, defined as osteolysis affecting ≥50% of the articular surface on both sides of the joints. All available radiographs (earliest to most recent) were quantitatively scored for osteolysis, erosion, joint space narrowing, and osteoproliferation. Radiographic progression was analysed using random effects models to allow for osteolysis affecting multiple joints (p = 0.001), but no more likely to have used a Biological (p = 0.53). 87.50% of PAM cases had used a DMARD before PAM-occurrence. A median of 5 radiographs were scored for each PAM case (IQR 3–7).

Conclusion: PAM is associated with worse physical function, more prevalent nail dystrophy, high-grade bilateral sacrolitiasis, greater DMARD use and earlier diagnosis when compared to cases without PAM. Osteolysis progresses most rapidly in early disease, slowing in established disease.

Disclosure: D. R. Jadon, None; G. Shaddick, None; W. Tillett, None; G. Robinson, None; C. Cavill, None; N. Waldron, None; E. Korendowych, None; N. J. McHugh, None.

Comparison of Clinical and Imaging Characteristics of Axial Psoriatic Arthritis and Axial Spondyloarthritis.

Neha Garg1, Abhiheet Danve2, Kiana Vakil-Gilan2 and Atul A. Deodhar3. 1Oregon Health and Sciences University, Portland, OR, 2Oregon Health & Science University, Portland, OR, 3Oregon Health and Science University, Portland, OR.

Background/Purpose: Few studies have compared the clinical and imaging (x-ray and MRI) characteristics between axial psoriatic arthritis (axPsA) and axial spondyloarthritis patients without psoriasis (axSpA). We compared the clinical and imaging characteristics in these two groups.

Methods: AxSpA patients were identified by searching electronic medical records of our university, and axPsA patients were identified from our existing cohort. Demographic and clinical data were collected by chart review. Disease activity was measured using BASDAI and RAPID3. For non-PAM cases (83.33 vs. 47.95%; p = 0.0002). At most recent assessment, PAM cases had a higher HAQ than non-PAM cases (median 1.25 vs. 0.63; p = 0.05), especially in domains relating to hand / foot function: HAQ-grip (p = 0.02); HAQ-eating (p = 0.03). In cases with ACPA serology available, PAM cases were no more likely to be ACPA positive (0/16) than non-PAM cases (8/226; p = 0.44). 16/28 PAM cases had radiographic sacrolitiasis, often bilateral (14/16) and of grade ≥3 (15/16). During their disease course, PAM cases were more likely than non-PAM cases to have used a DMARD (91.67 vs. 50.21%; p < 0.0001), but no more likely to have used a Biological (p = 0.53). 87.50% of PAM cases had used a DMARD before PAM-occurrence. A median of 5 radiographs were scored for each PAM case (IQR 3–7).

Conclusion: PAM is associated with worse physical function, more prevalent nail dystrophy, high-grade bilateral sacrolitiasis, greater DMARD use and earlier diagnosis when compared to cases without PAM. Osteolysis progresses most rapidly in early disease, slowing in established disease.

Disclosure: D. R. Jadon, None; G. Shaddick, None; W. Tillett, None; G. Robinson, None; C. Cavill, None; N. Waldron, None; E. Korendowych, None; N. J. McHugh, None.
imaging comparisons, the patients were divided into 2 gender and disease duration matched subgroups – 1) AS: ankylosing spondylitis patients without psoriasis fulfilling mNY criteria 2) axPsA: PsA patients fulfilling mNY criteria. Symmetry of sacroiliitis was defined as having same grade of sacroiliacitis on each side. Bilateralism was defined as having any grade sacroiliitis on either side. Categorical and continuous variables were reported using proportions and means. Statistical significance was estimated using Mann-Whitney, two mean comparison t-tests, and two sample proportion comparison tests as applicable.

**Results:** Of 168 SpA patients, 135 axSpA patients were compared with 33 axPsA patients (Table 1). Mean age, symptom duration, BMI were similar between the two groups. axSpA had lesser number of females compared to axPsA (33% vs. 57%, p<0.01), higher prevalence of uveitis (29% vs. 12%, p<0.04), higher HLA B27 (80% vs. 50%, p<0.007) and higher BASDAI and RAPID3 scores (BASDAI 4.4 vs 3.8, RAPID3 4.3 vs 3.6, p= ns). These scores were numerically higher in HLA-B27 positive compared to HLA-B27 negative patients (4.3 vs. 3.7, and 4.4 vs. 3.6, respectively; p= ns). Eighteen patients with axPsA were gender and disease duration matched with 86 patients with AS. Radiographic grading of sacroiliacitis, symmetry or bilateralism were not significantly different between AS and axSpA. RAPID3 and BASDAI scores did not correlate with radiographic grading in any group. No significant clinical or imaging differences were found between patients positive and negative for HLA B27.

**Conclusion:** In this comparative study between axPsA and axSpA patients, we found a higher prevalence of female gender, uveitis and positive HLA-B27 in the axSpA group. Our findings do not confirm the previous reports of more symmetry and more severe disease in AS compared to axPsA patients.

**Table 1:** Demographic and clinical characteristics of axSpA and axPsA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>axSpA All</th>
<th>axSpA N=135 (80.4%)</th>
<th>axPsA N=33 (19.6%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (6.8)</td>
<td>27.7 (6.9)</td>
<td>26.85 (6.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Smoking status</td>
<td>60 (35.7%)</td>
<td>47 (34.8%)</td>
<td>10 (30.3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sacroiliitis on x-rays*</td>
<td>118/131 (90.1%)</td>
<td>111/115 (94.1%)</td>
<td>32/32 (100%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sacroiliitis on MRI**</td>
<td>49/54 (90.7%)</td>
<td>33/37 (89.2%)</td>
<td>16/17 (94.1%)</td>
<td>0.56</td>
</tr>
<tr>
<td>HLA B27</td>
<td>91/119 (76.5%)</td>
<td>83/103 (80.6%)</td>
<td>8/16 (50%)</td>
<td>0.007</td>
</tr>
<tr>
<td>BASDAI</td>
<td>4.31 (2.4)</td>
<td>4.41 (2.5)</td>
<td>3.82 (2)</td>
<td>0.4</td>
</tr>
<tr>
<td>RAPID 3</td>
<td>4.18 (2.20)</td>
<td>4.32 (2.21)</td>
<td>3.67 (2.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>ESR mm/hr</td>
<td>28 (25.7)</td>
<td>27.4 (24.8)</td>
<td>29.5 (28.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>CRP mg/dl</td>
<td>2.6 (5.8)</td>
<td>2.89 (6.5)</td>
<td>1.88 (3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>42 (25%)</td>
<td>31 (22.9%)</td>
<td>11 (33)</td>
<td>0.22</td>
</tr>
<tr>
<td>Uveitis</td>
<td>44 (26.2%)</td>
<td>40 (29.6%)</td>
<td>6 (12%)</td>
<td>0.14</td>
</tr>
<tr>
<td>IBID</td>
<td>26 (15.5%)</td>
<td>22 (16.3%)</td>
<td>4 (12%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Depression</td>
<td>44 (26.2%)</td>
<td>34 (25.2%)</td>
<td>10 (30.3%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>15 (8.9%)</td>
<td>11 (8.2%)</td>
<td>4 (12%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Spinal Fractures</td>
<td>7 (4.2%)</td>
<td>7 (5.2%)</td>
<td>0 (0%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Ischimic Heart Disease</td>
<td>5 (2.9%)</td>
<td>5 (3.7%)</td>
<td>0 (0%)</td>
<td>0.26</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>129 (77.7%)</td>
<td>109 (81.9%)</td>
<td>20 (60.6%)</td>
<td>0.008</td>
</tr>
<tr>
<td>DMARDs any</td>
<td>68 (40.5%)</td>
<td>51 (37.8%)</td>
<td>17 (51.5%)</td>
<td>0.15</td>
</tr>
<tr>
<td>TNF inhibitors (%)</td>
<td>70 (8.0%)</td>
<td>95 (70.4%)</td>
<td>24 (72.7%)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*a*Sacroiliitis on X-Ray defined as either present or absent irrespective of Modified NY grading.

**Table 2:** Comparison of data for radiographic disease: AS vs axPsA, gender and duration matched

<table>
<thead>
<tr>
<th>Variable</th>
<th>AS (N=86)</th>
<th>axPsA (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X ray Grade Right</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>20 (23.3%)</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>2</td>
<td>22 (25.6%)</td>
<td>3 (16.7%)</td>
</tr>
</tbody>
</table>

**Discussion:**

**Disclosure:** N. Garg, None; A. Danve, None; K. Van-Vali-Gilani, None; A. A. Deodhar, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 2, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 5.

**Background/Purpose:** Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in patients with active PsA despite prior conventional disease-modifying anti-rheumatic drugs (DMARDs) and/or biologics, including biologic failures. We evaluated the impact of APR over 52 weeks on PsA disease activity.

**Methods:** Patients were randomized (1:1:1) to receive PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to PBO, or continued on their initial APR dose. At Week 24, all remaining PBO patients were re-randomized to APR20 or APR30. This analysis reports data over 52 weeks. Disease activity was evaluated using a modified American College of Rheumatology 20 (ACR20) response, 28-joint count Disease Activity Scale (DAS-28; C-reactive protein [CRP]), Maastricht Ankylosing Spondylitis Entheritis Score (MASES), dactylitis count, and 75% reduction from baseline Psoriasis Area and Severity Index (PASI-75) response.

**Results:** At Week 16, a significantly greater proportion of patients treated with APR achieved a modified ACR20 response vs PBO (primary endpoint). In patients initially randomized to APR and completing 52 weeks, ACR20 response was sustained over 52 weeks. APR20 and APR30 demonstrated improvement in disease activity vs PBO at Week 16.
mean change in DAS-28 (CRP), achievement of DAS-28 <2.6, median percent changes in MASES/dactylitis score, and PASI-75 response. Among patients who were continuously treated with APR through 52 weeks, sustained improvements were observed at Week 52 (Table 2). The most common adverse events reported during the PBO-controlled period (PALS 1–3; pooled) were diarrhea (12.2%), nausea (10.1%), and headache (8.0%). The safety profile of APR through 52 weeks was similar to that observed with APR for up to 24 weeks of treatment (PBO-controlled period). Marked laboratory abnormalities generally were infrequent and returned to baseline with continued treatment or were associated with a concurrent medical condition.

**Conclusion:** APR demonstrated sustained clinically meaningful improvements in measures of PsA disease activity through Week 52. APR demonstrated an acceptable safety profile and was generally well tolerated through 52 weeks.


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**Reliability and Construct Validity of the Psoriatic Arthritis Symptom Inventory in Subjects with Psoriatic Arthritis.** Philip Meese1, Mark C. Genovese2, Alex Mutebi3, Hilary Wilson2, Dennis Revicki2, Ngozi Erondu3, Ajay Nirula4, JingYuan Feng5 and Hema Viswanathan6.

1. Swedish Medical Center and University of Washington, Seattle, WA; 2. Stanford University Medical Center, Palo Alto, CA; 3. Amgen Inc, Thousand Oaks, CA; 4. Evidera, Bethesda, MD.

**Background/Purpose:** The Psoriasis Symptom Inventory (PSI) is an 8-item patient-reported outcome measure of psoriatic symptom severity. Data from a Phase 2 study of Brodalumab in subjects with plaque psoriasis demonstrated that PSI has good reliability, validity, and responsiveness to change. Psoriasis related symptoms are an important component of psoriatic arthritis (PsA). However, the measurement properties of the PSI have not been evaluated in the PsA population. This analysis sought to evaluate the reliability and construct validity of the PSI in subjects with PsA.

**Methods:** This was a secondary analysis of pooled data from treatment arms of a Phase 2 clinical trial (NCT01516957) evaluating the efficacy of Brodalumab in PsA. The PSIR17 R monoclonal antibody in PsA. Confirmatory factor analysis (CFA) and Rasch analysis were used to assess the dimensionality of the PSI. Item evaluation and internal consistency (Cronbach’s α) were conducted on baseline PSI data. Test-retest reliability was assessed using intraclass correlation coefficients (ICC) between PSI scores at week 2 and week 4 in stable subjects (i.e., ≤1% change ≤1 on the subject global assessment of disease (SGA)). Construct validity was evaluated based on correlations between PSI scores and body surface area (BSA) affected by psoriasis, and selected domains of the SF-36. Known groups validity was explored based on BSA severity categories (<5%, 5–10%, >10%) using analysis of variance. Ability to detect change was explored using t-tests comparing mean PSI scores in subjects reporting ≥30% versus <30% improvement from baseline to week 12 on the SGA.

**Results:** The analysis included 154 subjects: 93.5% White, 63.0% females, mean (SD) age was 52.2 (11.47) years. Mean (SD) duration of PsA and BSA at baseline was 88.7 (8.40) years and 10.4 (15.61) respectively. At baseline, 12% of subjects had no skin involvement and 63% had ≥5% skin involvement. Mean (SD) PSI total score at baseline was 12.2 (7.89). CFA and Rasch analysis supported unidimensionality. Rasch analysis also indicated good item fit and correctly ordered response categories.

This study provides evidence that the PSI is unidimensional, with excellent internal consistency, good test-retest reliability, construct validity, and ability to detect change in subjects with PsA. Based on the findings, the PSI is a robust yet simple and practical measure of psoriasis-related symptoms for use in PsA clinical trials.

**Disclosure:** P. Meese, Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; 2. Consulting fees from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; 5. Speakers’ bureau for AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Merck, and Pfizer, UCB, and Vertex; 8. M. C. Genovese, Research grants: Amgen Inc; 2. A. Mutemb, Shareholder of: Amgen Inc, 1, Employee of: Amgen Inc, 3. H. Viswanath, Shareholder of: Amgen Inc, 1, Employee of: Amgen Inc, 3.

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Secukinumab, an Anti-Interleukin-17A Monoclonal Antibody, Improves Physical Function, Quality of Life and Work Productivity in Patients with Active Psoriatic Arthritis: Results from a Phase 3 Randomized, Controlled Trial. Viveke Strand1, Philip Meese2, Ian B. McInnes3, Bruce Kirkham3, Arthur Kavanagh3,1, Proton Rahman4,5, P. Nash3, Luminia Pricop6,7, Jiacheng Yuan1, Hanno Richards3 and Shephard Mpofo1,2,6, Stanford University, Palo Alto, CA; 2. Swedish Medical Center, Seattle, WA; 3. University of Glasgow, Glasgow, United Kingdom; 4. ‘s-Gravenhage. Netherlands Foundation Trust, London, United Kingdom; 5. University of California San Diego, La Jolla, CA; 6. Memorial University of Newfoundland, St. John’s, NF; 7. Rheumatology, Nambour Hospital, Sunshine Coast and Department of Medicine, University of Queensland, Queensland, Australia; 8. Novartis Pharmaceuticals Corporation, East Hanover, NJ.

**Background/Purpose:** Psoriatic arthritis (PsA) has a significant adverse effect on patients’ health-related quality of life (HRQoL), affecting their physical and emotional functioning and psychological health. Here we present the impact of treatment with secukinumab on patient-reported outcomes (PROs) in patients enrolled in FUTURE 1 (NCT01392326), the first phase 3 trial to evaluate interleukin (IL)-17A inhibition in subjects with PsA.

**Methods:** Adults with active, moderate to severe PsA were randomized to secukinumab 120 mg i.v. at baseline. Weeks 2 and 4, then either 75 mg s.c. (10 IV → 75 SC; n = 202) or 150 mg s.c. (10 IV → 150 SC; n = 202) at Week 8 and every 4 weeks until end of study, or placebo (PBO; n = 202) on the same i.v. and s.c. schedules. PROs were measured using: Health Assessment Questionnaire – Disability Index (HAQ-DI); Short Form-36 Health Survey (SF-36); EuroQol (EQ-5D); PsAQoL; Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F); and Work Productivity and Activity Impairment – General Health (WPAI). PROs were reported using a mixed-effect model repeated measures analysis, except WPAI and SF-36 domains which were assessed using an observed analysis.

**Results:** At baseline, dose groups were comparable with respect to demographics and disease activity; subjects had moderate to severe physical impair-
ment, fatigue levels and impaired HRQOL. Secukinumab 10 IV → 75 SC and 10 IV → 150 SC significantly improved HAQ-DI (P < 0.0001), SF-36 physical component summary [PCS] score (P < 0.0001), EQ-5D (P < 0.001 and P < 0.0001) and PsAQoL (P < 0.0001) vs. PBO at Week 24; only 10 IV → 150 SC significantly improved FACIT-F (P < 0.05). Mean changes from baseline reported in HAQ-DI, PCS, mental component summary (MCS) and all domains of SF-36 and FACIT-F exceeded minimum clinically important differences (MCID; Table, in bold): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Various aspects of work productivity, as assessed by WPAI, were also improved with secukinumab vs. PBO. Improvements in all PROs were sustained or further increased over 52 weeks.

**Table.** Mean baseline scores and mean change from baseline (BL) in patient-reported outcomes (PROs) at Week 24 by treatment group

<table>
<thead>
<tr>
<th>PROs</th>
<th>Secukinumab 10 mg/kg i.v.</th>
<th>Secukinumab 150 mg s.c.</th>
<th>Placebo n = 202</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ-DI</td>
<td>1.25</td>
<td>1.23</td>
<td>1.19</td>
</tr>
<tr>
<td>(MCID ≥ 0.35) Change from BL at Week 24</td>
<td>-0.41*</td>
<td>-0.40*</td>
<td>-0.17</td>
</tr>
<tr>
<td>EQ-5D (VAS)</td>
<td>52.80</td>
<td>52.60</td>
<td>52.60</td>
</tr>
<tr>
<td>(MCID ≥ 4) Change from BL at Week 24</td>
<td>11.91*</td>
<td>13.36*</td>
<td>2.45</td>
</tr>
<tr>
<td>PsAQoL</td>
<td>10.65</td>
<td>10.27</td>
<td>10.65</td>
</tr>
<tr>
<td>(MCID ≥ 0.19) Change from BL at Week 24</td>
<td>-3.19*</td>
<td>-3.49*</td>
<td>-0.36</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>27.59</td>
<td>28.90</td>
<td>27.82</td>
</tr>
<tr>
<td>(MCID ≥ 4) Change from BL at Week 24</td>
<td>6.03</td>
<td>6.74*</td>
<td>4.0</td>
</tr>
<tr>
<td>SF–36 PCS</td>
<td>36.90</td>
<td>36.16</td>
<td>36.63</td>
</tr>
<tr>
<td>(MCID ≥ 0.51*) Change from BL at Week 24</td>
<td>5.41*</td>
<td>5.91*</td>
<td>1.82</td>
</tr>
<tr>
<td>SF–36 MCS</td>
<td>42.04</td>
<td>42.82</td>
<td>43.49</td>
</tr>
<tr>
<td>(MCID ≥ 2.5) Change from BL at Week 24</td>
<td>3.67</td>
<td>5.66*</td>
<td>2.39</td>
</tr>
<tr>
<td>SF–36 Domains</td>
<td>45.66</td>
<td>42.62</td>
<td>46.94</td>
</tr>
<tr>
<td>(MCID ≥ 5) Change from BL at Week 24</td>
<td>14.23</td>
<td>15.73</td>
<td>7.08</td>
</tr>
<tr>
<td>PF</td>
<td>47.32</td>
<td>45.99</td>
<td>47.01</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>13.68</td>
<td>18.52</td>
<td>9.27</td>
</tr>
<tr>
<td>RP</td>
<td>36.47</td>
<td>36.01</td>
<td>36.84</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>18.68</td>
<td>19.78</td>
<td>12.92</td>
</tr>
<tr>
<td>BP</td>
<td>40.91</td>
<td>42.42</td>
<td>41.72</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>8.81</td>
<td>12.03</td>
<td>6.33</td>
</tr>
<tr>
<td>GH</td>
<td>12.22</td>
<td>13.86</td>
<td>9.62</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>9.31</td>
<td>41.31</td>
<td>41.94</td>
</tr>
<tr>
<td>VT</td>
<td>56.71</td>
<td>56.15</td>
<td>57.81</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>13.80</td>
<td>17.41</td>
<td>10.53</td>
</tr>
<tr>
<td>RE</td>
<td>58.29</td>
<td>56.93</td>
<td>58.24</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>9.73</td>
<td>13.50</td>
<td>6.58</td>
</tr>
<tr>
<td>MH</td>
<td>56.28</td>
<td>58.97</td>
<td>61.09</td>
</tr>
<tr>
<td>Change from BL at Week 24</td>
<td>8.25</td>
<td>10.35</td>
<td>5.60</td>
</tr>
</tbody>
</table>

*P < 0.0001, †P < 0.001, ‡P < 0.01, §P < 0.05 vs. PBO

**Conclusion:** In patients with active PsA, selective inhibition of IL-17A with secukinumab improved physical function (HAQ-DI), fatigue (FACIT), and HRQOL by generic (SF-36, EQ-5D) and disease-specific (PsAQoL) measures, and reduced the impact of disease on work productivity (WPAI).

**Disclosure:** V. Strand, Consultant for AbbVie, Afferent, Amgen, Biogen Idec, Bioconectus, BMS, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCBB, and Vertex; 5; P. Mease, Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCBB, and Vertex; 2, Consulting fees from: AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCBB, and Vertex; 5; I. B. McNieces, Consulting fees from Novartis, Amgen, and Lilly; 5; B. Kirkham, Research grants from AbbVie and UCBB, 2, Consulting fees from Novartis, AbbVie, BMS, Lilly, and MSD, 5, speakers’ bureau for BMS, MSD, and UCBB, 8; A. Kavaughan, Consulting fees from Novartis, 5; P. Rahman, Consulting fees for Abbott, AbbVie, Amgen, BMS, Celgene, Janssen, Novartis, Pfizer and Roche, 5, Consultant to pharmaceutical companies dealing with biologic agents in rheumatology, 9; P. Nash, Research grants for clinical trials from Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene, 5, Honoraria for lectures and advice from Novartis, Abhbvie, Roche, Roche, Pfizer, BMS, Janssen, and Celgene, 9; L. Pricop, Novartis stock, 1, Employee of Novartis, 3; J. Yuan, Employee of Novartis, 3; H. Richards, Employee of Novartis, 3; S. Mpofo, Novartis stock, 1, Employee of Novartis, 3.

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**Predictors Associated with Rheumatologist Referral Time in Patients with Ankylosing Spondylitis.** Atul A, Deodhar1, Manish Mittal2, Patrick Reilly2, Yanjun Bao2, Shivaji Manthena2, Jaclyn K. Anderson2 and Avani D. Joshi2. 1Oregon Health and Sciences University, Portland, OR, 2AbbVie Inc., North Chicago, IL.

**Background/Purpose:** Average delay between symptom onset and diagnosis of ankylosing spondylitis (AS) has been reported as 8–12.8 years1,2. This study assessed delay in AS diagnosis following diagnosis of back pain (BP), and sought to identify factors affecting time from BP diagnosis to rheumatologist referral in AS patients (pts).

**Methods:** This longitudinal study used claims data from the large US MarketScan commercial insurance claims databases (total number of pts n = 127,137,195 between Jan 2000–Dec 2012). Pts aged 18–64 years with diagnosis of BP in a non-rheumatology setting followed by AS diagnosis in any setting were selected. Pts with a rheumatologist visit on/before AS diagnosis were considered to have been referred. A time-dependent Cox proportional hazard model was used to determine factors associated with referral time after adjusting for age, sex, comorbidities, physician specialty, drug therapy and imaging procedures.

**Conclusion:** Out of 3,336 pts diagnosed with AS after a diagnosis of BP, 1,244 (37%) were referred to and diagnosed by rheumatologists; remaining were diagnosed in a primary care (PCP; 25.7%), chiropractor/physical therapy (7%), orthopedic (3.8%), pain (3.6%), acute care (3.4%) or other (12.9%) setting. More referred pts were prescribed NSAIDs, DMARDs, corticosteroids and anti-TNF prior to diagnosis of AS, suggesting potentially more severe AS (Table 1). In the time between the diagnoses of BP and AS, 75% of referred patients were prescribed anti-TNF therapy by rheumatologists and 42% of non-referred patients were prescribed anti-TNF by PCPs. Referred pts were also more likely to have had spinal/pelvic imaging procedures (x-ray, MRI, CT scan). Median time from BP diagnosis to rheumatologist referral was 307 days and median time from first rheumatologist visit to AS diagnosis was 28 days. Referred pts were more likely to be younger, male, diagnosed with uveitis, referred by PCPs, prescribed NSAIDs, DMARDs, and anti-TNF prior to referral, and to have had spinal/pelvic x-ray (Table 2).

**Conclusion:** During 2000–2012, the majority of AS patients who presented with BP were diagnosed without rheumatologist referral. Among those referred, there was a delay of approximately 10 months before a rheumatologist referral was made. After a rheumatologist visit, diagnosis of AS generally followed within a month. Predictors of referral time included young age, male sex, presence of uveitis, use of drug therapy and imaging procedures, and referring physician specialty.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients referred to rheumatologist (n=1,244)</th>
<th>Patients not referred to rheumatologist (n=2,092)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.9</td>
<td>45.8</td>
</tr>
<tr>
<td>Female, %</td>
<td>50.7%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Comorbid condition, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.1%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>7.1%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18.4%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Cancer</td>
<td>17.3%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>4.3%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Table 2. Factors Associated with Rheumatologist Referral Time for Patients with Ankylosing Spondylitis in multivariate analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.986 (0.981, 0.991)</td>
</tr>
<tr>
<td>Sex (M vs F)</td>
<td>1.15 (1.03, 1.29)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1.49 (1.13, 1.96)</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>1.96 (1.64, 2.35)</td>
</tr>
<tr>
<td>Pain management</td>
<td>0.79 (0.69, 0.91)</td>
</tr>
<tr>
<td>NSAID</td>
<td>1.55 (1.35, 1.77)</td>
</tr>
<tr>
<td>DMARD</td>
<td>1.33 (1.16, 1.54)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>0.82 (0.72, 0.94)</td>
</tr>
<tr>
<td>CT scan</td>
<td>1.40 (1.12, 1.76)</td>
</tr>
<tr>
<td>MRI</td>
<td>0.71 (0.58, 0.87)</td>
</tr>
</tbody>
</table>

DMARDs=disease-modifying antirheumatic drug; MRI=magnetic resonance imaging; NSAIDS=non-steroidal antiinflammatory drug; TNF=tumor necrosis factor.

Conclusion: Treatment of nr-axSpA with ADA was associated with significant and sustained improvements in physical function, HRQOL, and work productivity over 3 years of the ABILITY-1 trial among patients with and without elevated CRP and/or positive MRI as well as the overall nr-axSpA population.

References:

Disclosure: D. van der Heijde, AbbVie, Agena, Astrozeneeca, Augurex, BMS, Celgene, Centocor, Chugui, Covagen, Daichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, 5; M. Mittal, AbbVie, 1, AbbVie, 3; N. Chen, AbbVie, 1, AbbVie, 3; A. L. Pangan, AbbVie, 1, AbbVie, 3; A. D. Joshi, AbbVie, 1, AbbVie, 3; 553

Comparison of Baseline Extra-Articular Manifestations, Comorbidities, and Long-Term Safety in Patients Treated with Adalimumab for Ankylosing Spondylitis and Non-Radiographic Axial Spondylarthropathy. Joachim Sieper 1, Desiré van der Heijde 1, Nupun A. Varothai 2 and Jacky K. Anderson 1.

1 Charité Universitätsmedizin Berlin, Berlin, Germany, 2 Leiden University Medical Center, Leiden, Netherlands, 3 AbbVie Inc., North Chicago, IL.

Background/Purpose: In the ABILITY-1 trial, adalimumab (ADA) treatment for 12 weeks was associated with improved clinical and health-related quality of life (HRQOL) outcomes among patients with nonradiographic axial spondylarthropathies (nr-axSpA). 1 We aimed to evaluate physical function, HRQOL, and work productivity over 3 years of ADA treatment in ABILITY-1.

Methods: ABILITY-1 was a 3-year, phase 3, multicenter, randomized, controlled trial of ADA versus placebo in patients with nr-axSpA (classified using the Assessment of SpondolyArthritis international Society axial SpA criteria). After a 12-week double-blind phase, all patients switched to open-label ADA for an additional 144 weeks (156 total). This post hoc analysis evaluated patient-reported outcomes through year 3 among 185 patients overall and among subgroups of 142/43 patients with/without elevated C-reactive protein (CRP) and/or MRI evidence of inflammation at baseline. Physical function was assessed using the disability index of the Health Assessment Questionnaire for Spondylarthropathies (HAQ-S) and HRQOL using the Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Productivity was assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI). Changes in HAQ-S, SF-36 PCS, and WPAI from baseline to years 1, 2, and 3 were reported for the ITT populations (LOCF).

Results: No significant differences were observed between patient cohorts in baseline HAQ-S, SF-36 PCS, or WPAI domain scores. Mean change from baseline in HAQ-S indicated sustained improvement over time among patients in the overall population at years 1, 2, or 3 (−0.39, −0.40, and −0.39, respectively); a majority of patients (56%, 55%, and 54%, respectively) achieved the minimum clinically important difference (MCID) of −0.26 2 (Table). Trends were similar for SF-36 PCS score; approximately 68% of patients achieved the MCID of 3.0 3 at each time point; mean scores were 41.8, 41.9, and 41.9 at years 1, 2, and 3, respectively, compared to the US general population norm of 50. 4 Mean changes from baseline in overall work impairment and activity impairment were stable over time, and >60% of patients achieved the MCID of -7.0% 5 at each time point. Improvements were sustained among patients with and without elevated CRP and/or positive MRI, and in observed case analysis.

Mean Change From Baseline Through Week 156 in HAQ-S, PCS, and WPAI Domain Scores Among nr-axSpA Patients 3 Mean ± SD; MCID = −0.26. Year 1 Year 2 Year 3 Year 1 Year 2 Year 3 Year 1 Year 2 Year 3

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.986 (0.981, 0.991)</td>
</tr>
<tr>
<td>Sex (M vs F)</td>
<td>1.15 (1.03, 1.29)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1.49 (1.13, 1.96)</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
</tr>
<tr>
<td>PCP</td>
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<td>CT scan</td>
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</tr>
<tr>
<td>MRI</td>
<td>0.71 (0.58, 0.87)</td>
</tr>
</tbody>
</table>

CT=conference interval; DMARDS=disease-modifying antirheumatic drug; HR= Hazard ratio; MRI=magnetic resonance imaging; NSAIDS=non-steroidal antinflammatory drug; PCP=primary care physician; TNF=tumor necrosis factor.

1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Leiden University Medical Center, Leiden, Netherlands, 3AbbVie Inc., North Chicago, IL.

Background/Purpose: To compare 1) extra-articular manifestations, 2) baseline comorbidities, and 3) adverse event (AE) rates with long-term adalimumab (ADA) therapy in patients (pts) treated in clinical trials for established ankylosing spondylitis (AS) and non-radiographic axial spondylarthropathy (nr-axSpA).

Methods: This post hoc analysis was performed in 3 studies: 1) ATLAS, a phase 3, randomized, double-blind (DB), multicenter study in US and Europe in pts with active AS who had inadequate response, or were intolerant to ≥1 nonsteroidal anti-inflammatory drug (NSAID); 2) M03–606, conducted in Canada with the same study design as ATLAS, and 3) ABILITY-1, a phase 3, multinational, randomized, DB, multicenter study in pts with active nr-axSpA (pts with past/present diagnosis of psoriasis were excluded). Pts were randomized to receive ADA 40 mg every other week (wk) or placebo for 24 wks followed by open-label ADA for up to 260 wks in ATLAS and M03–606, and up to 156 wks in ABILITY-1. Pts who received ≥1 dose of...
ADA at any time during the study were analyzed (Any ADA set). AE frequency and events/100 patient-years (E/100 PY) of ADA exposure were summarized by study indication with the AS studies combined.

**Results:** The Any ADA population in the ATLASM03–606/ABILITY-1 studies was N=311/82/183, respectively. The Any ADA safety population was n=393 for AS and n=190 for nr-axSpA. Mean age was similar in AS and nr-axSpA pts ranging from 37–42 yrs and about 80% of both AS and nr-axSpA pts were HLA-B27 positive. AS pts were predominantly male and had longer duration of disease diagnosis compared to nr-axSpA pts. Mean duration of SpA symptoms was >10 yrs in the AS study; however, it was not collected in the AS studies (Table 1). At BL uveitis and IBD were less frequent in nr-axSpA pts compared to AS pts. Among pts exposed to ADA (1543.9 PY of exposure in AS, 412.2 PY in nr-axSpA), the incidence of serious AE was similar in both populations (10.8 vs. 10.9 E/100 PY, AS vs. nr-axSpA). The malignancy rate in AS studies was 0.8 E/100 PY and 0 in nr-axSpA. There was 1 death in the AS studies (<0.1 E/100 PY) and 2 in nr-axSpA pts (0.5 E/100 PY); none were considered related to ADA. (Table 2)

**Table 1. Baseline Demographic and Disease Characteristics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>AS</th>
<th>M03-606</th>
<th>nr-axSpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (years)</td>
<td>42.3</td>
<td>40.9</td>
<td>37.9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>233 (74.9)</td>
<td>65 (79.3)</td>
<td>83 (45.4)</td>
</tr>
<tr>
<td>HLA-B27+, n (%)</td>
<td>245 (78.1)</td>
<td>69 (84.4)</td>
<td>144 (78.7)</td>
</tr>
<tr>
<td>Duration of disease diagnosis, mean (years)</td>
<td>10.9</td>
<td>13.3</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**SpA Disease Characteristics**

| Symptom duration, mean (years) | - | - | 10.1 |
| BasDAI, mean (0–10) | 6.3 | 6.3 | 6.5 |
| Total back pain, mean (VAS 0–10) | 6.5 | 7.0 | 7.0 |
| Uveitis, n (%) | 55 (17.3) | 27 (32.9) | 22 (12.0) |
| Uveitis (new onset or worsening) | 2.7 | 0.5 | 0.1 |
| Inflammatory bowel disease, n (%) | 27 (8.6) | 9 (11.0) | 8 (4.3) |
| Liver Events | 0.8 | 0.5 | 0.5 |
| Cardiac Disorders | 1.0 | 1.0 | 0.2 |
| Any Malignancy | 0.8 | 0.0 | 0.0 |
| Inflammatory bowel disease (new onset or worsening) | 0.6 | 0.6 | 0.6 |
| Postisar (n or worsening) | 2.7 | 0.5 | 0.5 |
| Deaths | <0.1 | 0.5 | 0.5 |

**Conclusion:** Enrolled pts with AS and nr-axSpA were generally similar in terms of demographics and BL disease activity. Although the SpA-related comorbid conditions and uveitis were more commonly reported in AS pts as compared to nr-axSpA pts at BL, reported AE rates were generally similar between pts with AS and nr-axSpA. This indicates a similar safety profile for ADA treatment in all pts with axial SpA.

**Disclosure:** J. Sieper, AbbVie, Merck, Pfizer, UCB, 2; AbbVie, Merck, Pfizer, UCB, 5; AbbVie, Merck, Pfizer, UCB, 8; D. van der Heijde, AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Covagen, Daichii, Eli Lilly, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, and Vertex, 2; AbbVie; 3; AbbVie; 1; J. K. Anderson, AbbVie, 1, AbbVie, 5.

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**Myocardial Infarction Risk with Diclofenac Use in Spondyloarthropathy Versus Non-Inflammatory Low Back Pain.** Maureen Dubreuil. Boston VA HealthCare System, Boston, MA.

**Background/Purpose:** Spondyloarthropathies (SpA) have been associated with increased risk of myocardial infarction (MI), however it remains unclear if the risk is related solely to the underlying inflammatory disease, or also due to use of medications that increase MI risk, such as certain non-steroidal anti-inflammatory drugs (NSAIDs). Alternatively, NSAIDs may reduce MI risk through reduction in systemic inflammation. Although diclofenac is commonly prescribed for treatment of SpA symptoms, its effect on MI in the SpA population has not been well quantified. By comparing risk of MI with diclofenac use in the SpA population with that in non-inflammatory back pain, we aimed to determine if the increased MI risk is solely due to the inflammatory disease or also the result of NSAID use.

**Methods:** We performed a cohort study assessing the effect of diclofenac on MI risk using 1995–2013 data from The Health Improvement Network, a medical record database from the United Kingdom, comprising records of over 11 million patients from over 600 general practitioners. We included adults with at least 1 year enrollment in the database, followed by a diagnosis of ankylosing spondylitis or psoriatic arthritis (combined SpA population) or who had a low back pain (LBP) diagnosis without any prior SpA history. From the SpA and LBP populations, we identified subjects who used either diclofenac or naproxen after SpA or LBP diagnosis and followed them until diagnosis of MI, death or end of the study period. We divided subjects into four categories: SpA/diclofenac, SpA/naproxen, LBP/diclofenac, and LBP/naproxen. We used Cox proportional hazards models with adjustment for potential confounders. The risk of MI in each cohort was compared to that in the LBP/naproxen cohort to estimate the effects of diclofenac and SpA on MI independently.

**Results:** We identified 2590 naproxen users and 3573 diclofenac users with SpA, as well as 47510 naproxen users and 280442 diclofenac users with LBP. SpA subjects tended to be younger, and less commonly female than LBP subjects. In all cohorts, baseline smoking, obesity, hypertension and use of cardioprotective medications was common. After adjustment for potential confounders, relative to the LBP/naproxen cohort, hazard ratios were 1.02 (985% CI 0.91–1.14) for LBP/diclofenac, 1.26 (0.71–2.23) for SpA/naproxen, and 1.50 (1.02–2.22) for SpA/diclofenac (Table).

**Conclusion:** Diclofenac use among SpA patients was associated with 50% increased risk of MI, while naproxen use did not significantly increase risk relative to its use in LBP patients. Notably in LBP patients, diclofenac use did not increase MI risk, potentially reflecting different patterns of use among LBP and SpA populations (eg, dose, frequency). These findings suggest that diclofenac use in SpA increases MI risk beyond any potential risk conferred by the underlying inflammatory disease.

**Table. Risk of Myocardial Infarction (MI) according to low back pain or spondyloarthropathy diagnosis and use of naproxen or diclofenac**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects, N</th>
<th>NLN (%)</th>
<th>Follow-up time (PS)</th>
<th>Incidence rate (1000 PY)</th>
<th>Odds RR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Multivariable Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBP/naproxen</td>
<td>147710</td>
<td>1156</td>
<td>518282</td>
<td>2.23</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>LBP/diclofenac</td>
<td>208442</td>
<td>379</td>
<td>1788180</td>
<td>2.11</td>
<td>0.83</td>
<td>0.83</td>
<td>0.89 (0.71,1.09)</td>
</tr>
<tr>
<td>SpA/naproxen</td>
<td>2590</td>
<td>27</td>
<td>10173</td>
<td>2.60</td>
<td>1.06</td>
<td>1.06</td>
<td>1.26 (0.91,1.75)</td>
</tr>
<tr>
<td>SpA/diclofenac</td>
<td>3573</td>
<td>61</td>
<td>23498</td>
<td>2.20</td>
<td>1.26</td>
<td>1.26</td>
<td>1.26 (0.91,1.75)</td>
</tr>
</tbody>
</table>

**Disclosure:** M. Dubreuil, None.

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**Urinary Excretion of Type II Collagen C-Telopeptide and Glucosyl-Galactosyl-Pyridinoline As Prognostic Biomarkers in Early Spondyloarthropathies.** Elisa Trujillo1 and Maria del Mar Trujillo2. 1Hospital Universitario de Canarias, La Laguna, Tenerife, Spain, 2Servicio Canario de la Salud, Tenerife, Spain.
Background/Purpose: The search for biomarkers in spondyloarthritis (SpA) is of great interest because of their diagnostic and prognostic role in the treatment of these diseases. In recent years cartilage has been shown to be a major target organ in spondyloarthritis. In other diseases of the joints, elevated levels of urinary CTX-II (C-telopeptide fragments of type II collagen) and Glc-Gal-PYD (glucosyl-galactosyl-pyridinoline) have been associated with progression of radiological damage. Objectives: 1. To compare the level of urinary CTX-II and Glc-Gal-PYD in patients with early-stage SpA with urinary levels in healthy people of similar age and gender. 2. To analyze the association between the level of urinary CTX-II and Glc-Gal-PYD with patient variables and diagnosis at 3 years of follow up.

Methods: We included 68 patients aged <45 years who came to the service with some of the suggestive information of ESP of the table and who later completed three years of follow-up and they fulfill nowadays criteria for the Classification of Spondyloarthropathy of The European Spondyloarthropathy Study Group (ESSG):

- inflammatory back pain,
- asymmetrical arthritis especially in lower limbs, dactylitis,
- uveitis or arthralgia, plus one of the following: psoriasis, enthesitis, IBD, anterior uveitis, family history of spondyloarthritides, radiographic sacrorrheitis, HLA-B27+, cervicitis/urethritis/diarrhea in the previous month.

Urinary samples were taken from all patients attending for the first time with suspected early SpA. Urinary excretion of CTX-II was determined by immunoassay (ELISA). Urinary excretion of Glc-Gal-PYD was determined by High performance liquid chromatography. We also determined CTX-II and Glc-Gal-PYD urinary excretion in a healthy control group (n = 25) of similar age and sex.

Association analysis was performed with the following variables at 3 years: final diagnosis, HLA-B27, SpA axial / peripheral ASAS, early involvement of large joints (hips/knees), presence of extra-articular manifestations (anterior uveitis, psoriasis or IBD) and anti-TNF therapy.

Results: Urinary excretion of CTX-II and Glc-Gal-PYD in patients presenting for the first time with suspected early SpA was significantly higher in 10 than in the healthy control group matched for age and sex (p <0.001).

Urinary excretion of CTX-II and Glc-Gal-PYD in patients presenting for the first time with suspected early SpA were significantly higher in those who had predominantly peripheral involvement (SpA peripheral ASAS) versus axial involvement and in those due to high clinical activity and functional deficits (BASDAI and BASFI) required biological treatment at 3 years follow up. Urinary excretion of CTX-II was also significantly higher in patients developed early large joint involvement at 3 years follow up.

Conclusion: Urinary excretion of CTX-II and Glc-Gal-PYD in patients with early SpA may be a prognostic biomarker since in our series it was associated with peripheral involvement and early large joint involvement, and the need for biological treatment in the first three years of follow-up.

Disclosure: E. Trujillo, None; M. D. M. Trujillo, None.

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Defining Flare in Spondyloarthritis: Thresholds of Disease Activity Variations. Marie Godfroin-Valnet1, Marc Puhyraveau1 and Daniel Wending1, 1CHR, Besançon, France, 2CHU J Minjot, Besancon, France.

Background/Purpose: Spondyloarthritis (SpA) activity varies with time and treatment, but to date no clear definition of a flare of the disease is available. The aim of this study was to evaluate thresholds of disease activity variations using validated composite indexes.

Methods: 50 SpA patients fulfilling ASAS criteria and prospectively followed with at least 2 visits were evaluated using BASDAI, ASDAS-CRP and ASDAS-ESR. Patients and physician answered at each visit the question: “do you consider your SpA in a state of flare?”. Variations of BASDAI and ASDAS between visits were assessed and associated to the change of perception of a flare (yes/no). ROC curves were built to assess thresholds of variation in BASDAI and ASDAS associated with the change flare: no to yes between visits.

Results: The patients were issued from a prospective series of 250 SpA 99 situations with at least 2 visits were analyzed. The main characteristics of this cohort were: 67 % men, mean age 45 ± 12 years; disease duration: 16 ± 10 y; 84 % HLA-B27 positive; purely axial SpA: 81 %; PASS at baseline: 56 %; mean CRP: 8.6 ± 13.5 mg/l. Mean BASDAI and ASDAS-CRP at baseline were 4.3 ± 2.2 and 5.1 ± 1.1 respectively. The kappa coefficient of agreement between patient and physician for considering a flare was 0.68.

Conclusion: According to these results, an increase from a non-flare state of at least 2.1 units in BASDAI, 0.8 units in ASDAS-ESR or 1.3 units in ASDAS-CRP is associated to (and may define) a flare, as considered by the patient and the physician.

Disclosure: M. Godfrin-Valnet, None; M. Puhyraveau, None; D. Wending, None.

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The aim of this study was to assess, in current practice, thresholds of variation of activity score associated with a flare in SpA. This may help physicians in the evaluation and management of the patients with SpA.

Disclosure: M. Godfrin-Valnet, None; M. Puhyraveau, None; D. Wending, None.
the EF Item Set cross-culturally into 15 languages with 17 versions and to field test the new versions in patients with axial SpA (axSpA).

Methods: Translation and cross-cultural adaptation was done in 20 countries according to published recommendations (forward-backward procedure) in 5 steps: translation, synthesis of translation, back translation, expert committee review and pre-testing in a field test. The field test was conducted in patients with axSpA to test its applicability in patients with all forms of SpA.

Results: The ASAS HI and EF Item Set was translated into Arabic, Chinese, Croatian, Dutch/Flemish, French, German, Greek, Hungarian, Italian, Korean, Portuguese, Russian, Spanish (Colombia, Mexico, Spain), Thai, and Turkish. 206 patients (approximately 10 patients/country, 59.7% male, mean (SD) age 42.4 (13.9) years, mean (SD) BASDAI 3.8 (2.3)) with axSpA underwent qualitative interviews during field testing in 23 countries (19 non-English speaking countries, 4 English-speaking countries). 65% of the patients were diagnosed with AS, 35% with non-radiographic axSpA and 33% of the total sample size suffered from peripheral involvement. Interviews showed the English questionnaire and the translations to be clear, relevant and comprehensive. All versions were accepted with minor modifications. The total sum of the ASAS HI (range 0–17, with a lower score indicating a better health status) was 7.1 ± 4.4 (mean ± SD). Completion times for ASAS HI and for EF Item Set were respectively, 2.6 ± 1.6 and 2.1 ± 1.5 (mean ± SD) minutes.

Conclusion: The ASAS HI and the EF Item Set were successfully translated into 15 languages with 17 versions. This study showed the ASAS HI items to be readily adaptable throughout countries, indicating the concepts covered may be meaningful in many cultures. In the other hand, more difficulties were experienced with the contextual factors indicating these concepts may be more culture-dependent. The field test suggested that the English and the non-English versions have high face and content validity. By investigating patients with axSpA and with and without peripheral manifestations it could be shown that the ASAS HI and EF Item Set are valid to be applied in patients with all forms of SpA. Further validation is underway to test the psychometric properties of this new disease-specific questionnaire.

Disclosure: U. Kiltz; None; D. van der Heijde; None; A. Boonen; None; W. Bautista - Molano; None; R. Burgos-Vargas; None; P. Chiovancanavakoti; None; M. T. Durouz; None; E. El-Zorkany; None; L. Gossec; None; L. Greydouka; None; L. Issers; None; P. Gehler; None; L. Gossec; None; S. Grazio; None; J. Gu; None; M. A. Khan; None; T. J. Kim; None; W. P. Maksymykovych; None; H. Marzo-Ortega; UCSB Pharma; S. V. Navarro-Compan; None; I. Olivieri; None; D. Patrakis; None; F. Pimentel-Santos; None; F. van Den Bosch; None; J. Zochling; None; J. Braun; AbbVie (Abbott); Angen, BMS, Boehringer, Celgene, Celtirion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Scherling-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB; 9, AbbVie (Abbott); Angen, BMS, Boehringer, Celgene, Celtirion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Scherling-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB; 5, AbbVie (Abbott), Angen, BMS, Boehringer, Celgene, Celtirion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Scherling-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB; 2.

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Therapeutic Response in Adalimumab-Treated Patients with Non-Radiographic Axial Spondyloarthritis Is Similar Regardless of Body Mass Index, Philip Mease1, Denis Podubinsky2, Su Chen2 and Jaclyn K. Anderson3. 1Swedish Medical Center and University of Washington, Seattle, WA; 2Charité Universitätsmedizin Berlin, Berlin, Germany; 3AbbVie Inc., North Chicago, IL.

Background/Purpose: C-reactive protein (CRP), an objective measure of active inflammation, has been associated with obesity, with both overweight and obese individuals more likely to have elevated CRP levels than their normal-weight counterparts. The objective of this analysis was to assess the relationship between elevated CRP and clinical response in non-obese and non-obese subgroups of non-radiographic axial SpA (nr-axSpA) patients (pts).

Methods: This post hoc analysis was performed in ABILITY-1, a phase 3, randomized, double-blind, multicenter study in pts with active nr-axSpA. Pts were randomized to receive adalimumab (ADA) 40 mg every other week (wk) [or placebo (PBO)] for 12 wks following randomization with an optional-label (OL) ADA for up to 156 wks. The MRI+elevated CRP subgroup included pts with a positive baseline MRI (Spondyloarthritis Research Consortium of Canada [SPARCC] score ≥2 for either the sacroiliac joints or spine) and/or elevated baseline CRP. Pts with BMI ≥25 kg/m² were considered obese. Clinical response variables were analyzed by BMI subgroups at wk 12.

Results: BMI was ≥25 in 85/185 (45.9%) pts in the overall population (PBO/ADA, n=43/42) and in 57/141 (40.1%) in the MRI+elevated CRP subgroup (PBO/ADA, n=30/27); BMI was <20 in 149/185 (80.5%) pts in the overall population (PBO/ADA, n=70/79) and in 110/141 (77.5%) in the MRI+elevated CRP subgroup (PBO/ADA, n=52/58). In the overall population CRP was elevated in 43/100 (43%) pts with BMI ≥25 and in 22/56 (61.1%) pts with BMI <20. BMI and CRP were weakly correlated (0.23, P=0.002); however, in pts with elevated CRP, mean BMI was significantly higher than in pts with normal CRP (28.8 vs 25.0, P<0.0001). ASAS40 response at wk 12 was similar in the overall population when evaluating overweight and obese pts. (Table 1) A comparable effect was seen in the MRI+elevated CRP subgroup with the exception of a slightly higher ASAS40 response in the MRI+elevated CRP subgroup with BMI <25; however, this should be interpreted with caution due to small sample size. (Table 2) ASAS40 response for the subgroup BMI ≥25 for the overall and MRI+elevated CRP populations was consistent with the overall population (PBO 15.7% vs ADA 34.7%, and PBO 16.3% vs ADA 33.3%, respectively).

Table 1. Clinical Response in the Overall Population at Week 12

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>BMI ≥25 kg/m²</th>
<th>BMI &lt;30 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=185)</td>
<td>(N=85)</td>
<td>(N=100)</td>
</tr>
<tr>
<td>PBO N=70</td>
<td>BMI N=39</td>
<td>BMI N=39</td>
</tr>
<tr>
<td>ACR N=42</td>
<td>ACR N=24</td>
<td>ACR N=24</td>
</tr>
<tr>
<td>ASAS40</td>
<td>28 (40.6)</td>
<td>28 (37.5)</td>
</tr>
<tr>
<td>ASAS20</td>
<td>27 (37.1)</td>
<td>27 (41.0)</td>
</tr>
<tr>
<td>ASAS40</td>
<td>17 (26.4)</td>
<td>17 (26.4)</td>
</tr>
<tr>
<td>HAQ-S</td>
<td>0.1 (0.4)</td>
<td>0.1 (0.4)</td>
</tr>
<tr>
<td>SF-36v2 PCS</td>
<td>0.4 (0.7)</td>
<td>0.4 (0.7)</td>
</tr>
</tbody>
</table>

Change from Baseline

| -0.4 (0.6) -0.5 (12.5) | 0.4 (5.8) -0.7 (15.7) | 0.1 (5.2) -0.5 (19.1) |

Table 2. Clinical Response in the MRI+elevated CRP Subpopulation at Week 12

<table>
<thead>
<tr>
<th>MRI+elevated CRP Subpopulation</th>
<th>BMI ≥25 kg/m²</th>
<th>BMI &lt;30 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=71)</td>
<td>(N=42)</td>
<td>(N=29)</td>
</tr>
<tr>
<td>PBO N=25</td>
<td>BMI N=14</td>
<td>BMI N=15</td>
</tr>
<tr>
<td>ACR N=20</td>
<td>ACR N=11</td>
<td>ACR N=9</td>
</tr>
<tr>
<td>ASAS40</td>
<td>20 (30.5)</td>
<td>20 (30.5)</td>
</tr>
<tr>
<td>ASAS20</td>
<td>19 (26.4)</td>
<td>19 (26.4)</td>
</tr>
<tr>
<td>ASAS40</td>
<td>12 (17.1)</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>HAQ-S</td>
<td>0.1 (0.4)</td>
<td>0.1 (0.4)</td>
</tr>
<tr>
<td>SF-36v2 PCS</td>
<td>0.4 (0.7)</td>
<td>0.4 (0.7)</td>
</tr>
</tbody>
</table>

Change from Baseline

| 0.3 (0.5) 0.4 (0.5) | 0.5 (1.0) 0.5 (1.0) | 0.6 (0.8) 0.6 (0.8) |

Conclusion: In ABILITY-1, ADA showed similar clinical responses in subgroups excluding overweight and obese pts compared to the overall study population. These data suggest nr-axSpA pts have a general inflammatory
state which is unrelated to obesity-related CRP elevations and that response to ADA is not driven by CRP elevations related to obesity.

**Disclosure:** P. Mease, AbbVie, Amgen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; 2, AbbVie, Amgen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; 5, AbbVie, Amgen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; 8, D. Poddubny, AbbVie, Janssen, MSD, Novartis, Pfizer, Roche, and UCB; 5, AbbVie, Janssen, MSD, Novartis, Pfizer, Roche, and UCB; 8, S. Chen, AbbVie, 1, AbbVie, 3, J. K. Anderson, AbbVie, 1, AbbVie, 3.

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**Ultra Sonographic Evaluation of the Anterior Chest Wall in Spondyloarthritides, a Prospective Study.** Frank Verhoeven1, Xavier Guillot, Marie Godfrin-Vaelnet2, Clément Prati3 and Daniel Wendling. 1CHU Jean Minjoz, Besançon, France, 2Rheumatology, Besançon, France, 3CHRU, Besançon, France, 4CHU J Minjoz, Besançon, France.

**Background/Purpose:** Anterior chest wall (ACW) involvement is a characteristic feature of spondyloarthritides (SpA), even in early stages, but its paraclinical exploration is not standardized. The aim of this study was to evaluate prevalence and type of ultrasonic (US) ACW involvement in SpA, and to look for factors associated to this involvement.

**Methods:** This prospective monocentric study included consecutive SpA (ASAS criteria) patients and a control group (healthy subjects, disca sciatica). Clinical (pain, swelling) and US evaluation (synovitis, joint effusion, erosion, joint space narrowing, ankylosis, power Doppler activity) were performed on manubriosternal and sternoclavicular joints. The main characteristics of SpA were recorded (disease duration, biologic features, BASDAI, ASDAS, radiographic and extra articular involvement). Patients were compared to controls (C).

**Results:** 131 SpA and 49 control patients (same age and sex ratio) were included. Clinical and US ACW involvement was found respectively in 36 and 39 patients (p < 0.01). US findings were: synovitis (9 SpA vs 2 C), joint space narrowing (12 vs 0), erosions (34 vs 0), manubriosternal ankylosis (24 vs 3), power Doppler activity (12 vs 2). US involvement in SpA is associated to smoking (p < 0.05), history of ACW pain (p < 0.05), to radiographic changes of sacro iliac joint (p = 0.05), to age (45 vs 41 y, p = 0.004), disease duration (14.9 vs 11.1 y, p = 0.04) and presence of inflammatory bowel disease (p = 0.03). US involvement is not associated to HLA-B27, enthesitis, psoriasis or uveitis, whereas clinical ACW involvement is associated with higher BASDAI (47 vs 32; p = 0.0009) and ASDAS (29.2 vs 2.2; p = 0.006). There is only a weak correlation between clinical and US involvement of ACW in these patients and controls.

**Conclusion:** US involvement of ACW is frequent in SpA, associated to disease duration, smoking and bowel involvement.

**Disclosure:** F. Verhoeven, None; X. Guillot, None; M. Godfrin-Vaelnet, None; C. Prati, None; D. Wendling, None.

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**High Sensitivity of the ASAS Classification Criteria in Patients with HLA-B27 Positive Undifferentiated Spondyloarthritides with Onset of Disease after Age 45.** Ignazio Olivieri1, Michele Gili1, Salvatore D’Angelo1, Angela Paullia, Pietro Leccece1, Silvana Di Bello1, Noruilah Akkok6, Nicola Ferrara6 and Carlo Palazzi. 1Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy, 2Department of Internal Medicine, Division of Rheumatology, Dokuz Eylul University School of Medicine, Izmir, Turkey, 3Department of Translational Medical Sciences, Federico II University, Naples, Italy.

**Background/Purpose:** The spondyloarthritides (SpA) complex also includes forms that do not meet criteria for the definite forms and are called undifferentiated SpA (uSpA). Recently the Assessment in SpondyloArthritis international Society (ASAS) suggested criteria for axial and peripheral SpA that have substituted the Amor and the European Spondylarthritis Study Group (ESSG) criteria for all forms of SpA. In the ASAS criteria for axial disease the entry criterion is chronic low back pain in a patient with an age less than 45 years. Only 15% of the patients included in the study for the ASAS criteria for peripheral disease were older than 45 years. The objective of our study was to evaluate the sensitivity of the ASAS criteria for axial and peripheral SpA in a cohort of consecutive patients with HLA-B27-positive uSpA with onset after the age of 45 (late onset uSpA) consecutively recruited in a 12-year period in comparison with a cohort of consecutive patients with HLA-B27-positive uSpA with onset before age 45 (ordinary onset uSpA) recruited in the same period.

**Methods:** Patients HLA-B27-positive with at least one clinical manifestation of SpA and not meeting the New York criteria for ankylosing spondylitis (AS) and with a negative personal history for psoriasis, inflammatory bowel disease and preceding infection seen since January 2001 were entered in a special register and were followed prospectively. Each patient was examined at 6-month even if asymptomatic.

**Results:** During the 12-year recruitment period, 93 patients (35 M, 58 F; age 58 ± 9.8) with late onset uSpA were seen. The first 93 consecutive patients (54 M, 39 F; age 29.6 ± 8.6) with ordinary onset uSpA seen in the same period were evaluated for comparison. Compared to the 93 patients with ordinary onset uSpA, the 93 patients with late onset uSpA were more frequently females (62.4% vs. 41.9%, p < 0.05) and had a shorter diagnostic delay (time elapsed between the day of onset and the day of diagnosis: 20 ± 7 vs. 63 ± 3177 months, p < 0.01) and showed more frequently increased levels of ESR (Erythrocite Sedimentation Rate)57% vs. 33.3%, p = 0.05) and CR (C-reactive protein) 62.4% vs. 48.4%, p = 0.07). In addition, patients with late onset uSpA developed more frequently inflammatory extremity swelling with pitting edema (IIESPE) over the dorsum of hands and/or of the feet (25.8% vs. 4.3%, p < 0.01) and peripheral enthesitis (48.4% vs.31.2%, p < 0.05). In contrast, patients with ordinary onset uSpA showed more frequently acute anterior uveitis (20.4% vs. 7.5%, p < 0.05). The sensitivity of the ASAS criteria was similar in the ordinary cohort (90.3%) and the late onset (91.4%) cohorts of patients with uSpA.

**Conclusion:** The ASAS classification criteria for axial and peripheral SpA showed a similar high sensitivity in patients with ordinary and late onset uSpA. In addition, this study confirms that some clinical and laboratory features of SpA may differ with the age at onset of the disease.

**Disclosure:** I. Olivier, None; M. Gili, None; S. D’Angelo, None; A. Padula, None; P. Lecese, None; S. Di Bello, None; N. Akkok, None; N. Ferrara, None; C. Palazzi, None.

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**A Psychometric Analysis of Outcome Measures in Trials of Peripheral Spondyloarthritides.** Sofia Ramiro1, Maureen C. Turina2, Dominique L. Baer3, Philip Mease4, Jannik Glueck4, Francois F. Papatheodorou4, Ingrid P. Pangan5 and Robert Landewe6. 1Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, 2Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 3Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 4Swedish Medical Center and University of Washington, Seattle, WA, 5AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, 6AbbVie Inc., North Chicagio, IL.

**Background/Purpose:** We assessed the discriminative aspects of disease activity measures and response criteria between adalimumab (ADA) and placebo (PBO) in 2 studies of patients (pts) with peripheral spondyloarthritides (pSpA).

**Methods:** ABILITY-2 is an ongoing randomized controlled trial of ADA in pts with pSpA fulfilling ASAS peripheral SpA criteria. Primary endpoint was peripheral SpA response criteria (PSpARC)40 at wk 12, defined as ≥40% improvement from baseline (BL) (≥20 mm absolute improvement on a visual analog scale) in Patient Global Assessments of Disease Activity (PGA) and Pain (PGA-pain) and ≥40% improvement in ≥1 of the following: swollen joint count (SJC) and tender joint counts (TJC); enthesitis count; or dactylitis count. In an investigator-initiated study (AMC) in the Netherlands, pts fulfilling ESSG and/or AMOR criteria for SpA for ≥3 months but not criteria for ankylosing spondylitis or psoriatic arthropitids were randomized to ADA or PBO. Primary endpoint was change in PGA at wk 12. Analyses to determine the discriminative capacity of disease activity measures between ADA and PBO groups included standardized mean difference (SMD) of the mean change from BL; for categorical response criteria Pearson’s χ2 between treatments were calculated. Higher the SMD and χ2, the higher the discriminatory capacity. Variables evaluated included PGA, PGA-pain, Physician’s Global Assessment of Disease Activity (PGA), CRP, TJC, SJC, BASDAI, SF-36, HAQ-S, ASDAS, PSpARC0/50/70, ACR20/50/70, ASDAS major improvement/inactive disease, and BASDAI50.

**Results:** ABILITY-2 randomized 165 pts (ADA 84, PBO 81); AMC enrolled 40 pts (ADA 20, PBO 20). Among the continuous variables, ASDAS
discriminates better than BASDAI or individual measures such as CRP as shown by higher SMD values (Table). For clinical response criteria, PsPARC0, PsParc50, ASDAS inactive disease and BASDAI50 performed well in differentiating between ADA vs. PBO treatment as shown by the χ² in the table. ACR20 and ACR50 performed better than ACR70 in differentiating between ADA vs. PBO.

Discrimination between patients on adalimumab vs. placebo at week 12

<table>
<thead>
<tr>
<th>Mean Change from Baseline</th>
<th>ADA (n)</th>
<th>PBO (n)</th>
<th>SMD</th>
<th>Gartit’s ES</th>
<th>ADA (n)</th>
<th>PBO (n)</th>
<th>SMD</th>
<th>Gartit’s ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS</td>
<td>-1.1 (0.8)</td>
<td>-0.5 (0.7)</td>
<td>-0.65</td>
<td>-1.18</td>
<td>-1.3 (0.9)</td>
<td>-0.6 (0.9)</td>
<td>-0.9</td>
<td>-0.89</td>
</tr>
<tr>
<td>BASDAI</td>
<td>-2.1 (0.9)</td>
<td>-1.0 (0.9)</td>
<td>-0.9</td>
<td>-0.976</td>
<td>-1.5 (0.9)</td>
<td>-0.3 (1.0)</td>
<td>-0.73</td>
<td>-1.26</td>
</tr>
<tr>
<td>PGA (0–100 mm Hg)</td>
<td>-28.6 (16.1)</td>
<td>-16.2 (10.8)</td>
<td>-4.74</td>
<td>-11.3 (10.9)</td>
<td>-5.9 (11.2)</td>
<td>-1.12</td>
<td>-1.45</td>
<td></td>
</tr>
<tr>
<td>PGA (&gt;100 mm Hg)</td>
<td>-32.7 (15)</td>
<td>-24.8 (16)</td>
<td>-0.44</td>
<td>-1.43</td>
<td>-19.4 (18)</td>
<td>-4.4 (18)</td>
<td>-0.87</td>
<td>-1.21</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>-5.8 (0.8)</td>
<td>-2.8 (0.8)</td>
<td>-1.08</td>
<td>-0.82</td>
<td>-5.7 (0.9)</td>
<td>0.3 (0.9)</td>
<td>-0.53</td>
<td>-0.25</td>
</tr>
<tr>
<td>SJC 76</td>
<td>-3.6 (3.2)</td>
<td>-3.1 (2.8)</td>
<td>-0.1</td>
<td>-0.46</td>
<td>-2.3 (0.4)</td>
<td>0.4 (0.4)</td>
<td>-0.9</td>
<td>-1.40</td>
</tr>
<tr>
<td>TJC 78</td>
<td>-6.0 (3.2)</td>
<td>-1.8 (1.8)</td>
<td>-0.5</td>
<td>-0.57</td>
<td>-1.8 (1.9)</td>
<td>1.7 (1.9)</td>
<td>-0.45</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

Table: Long-term clinical response and remission at Years 2 and 3

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>NRI</td>
<td>Observed Data NRI = 128</td>
</tr>
<tr>
<td>ADA PBO Pearson’s r, F-value</td>
<td>ADA PBO Pearson’s r, F-value</td>
<td>ADA PBO Pearson’s r, F-value</td>
</tr>
<tr>
<td>ASDAS</td>
<td>0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>PsParc50</td>
<td>0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>PsParc10</td>
<td>0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>ASDAS Major Improvement</td>
<td>0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>ASDAS Inactive</td>
<td>0.9</td>
<td>0.004</td>
</tr>
</tbody>
</table>

As seen in Table 2, ADA had significantly better clinical outcomes compared to PBO at both Year 2 and Year 3, as evidenced by the observed NRI values and the corresponding P-values.

Results: Of the 185 pts enrolled in ABILITY-1, 122 (66%) had data available at wk 156 and 97 of 142 (68%) from the MRI-elevated CRP sub-population. Clinical responses and remission rates were generally sustained between Year 2 and Year 3 of the study (Table). Through 412.2 patient-years (PYs) of exposure to ADA, the serious infection rate observed was 2.4 events/100 PYs, including 1 case of disseminated TB. There were 2 deaths – 1 due to suicide and another due to opiate toxicity. There were no malignancies reported.

Conclusion: Composite indices (ASDAS and BASDAI) outperformed individual measures (TJC, SJC, CRP) in sensitivity to change and discriminatory properties. The PsParc response criteria developed for psPsA, as well as ACR20 and ACR50, have good discriminatory ability in patients with psPsA. Although the ASDAS and to some extent BASDAI, which were developed for AS, performed reasonably well in being able to discriminate between active treatment and placebo in patients with periarticular SpA, there may be problems regarding face validity.

Disclosure: S. Ramiro, None; M. C. Turina, None; D. L. Baeten, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, UC, 2, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, UC, 5, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, UC, 8; P. Mose, AbbVie, Aigen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UC, 2, AbbVie, Aigen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UC, 27; A. L. Pangan, AbbVie, 1, A. L. Pangan, AbbVie, 1, A. L. Pangan, AbbVie, 3; R. Landévez, AbbVie, Aigen, BMS, Centocor, GSK, Merck, Novartis, Pfizer, Roche, Schering-Plough, UCB, Vertex, 5, A. L. Pangan, AbbVie, 1; I. H. Song, AbbVie, 5, Imaging Rheumatology BV, 9; R. Landévez, AbbVie, Aigen, BMS, Centocor, GSK, Merck, Novartis, Pfizer, Roche, Schering-Plough, UCB, Vertex, 5, A. L. Pangan, AbbVie, 1; I. H. Song, AbbVie, 5, Imaging Rheumatology BV, 9; R. Landévez, AbbVie, Aigen, BMS, Centocor, GSK, Merck, Novartis, Pfizer, Roche, Schering-Plough, UCB, Vertex, 5, A. L. Pangan, AbbVie, 1; I. H. Song, AbbVie, 5, Imaging Rheumatology BV, 9.

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Evaluation of Clinical Parameters and Quality of Life in Smokers with Ankylosing Spondylitis: Results from the Scotland Registry for Ankylosing Spondylitis.

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Background/Purpose: Several studies have shown that smoking is associated with increased disease activity, worse physical function and poor quality of life in ankylosing spondylitis (AS). However, other than as part of general health advice, recommendations on smoking cessation are not commonly given by physicians, nor perceived as of high importance by AS.

1Ruhr-University Bochum, Herne, Germany, 2University of Alberta, Edmonton, AB, 3Amsterdam Rheumatology Center, Amsterdam, Netherlands, 4UCB Pharma, Monheim, Germany, 5UCB Pharma, Slough, United Kingdom, 6Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Previous results from RAPID-axSpA (NCT01087762) demonstrated that certolizumab pegol (CZP) reduced inflammation in the sacroiliac joints (SIJ) and spine, as assessed by Magnetic Resonance Imaging (MRI), after 12 weeks (wks) of therapy in patients (pts) with axial spondyloarthritis (axSpA) and in both ankylosing spondylitis (AS) and non-radiographic (nr-) axSpA subpopulations. 1 The objective of this report is to present MRI outcomes from RAPID-axSpA to Wk96.

Methods: RAPID-axSpA,2 a Phase 3 study in axSpA pts, is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4), continued on their assigned dose in dose-blind and OL phases. MRI scans of the SIJ and spine,3 using short-tau-inversion recovery sequences, were performed at baseline (BL) (≥3 days), Wk12, Wk24 and Wk96. MRI endpoints were change from BL in the Spondyloarthritis Research Consortium of Canada (SPARC) SIJ score for inflammation and in the Berlin modification of AS spine MRI score for disease activity in the spine (ASpMRAI-a). MRIs were recorded in a subset of pts, and results reported for pts randomized to CZP using all observed MRI measurements.

Results: 218 pts were randomized to receive CZP, of which 109 were included in the MRI set. 726 MI were reported in AS patients (N=18,916) over mean follow-up of sixteen years: incidence 5.5% [3.9%, 7.4%], i.e. 0.4/100 yrs. Seven studies revealed 17,410 MI (2.5% [1.8%, 3.4%]) in the control group (N=1,349,964). Meta-analysis of the seven longitudinal studies showed a significant increase in MI (RR=1.46 [1.33, 1.60]) in AS patients. 2 Stroke.In ten longitudinal studies (N=43,374), 1,370 strokes were reported in AS patients over 18.5 years of follow-up: incidence 3.4% [1.2%, 6.8%], i.e. 0.1/100 yrs. Three studies reported 22,899 strokes in controls (N=1,239,041), giving an incidence of 1.78% [1.75%, 1.80%]. A significant increase in stroke (RR=1.50 [1.39, 1.62]) in AS patients was found.

Conclusion: AS patients appear to have a higher risk of MI and stroke. Management of cardiovascular risk factors and control of systemic inflammation should be taken into account in AS.

Disclosure: J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma; 2 W. P. Maksymowych, AbbVie, Amgen, BMS, Eli Lilly, Janssen, Merck, Pfizer, Synarc, UCB Pharma; 3 R. B. M. Landewé, Abbott, Ablinis, AstraZeneca, Bristol Myers Squibb, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma; 4 V. Plough, UCB Pharma, Wyeth; 5 A. H. St Clair, AbbVie, Amgen, BMS, Eli Lilly, Janssen, Merck, Pfizer, Synarc, UCB Pharma; 6 T. Ratz, AbbVie, Amgen, BMS, Eli Lilly, Janssen, Merck, Pfizer, Synarc, UCB Pharma; 7 D. van der Heijde, AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Chugai, Covagen, Daiichi, Eli Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma, Vertex, 5 Imaging Rheumatonomy bv, 9.


Table: Mean change from BL in SPARC and ASpMRAI-a in patients with axSpA

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean score (SD)</td>
<td>Mean change from BL (SD)</td>
</tr>
<tr>
<td>SPARC</td>
<td>axSpA</td>
<td>97</td>
</tr>
<tr>
<td>AS</td>
<td>58</td>
<td>1.3 (3.6)</td>
</tr>
<tr>
<td>ASpMRAI-a</td>
<td>axSpA</td>
<td>99</td>
</tr>
<tr>
<td>AS</td>
<td>60</td>
<td>1.8 (3.8)</td>
</tr>
<tr>
<td>nr-axSpA</td>
<td>axSpA</td>
<td>60</td>
</tr>
<tr>
<td>AS</td>
<td>33</td>
<td>0.9 (1.5)</td>
</tr>
</tbody>
</table>

Disclosure: L. E. Dean, None; F. Azemi, None; T. Ratze, None; A. G. MacDonald, None; R. D. Sturrock, None; J. Hunter, None; D. Marshall, Abbvie, 5, Chugai-Roche, 5, MSD, 5, Chugai-Roche, 8, Celgene, 8, Novartis Pharmaceutical Corporation, 8; G. J. Macfarlane, Pfizer Inc. 2, Abbo Ltd, 2, Pfizer Inc, 5; G. T. Jones, Pfizer Inc. 2, Abbvie Ltd, 2.
Background/Purpose: The impact of certolizumab pegol (CZP) on clinical and Magnetic Resonance Imaging outcomes in patients (pts) with axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic (nr-) axSpA, has been described previously.1 However, structural progression in these pts measured by X-ray has not been previously reported. The objective of this report is to present structural progression, assessed using X-ray, over 96 weeks (wks) of CZP treatment in the RAPID-axSpA study (NCT01087762).2

Methods: RAPID-axSpA, a Phase 3 study in axSpA pts, is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts had adult-onset active axSpA. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4), continued on their assigned dose in dose-blind and OL phases. X-ray assessment of the anterior vertebral edges of the cervical and lumbar spine was conducted using the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) at baseline (BL) and Wk96. X-rays were recorded in a subset of pts, and results reported for pts initially randomized to CZP with both available BL and Wk96 X-ray measurements (observed case). Definite mSASSS progression was defined as an mSASSS increase of 2 units. Unadjusted descriptive analyses investigated mSASSS disease activity and response in subgroups of pts.

Results: 218 pts were randomized to receive CZP, of which 109 were included in the imaging set, and 89 had both BL and Wk96 X-rays available for analysis. 22.2% of CZP pts in the imaging set had evidence of structural changes in the spine (mSASSS≥2, with ≥1 syndesmophyte) at BL (32.3% of AS and 8.7% of nr-axSpA pts). Mean mSASSS at BL was 8.0 in axSpA pts. As expected, BL damage was more severe in AS pts compared to the nr-axSpA population (11.1 vs 3.2, Table). Over 96 wks of CZP treatment, mean mSASSS score of the axSpA population increased by 0.4 units, and 9.0% of pts experienced definite mSASSS progression ≥2 units. Radiographic progression was greater in AS pts compared to nr-axSpA pts (change from BL: 0.6 vs 0.2, definite mSASSS progression 13.0% vs 2.9%).

Conclusion: Limited radiographic progression was seen over 96 wks in CZP-treated pts. Further analyses are needed to confirm which subgroups of pts have an increased risk of progression.

References
1. van der Heijde D. Arthritis Rheum 2012;64(Suppl 10):S730

Disclosure: D. M. van der Heijde, AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma, Vertex, 5, Imaging Rheumatology bv, 9; W. P. Maksymowych, AbbVie, Amgen, BMS, Eli Lilly, Janssen, Merck, Pfizer, Synarc, UCB Pharma, 1, AbbVie, Amgen, Eli Lilly, Janssen, Merck, Pfizer, Synarc, UCB Pharma, 5; R. B. M. Landewe, Abbott, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Centocor, Glaxo-Smith-Kline, Novartis, Merck, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 7, Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 2, Abb, Abbott, Amgen, Bristol Myers Squibb, Centocor, Merck, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 8; C. Stach, UCB Pharma, 3, UCB Pharma, 1; O. Davies, UCB Pharma, 3, UCB Pharma, 1; T. Nurminen, UCB Pharma, 3; J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.

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Use of Monotherapy Anti-Tnf Agents in Ankylosing Spondylitis Patients from the rhumadata® Registry: 8-Year Comparative Effectiveness of Discontinuation, Etanercept and Infliximab

Background/Purpose: Anti-TNF agents namely adalimumab (ADA), etanercept (ETA) and infliximab (INF) are approved for the treatment of signs and symptoms of ankylosing spondylitis. Their efficacy has been demonstrated in randomized controlled trials against placebo. They have also been shown effective in the treatment of extra-articular features such as enthesitis, inflammatory bowel entities such as Crohn’s disease and ulcerative colitis and uveitis. Antibodies and fusion receptors may have a different mechanism of action. Our objective is to assess the retention rates of adalimumab (ADA), etanercept (ETA) and infliximab (INF) in patients diagnosed with ankylosing spondylitis (AS) and to compare patient reported response over time.

Methods: Data of AS patients who had been prescribed adalimumab (ADA), etanercept (ETA) or infliximab (INF) in monotherapy on or after January 1st 2004 was extracted. Baseline demographics included age, gender, disease duration, HAQ-DI fatigue and pain visual analog scale, extra-articular features such as enthesitis, inflammatory bowel entities such as Crohn’s disease and ulcerative colitis and uveitis. Antibodies and fusion receptors may have a different mechanism of action. Our objective is to assess the retention rates of adalimumab (ADA), etanercept (ETA) and infliximab (INF) in patients diagnosed with ankylosing spondylitis (AS) and to compare patient reported response over time.

Results: Data from 170 patients diagnoses with AS was extracted and no significant differences in baseline characteristics were observed between treatment groups except for age and disease duration. The 8-year retention rate of ADA, ETA and INF were 62%, 55% and 54% respectively and were not statistically different (Log-Rank p=0.90). Seventy-five patients were used to analyse time required to reach a BASDAI of 2 and compare rates of response. At baseline, ADA, ETA and INF BASDAI were 6.6, 6.2, 6.5 respectively. The adjusted hazard ratio for reaching a BASDAI of two was found to be 0.77 (95% CI = [0.52, 1.07]) and 0.82 (95% CI = [0.55, 1.18]) when comparing ETA and INF to ADA respectively. Overall 42%, 49% and 54% of ADA, ETA and INF patients reached a target BASDAI of 2 in average adjusted times of 9.6, 19.0 and 15.6 months (p-value=0.31).

Conclusion: Monotherapy adalimumab, etanercept and infliximab in AS patients show similar 8-years retention rates and similar improvement in BASDAI. They all represent good options for the treatment of AS in monotherapy.

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Secondary Amyloidosis Complicating Spondyloarthritis: Still Present after All These Years. Samantha Rodríguez-Muguruzal, Melissa Martínez-Morillo, Susana Holgado, María Lourdes Mateo, Juana Sanit, Anne Riveros-Frutos, Jeronima Canellas, Xavier Tena and Alejandro Olivé Marqués. 1Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, 2Hospital Universitari Germans Trias i Pujol, Badalona, Spain.

Background/Purpose: Secondary amyloidosis (AA) is a disorder caused by deposition of insoluble amyloid A fibrils in different tissues and organs. It is a rare and serious complication of rheumatic diseases including spondyloarthropathies (SpA).

The aim of this study was to determine the clinical features, laboratory data, treatment and clinical outcome of patients with SpA who developed AA amyloidosis.

Methods: Design: retrospective (1984–2013). Hospital: academic tertiary hospital. Referral area: 850,000 inhabitants. We reviewed the medical records of 1125 patients with SpA: 509 (45%) psoriatic arthritis (PsA), 263 (23%) ankylosing spondylitis (AS), 128 (11.3%) spondylitis associated with inflammatory bowel disease (IBD), 190 (16.8%) undifferentiated spondyloarthropathies, and 35 (3.1%) reactive arthritis. We selected patients who had a histological diagnosis of AA amyloidosis. Patients with comorbidities that might be associated with AA amyloidosis were excluded.

Results: Fifteen (1.3%) patients with AA amyloidosis were recruited: 11 (73.3%) males and 4 (26.7%) females. Five (33.3%) AS, 5 (33.3%) spondylitis associated with IBD, 4 (26.7%) PsA, and 1 (6.7%) reactive arthritis. Mean age at SpA and AA amyloidosis diagnosis: 35.13 and 57.7 years, respectively. Mean disease duration: 23.9 years. Eleven patients with AA amyloidosis were diagnosed in 1984–2000 and 4 in 2001–2013. Amyloid deposits were observed on biopsy of: rectum (6 cases), kidney (3 cases), subcutaneous fat (4 cases) and bladder (1 case). In one case diagnosis was made incidentally (gallbladder), in the others diagnosis was symptomatic and suspected due to nephrotic syndrome (4), acute renal failure (ARF) (3), non-nephrotic-range proteinuria (3), chronic renal failure (CRF) (2), diarrhoea (1) and macroscopic haematuria (1). The mean values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at diagnosis were 65.4 mm and 25.22 mg/L, respectively. Five patients were treated with infliximab: three showed a clinical improvement, with decreased ESR and CRP, and two patients were treated with TNF inhibitor alone.

Conclusion: The frequency of clinically apparent AA amyloidosis in our patients was 1.3%. There was a marked male predominance. Clinical AA amyloidosis was diagnosed at a relatively late stage in SpA. The predominant clinical picture was nephrotic syndrome. The frequency of AA amyloidosis decreases between decades, reflecting better control of the disease with novel therapies. Mortality is high.

Disclosure: S. Rodríguez-Muguruzal, None; M. Martínez-Morillo, None; S. Holgado, None; M. L. Mateo, None; J. Sanit, None; A. Riveros-Frutos, None; J. Canellas, None; X. Tena, None; A. Olivé Marqués, None.

Better Outcomes in Ankylosing Spondylitis: The Synergistic Association Between Exercise and Tumor Necrosis Factor Inhibitors. Sarah L. Patterson, John D. Reveille, Minee Lee, Michael M. Ward, Mohammad H. Rahbar, Matthew A. Brown, Michael H. Weissman and Lianne S. Gensler. 1University of California, San Francisco, San Francisco, CA, 2University of Texas Health Science Center at Houston, Houston, TX, 3NIAMS/NIH, Bethesda, MD, 4The University of Texas Health Science Center at Houston, Houston, TX, 5University of Queensland Diamantina Institute, Brisbane, Australia, 6Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Exercise is an important component of Ankylosing Spondylitis (AS) management. The purpose of this study was to determine if the amount patients exercise associates with better functional outcomes and to assess if medication use contributes to this relationship.

Methods: This is a prospective cohort of 623 AS patients, meeting modified New York criteria followed up to 4 years. We collected demographic, clinical and self-reported outcomes every 6 months. Participants were queried about exercise habits including number of days per week and minutes per time exercise. A moderate exercise dose was defined as ≥120 minutes per week. Using a mixed effects Poisson regression model, we assessed multivariable associations between independent variables and the Bath Ankylosing Spondylitis Functional Index (BASFI). This accounted for correlation of repeated measures over time. Potential confounding, including baseline function, and effect modifications were examined and addressed while developing a final longitudinal multivariable model.

Results: The mean age of patients was 43 ± 14.0 years. The cohort was 72% male and 78% of patients were white. Mean disease duration was 19 ± 13.4 years. Findings from our final multivariable model indicated BASFI scores for the moderate exercise group were significantly lower than those who exercised less than 120 minutes per week at 1, 2, 3, and 4 years of follow-up (Table 1).

Conclusion: AS patients who exercise for at least 120 minutes per week have significantly better long-term function than those who do not. Additionally, there is a greater likelihood of functional improvement in those on both a TNF inhibitor and moderate exercise program compared to those using a TNF inhibitor alone.

Table 1. Adjusted Associations of Exercise and Other Covariates on Function (BASFI)

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Adjusted Rate Ratio*</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise &amp; Time Interaction</td>
<td></td>
<td></td>
<td>0.0349</td>
</tr>
<tr>
<td>Exercise &gt; 120*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.00</td>
<td>0.96–1.05</td>
<td>0.96</td>
</tr>
<tr>
<td>Year 1</td>
<td>0.93</td>
<td>0.90–0.96 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>0.95</td>
<td>0.91–0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.93</td>
<td>0.88–0.97 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>0.95</td>
<td>0.90–1.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Exercise &amp; TNF inhibitor Interaction</td>
<td></td>
<td></td>
<td>0.0464</td>
</tr>
<tr>
<td>Exercise &gt; 120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF inhibitor Use</td>
<td>0.99</td>
<td>0.93–1.06</td>
<td>0.83</td>
</tr>
<tr>
<td>No TNF inhibitor</td>
<td>1.04</td>
<td>0.97–1.11</td>
<td>0.32</td>
</tr>
<tr>
<td>TNF inhibitor Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise &gt; 120</td>
<td>0.87</td>
<td>0.84–0.91 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Exercise &lt; 120</td>
<td>0.91</td>
<td>0.88–0.95 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BASFI at Baseline</td>
<td>1.03</td>
<td>1.03–1.03 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age at least 50 years</td>
<td>1.12</td>
<td>1.05–1.19</td>
<td>0.0003</td>
</tr>
<tr>
<td>Male</td>
<td>1.01</td>
<td>0.91–1.13</td>
<td>0.85</td>
</tr>
<tr>
<td>Postgraduate Education</td>
<td>0.96</td>
<td>0.84–1.10</td>
<td>0.58</td>
</tr>
<tr>
<td>BASDAI score at least 40</td>
<td>1.33</td>
<td>1.29–1.36</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total CES-D score at least 8</td>
<td>1.14</td>
<td>1.11–1.16</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>0.93</td>
<td>0.79–1.08</td>
<td>0.32</td>
</tr>
<tr>
<td>At least 1 comorbidity</td>
<td>1.04</td>
<td>0.93–1.18</td>
<td>0.48</td>
</tr>
<tr>
<td>Disabled</td>
<td>0.91</td>
<td>0.76–1.10</td>
<td>0.28</td>
</tr>
<tr>
<td>NSAID Use</td>
<td>1.07</td>
<td>1.04–1.09 &lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Rate Ratio of a higher BASFI score based on the independent variables in column 1 adjusted for BASFI at baseline, and all other covariates above.

Report of exercise for at least 120 minutes per week.
Sleep disturbances are prevalent amongst Korean patients with ankylosing spondylitis (AS). Inadequate sleep in AS patients is associated with multiple factors including pain, fatigue, disease activity and depression. In this study, we evaluated the prevalence of sleep disturbance in Korean patients with ankylosing spondylitis, and its association with disease activity and depression.

Methods: Forty patients with AS and eighty healthy controls were included in the study. Participants completed questionnaires. Sleep quality was assessed using the Korean version of the Pittsburgh sleep quality index (PSQI). Depression was assessed by the Korean version of the Beck depression inventory second edition (BDI-2). The Bath ankylosing spondylitis disease activity index (BASDAI) and ankylosing spondylitis disease activity score-C-reactive protein (ASDAS-CRP) were used to evaluate disease activity. Patients were dichotomized into a good sleeper group (PSQI ≤ 5) and a poor sleeper group (PSQI > 5).

Results: The mean total PSQI score of patients with AS was 7.23 ± 3.84. It was higher than that of control subjects (p < 0.001). AS patients had higher scores in the subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance and daytime dysfunction components. 60% of the AS patients classified as poor sleeper group. The mean ASDAS-CRP and BDI-2 score of poor sleeper group were higher than that of good sleeper group. Significantly, higher disease activity according to ASDAS-CRP was associated with poor sleep quality and depression. Stepwise multiple regression analysis revealed that duration of morning stiffness and depression were independent risk factors that influenced poor sleep quality. Therefore, evaluation and optimal management of morning stiffness and depression to improve sleep quality in patients with AS is important.

Conclusion: Sleep disturbances are prevalent amongst Korean patients with AS. Lower quality of sleep is significantly associated with higher disease activity and depression. Morning stiffness and depression were independent risk factors that influenced poor sleep quality. Therefore, evaluation and optimal management of morning stiffness and depression to improve sleep quality in patients with AS is important.

Disclosure: S. L. Patterson, None; J. D. Reveille, None; M. Lee, None; M. M. Ward, None; M. H. Rahbar, None; M. A. Brown, None; M. H. Weisman, None; L. S. Gensler, UCB, 5, AbbVie, 5.

570 Sleep Disturbances in Korean Patients with Ankylosing Spondylitis Are Associated with Increased Disease Activity. Hye Jin Jeong1, Yun Sung Kim1, Chang-Nam Son3, Ji-Min Kim3 and Sang-Hyon Kim3. 1Keimyung University Dongsan Medical Center, Daegu, South Korea, 3Chosun University Hospital, Gwangju, South Korea, 3Keimyung University School of Medicine, Daegu, South Korea.

Background/Purpose: Sleep problems have been reported to be more frequent in rheumatic disease than normal population. Other studies indicate various sleep problems have been reported in ankylosing spondylitis (AS). Inadequate sleep in AS patients is associated with multiple factors including pain, fatigue, disease activity and depression. In this study, we evaluated the prevalence of sleep disturbance in Korean patients with ankylosing spondylitis, and its association with disease activity.

Methods: Forty patients with AS and eighty healthy controls were included in the study. Participants completed questionnaires. Sleep quality was assessed using the Korean version of the Pittsburgh sleep quality index (PSQI). Depression was assessed by the Korean version of the Beck depression inventory second edition (BDI-2). The Bath ankylosing spondylitis disease activity index (BASDAI) and ankylosing spondylitis disease activity score-C-reactive protein (ASDAS-CRP) were used to evaluate disease activity. Patients were dichotomized into a good sleeper group (PSQI ≤ 5) and a poor sleeper group (PSQI > 5).

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Conclusion: Sleep disturbances are prevalent amongst Korean patients with AS. Lower quality of sleep is significantly associated with higher disease activity and depression. Morning stiffness and depression were independent risk factors that influenced poor sleep quality. Therefore, evaluation and optimal management of morning stiffness and depression to improve sleep quality in patients with AS is important.

Disclosure: H. J. Jeong, None; Y. S. Kim, None; C. N. Son, None; J. M. Kim, None; S. H. Kim, None.

571 Unraveling the Familial Tendency for Ankylosing Spondylitis in Korea. Hye Won Kim1, Hye Rim Choe2, Won Ik Chang2, Yong-Gil Kim3, Bin Yoo3, Jin Wook Hur1, Tae-Hwan Kim4, Sungim Lee5 and Eun Young Lee5. 1Eulji University of Medicine, Eulji General Hospital, Seoul, South Korea, 2Seoul National University College of Medicine, Seoul, South Korea, 3University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, 4Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 5Dankook University, Yongin, South Korea.

Background/Purpose: Despite of the evidence of familial aggregation of ankylosing spondylitis (AS), familial tendencies are not fully explored. The purpose of this study was to examine the recurrence risk (RR) ratios in different degrees of relatives for Korean AS patients.

Methods: 526 consecutive unrelated AS probands (101 female, 425 male, mean age 35.5 years, mean disease duration 12.3 years, 88.7% HLA-B27 positive) fulfilling the modified New York criteria were face-to-face-interviewed by physicians, with elaborated questionnaire to investigate AS in other family members by the same criteria. A total of 12,051 relatives (2284, 5342 and 4425 for first, second and third-degree relatives (TDR), respectively) were included. The RR ratios for different degrees of relatives were elicited and subsequently stratified by gender and HLA-B27 status. The prevalence of AS among Korean in 2013 was estimated by the Korean National Health Insurance Service at 0.07%.

Results: The RR ratio was 53.8 for first-degree relatives (FDR) followed by 10.8, 9.0 for second-degree relatives (SDR) and TDR, respectively, indicating strictly decreasing in familiality. Among FDRs, siblings were more frequently affected than offspring or parents. For male probands, the overall RR ratio for FDR was 55.5, and 65 for female, implying higher familiality of female over male. Remarkably, all of affected SDRs and beyond were relatives of HLA-B27 positive probands.

Conclusion: We demonstrated strongest familiality of AS in FDRs, particularly in siblings. Despite of similar sharp decline pattern of familiality beyond SDR, lower RR ratio in FDR was 55.5, and 65 for female, implying higher familiality of female over male. Remarkably, all of affected SDRs and beyond were relatives of HLA-B27 positive probands.

Table. The relative recurrence risk ratio by gender in Korean AS patients.

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean population prevalence (%)</td>
<td>0.04</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>RR ratio</td>
<td>RR (95% CI)</td>
<td>RR ratio</td>
</tr>
<tr>
<td>Overall familial</td>
<td>0.0 (0.5-4.3)</td>
<td>0.93</td>
<td>1.1(1.4-2.2)</td>
</tr>
<tr>
<td>First degree</td>
<td>2.6 (1.7-3.5)</td>
<td>65.0</td>
<td>5.0 (3.8-6.3)</td>
</tr>
<tr>
<td>Parent</td>
<td>1.0 (0.6-3.0)</td>
<td>85.0</td>
<td>5.7 (3.0-7.3)</td>
</tr>
<tr>
<td>Offspring</td>
<td>2.5 (1.4-4.1)</td>
<td>62.5</td>
<td>5.1 (3.9-6.3)</td>
</tr>
<tr>
<td>Sibling</td>
<td>3.3 (1.7-6.0)</td>
<td>82.5</td>
<td>6.6 (4.5-9.9)</td>
</tr>
<tr>
<td>Second degree</td>
<td>0.4 (0.2-0.7)</td>
<td>10.0</td>
<td>1.1 (0.7-1.5)</td>
</tr>
<tr>
<td>Third degree</td>
<td>0.2 (0.0-0.4)</td>
<td>5.0</td>
<td>1.0 (0.6-1.4)</td>
</tr>
</tbody>
</table>
Objective Evaluation of Physical Functioning after TNFi Therapy in Ankylosing Spondylitis Patients: A Selection of Three Feasible Performance-Based Tests. Salima F.E. van Weely1, Joost Dekker2, Martijn P.M. Steultjens3, Christiana J. Van Denderen4, Mike T. Nurmohamed5, Ben A.C. Dijkman6 and Irene E. van der Horst-Bruinsma7. 1Reade, centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands, 2VU University Medical Center, Amsterdam, Netherlands, 3Glasgow Caledonian University, Glasgow, Scotland, 4VU University Medical Centre, Amsterdam, Netherlands.

Background/Purpose: Physical functioning is considered an important outcome domain for the evaluation of the effectiveness of therapy and the course of the disease. In an effort to find objective outcome measures that assess limitations in physical functioning in Ankylosing Spondylitis (AS) patients, eight performance-based tests based on items of the Bath AS Functional Index (BASFI) were developed. Here, in research and clinical practice it is important to eliminate redundant testing in order to safe energy, time and money. Therefore, this study aimed (i) to select a limited number of performance-based tests that are reliable, show improvement in physical functioning after TNFi therapy and generate the equivalent information as the full set of tests and (ii) to be feasible for use in daily clinical practice.

Methods: Eight performance-based tests were evaluated: (1) climbing stairs, (2) bending, (3) reaching up, (4) putting on socks, (5) rising up and sitting down on a chair, (6) getting up from the floor, (7) looking over the shoulder and (8) a physically demanding activity. The tests that showed adequate reliability, highest Standardized Response Means (SRM) and the largest proportion of patients with an improved performance-based physical functioning were selected. The selected tests were combined into a new criterion for improvement in physical functioning (AS Performance-based Improvement, ASPI). The number and percentage of improved patients identified with the ASPI and identified with the full set of performance tests were compared.

Results: Reliability for all tests was adequate to excellent (Intraclass Correlation Coefficients 0.73–0.96). The tests for bending, putting on socks and getting up from the floor had the highest SRM’s (0.52–0.74) and showed the largest proportion of improved patients after TNFi therapy. The combination of these three tests is feasible in daily clinical practice and showed improved physical functioning after TNFi therapy in 67% of the patients. Coefficients of correlation for Test-Baseline (measures for the floor are recommended for use in daily practice, because they generate comparable information as the full set and are feasible for use in daily clinical practice. A new criterion, the ASPI, using a combination of these three tests showed an improved physical functioning after TNFi therapy in 67% of the patients. By performing only three instead of all performance-based tests, redundant testing is eliminated. In future, evaluations of the effectiveness of TNFi therapy in AS patients might be improved by adding these tests to other outcome measures.

Conclusion: Improvement of physical functioning in TNFi treated AS patients continues up to 24-weeks and stabilizes thereafter. Therefore, the efficacy of treatment should be determined at 6 months. Predictors for the level and course of physical functioning and spinal mobility after 3-years of TNFi treatment include baseline BASFI, BASMI, absence of comorbidity, physical activity and BMI.
Results: 216 Patients were included (154 (71%) men, mean age 43.6 years (SD 12.7), mean symptom duration 20.5 years (SD 11.7), and mean follow-up 8.3 years (SD 4.1)). At baseline, 39 (18%) patients had AAU, 15 (7%) IBD, and 9 (4%) psoriasis (prevalent cases). During follow-up, 19 patients developed AAU, 9 IBD, and 5 psoriasis (incident cases). Psoriasis was excluded from further analyses, because of a low prevalence and incidence in this cohort. Prevalent AAU was univariably associated with more radiographic damage (B=7.19, 95%-Confidence Interval [CI] 0.19 to 14.19, p=0.04) over time, but in a multivariable model this association was no longer significant (B=1.12, 95%-CI -3.81 to 6.26, p=0.64). Prevalent IBD was not associated with any of the clinical outcomes over time. Incident AAU was also not associated with clinical outcomes over time. Incident IBD, however, showed a trend towards worse function (BASF) over time in a univariable model (B=-1.86, 95%-CI -4.08 to 3.80, p=0.06), and also in a multivariable model (B=-1.40, 95%-CI -0.04 to 2.84, p=0.06).

Conclusion: Prevalent AAU and IBD at baseline were not associated with a worse course of QoL function, or radiographic damage over time. However, patients with new-onset IBD tended to have more functional disability over time in comparison with patients who do not develop IBD.

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Disease Activity Strongly Influences Work Productivity and Physical Health Related Quality of Life in Early Axial Spondyloarthritis: Data from the SPACE-Cohort.

A Roeterink1, M de Hooge1, R. van den Berg1, H Dagfinrud2, R. Landewé3, M. van Oosterhout4, R. Ramonda5, D. van der Heijde1 and F. van Gaalen 1.

1. Leiden University Medical Center, Leiden, Netherlands, 2. Diakonhjemmet Hospital, Oslo, Norway, 3. Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 4. Groene Hartziekenhuis, Gouda, Netherlands, 5. University of Padova, Padova, Italy.

Background/Purpose: In early onset axial spondyloarthritis (axSpA), not much is known about the relationship between disease activity and work productivity loss (WPL) or disease activity and health-related quality of life (HRQoL) in this study we assessed the relationship between disease activity and WPL and HRQoL in early axSpA.

Methods: The SPACE cohort recruited patients (n=345) with chronic back pain (≥3 months, ≤2 years, onset ≤45 years) in 5 European centres. In patients fulfilling the ASAS axSpA criteria (n=131), the following assessments were done: ASDAS and BASDAI (disease activity), BASFI (functional ability), SF-36 (HRQoL) and Work Productivity and Activity Impairment (WPAF). Patients were grouped according to ASDAS: inactive disease (<1.3), moderate disease (1.3-2.1), high disease (2.1-3.5) and very high disease activity (>3.5). BASDAI and BASFI scores ≥4 were considered as high disease activity and impaired function, respectively. HRQoL was reported as the SF-36 physical (PCS) and mental component summary (MCS) scores. Lower scores indicate decreased quality of life compared to the general population. Impact of disease on work productivity (WP) was defined as percentage of absenteeism, presenteeism and WPL (combines absenteeism and presenteeism) with greater scores indicating greater impairment.

Results: Figure 1 shows that physical health-related quality of life (PCS) decreased significantly with increasing ASDAS. For example, in patients with inactive disease, the PCS was 42.5 compared to 17.3 in patients with very high disease activity. Moreover, absenteeism, presenteeism and WPL increased as ASDAS increased (figure 1b). MCS was not influenced by disease activity. PCS and WPL had a similar association with BASDAI (not shown) and BASFI (low vs high BASFI, PCS 46.3 vs 47.2, p=0.06; WPL: 30.9% vs. 66.7%; absenteeism: 7.1% vs. 24.9%; presenteeism: 28.9% vs. 61.1%; all P<0.001).

Conclusion: In early axial SpA, disease activity highly influences physical health-related quality of life and work productivity. These findings support aiming for clinical remission in patients with early axial SpA.

Disclosure: A. Roeterink, None; M. de Hooge, None; R. van den Berg, None; H. Dagfinrud, None; R. Landewé, None; M. van Oosterhout, None; R. Ramonda, None; D. van der Heijde, None; F. van Gaalen, None.

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Dkkkopf-1 (Dkk-1) Serum Levels in Axial Spondyloarthritis (axSpA) Are Related to Disease Duration. Victoria Navarro-Compáñ1, Enrique Melguizo-Madrid2, Concepción González-Rodríguez2, Federico Navarro-Sarabia2 and Rafael Ariza-Ariz2. 1. University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, 2. University Hospital Virgen Macarena, Seville, Spain.

Background/Purpose: Tumor necrosis factor (TNF) alpha is responsible for induction of dkk-1 which down-regulates bone formation. Therefore, it was expected that TNF-blocker therapy would inhibit radiographic progression in patients with axSpA but this effect has not been observed yet. Nevertheless, most of the studies have included patients with long disease duration and it is unknown whether or not this effect would be the same in patients with an early stage of the disease. The objective of this study was to investigate if disease duration influences on the serum levels of dkk-1 in patients with axSpA.

Methods: Observational study including consecutive patients with axSpA according to ASAS criteria visiting a tertiary hospital between January 2011 and June 2013. All patients were receiving NSAIDs and none of them was under biologic therapy. The following characteristics were recorded at one visit: Demographic (age, gender), symptoms duration, HLA-B27, disease activity indices (BASDAI, CRP, ESR) and function (BASFI), Blood samples to determine dkk-1 serum levels by enzyme immunoassay were collected at the same visit too. Patients were classified as early axSpA (symptoms duration ≤5 years) and established axSpA (>5 years) and the characteristics enumerated above were compared between both groups. Univariate and multivariate linear regression models were employed to identify the characteristics related to dkk-1 serum levels.

Results: Fifty one patients (31 with early axSpA and 21 with established disease) were included this study. Patients with early axSpA were younger (32.6 ± 9.3 vs 41.0 ± 10.2 years; p<0.01), had lower degree of disease activity (BASDAI: 4.6 ± 2.7 vs 6.6 ± 1.9; p<0.01 and ESR: 7.7 ± 9.2 vs 18.1 ± 15 mmHg; p<0.05) and worst function (3.2 ± 2.9 vs 5.8 ± 2.5; p<0.01) compared with patients with established disease. Serum levels of dkk-1 were significantly higher in patients with early disease (25.9 ± 11.5 vs 13.9 ± 13.5; p<0.001 ng/dl). No statistically significant differences were found between both groups for the rest of characteristics. In the univariable analysis, symptoms duration and BASDAI were inversely related to dkk-1 levels (standard β: -0.435; p<0.01 and standard β: -0.283; p<0.05, respectively). However, only the relationship with symptoms duration remained statistically significant in the multivariable analysis (standard β: -0.415; p<0.01).

Conclusion: Serum Dkk-1 levels in patients with axSpA depend on disease duration, being higher in patients with recent onset of the disease. The effect of TNF-blocker therapy on radiographic progression may be different in patients with an early stage of the disease compared with patients with established disease.

Disclosure: V. Navarro-Compáñ, None; E. Melguizo-Madrid, None; C. González-Rodríguez, None; F. Navarro-Sarabia, None; R. Ariza-Ariz, None.
A Substantial Decrease in Work Productivity and Physical Health-Related Quality of Life in Chronic Back Pain of Recent Onset: Data from the SPACE-Cohort. A Roeterink¹, M de Hooge¹, R van den Berg², H Dagfinrud³, M Tuinna¹, M van Oosterhout¹, D van der Heijde¹ and F van Gaalen¹. ¹Leiden University Medical Center, Leiden, Netherlands, ²Diakoniehjemmet Hospital, Oslo, Norway, ³Academic Medical Center/University of Amsterdam, Amsterdam, Amsterdam, Netherlands, ⁴Groene Hartziekenhuis, Gouda, Netherlands.

Background/Purpose: Ankylosing spondylitis is associated with work productivity (WP) loss and a decreased health-related quality of life (HRQoL). Little is known about WP loss and HRQoL in early axial spondyloarthritis (SpA). Aim of the study was to determine the impact of chronic back pain (CBP) of recent onset on HRQoL and work productivity in young patients.

Methods: The SPACE-cohort includes patients with CBP (≥3 months, ≤2 years, onset <45 years) in 5 European centers (n = 345). Patients who met the ASAS axial SpA criteria were classified as axSpA (n = 131). Patients with 1 SpA feature were defined as possible SpA (n = 167), and those with no SpA features as no SpA (n = 47). The 36-item Short-Form (SF-36) and Work Productivity and Activity Impairment (WPAI) surveys were used to assess HRQoL and WP. SF-36 physical (PCS) and mental component summary (MCS) scores were compared to the general population (a score of 50 ± 10 SD represents the general population). Impact of disease on WP was defined as percentage of absenteeism, presenteeism and WP loss (which combines absenteeism and presenteeism) with greater scores indicating greater impairments.

Results: 304 patients completed the SF-36 and 230 the WPAI. Figure 1 shows a significant reduction of ≥2 SD in mean physical component scores (PCS) in all subgroups compared to the general population (25.9 in no SpA, 23.5 in possible SpA and 28.3 in axial SpA). Mental component scores (MCS) were not significantly reduced in patients with CBP compared to the general population. Considerable absenteeism and presenteeism was present in all subgroups with CBP. Absenteeism was highest in no SpA and possible SpA (21.6% and 18.5%; compared to axSpA (10.3%) (p = 0.10 and p = 0.05, respectively). Presenteeism was highest in no SpA and possible SpA (46.9% and 44.7%, compared to axSpA (34.7%). Total WPL was highest in no SpA and possible SpA (55.2% and 48.3%) compared to axSpA (37.5%).

Conclusion: Work productivity and physical health-related quality of life are already greatly reduced in young patients with chronic back pain of less than two years duration.

Disclosure: A. Roeterink, None; M. de Hooge, None; R. van den Berg, None; H. Dagfinrud, None; M. Tuinna, None; M. van Oosterhout, None; D. van der Heijde, None; F. van Gaalen, None.

Background/Purpose: It is well recognized that rheumatoid arthritis is an independent risk factor for cardiovascular disease. For ankylosing spondylitis (AS), the literature on this risk is relatively scarce, and shows conflicting results. Furthermore, these studies did not explore the role of non-steroidal anti-inflammatory drugs (NSAIDs) use on this risk. Therefore, the aim of the present study was to investigate the incidence and risk of ischemic heart disease (IHD) and acute myocardial infarction (AMI), including the role of NSAIDs, in patients with AS compared with matched population controls.

Methods: All patients with newly diagnosed AS from the Dutch Clinical Practice Research Datalink (1987–2012) were matched with up to 7 persons without AS by year of birth, gender, and practice. Incidence rate ratios (IRR) and hazard ratios (HR) for development of IHD and AMI were calculated. Stepwise analyses were performed adjusting for age, gender, comorbidity, and drug use, including NSAIDs. Results: In total, 3,809 patients with AS were matched with 26,196 population-based controls. The number of men (70.5% vs 70.7%), and the mean age (43.7 years vs. 43.3 years) were comparable for patients with AS and controls. The mean duration of follow up for patients and controls was 6.6 years. At baseline, 4.3% of the patients had a history of IHD, and 1.8% had a history of AMI, compared with 3.4% and 1.4% of the controls, respectively (p < 0.01 and p = 0.02, respectively). After excluding subjects with pre-existing cardiovascular disease, the overall IRR for IHD was 1.18 (95%-confidence interval [CI] 0.96–1.46) and for AMI 0.91 (95%-CI 0.65–1.27). Compared with controls, the age-adjusted HR for developing IHD was 1.20 (95%-CI 0.97–1.48), and for AMI 0.91 (95%-CI 0.65–1.28) for patients with AS. In female patients, the increased risk of developing IHD was statistically significant (HR 1.81, 95%-CI 1.18–2.79), but after adjustment for all possible risk factors only a non-significant trend towards increased risk was found (HR 1.36, 95%-CI 0.86–2.14). In particular, recent NSAID use explained the change in risk (female HR IHD adjusted for age-gender-NSAID use 1.47, 95%-CI 0.93–1.36). After stratification for the use of NSAIDs, the overall risk of IHD in patients with AS was 1.36-fold (95%-CI 1.00–1.87) increased with recent use of NSAIDs. This was particularly increased in female patients (HR fully adjusted 2.52, 95%-CI 1.41–4.51), but not in male patients (HR fully adjusted 1.13, 95%-CI 0.78–1.64).

Conclusion: Female patients with AS are at increased risk of developing IHD, but this effect is associated with recent NSAID use. However, it cannot be excluded that NSAID use is (partly) a reflection of active disease.

Disclosure: I. Essers, None; C. Stolwijk, None; A. Boonen, None; M. L. De Bruin, None; M. Bazelier, None; F. de Vries, None; A. Van Tubergen, None.
Results: 86 Patients contributed to the current analyses (mean age 39.6 years (SD 10.6); mean disease duration 9.7 years (SD 8.1), and 68/86 (79.1%) patients had an ASAS20 response). At baseline, the BAS-G in ASSERT was 7.0 (SD 1.6), and patients retrospectively re-rated their BAS-G, using the ‘then test’, at 7.2 (SD 2.3), revealing a non-significant and non-relevant gap (H11021). Baseline BAS-G of ASSERT and retrospective BAS-G of ASSERT was INF.

Disclosure: I. Essers, None; A. Van Tubergen, None; J. Braun, None; X. Baraliakos, None; F. Heldmann, None; A. Boonen, None.

S80 MRI Is Often Negative in Clinically Suspected Non-Radiographic Axial Spondyloarthritis. M. L. John1, M. A. C. van der Weijden2, C. M. A. van der Bijl3, S. T. G. Bruijnen1, C. J. van der Laken1, M. T. Nurmohamed1 and I. E. van der Horst-Bruinsma1. 1VU University Medical Center, Amsterdam, Netherlands; 2Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands; 3Jan van Breemen Research Institute Reade, Amsterdam, Netherlands.

Background/Purpose: The diagnosis of ankylosing spondylitis (AS) is based on disease specific bone damage seen on plain radiography of the pelvis. Recent developments in magnetic resonance imaging (MRI) techniques have demonstrated that active inflammation in the sacroiliac joints (SIJ) and/or spine is detectable by MRI and might even be visible before the appearance of chronic changes on plain radiography. However, the current literature discussing the actual diagnostic properties of MRI in early spondyloarthritis (SpA) non-radiographic axial SpA remains controversial and its prognostic value regarding the future development of AS has yet to be determined.

Methods: In this cross-sectional study, we recruited 70 patients with chronic inflammatory back pain (mean disease duration of 5 years) and high disease activity (BASDAI≥4) who had to be either HLA-B27 positive with ≥1 SpA-feature or HLA-B27 negative with ≥2 Sp-A-features. All patients underwent MRI of the SIJ and 50 patients underwent additional MRI of the spine on baseline. A positive MRI was defined by the presence of either BMO and/or osteitis, a negative MRI by the absence of both. Patients with a negative baseline MRI were asked to undergo a second MRI after 6 months. Eventually, 29 out of 49 patients with a negative baseline MRI SIJ and 22 out of 47 patients with a negative baseline MRI spine were willing and eligible to undergo the second MRI. Additionally, all patients were tested for CRP levels, ESR levels, X-rays of the pelvis were made and several patient features were recorded. Correlation analysis was performed between the different collected variables.

Results: At baseline, only 21 of the 70 patients (30%) showed signs of inflammation on MRI: 18 had sacroiliitis, 2 had spinal involvement and one patient had both. In total, only 4 patients presented with inflammation of the spine at baseline and six months, of which 2 also suffered from sacroilitis. Comparison of the two consecutive MRIs revealed that, in two patients, the inflammatory process spread from the SIJ to the spine or the other way around. Only one patient with a negative baseline MRI SIJ developed apparent sacroilitis over time. Furthermore, three patient characteristics were significantly associated with a positive MRI outcome at any point in time: raised ESR-level (p=0.003), family history of uveitis (p=0.028) and the number of swollen joints (SJC, p=0.023). We also observed a slight difference regarding HLA-B27-status and medical history of uveitis, in favor of the positive MRI group.

Conclusion: Only a small number of patients with clinically suspected non-radiographic axial SpA showed signs of inflammation on MRI SIJ and/or spine, questioning the sensitivity and with this the value of this new imaging tool in early SpA. Even though, some patient characteristics seem to be positively associated with MRI outcome, defining the right place of MRI in the diagnosis of early SpA remains difficult. The diagnostic properties of MRI in this particular patient group should be weighted carefully because patients with a negative MRI might also have severe complaints.

Disclosure: M. L. John, None; M. A. C. van der Weijden, None; C. M. A. van der Bijl, None; S. T. G. Bruijnen, None; C. J. van der Laken, None; M. T. Nurmohamed, None; I. E. van der Horst-Bruinsma, None.

581 Evaluation of the Nonsteroidal Anti-Inflammatory Drug-Sparing Effect of Etanercept in Axial Spondyloarthritides: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Maxime Dougados1, Emily Wood1, Bernard Combe2, Corinne Miceli-Richard3, Francis Berenbaum4, Nadine Koppiker5, F. Berenbaum5, Nandan Koppiker6, Arnaud Dubanchet7 and Isabelle Logeart7. 1Université Paris René Descartes and Hôpital Cochin, Paris, France; 2Quanticare, Hitchin, England; 3Hôpital Lapeyronie, Montpellier, France; 4Université Paris-Sud 11, Bièvre Hospital, Kremlin Bicêtre, France; 5Saint-Antoine Hospital, Paris, France; 6Pfizer PGRD, Sandwich, United Kingdom; 7Pfizer, Paris, France.

Background/Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line pharmacotherapy in axial spondyloarthritis (axSpA) but are recommended for use at the lowest effective dose for the shortest possible time due to safety concerns. Although NSAID discontinuation is common in clinical practice after response to biologic therapy in axSpA patients, its impact has not been evaluated in prospective controlled trials. The SPARSE trial was conducted to assess the effects of etanercept (ETN) on NSAID intake as measured by the ASAS-NSAID score and conventional clinical outcomes in axSpA.

Methods: In the initial 8-week, double-blind (DB), placebo (PBO)-controlled period, patients with active (mini BASDAI≥4) axSpA (ASAS criteria) despite optimal NSAID intake were randomized to ETN 50 mg or PBO once weekly for 8 weeks. All patients were advised to taper/stop their NSAID intake (self-reported diary) during the study treatment period. Completers were eligible for ETN 50 mg in the subsequent 8-week open-label period (OL). ASAS-NSAID scores were calculated according to ASAS recommendations.1 The primary endpoint, the change from baseline (BL) to week 8 in the ASAS-NSAID score, was analyzed using an analysis of covariance (ANCOVA).

Results: In 90 randomized patients at BL, mean age (±SD) was 39.9±11.8 years; disease duration, 5.7±8.1 years; 62% were male; 66% were HLA-B27 positive; and 50% were MRI sacroiliitis positive. Mean ASAS-NSAID scores at BL (ETN vs PBO: 98.2±39.0 vs 93.0±23.4); BASDAI (6.0±1.7 vs 5.9±1.5); and BASFI (5.2±2.1 vs 5.1±2.2) were similar between groups. A between-group difference in changes in ASAS-NSAID scores of -27.3 (P=0.002) favoring ETN was observed at week 8 (table). Significantly more patients in the ETN vs PBO group achieved BASDAI50 and ASAS40 at week 8. Significant reductions in ASAS-NSAID scores were seen in the ETN/ETN group from BL to week 16 and in the PBO/ETN group from week 8 to 16 (table); response rates increased in the ETN/ETN and PBO/ETN groups for most clinical endpoints in the OL period.

Table. Effects of ETN vs PBO in patients with axSpA (ITT).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Change (95%CI/SD)</th>
<th>ETN/ETN</th>
<th>PBO/ETN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS-NSAID score</td>
<td>63.9 (51.8, 76.0)</td>
<td>65.9 (52.9, 78.9)</td>
<td>39.2 (25.5, 53.5)</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2.1 (1.0, 3.2)</td>
<td>2.1 (0.9, 3.3)</td>
<td>2.3 (1.0, 3.6)</td>
</tr>
<tr>
<td>BASFI</td>
<td>1.7 (1.0, 2.4)</td>
<td>1.8 (1.1, 2.5)</td>
<td>2.3 (1.9, 2.6)</td>
</tr>
<tr>
<td>ASAS40</td>
<td>1.7 (1.0, 2.4)</td>
<td>1.8 (1.1, 2.5)</td>
<td>2.3 (1.9, 2.6)</td>
</tr>
<tr>
<td>ASAS50</td>
<td>1.7 (1.0, 2.4)</td>
<td>1.8 (1.1, 2.5)</td>
<td>2.3 (1.9, 2.6)</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2.0 (1.2, 3.0)</td>
<td>2.1 (1.3, 3.0)</td>
<td>2.3 (1.5, 2.6)</td>
</tr>
<tr>
<td>BASFI</td>
<td>1.7 (1.0, 2.4)</td>
<td>1.8 (1.1, 2.5)</td>
<td>2.3 (1.9, 2.6)</td>
</tr>
</tbody>
</table>

*P<0.05, ETN vs PBO. †P<0.005, ETN vs PBO. ‡P<0.0001, BL vs wk 16.

Conclusion: In this population of patients with axSpA, etanercept was associated with very significant NSAID-sparing effects in addition to significant improvements in conventional clinical outcomes.


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Background/Purpose: We performed a Cochrane systematic review to determine the benefits and harms of non-steroidal anti-inflammatory drugs (NSAIDs) in axial spondyloarthritis (axSpA).

Methods: We included all published randomised controlled trials (RCTs) of NSAIDs versus any comparator in adult patients with axial SpA identified by searches in MEDLINE, EMBASE and CENTRAL (until April 2014). The comparisons investigated were traditional NSAIDs versus placebo, COX-2 NSAIDs versus placebo, traditional NSAIDs versus COX-2 NSAIDs, NSAIDs in low versus high dose and NSAIDs versus NSAIDs. Main efficacy outcomes were pain, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI) and radiographic progression. Main safety outcomes were number of withdrawals due to adverse events and number of serious adverse events. Risk of bias of included studies was assessed according to the Cochrane risk of bias tool.

Results: Forty-one trials (n=6073) with a median duration of 12 weeks (range 1 week to 2 years) met inclusion criteria. Thirty-one studies (n=1135) showed that indomethacin resulted in more adverse events than other NSAIDs (RR 3.57, 95% CI 1.06 to 1.49), in particular neurological adverse events like headache and dizziness (RR 1.96, 95% CI 1.06 to 3.57), although there were not more withdrawals due to adverse events.

Conclusion: In patients with axial SpA, overall high quality trials indicate that traditional and COX-2 NSAIDs are consistently more efficacious than placebo, without a significant difference between the two NSAIDs classes. Various NSAIDs do not differ in efficacy in low to moderate quality trials, although indomethacin seems to result in more, mainly neurological, adverse events, even though this did not lead to more withdrawals. Results of this review support current recommendations for treatment of axial SpA with NSAIDs.

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Background/Purpose: Despite the importance of the Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in assessing patient-reported functional status and disease activity, they have been critiqued for being time-consuming, not convenient on a daily basis and thus not contributing to decisions in real-time. The aim of this analysis was to describe the correlation of individual HAQ and BASDAI questions with patient and physician reported measures used in ankylosing spondylitis (AS) and to examine whether the instruments could be reduced to better reflect routine clinical practice.

Methods: BioTRAC is an ongoing prospective registry of patients initiating infliximab or golimumab as first biologics or after <6 months of biologic treatment. Data from AS patients treated in 2005–2014 were used. The correlation of individual HAQ and BASDAI questions with patient (pain, BASDAI, HAQ and BASFI) and physician (MDGA) reported measures was described with the Pearson’s correlation coefficient. The impact of each question on the need for help in each HAQ domain was assessed with logistic regression. Factor analysis was used to assess the variability due to each individual question in HAQ and BASDAI.

Results: A total of 413 AS patients with 1660 BASDAI and 1654 HAQ assessments were included. HAQ and BASDAI questions correlated at different extents with each AS measure (Table 1). Questions related to “eating” and “gripping” showed the lowest correlation with patient and physician reported measures. All HAQ questions had higher correlations with patient reported measures than with MDGA. The BASDAI question on “fatigue and tiredness” showed the highest correlation with BASFI, while the question on “other joint pain/swelling” showed the lowest correlation with MDGA. None of the HAQ and BASDAI questions were associated with needing help for eating. All other HAQ individual questions were significantly associated with the need for help within their corresponding category, with the exception of Q5C and Q7A. BASDAI question on level of discomfort was significantly associated with the need for help in all HAQ categories, with the exception of “eating” and “walking”. Q2A and Q7C accounted for 59.6% of the HAQ variance. The level of morning stiffness accounted for 73.8% of the BASDAI variance. When combining the HAQ and BASDAI, Q2A and Q3A from HAQ and Q1 from BASDAI accounted for 63.5% of the variance.

Conclusion: Variability exists in the correlation of HAQ and BASDAS questions with patient and physician reported AS measures. The results suggest that “standing up straight from an armless chair” and “turning faucets on/off” are the main drivers of HAQ, while the level of morning stiffness drives the BASDAI. Three questions were found to cover the combined HAQ and BASDAI which may have implications in the design of self-report instruments.

Table 1. Correlation between Individual HAQ / BASDAI Questions and Disease Activity Measures

<table>
<thead>
<tr>
<th>HAQ Questions</th>
<th>Pain</th>
<th>BASDAI</th>
<th>BASFI</th>
<th>MDGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing and Grooming (Q.1 A/B)</td>
<td>0.560.41</td>
<td>0.530.45</td>
<td>0.680.52</td>
<td>0.470.37</td>
</tr>
<tr>
<td>Arising (Q.2 A/B)</td>
<td>0.600.63</td>
<td>0.630.66</td>
<td>0.740.66</td>
<td>0.500.54</td>
</tr>
<tr>
<td>Eating (Q.3 A/B/C)</td>
<td>0.520.50</td>
<td>0.550.58</td>
<td>0.630.68</td>
<td>0.430.45</td>
</tr>
<tr>
<td>Walking (Q.4 A/B/C)</td>
<td>0.720.40</td>
<td>0.740.45</td>
<td>0.630.60</td>
<td>0.430.55</td>
</tr>
<tr>
<td>Hygiene (Q.5 A/B/C)</td>
<td>0.510.40</td>
<td>0.540.45</td>
<td>0.600.60</td>
<td>0.430.55</td>
</tr>
<tr>
<td>Reach (Q.6 A/B)</td>
<td>0.470.50</td>
<td>0.520.57</td>
<td>0.680.72</td>
<td>0.370.44</td>
</tr>
<tr>
<td>Grip (Q.7 A/B/C)</td>
<td>0.300.30</td>
<td>0.280.40</td>
<td>0.380.49</td>
<td>0.260.26</td>
</tr>
<tr>
<td>Activities (Q.8 A/B/C)</td>
<td>0.580.70</td>
<td>0.580.62</td>
<td>0.670.67</td>
<td>0.460.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BASDAI Questions</th>
<th>Pain</th>
<th>HAQ-DI</th>
<th>BASFI</th>
<th>MDGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue and tiredness (Q.1)</td>
<td>0.74</td>
<td>0.58</td>
<td>0.87</td>
<td>0.62</td>
</tr>
<tr>
<td>Neck, back or hip pain (Q.2)</td>
<td>0.85</td>
<td>0.66</td>
<td>0.77</td>
<td>0.67</td>
</tr>
<tr>
<td>Other joints pain/swelling (Q.3)</td>
<td>0.66</td>
<td>0.60</td>
<td>0.67</td>
<td>0.53</td>
</tr>
<tr>
<td>Level of discomfort (Q.4)</td>
<td>0.72</td>
<td>0.63</td>
<td>0.71</td>
<td>0.60</td>
</tr>
<tr>
<td>Level of morning stiffness (Q.5)</td>
<td>0.80</td>
<td>0.64</td>
<td>0.76</td>
<td>0.69</td>
</tr>
<tr>
<td>Morning stiffness duration (Q.6)</td>
<td>0.85</td>
<td>0.67</td>
<td>0.82</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* Levels of correlation are Weak: r 0.30 - 0.39; Moderate: r 0.40 - 0.69; and Very Strong: r 0.70.

Flare in Spondyloarthritis: Proposal of a Meaningful Change in Symptomatic Outcome Measures in Axial Spondyloarthritis. Maxime Dougdos1, Emily Wood2, Laure Gossec3, Désirée van der Heijde4 and Isabelle Logeart5.

Background/Purpose: Recognition of flare is important in both daily practice and clinical trial setting. However, there is no clear definition of flare in patients with axial spondyloarthritis. SPARSE was a randomized controlled trial evaluating the NSAID-sparing effect of etanercept in axial spondyloarthritis. All patients had to be on NSAIDs prior to screening and were requested to discontinue their NSAID therapy at screening. The objective of this post-hoc analysis was to evaluate the threshold in the changes in symptomatic outcome measures in case of a restart of NSAID, which was considered as a flare.

Methods: Patients: Axial spondyloarthritis (ASAS criteria) with active disease (BASDAI ≥ 4) refractory to NSAIDs and justifying anti-TNF therapy. Design: Prospective randomized controlled trial. Study period of interest: This analysis was focused on the period between screening and baseline. During this period, patients were requested to stop their NSAID therapy and to restart the NSAID only if they experienced clinical deterioration. In this case, patients were asked to complete a diary. Analysis: The proposal of a meaningful change in symptomatic outcome measures was based on the 75th percentile technique. The 75th percentiles of the change in the evaluated outcome measures between screening and re-starting NSAIDs were examined for the subgroup of patients who were able to stop NSAID therapy for at least 2 consecutive days and subsequently had to restart their NSAID therapy (i.e. those patients who flared). Evaluated outcome measures: The BASDAI score and each component of the BASDAI.

Results: Of the 128 screened patients, 91 (71.1%) had an available BASDAI at the screening visit and 45 (35.2 %) were able to stop their NSAID therapy for at least 2 consecutive days. Of these 45 patients, 32 optimally completed their diary the day they had to restart their NSAID. The table summarizes the observed values for the study variables at screening and flare (time of NSAID restarting) in these 32 patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Changes from Screening to Flare</th>
<th>75th Percentile [% CI]</th>
<th>Screening</th>
<th>Absolute</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI total score</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>5.8 ± 1.2</td>
<td>1.5 [1.2, 1.9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(5.8)</td>
<td>(28 [20, 38])</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(14)</td>
<td></td>
</tr>
<tr>
<td>BASDAI question 1 (fatigue)</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>6.7 ± 1.6</td>
<td>0.8 ± 1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(7.0)</td>
<td>(23 ± 54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(13.0)</td>
<td></td>
</tr>
<tr>
<td>BASDAI question 2 (axial)</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>6.6 ± 1.5</td>
<td>0.8 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(7.0)</td>
<td>(16 ± 27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(14)</td>
<td></td>
</tr>
<tr>
<td>BASDAI question 3 (peripheral)</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>4.3 ± 2.8</td>
<td>0.2 ± 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(5.0)</td>
<td>(16 ± 80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>BASDAI question 4 (enthesitis)</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>5.0 ± 2.3</td>
<td>0.9 ± 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(5.0)</td>
<td>(43 ± 128)</td>
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<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>BASDAI question 5/6 (morning stiffness)</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>6.5 ± 1.7</td>
<td>0.6 ± 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Median)</td>
<td>(6.5)</td>
<td>(12 ± 23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th Percentage [% CI]</td>
<td>(7)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: This study suggests that there is no universal change that is applicable to all variables. However, an absolute change of at least 2 on a scale of 10 or a relative change of 30% is indicative of a meaningful symptom deterioration for most of the symptomatic variables included in the BASDAI score.

Disclosure: M. Dougdos, Pfizer Inc. 2, Pfizer Inc. 5; E. Wood, Pfizer Inc. 5; L. Gossec, None; D. van der Heijde, None; I. Logeart, Pfizer Inc. 1, Pfizer Inc. 3.

Optimism Levels Are Moderately and Similar in Patients with Axial Spondyloarthritides and Chronic Low Back Pain, and Are Related to Mental Quality of Life but Not Physical Quality of Life. A Cross Sectional Study of 277 Patients. Sarah Kreis1, Anna Molto2, Florian Bailly3, Sabrina Dadoun4, Stephanie Fabre5, Katherine J. Halpern6, Ioana Itiner7, Sylvie Rozenberg8, Edouard Pertheuis9, Bruno Fautrel3 and Laure Gossec3.

Background/Purpose: Axial Spondyloarthritis (AxSpA) and chronic low back pain (LBP) are very different chronic rheumatic diseases in terms of physiopathology and prognosis but both have a strong impact on patients' health-related quality of life (HRQoL). Dispositional optimism is defined as a stable personality trait consisting of a general positive mood or attitude about the future with a tendency to expect favorable outcomes in life situations. It has been shown in some chronic disease groups (e.g cancer) that dispositional optimism is related to both physical and psychological outcomes and seems to lead to better HRQoL. The objective of this study was to explore the relationship between optimism and HRQoL in both chronic diseases: AxSpA and LBP.

Methods: A cross-sectional study was performed in two tertiary care hospitals and two private practices in France. Patients were diagnosed with definite AxSpA or chronic LBP according to the rheumatologist. HRQoL was collected using a generic HRQoL questionnaire (Short Form, SF-12) with physical and mental composite scores (PCS and MCS respectively) and optimism was collected using the Life Orientation Test-revised (LOT-R) questionnaire. Analyses included descriptive statistics, non-parametric correlations and multiple regression analyses to study the effect of optimism on physical and mental HRQoL.

Results: In all, 277 patients (188 AxSpA and 89 LBP) were included: mean age, 47.3±11.9 years, 49.1% were males. BASDAI in AxSpA was 3.8±2.0 and the LBP patients’ pain visual analog scale was 4.3±2.3. HRQoL was similarly altered in both diseases, for both physical and mental composite scores (mean: PCS: 43.4±8.4 vs. 41.9±7.1; mean: MCS: 45.7±7.9 vs. 46.7±8.1 for AxSpA and LBP respectively). Optimism was moderate and similar in both populations. Optimism was positively correlated to MCS in both diseases (r=0.57 vs. 0.54, for AxSpA and LBP respectively, both p<0.0001) and these relations persisted in multivariate analyses (beta=0.77 vs. 1.21, both p<0.0001).

Conclusion: Optimism was similar in these two chronic diseases and was an explanatory factor of mental HRQoL, but not physical HRQoL. Physical HRQoL may reflect more the disease process than character traits.

Disclosure: S. Kreis, None; A. Molto, None; F. Bailly, None; S. Dadoun, None; S. Fabre, None; C. Hudry, None; F. Zenasni, None; S. Rozenberg, None; E. Pertheuis, None; B. Fautrel, None; L. Gossec, None.

Helplessness in Coping Is Associated with Worse Patient Reported Outcomes Among Patients with Ankylosing Spondylitis: A Longitudinal Multi-Country Cohort Study. Walter P Maksymowych1, Annelies Bloom2, Heleno Marzo-Ortega3, Marina N. Magrey4, Manish Mittal5, Michael Haldern6, Jeannette Renaud6, Yanjun Bao5 and Avani D. Joshi5.

Methods: A prospective Patient Reported Outcomes Survey of Employment in Patients with AS (PROSE-AS) was conducted at rheumatologists’ clinical practice sites in Canada (n=234), the Netherlands (n=131), the
United Kingdom (n = 144) and the United States (n = 46). Patients ≥18 years of age completed surveys at baseline, 3, 6, 9, and 12 months. Helplessness was assessed using the helplessness subscale of the Rheumatology Attitudes Index (RAI; scale 5–25), and patients were stratified according to low (RAI <11), moderate (RAI 11–19) or high (RAI ≥20) helplessness for analysis 3. Depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D) scale. Work outcomes were assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. Disease activity and functional impairment were assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI) scales, respectively. HRQoL was assessed using the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short Form 36 Health Survey (SF-36) and the AS Quality of Life (ASQoL) questionnaires. Associations between helplessness and outcome variables over time were analyzed using multivariable generalized estimating equations (GEE), with adjustment for baseline patient socio-demographics, disease characteristics, medication use and country.

Results: Mean AS duration among 553 patients was 13.9 years; 194 (35.1%), 317 (57.3%) and 42 (7.6%) were classified with low, moderate and high helplessness, respectively. Patients with moderate and high helplessness were significantly more likely than patients with low helplessness to be depressed, unemployed and exhibit overall work and activity impairment (Table). High helplessness was also significantly associated with greater clinical severity as measured by BASDAI and BASFI, and with greater HRQoL impairment as measured by ASQoL, SF-36 PCS and MCS scores, compared with low helplessness.

**Association Between RAI Helplessness Category and Outcome Variables Over Time**

<table>
<thead>
<tr>
<th>Outcome Variables (Categorical)</th>
<th>Moderate vs Low Helplessness (b, 95% CI)</th>
<th>High vs Low Helplessness (b, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D (scale 0–60)</td>
<td>3.56 (2.72 to 4.46)</td>
<td>12.91 (8.20 to 20.32)</td>
</tr>
<tr>
<td>Work Status</td>
<td>1.14 (0.99 to 1.33)</td>
<td>1.69 (1.30 to 2.21)</td>
</tr>
<tr>
<td>WPAI (a)</td>
<td>3.41 (2.07 to 5.62)</td>
<td>5.16 (2.35 to 11.33)</td>
</tr>
<tr>
<td>BASDAI Score (n = 553, scale 0–10)</td>
<td>1.01 (0.85 to 1.16)</td>
<td>2.28 (1.99 to 2.58)</td>
</tr>
<tr>
<td>SF-36 PCS Score (n = 553, scale 0–100)</td>
<td>-4.40 (–5.04 to -3.75)</td>
<td>-8.31 (–9.96 to –7.07)</td>
</tr>
<tr>
<td>SF-36 MCS Score (n = 553, scale 0–100)</td>
<td>-4.03 (–4.88 to -3.17)</td>
<td>-9.92 (–11.57 to –8.28)</td>
</tr>
<tr>
<td>Activity impairment (n = 317)</td>
<td>0.33 (0.01 to 0.67)</td>
<td>0.74 (0.26 to 1.22)</td>
</tr>
<tr>
<td>Synthetic spondylitis</td>
<td>3.56 (2.72 to 4.46)</td>
<td>12.91 (8.20 to 20.32)</td>
</tr>
<tr>
<td>Moderate vs Low Helplessness</td>
<td>1.01 (0.85 to 1.16)</td>
<td>2.28 (1.99 to 2.58)</td>
</tr>
<tr>
<td>High vs Low Helplessness</td>
<td>1.69 (1.30 to 2.21)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** High helplessness in coping with AS was associated with depression, poor work productivity and employment outcomes, greater disease activity and functional impairment, and worse HRQoL. Helplessness should receive more attention in clinical care.

References:

Disclosure: W. P. Maksymowych, AbbVie, 5, AbbVie, 2, AbbVie, 8, A. Boonen, Amgen, AbbVie, Merck and Pfizer, 2, UCB and Pfizer, 2, H. Marzo-Ortega, AbbVie, MSD, UCB, Pfizer, Janssen, 2, M. N. Magrey, MetroHealth, 3, AbbVie, 5, AbbVie, 9, M. Mittal, AbbVie, 1, AbbVie, 3, M. Halpen, AbbVie, 2, J. Renaud, AbbVie, 2, Y. Bao, AbbVie, 1, AbbVie, 3, A. D. Joshi, AbbVie, 1, AbbVie, 3.

**587 Clinical Characteristics of Nonradiographic Axial Spondyloarthritis in Korea: A Comparison with Ankylosing Spondylitis.** Hyunjin Kim1, Hyemin Jeong2, Seulkie Lee3, Inyoung Kim1, Jiwon Hwang4, Jaejoon Lee5, Jinseok Kim4, Eun-Mi Koh6 and Hoon-Suk Cha7. 1Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 2Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 3Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 4Jeju National University Hospital, Jeju, South Korea.

**Background/Purpose:** To evaluate the clinical characteristics and outcomes of nonradiographic axial spondyloarthritis (nr-axSpA) in Korean patients.

**Methods:** A retrospective analysis evaluated 155 patients with nr-axSpA at a single tertiary hospital between January 2001 and January 2011. Baseline characteristics and clinical courses were reviewed and compared with those of patients with ankylosing spondylitis (AS).

**Results:** The mean age at disease onset was 29.5 ± 10.8 years, and 52 (33.5%) patients were female. The mean age at symptom onset was older (29.3 ± 10.8 vs 25.9 ± 9.2, respectively, p < 0.001) in the male to female ratio was lower (2:1 vs 5:1, respectively, p = 0.001) in patients with nr-axSpA compared with patients with AS. The proportion of females was higher among patients with late onset-SpA than early-onset nr-axSpA (55.0 vs. 30.1%, respectively, p = 0.029). Among 74 patients with nr-axSpA, whose follow-up duration was more than 1.5 years, 29 (39.2%) patients progressed to AS during the follow-up period. The proportion of females was lower in progressors that of non-progressors (13.8 vs. 44.4%, respectively, p = 0.010), Presence of syndesmophyte and minimal X-ray changes at baseline were frequently observed in progressors compared with non-progressors (26.7 vs. 0.0%, p = 0.006 and 69.0 vs. 35.6%, p = 0.005, respectively).

**Conclusion:** The predominance of male patients is more prominent among Korean patients with SpA compared with Caucasians. Female nr-axSpA patients had late symptom onset and less progression to AS. X-ray changes at baseline were associated with radiographic progression.

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588 Blacks with As Have Greater Disease Severity Than Whites. Forokh Jamalyaria1, Michael M. Ward1, Mindae Lee1, Lianne S. Gensler2, Laura A. Diekema3, Mohammad H. Raha1, Amiri1, 1S. Annasaj3, Michael H. Weissman4 and John D. Revelle5. 1University of Texas Health Science Center at Houston, Houston, TX, 2NIAMS/NIH, Bethesda, MD, 3University of California, San Francisco, San Francisco, CA, 4The University of Texas Health Science Center at Houston, Houston, TX, 5Cedars-Sinai Medical Center, Los Angeles, CA.

**Background/Purpose:** To compare clinical parameters in African American (AA) patients with ankylosing spondylitis (AS) to white patients.

**Methods:** 539 AS patients (47 B, 492 W), meeting the modified New York criteria 1 enrolled in a longitudinal outcome study were assessed cross-sectionally at the baseline visit. Disease activity was defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional outcomes by the Bath Ankylosing Spondylitis Functional Index (BASFI) and radiographic severity by the Bath Ankylosing Spondylitis Radiographic Index (mSASSS). Univariable comparisons of clinical characteristics for African-American and White patients were done using Chi-square test and Student t test and their non-parametric counterparts when necessary in both cohorts. We compared the baseline BASRI total score for African-American and White patients by constructing multivariable mixed effect models to account for intra-family correlation (539 patients from 449 families). Possible founders were examined by identifying variables that were significantly associated with race and effect modifications were also tested while developing a final multivariable model. Analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC) at a statistical significance level of 0.05.

**Results:** Blacks had greater radiographic severity as seen by higher BASRI scores (9.12 versus 6.41, p = 0.0001), greater functional impairment as measured by the BASFI (53.65 versus 31.94, p = 0.0001) and higher disease activity as determined by the BASDAI (5.52 versus 4.11, p = 0.007) compared to whites. There was no difference between disease duration or age. A significant interaction effect was found between race and disease duration. Table 1 shows the associations between baseline BASRI score and race at different levels of disease duration from the unadjusted and adjusted mixed effect model. Sex, B27+, study site and comorbidities (heart attack and diabetes) were adjusted in the final multivariable model. Subjective disease activity (BASDAI) and functional impairment (BASFI) were not included.
Conclusion: Although we cannot rule out the possibility that the more severely affected AA with AS are properly diagnosed and/or volunteer for study, these data confirm and extend prior subjective assessments of greater disease severity in African Americans using objective clinical and radiographic measurements and validated outcome tools.

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Patients with Nr-AxSpa Show a Statistically Higher Disease Burden in Clinical Practice Compared with Patients with Radiographic Axial SpA. Lennart TH Jacobsson1, Tomas Husmark2, Elke Theander3, Kenneth Henriksson4, Catharina Büsch5 and Martin Johansson5. 1Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 2Falu Hospital, Falun, Sweden, 3Skane University Hospital Malmö, Lund University, Malmö, Sweden, 4Rheumatology city clinic, Stockholm, Sweden, 5AbbVie AB, Stockholm, Sweden, Stockholms, Sweden.

Background/Purpose: The ASAS axial SpA classification criteria was published in 2009 but so far there has been limited research on axial SpA patients in clinical practice. There is no diagnose code for non-radiographic axial SpA (nr-axSpA) and it is unclear which diagnosis these patients receive in clinical practice. Characterization of nr-axSpA patients in clinical practice is lacking in comparison with radiographic axial SpA (rad-axSpA). The aim of this study was to characterize patients with axial SpA in clinical practice and to investigate similarities/differences between radiographic and non-radiographic axial SpA.

Methods: This is a prospective, cross-sectional, multi-center cohort study from Sweden. SpA patients (diagnosed with Psoriatic Spondylitis (M07.2), Ankylosing Spondylitis (M45.4), Spinal enthesopathy (M46.0), Sacroilitis, not elsewhere classified (M46.1), Other specified inflammatory spondylopathies (M46.8), or Inflammatory spondylopathy, unspecified (M46.9)) were consecutively recruited from the clinical settings of the participating study centers. Patients were followed for three months via an online questionnaire. At baseline, the rheumatologist assessed the ASAS axial SpA criteria and registered information on disease history, extra articular manifestations, and treatments. The patients answered online questionnaires capturing patient demographics, disease activity and function (BASDAI, BASFI, HAQ-S, etc.), QoL (EQ-5D, AS-QoL), health care resource use, and work ability (WPAI). P-values, unadjusted for covariates, were calculated using chi-square tests for categorical variables and t-tests for continuous variables.

Results: 251 patients were included of whom 197 (78%) were classified as axSpA. Of those, 125 (63%) were classified as rad-axSpA and 72 (37%) were classified as nr-axSpA according to the ASAS axial SpA criteria. The nr-axSpA patients were diagnosed with AS (35%), other specific inflammatory spondylopathies (31%), inflammatory spondylopathy unspecified (19%), psoriatic spondylitis (11%), and sacroilitis, not elsewhere classified (4%). Time between symptom onset and diagnosis was 9.0 (8.4) years for rad-axSpA and 6.7 (7.1) years for nr-axSpA. The nr-axSpA patients showed a higher disease burden compared with rad-axSpA patients, e.g. higher BASDAI (4.1 vs. 2.7), VAS global (4.3 vs. 2.9), VAS pain (4.4 vs. 2.9), and ASDAS(CRP) (2.3 vs. 1.9).

Conclusion: In this study, from Swedish clinical practice, we included patients from rheumatology clinics with pre-specified diagnoses most likely to be classified as axial SpA. The results show that the nr-axSpA patients have a statistically higher burden of disease than patients with rad-axSpA.

Disclosure: L. T. Jacobsson, AbbVie, Pfizer, UCB, 5; T. Husmark, AbbVie, 5; E. Theander, AbbVie, 5; K. Henriksson, AbbVie, 5; K. Büsch, AbbVie, 1, AbbVie, 3; M. Johansson, AbbVie, 3.

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Factors Associated with a Poor Functional Prognosis in Early Inflammatory Back Pain: Results from the DESIR Cohort. Cédric Lukas1, Maxime Dougdas2 and Bernard Combe3, 1Hospital Lapeyronie, Montpellier, France, 2Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: Spondyloarthropathy is a heterogeneous disease, with various and hardly predictable potential courses. We aimed at determining prognostic factors of a bad functional outcome at 2 years in patients with early inflammatory back pain.

Methods: Data from patients included in the French multicenter DESIR cohort, i.e. suffering from inflammatory back pain (IBP) starting before 50 years of age and lasting for between 3 months and 3 years, were used in this work. A bad functional outcome was defined as an increase in BASFI superior to 75th percentile of observed progression in the cohort from inclusion visit to 24-months assessment, or a BASFI at 2 years higher than 75th percentile at this latter timepoint. Demographic, clinical, biological and radiological data collected at inclusion were compared in patients with bad functional outcome versus others, first by Chi2 test (numeric data were dichotomized according to observed median values), then by multivariate logistic regression model with stepwise selection of relevant factors.

Results: 513 patients (54.4% females, mean age 34 ± 8 years, 72.2% fulfilling ASAS criteria) were assessed. Of those, 130 (25.3%) fulfilled the aforementioned criteria of a bad functional outcome (with BASFI increase of at least 4 units or value at 2 years ≥60). A bad outcome was more frequently observed in “older” patients aged over 33 years at disease onset, or with educational level lower than college (both p<0.0001). Smoking patients (p<0.0001) and female patients (p<0.008) also had more frequently an unfavourable course of disease. Patients not fulfilling ASAS criteria, having negative X-Rays or MRI of sacroiliac joints, with a history or active peripheral arthritis were also more prone to have poor functional outcome (all p<0.05). A high disease activity at baseline (ASDAS CRP>3.5 and BASDAI >45) was also associated with a bad functional evolution (p<0.0001). Multivariate analysis revealed that not fulfilling ASAS criteria, a female sex, an age >33 years, a lower educational level, an active smoking status and a high disease activity according to BASDAI at baseline were independently associated with a bad functional outcome at 24 months follow-up (Table).

Factors associated with a bad functional outcome at 24 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiographic Axial SpA</th>
<th>Non-radiographic Axial SpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI mean, n (%)</td>
<td>2.7 (65)</td>
<td>4.1 (61)</td>
</tr>
<tr>
<td>ASDAS &gt;=40 %, n (%)</td>
<td>28 (65)</td>
<td>55 (61)</td>
</tr>
<tr>
<td>BASFI, mean, n (%)</td>
<td>2.5 (65)</td>
<td>3.0 (61)</td>
</tr>
<tr>
<td>VAS global, mean, n (%)</td>
<td>2.9 (65)</td>
<td>4.3 (61)</td>
</tr>
<tr>
<td>VAS pain, mean, n (%)</td>
<td>2.9 (65)</td>
<td>4.4 (61)</td>
</tr>
<tr>
<td>ASDAS CRP, n (%)</td>
<td>1.9 (58)</td>
<td>2.3 (57)</td>
</tr>
<tr>
<td>ASDAS ESR, mean, n (%)</td>
<td>1.8 (58)</td>
<td>2.3 (56)</td>
</tr>
<tr>
<td>Current NSAID use, %, n (%)</td>
<td>60 (100)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>Current MTX or SSZ use, %, n (%)</td>
<td>28 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Current anti-TNF use, %, n (%)</td>
<td>50 (100)</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

Conclusion: We confirmed, in a large prospective cohort of early IBP patients, bad prognostic factors formerly described in ankylosing spondylitis, especially a low educational level, a (relatively) older age and a high disease burden.

Disclosure: L. A. Diekman, None; M. Lee, None; J. D. Reveille, None; M. Johansson, AbbVie, 3.
activity at onset, and revealed that an active smoking status was also independently associated with a poor outcome. Fulfilment of ASAS criteria on the other hand was predictive of a better outcome, likely due to more consensual management of a defined disease. Female sex however, usually regarded as a protective factor in AS, was related with a (self-assessed) poorer functional outcome after 2 years of follow-up.

Disclosure: C. Lukas, None; M. Dougados, None; B. Combe, None.

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The Fat Spondyloarthritis Spine Score (FASSS) Independently Predicts Radiographic Progression in Patients with Ankylosing Spondylitis. Susanne Juhl Pedersen1, Stephanie Wichuk2, Praveena Chiovchanwisawakit3, Zheng Zhao4, Robert GW Lambert5 and Walter P. Maksymowycz6. 1Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, 2University of Alberta, Edmonton, AB, 3Mahidol University, Bangkok, Thailand, 4PLA General Hospital, Beijing, China.

The Fat Spondyloarthritis Spine Score (FASSS) independently predicts radiographic progression in patients with ankylosing spondylitis. Background/Purpose: Vertebral corner fat lesions have been shown to be associated with later development of new syndesmophytes in the same vertebral corner.1,2 The aim of this study was to investigate the association between fat lesions and radiographic progression at the patient level using the novel Fat Spondyloarthritis Spine Score (FASSS). This could lead to an important target for therapeutic intervention.

Methods: 157 patients with AS (N (%): male sex: 121 (77%); receiving TNFα-inhibitors: 93 (59%); mean (SD) age: 39.4 (11.7); symptom duration: 15.9 (10.2)) had MRIs and X-rays performed with a mean (SD) follow-up of 2.3 (0.7) years and 2.2 (0.68) years. Status and change in fat lesions were assessed with FASSS and radiographic progression with the modified Stoke AS Spine Score (mSASSS). Two readers independently read MRIs scans and radiographs, and an adjudicator re-assessed discrepant cases according to pre-specified rules. Multivariate stepwise regression analysis included variables significant in univariable analyses (age, sex, symptom duration, baseline CRP, baseline mSASSS) and treatment.

Results: When mSASSS progression was dichotomized (mSASSS progression yes/no), baseline FASSS scores were significantly higher in the progression group as compared to the non-progression group (20.0 (21.6) vs. 12.9 (22.5), p<0.001). When a pre-specified FASSS cut-off of 5 was used, which has been suggested as a definition of a “positive spine MRI”4, higher rates of radiographic progression were seen in patients with score ≥5 vs. <5 (1.19 (1.52) vs. 0.34 (0.72), p<0.001). In the regression analyses baseline FASSS score was the only independent predictor of radiographic progression (β=0.008, p=0.0004). Figure 1 shows patients with a baseline FASSS scores ≥5 had a higher cumulative probability of radiographic progression.

Conclusion: A positive spine MRI for fat assessed with FASSS, and the degree of spinal fat are significantly associated with radiographic progression in patients with AS.

References
1Baraliakos X et al. Ann Rheum Dis, 2013 (online)

Disclosure: S. J. Pedersen, None; S. Wichuk, None; P. Chiovchanwisawakit, None; Z. Zhao, None; R. G. Lambert, None; W. P. Maksymowycz, None.

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Clinical and Psychological Correlates of Sleep Difficulties in Patients with Spondyloarthropathies Compared to Patients with Rheumatoid Arthritis. Konstantinos Kotsis1, Thomas Hyphantis2, Paraskevi V. Voulgari3, Andre F. Carvalho3 and Alexandros A. Drosos4. 1Department of Psychiatry, Medical School, University of Ioannina, 45110, Ioannina, Greece, 2Department of Psychiatry, Medical School, University of Ioannina, Ioannina, Greece, 3Department of Rheumatology, Ioannina, Greece, 4Department of Rheumatology, Ioannina, Greece.

Background/Purpose: Sleep difficulties are common in patients with rheumatological disorders. Patients with Rheumatoid Arthritis (RA) report frequently poor quality sleep, numerous night awakening and difficulty falling asleep; complaints of patients with Spondyloarthropathies (SpA) often include poor sleep quality, sleep-onset insomnia and difficulty awakening. The aim of the present study was to test whether the clinical and psychological factors associated with sleep difficulties are different in patients with SpA compared to RA patients.

Methods: In 138 consecutive SpA patients (55 with Ankylosing Spondylitis (AS) and 83 with Psoriatic Arthritis) we assessed disease’s parameters, pain, depressive symptom severity (PHQ-9), Illness Perceptions (B-IPOQ) and sleep difficulties (SCL-90-R). One hundred and ninety-nine consecutive RA patients served as disease control group. Multiple regression models determined the associations of clinical and psychological variables with sleep difficulties separately for each disease-group.

Results: SpA patients reported more waking up early in the morning (p=0.012) and less difficulties in falling asleep (p<0.001) and restless sleep (p=0.002) compared to RA patients. Depressive symptoms were associated with sleep difficulties in both disease-groups. In RA, older age (p=0.038) and female gender (p=0.016) were associated with more difficulties in falling asleep; female gender was correlated with waking up early in the morning (p=0.028), and disease activity, as measured by the DAS-28, was associated with restless sleep (p=0.004). However, pain was associated with troubles falling asleep (p=0.009) and sleep restlessness (p<0.001) only in patients with SpA. In addition, in patients with SpA, the higher the number of bodily symptoms attributed to the illness (illness identity), the greater the waking up early in the morning (p=0.05).

Conclusion: Apart from early recognition and treatment of depressive symptoms in both SpA and RA, addressing pain issues should be considered a priority in patients with SpA, as axial pain and stiffness in the latter half of the night are an important characteristic of the inflammatory back pain in those patients with AS, resulting in sleep disturbances, as the present findings showed. Attention to patients’ illness perceptions and their concerns about numerous bodily symptoms attributed to the illness may also enable rheumatologists to identify and manage treatable aspects of sleep difficulties in patients with SpA.

Disclosure: K. Kotsis, None; T. Hyphantis, None; P. V. Voulgari, None; A. F. Carvalho, None; A. A. Drosos, None.

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The Clinimetric Outcomes of Two Bath Ankylosing Spondylitis Metrology Indices in Treatment with TNF-α Blockers. Eun Jeong Nam1, Jeong Soo Eun1, Sang Hoon Kwon1 and Young Mo Kang2. 1Kyungpook National University School of Medicine, Daegu, South Korea, 2Kyungpook National Univ Hosp, Daegu, South Korea.

Background/Purpose: Bath Ankylosing Spondylitis Metrology Index (BASMI) was developed to quantify the accurate axial status and to assess the clinical changes in spinal movement. The original BASMI was a 3-point scale (range 0–2; BASMI3), which was refined to an 11-point scale, BASMI11 (range 0–10) to increase the sensitivity to changes in axial status in ankylosing spondylitis (AS). In this study, we compared these BASMI scoring methods in AS patients who were treated with TNF-α blockers.

Methods: A retrospective study was conducted in a total of 116 patients who were treated with TNF-α blockers (137 cases; 96 patients with single agent, 19 patients with two, and 1 patient with three). Clinical efficacy was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BAS- DAI), ASAS20, ASAS40, ASAS6/6, BASDAI50, and acute phase reactants including ESR and CRP at baseline and month 3, and then every six months up to 27 months. Metrology outcome was also evaluated by chest expansion, BASMI11 and BASMI10 methods at the same time.

Disclosure: None.
Results: Three TNF-α blockers including etanercept (60 cases), adalimumab (62 cases), and infliximab (15 cases) showed a similar clinical efficacy. ASAS20 response rate was 87.3%, 91.3%, 91.9%, 90.3%, and 90.9% at months 3, 9, 15, 21, and 27, respectively. ASAS20 responders at month 3 (3MoASAS20) showed a significant improvement of BASMI2 and BASMI10 scores and chest expansion, compared to those of baseline, while 3MoASAS20 non-responders did not show a significant change until month 27. BASMI2 scores at baseline and months 3, 9, 15, 21, and 27, were not significantly different from those of BASMI10 scores at the same time points. Both BASMI2 and BASMI10 scores were significantly correlated with components of ASAS20 response criteria including Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI-spondylitis inflammation (BASDAI-SI), patient’s global assessment, and pain. The change of BASMI2 and BASMI10 in 3MoASAS responders was most prominent from baseline to month 3, but still significant from month 3 to month 9. The change of lumbar flexion and lumbar side flexion components of both BASMI2 and BASMI10 in 3MoASAS20 responders were statistically significant until month 9, while that of other components was only significant until month 3. The improvement of both BASMI2 and BASMI10 was significantly associated with changes of BASDAI-SI, BASFI and pain at month 3, 9, 15, 21, and 27.

Conclusion: The BASMI2 method showed similar sensitivity to changes in range of axial motion in patients with AS who were treated with TNF-α blockers. Further studies are required to determine whether BASMI2 method is as sensitive as BASMI10 method for assessment of axial involvement in AS patient with TNF-α blocker treatment.

Disclosure: E. J. Nam, None; J. S. Eun, None; S. H. Kwon, None; Y. M. Kang, None.

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Do Bone Marrow Edema Lesions in the Sacroiliac Joint Change into Fatty Lesions over a 1-Year Period in Patients with Axial Spondyloarthritis or Possible Spondyloarthritis? Pauline Bakker1, Rosaline van den Berg1, Manouk de Hooge1, Floris van Gaalen1, Monique Reinierse1, T.W.J. Huizinga1 and Désirée van der Heijde2.

Background/Purpose: Bone marrow edema (BME) lesions in the sacroiliac joint (SIJ) may change into fatty lesions over time. Fatty lesions are regarded as the earliest sign of chronic changes as a consequence of inflammation but are sometimes also found healthy controls.1 At the moment, there is little information on the course over time in patients without treatment of TNF-inhibitors. The aim is to investigate whether BME lesions in the sacroiliac joint change into fatty lesions over 1 year in patients with axial SpondyloArthritis (axSpA) or possible SpA and to evaluate the volatility of both lesions general.

Methods: Patients in the SPACE cohort (back pain: \(\geq 3\) months, \(\geq 2\) years, with suspicion of axSpA underwent MRI of the SIJ at baseline and 1-year follow-up (n=76). MRI readings were independently by 3 well-calibrated readers, blinded for time sequence and patient characteristics (STIR and MRI T1-weighted sequences viewed simultaneously). The presence of BME and fatty lesions was scored. Both lesions were defined present (STIR and MRI T1-weighted sequences viewed simultaneously). The presence of BME and fatty lesions was scored. Both lesions were defined present.

Results: 76 patients were completed in the analyses (number of Q=608); of which 39 (51%) were classified axSpA at baseline (ASAS classification criteria), and 37 (49%) as possible SpA. BME or fatty lesions at any time point was found in 74/76 patients (97%) over 1 year time with agreement on 5 patients among the two readers (mNYc). The readers scored images of both time points randomly and blinded by two trained readers, according to ASAS definition for bone marrow oedema (BME). Descriptive analysis was performed using SPSS program v.21.0. Cohen’s kappa coefficients were also calculated to assess agreement between the two readers (mNYc for x-Rays and ASAS definition for a positive MRI).

Results: Forty four patients (52% male) were included. Mean age was 34.4 years (range: 21–45) and 52.3% were HLA-B27 positive. Mean time since symptoms onset until baseline visit was 10.4 months (range: 3–24). Mean (SD) follow up period (between baseline x-Ray and last follow up x-Ray) was 3.6 (1.4) years (median 4 years). All patients fulfilled ASAS criteria for axSpA and 16 of them had AS according to mNYc at baseline, in the opinion of both readers. Interobserver agreement for the x-Ray reading at baseline visit (44 x-Rays) was at the limit between moderate and good (kappa 0.62), but it increased to very good agreement (kappa 0.90) at the x-Rays reading corresponding to the follow-up visit. Regarding MRI, data from 27 images were available for analysis and the kappa value for the ASAS definition of BME was 0.76 at baseline. Progression of sacroiliitis over follow up period by at least one grade at one side was found in 43.2% (19/44), in the opinion of both readers. Among the 28 nr-axSpA patients at baseline, 3 of them (11%) progressed to AS according to NYmc in the opinion of both readers. We also analyzed the possible association between all variables

References:
2. Song ARD 2011:70:1257.

Volatility of BME and fatty lesions in the SIJs over 1 year time

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<th>Reader 1</th>
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</table>

8 quadrants per patient (n = 76); 608 quadrants in total

Disclosure: P. Bakker, None; R. van den Berg, None; M. de Hooge, None; F. van Gaalen, None; M. Reinierse, None; T. W. J. Huizinga, None; D. van der Heijde, None.

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Radiographic Sacroiliitis Progression in an Early Axial Spondyloarthritis Cohort. Concepcion Castillo-Gallejo1, Jesus Sanz2, Carmen Martin-Hervas1, Mireia Moreno1, Victoria Navarro-Compán1, Diana Peiteado1, Jorge Gratacos-Masmithia1, Eugenio De Miguel1 and Emilio Martin-Mola1.

Background/Purpose: The current concept of axial Spondyloarthritis (axSpA) considers non-radiographic axSpA (nr-axSpA) and Ankylosing Spondylitis (AS) as two stages of one disease. There are limited data available regarding rate of radiographic progression of the sacroiliac joints (SIJ) and the rate of transition from nr-axSpA to AS. The aim of the current study was to investigate radiographic progression in the SIJ in an early axSpA cohort.

Methods: Patients included in the study came from an early SpA cohort, from three centers of the ESPERANZA programme, a Spanish nationwide health management programme designed to provide excellence in care for early SpA. One of the inclusion criteria was symptom duration between 3 and 24 months. Each patient had a complete examination at baseline that included ESR, CRP, ASAS-CRP, ASAS-ESR, BASDAI, HLA-B27, pelvis X-Rays and Magnetic resonance (MRI) of the SIJ. Pelvis x-Rays at baseline and at follow up were performed for every patient. These x-Rays were centrally digitized, anonymised and the SIJ were scored independently by two trained readers, according to the grading system of the modified New York criteria (mNYc). The readers scored images of both time points randomly and were blinded for all clinical data. MRI of the SIJ were assessed independently and blinded by two trained readers, according to ASAS definition for bone marrow oedema (BME). Descriptive analysis was performed using SPSS program v.21.0. Cohen’s kappa coefficients were also calculated to assess agreement between the two readers (mNYc for x-Rays and ASAS definition for a positive MRI).

Results: Forty four patients (52% male) were included. Mean age was 34.4 years (range: 21–45) and 52.3% were HLA-B27 positive. Mean time since symptoms onset until baseline visit was 10.4 months (range: 3–24). Mean (SD) follow up period (between baseline x-Ray and last follow up x-Ray) was 3.6 (1.4) years (median 4 years). All patients fulfilled ASAS criteria for axSpA and 16 of them had AS according to mNYc at baseline, in the opinion of both readers. Interobserver agreement for the x-Ray reading at baseline visit (44 x-Rays) was at the limit between moderate and good (kappa 0.62), but it increased to very good agreement (kappa 0.90) at the x-Rays reading corresponding to the follow-up visit. Regarding MRI, data from 27 images were available for analysis and the kappa value for the ASAS definition of BME was 0.76 at baseline. Progression of sacroiliitis over follow up period by at least one grade at one side was found in 43.2% (19/44), in the opinion of both readers. Among the 28 nr-axSpA patients at baseline, 3 of them (11%) progressed to AS according to NYmc in the opinion of both readers. We also analyzed the possible association between all variables

Disclosure: P. Bakker, None; R. van den Berg, None; M. de Hooge. None; F. van Gaalen, None; M. Reinierse, None; T. W. J. Huizinga, None; D. van der Heijde, None.
collected at baseline with radiographic progression but we did not find any statistically significant association for any of them.

**Conclusion:** Progression of radiographic sacroiliitis by at least one grade after a mean time of follow-up of 3.6 years occurs in almost half of the patients. The rate of progression from nrax-SpA to AS was 11%. The inter-reader reliability of pelvis x-Ray improves as disease progresses. Regarding to these results, pelvis x-Ray has a limited utility at early stages of axSpA.

Disclosure: C. Castillo-Gallego, None; J. Sanz, None; C. Martín-Hervas, None; M. Moreno, None; V. Navarro-Compan, None; D. Peitdeo, None; J. Gratacos-Masmitjà, None; E. De Miguel, None; E. Martín-Mola, None.

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Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis, Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis

**Conclusion:** The ASDAS (ankylosing spondylitis disease activity score) was developed to overcome some of the deficiencies of BASDAI (Bath Ankylosing Disease Activity Spondylitis Index). In this prospective study merits of both scores are compared.

**Methods:** Patients with AS according to mNY criteria and BASDAI ≥ 4 were enrolled at 30 Spanish centers and followed during 1 year. Follow-up visits were scheduled every 4 months. Physical examination, CRP and ESR, Patient Global disease activity visual analogue scale (VAS), PG-VAS, pain due to AS (VAS), BASDAI, BASMI, BASFI, ASAS, patient acceptable symptom state (PASS), SF-36, ASQoL, work productivity and activity impairment (WPAI) questionnaire data were recorded at each visit.

**Results:** A total of 127 evaluable patients, 75.6% men, with median age of 48 years and median time from diagnosis of 10 years, were recruited. **Criterion validity:** across follow-up correlations between ASDAS and PG-VAS ranged from 0.560 to 0.736, and from 0.758 to 0.840 between BASDAI and PG-VAS. **Construct validity:** ASDAS correlation with BASDAI (0.73), ASDAS correlation with BASMI (0.78), BASDAI (0.725 to 0.552), BASFI (0.476 to 0.591), lumbar pain VAS, (0.691 to 0.702) and lumbar right pain VAS (0.648 to 0.702) were found. **Discriminant validity:** mean ASDAS and mean BASDAI were significantly higher in patients with non-acceptable PASS than in patients with acceptable PASS. Patients below median PG-VAS showed significantly lower mean ASDAS and BASDAI than patients above median PG-VAS. ASDAS, but not BASDAI, distinguished between patients below and above median CRP. Patients in different ASDAS categories showed significant differences in CRP, PG-VAS, BASMI, BASDAI, BASFI and pain VAS across follow-up, but significant differences in TJC and SJC were not found at any visit. **Sensitivity to change:** significant reductions in mean ASDAS and BASDAI were observed in patients changing from non acceptable PASS at baseline to acceptable PASS across the follow-up, and a significant proportion of patients had a reduction in disease activity level according to their ASDAS categories. ASDAS was sensitive to patients achieving a 50% reduction in BASDAI, Concerning treatments, ASDAS and BASDAI were sensitive to changes in PASS in patients treated with biological therapies, but only BASDAI was sensitive to changes in patients treated with DMARDs. An inverse relationship was detected between ASDAS and physical and mental subscales of SF36, and changes in ASDAS were significantly related with changes in ASQoL. Concerning WPAI, the work time missed increased as ASDAS score increased.

**Conclusion:** ASDAS has shown good metric properties in patients with AS, performing as well as BASDAI, but with higher sensitivity to inflammatory signs. Patients’ quality of life and impairment of productive activity are associated with ASDAS scores.

Disclosure: A. Sellas-Fernandez, None; J. L. Guerra Vázquez, None; J. L. Casals, None; C. Gonzalez Fernandez, None; R. Miguel, None; J. Rosas, None; A. Fernandez-Nebro, None; C. Peralta Ginés, None; C. Montilla-Morales, None; X. Juanola, None; M. Abad, None; A. Alonso, None; A. Hernández-Sanz, None; L. F. Linares, None; J. Medina, None; J. Rovira, None; J. C. Torre-Alonso, None; A. Willisch, None; E. Collantes-Estevez, None; A. Ruiz-Zorrilla, Abbvie, 3.

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**Inflammatory Burden in Recent-Onset Axial Spondyloarthritis.** Juan Jose Aznar Sanchez, Raul Veron Gonzalez, Adela Gallego Flores, Tamara Libert Rodrigo Araya, Piter Jose Cossio Jimenez and Eugenio Chamizo Carmona. Hospital de Mèrida, Mèrida, Spain.

**Background/Purpose:** Patients with Non-Radiographic Axial Spondyloarthritis (non-Rx AxSpA) don’t present with different clinical manifestations than patients with Ankylosing Spondylitis (AS), although the inflammatory burden measured by ASDAS and CPR is higher in the latter. Studies have still yet to discover any difference in inflammatory burden between patients with non-Rx SpA classified by ASAS criteria by the pathway of imaging (active inflammatory lesions in sacroiliac joints detected by MRI) and that classified by the clinical pathway (HLA-B27). The aim of this study is to analyze the clinical characteristics and the inflammatory burden of patients classified of Axial Spondyloarthritis (AxSpA) by ASAS criteria attended in recent-onset Spondyloarthritis Unit (RSpAU).

**Methods:** We included adult patients younger than 45 years old attended the RSpAU of the General Hospital in Mérida (Spain) between May 2008 and May 2014 with inflammatory low back pain more than 3 months and less than 2 years, asymmetric arthritis and/or mechanical low back pain/arthritisg accompanied by, at least, one of the following: psoriasis, uveitis, inflammatory bowel disease (IBD), entesitis, sacroiliitis on imaging, HLA-B27 (+) or family history of SpA. Patients with previous diagnosis of SpA were however excluded.

**Results:** We studied 132 patients, 36 patients fulfilled ASAS criteria for SpA. Of this group, 8 patients fulfilled NY criteria for EA, and 28 were diagnosed with non-Rx SpA. Of the patients with non-Rx SpA, 16 entered through the clinical pathway (HLA-B27) and 12 through the pathway of imaging (MRI of sacroiliac joints with active inflammatory lesions or bone marrow edema). The age at the diagnosis was 29.5 year for both EA and non-Rx SpA. In the group of non-Rx SpA we found female predominance (16 women/12 men), in particular in the group with MRI positive and HLA-B27 negative (4 women/2 men). The measures of BASDAI and BASFI indexes were higher in the group of non-Rx SpA, but without statistically significance.

In patients with non-Rx SpA, the median level of CRP was higher in patients with positive MRI than patients that entered by the clinical pathway, but without statistically significance.

**Conclusion:** In the non-Rx SpA there is a female predominance and a lower rate of HLA B27 (+) than in radiological EA. We didn’t find any significant differences in the indexes used to measure the inflammatory burden between both groups. There is a trend to higher inflammatory burden measured by CPR and ASDAS in EA than in non-Rx SpA and in the last group, higher in patients with active inflammatory lesions in sacroiliac joints by MRI.
Anti-Drug Antibodies As a Predictor for the Discontinuation of Anti-TNF Agents in Patients with Spondyloarthritis. Jiwon Hwang, In young Kim, Seulkkee Lee, Hyemin Jeong, Hyungjin Kim, Jaejoon Lee, Eun-mi Koh and Hoon-Suk Cha. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

**Background/Purpose:** Tumor necrosis factor (TNF) blocking agent has shown to be effective in patients with axial spondyloarthritis (SpA) including ankylosing spondylitis (AS) as up to 60–70%. However, the other 30–40% of patients fails to respond. This non-responsiveness to TNF blocking agent has been suggested as the result of the development of antibodies against anti-drug antibodies (ADA), which have been described well in patients with rheumatoid arthritis and Crohn’s disease. The aim is to assess whether ADA is related to the clinical efficacy in SpA patients on anti-TNF agents.

**Methods:** According to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA, consecutive patients were recruited at a single tertiary hospital who received treatment with adalimumab (Ada) or infliximab (Ixf); 86 AS, 11 inflammatory bowel disease associated SpA, 3 psoriatic SpA and 2 undifferentiated SpA. Serum samples were collected at the enrolment for the drug and ADA levels, which were measured by ELISA.

Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at baseline (at the beginning of the current anti-TNF agents), at 3 month and then every 6 months. The reactivation of tuberculosis infections, side-effects or infusion reactions, and the cause for discontinuation of therapy were assessed prospectively.

**Results:** A total of 102 patients were studied (89.2% male; mean age at sampling 35.2 ± 18.0 years; mean disease duration 11.3 ± 7.9 years). HLA-B27 was positive in 65 of 76 patients (85.5%). Among 102 patients, 74 were treated with Ada and 28 with Ixf. Eighteen patients (17.6%) had switched from other kinds of anti-TNF agents including Ada, Ixf and etanercept. Latent tuberculosis (TB) infection was detected in 22 patients (21.6%) before starting anti-TNF agents and the treatment regimen with isoniazid and rifampin was commenced by a TB expert. ADA was demonstrated in 8 patients (7.8%) (5 of Ada and 3 of Ixf) and all of them were anti-TNF naïve patients. Patients who developed ADA had lower levels of the corresponding drugs (Ada level: 0.45 ± 0.68 vs 4.42 ± 2.12, p < 0.0001; Ixf level 0.91 ± 1.36 vs 3.38 ± 2.24, p = 0.076). At baseline, no differences in BASDAI were found in patients with or without ADA, and neither ESR nor CRP was different. The median period under prospective observation was 15 months (range 0 – 17, mean 12.7 ± 7.8). ADA-positive patients had a significantly higher cumulative drug discontinuation rate due to inefficacy and adverse events (37.5% vs 6.4%, p = 0.022). There was no reactivation of tuberculosis during anti-TNF treatment.

**Conclusion:** Our result suggests that in SpA patients the presence of ADA to current Ada or Ixf can predict the drug discontinuation in future due to inefficacy or adverse events.

Disclosure: J. Hwang, None; I. Y. Kim, None; S. Lee, None; H. Jeong, None; H. Kim, None; J. Lee, None; E. M. Koh, None; H. S. Cha, None.

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Is There Any Gender Specific Difference in the Cut Off Values of Ankylosing Spondylitis Disease Activity Score (ASDAS) in Patients with Axial Spondyloarthritis? Erkan Kilic, Gamze Kilic and Salih Ozgocmen. Erceyis University, Faculty of Medicine, Kayseri, Turkey.

**Background/Purpose:** Axial spondyloarthritis (axSpA) consists patients with advanced axial SpA or ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA). Evaluation of disease activity in axSpA is complex due to the phenotypic heterogeneity of the disease. Assessment in Spondyloarthritis International Society (ASAS) endorsed the cut off values for ASDAS-CRP. The aim of this study was to assess the validity of AS Disease Activity Score (ASDAS)-CRP and ASDAS-ESR as clinical tools for assessing disease activity in axSpA and to estimate the cut-off values of ASDAS-CRP and ASDAS-ESR for male and female patients with axSpA.

**Methods:** Patients with axSpA were recruited from Erceyis Spondyloarthritis Cohort (ESPAC) and assessed for BASDAI, ASDAS, BASMI, Ankylosing Spondylitis Quality of Life (ASQoL), and VAS-pain. Patients were grouped into low and high disease activity according to the physician’s (DrG) and patient’s global (PtG) assessment score (>6/10 vs <4/10), ASAS partial remission criteria, treatments and presence of peripheral arthritis. The discriminant ability of ASDAS-CRP and ASDAS-ESR was assessed using standardized mean differences. Receiver operating characteristic (ROC) curves were used for comparisons. Optimal cut-off values of ASDAS-CRP and ESR were calculated for both genders and for the whole group.

**Results:** Three hundred fifty-eight patients with axSpA (138 F, 220 M) were included in this study. One hundred sixty two patients met criteria for non-radiographic axSpA (nr-axSpA) and 196 for ankylosing spondylitis. Two ASDAS versions and BASDAI had good correlations with PtG and DrG in both groups, however correlation coefficients were relatively higher in men. Women had significantly higher VAS-pain, BASDAI item scores, PtG and DrG and ESR. Discriminant ability of ASDAS-CRP, ASDAS-ESR and BASDAI were similar in men and women when patients were assigned into low and high disease activity based on the ASAS partial remission, PtG and DrG scores (assessed by comparing AUC of ROC curves). ASDAS cut-off values are quite similar in all groups indicating that ASDAS-CRP works similarly well in male and female patients with axSpA. The calculated ASDAS-CRP cut-offs in both genders were very similar to predefined values by ASAS except the cut off for in-active to moderate disease activity. The cut-off values for ASDAS-ESR seem to be lower than predefined values and women tent to have higher cut-offs compared to males.

**Conclusion:** The construct validity of ASDAS-CRP to discriminate low and high disease activity and cut off values are similar in male and female patients with axSpA, however cut off for ASDAS-ESR need to be redefined.

Disclosure: E. Kilic, None; G. Kilic, None; S. Ozgocmen, None.

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Differing Patterns of Axial Spondyloarthritis in Females and Males. Ibrahim Almaghlouth1, Arane Thava1, Nigil Haroon2 and Robert D. Innam3. 1Toronto Western Hospital, Toronto, ON, 2Toronto Western Research Institute, Toronto, ON, 3Department of Medicine, University of Toronto, Toronto, ON.

**Background/Purpose:** Sex effects have been noted in axial spondyloarthritis (AS) however controversy still exists regarding male and female clinical manifestations of AS. This includes uncertainty regarding pattern of spinal disease, peripheral joint involvement, and clinical burden of disease. Prior studies have often been limited by numbers and lack of contemporaneous comparators. In this study we examine sex effects on a longitudinal observation cohort of AS.

**Methods:** A systematic review of 950 AS patients (671 male and 279 female) followed in a longitudinal clinic which entails regular clinic visits using a standardized protocol. Patients were stratified by sex. Descriptive characteristics using means (sd) and frequencies (%) can be seen in Table 1. Tests were used to compare continuous variables and Chi-Squared tests for categorical variables. P-value <0.05 was used to define statistical significance.

**Results:** We observed that age of onset of back pain was higher in females, and that there was a significant longer delay in diagnosis in females. CRP levels were lower among female patients. This finding parallels previous reports of lower CRP among female with non-radiographic axSpA. We noticed no difference between sex in terms of affected joints, nor with respect to key extra-articular manifestations (iritis, psoriasis, inflammatory bowel disease). Significant differences in BASMI indicate less impairment of spinal mobility, which may reflect both lower levels of CRP and lower rates of smoking, both of which have been previously associated with structural progression of AS. The use of biologic agents as a surrogate marker of symptomatic burden of disease did not differ between females and males but comparative ASQoL scores reflected greater impact on quality of life in females.

**Conclusion:** Our large cohort documents later onset of AS symptoms and longer delay in diagnosis in female AS patients compared with males. Difference in inflammatory markers might be a reflection of different disease pathogenesis but environmental factors such as smoking also contribute to the difference in clinical expression of the disease.

**TABLE 1:** Comparison of Baseline Demographic and Disease Characteristics by Sex (n=950)

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Sunday, November 16

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**Combined Hip Abduction Angle Measured By Using Iphone Compass Application; A Novel Measurement Tool to Asses Hip Mobility.** Handan Yarkan, Berrin Zengin, Gokce Kenar, Pinar Cetin, Ismail Sarli, Fatos Onen and Nurullah Akkoç. Dokuz Eylül University School of Medicine, Izmir, Turkey.

**Background/Purpose:** Inter-malleolar distance (IMD) is a component of the Bath ankylosing spondylitis metrology index (BASM1) and measures abduction of the hips. New generations of smartphones are equipped with a gyroscope and an accelerometer which in combination with a smartphone’s operating system or specific software applications can be used for various clinical applications. Intra-rater and inter-rater reliability were examined with standard method at two different time points with the patient lying in a supine position. New generations of smartphones are equipped with a gyroscope and an accelerometer which in combination with a smartphone’s operating system or specific software applications can be used for various clinical applications. Intra-rater and inter-rater reliability were examined with standard method at two different time points with the patient lying in a supine position.

**Results:** The study sample included 20 AS patients (6 females, 14 males) with a mean age of 47.8 (± 10.2) years. BASMI scores were obtained from patient charts. Two examiners measured inter-malleolar distance as the standard method at two different time points with the patient lying in a supine position. Then combined abduction of the hips angle (CAHA) was measured by iphone compass application twice. To stabilize the iphone’s position during measurements an iphone case and an elastic bandage with velcro patches were used. Intra-rater and inter-rater reliability were examined with intra-class correlation coefficients (ICC). The validity was assessed by Pearson Correlation analysis.

**Conclusions:** The results of this study suggest that measurement of combined hip abduction angle using iphone, which is not be affected by patients’ height, can be used as a novel hip mobility measure.

**Disclosure:** I. Almaghlouth. None; A. Thava. None; N. Haroon. None; R. D. Inman. Advisory board and grant, 5.

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**Table:** Intra-rater and inter-rater reliability of the two methods to assess the hip mobility

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<td><strong>Combined hip abduction Angle</strong></td>
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**Disclosure:** H. Yarkan. None; B. Zengin. None; G. Kenar. None; P. Cetin. None; I. Sarli. None; F. Onen. None; N. Akkoç. None.

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A Phase 3, Randomized, Controlled Trial of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, for Treatment of Psoriatic Arthritis: Long-Term (52-Week) Improvements in Physical Function. Alvin Wells1, Jacob A. Aelion2, Adewale O. Adebojo1, Alan Kivitz3, Paul Bird, Chia-Chi Hu6, Randall McStevens4,5, Daniel W. Hunder4,6,7, Ruoyu Wang, John F. D. McQueen8, Lisa M. Gordon9, William O. Brandt10, Jonathan M. Stein11,12, Skip C. Braverman13,14,15, Revicki DA16,17, Handan Yarkan18, Nurullah Akkoç19, Handan Yarkan20.

**Background/Purpose:** Apremilast (APR) is a phosphodiesterase 4 inhibitor that helps regulate T cell activation and is undergoing development as a novel treatment for rheumatoid arthritis.

**Aims:** This study evaluated the mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) and 36-item Short Form Health Survey (SF-36v2) Physical Function (PF) domain in PsA patients treated with APR or placebo over 52 weeks.

**Methods:** Patients were randomized to receive APR or placebo. Aims were non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial apramistel dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. This analysis reports data for Weeks 0 to 52. Physical function was measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI) and 36-item Short Form Health Survey (SF-36v2) Physical Function (PF) domain.

**Results:** At Week 16, a significantly greater proportion of patients treated with APR achieved a modified ACR20 response vs placebo (primary endpoint). Mean changes in HAQ-DI at Week 16 (key secondary endpoint) were -0.17 (placebo), -0.0008, and -0.23 (APR; P<0.0001). Among patients who were treated with APR continuously through 52 weeks, sustained improvement in HAQ-DI was observed. Mean change in HAQ-DI was -0.39 (APR20) and -0.39 (APR30) at Week 52, exceeding MCID thresholds of ≥0.13 or ≥0.30 (Table). At Week 52, 36.8% (APR20) and 59.0% (APR30) achieved HAQ-DI ≥0.13 or ≥0.30, respectively. Week 52 mean changes from baseline in SF-36v2 PF (APR20: 4.61; APR30: 5.55; APR30: 6.67) exceeded the MCID threshold (≥2.5). At Week 52, 57.6% of APR20 and 60.6% of APR30 patients achieved SF-36v2 PF MCID. The most common adverse events reported during the placebo-controlled period were nausea (12.6%), diarrhea (9.4%), and headache (6.0%). The safety profile of APR for up to 52 weeks was similar to that observed with APR for up to 24 weeks of treatment (placebo-controlled period).

**Conclusions:** Over 52 weeks, APR continued to demonstrate clinically meaningful improvements in physical function in active PsA patients who were DMARD-naïve. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 weeks.

**Disclosure:** I. Almaghlouth. None; A. Thava. None; N. Haroon. None; R. D. Inman. Advisory board and grant, 5.
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Periostin May Have a Role in Ankylosing Spondylitis and It Is Associated with Wnt Signalling Pathway Regulators. Servet Akar1, Saadettin Uslu2, Leyla Didem Kocaz2, Gerek Can2, Neslihan Karaca3, Eminie Figen Tarhan4, Mustafa Ozmen5 and Dilek Solmaz6. 1Izmir Katip Celebi University School of Medicine, Izmir, Turkey, 2Izmir Katip Celebi University School of Medicine, Izmir, Turkey, 3Adnan Menderes University School of Medicine, Aydin, Turkey, 4Izmir Ataturk Education and Research Hospital, Izmir, Turkey, 5Adnan Menderes University, Science Thecnology Research and Application Center, Aydin, Turkey, 6Namik Kemal University School of Medicine, Tekirdag, Turkey.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic rheumatic disease characterized by sacroiliac and spinal inflammation and new bone formation (synodesmophyte). Molecular mechanisms underlying this process have not been yet fully understood however differentiation of mesenchymal cells into bone-forming osteoblasts appears to be a key pathogenic event. Periostin is an extracellular matrix protein and primarily secreted by osteoblasts. It was shown that periostin has a role in bone anabolism by the regulation of Wnt-β-catenin signalling, therefore it may be one of the pathogenic mechanisms in syndesmophyte formation in AS. To evaluate the serum periostin levels in patients with AS. We also assessed the relationship among periostin levels and other biomarkers of bone formation and the role of periostin in disease outcomes, radiographic changes in particular.

Methods: In total 98 consecutive AS patients (77 males [79%]; with a mean age of 39.3 ± 10.8years) according to the modified New York criteria (n=17) and controls (n=11) were included in the study. Serum periostin, interleukin (IL)-8, dickkopf-1 (Dkk-1) and sclerostin levels were measured by commercially available ELISA kits. We also determined the serum high-sensitivity C-reactive protein (hs-CRP) levels. Disease related characteristics of patients were assessed by using BASDAI, BASFI, BASMI. Radiographs of the pelvis, cervical and lumbar spine were scored by using the modified New York and modified Stokes ankylosing spondylitis spinal score (mSASSS).

Results: As expected hs-CRP levels and erythrocyte sedimentation rate were higher in AS patients in comparison with controls. Serum periostin and Dkk-1 levels were significantly lower in AS patients compared with controls. Moreover periostin level was particularly lower in patients with active (35.4 ± 25.8 vs 53.9 ± 42.1 ng/mL and P=0.014) disease (BASDAI ≥4). There was also a trend towards higher periostin levels in patients with syndesmophyte, hip involvement and sacroiliac ankylosis however these were not reached statistical significance. Regression analysis showed that serum periostin levels were independently predicted by Dkk-1, IL-8 levels.

Conclusion: Our results suggested that periostin may play a role in disease outcome, radiographic changes, and the role of periostin in disease outcomes, radiographic changes in particular.

| Mean BASMI | N/A | N/A | 3.8 ± 1.7 | N/A |
| Mean BASDAI-CRP | 3.0 ± 0.9 | N/A | N/A |
| Median m SASSS score | 6 (0-72) | N/A | N/A |
| Serum periostin (ng/mL) | 43.8 ± 35.0 | 72.5 ± 50.0 | 0.001 |
| Dkk-1 (ng/mL) | 49.2 ± 35.1 | 68.6 ± 37.8 | 0.040 |
| IL-8 (pg/mL) | 103.7 ± 270.2 | 66.9 ± 60.1 | 0.390 |
| hsCRP (µg/mL) | 5.2 ± 8.4 | 0.7 ± 1.3 | <0.001 |
| Creatinine (mg/dL) | 0.76 ± 0.15 | 0.82 ± 0.14 | 0.017 |

Disclosure: S. Akar, None; S. Uslu, None; L. D. Kocaz, None; G. Can, None; N. Karaca, None; E. F. Tarhan, None; M. Ozmen, None; D. Solmaz, None.

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Characterisation of Mucosal-Associated Invariant T (MAIT) Cells in Ankylosing Spondylitis Patients. Ibrahim Almaghlouth1, Eric Gracey2, Zoya Qaiyum3, Robert D. Inman4 and Ammepa Anton5. 1Toronto Western Hospital, Toronto, ON, 2University of Toronto, Toronto, ON, 3Department of Medicine, University of Toronto, Toronto, ON, 4University Health Network, Toronto, ON, 5University of Toronto, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is chronic inflammatory disease of unknown origin. Studies into the molecular basis of AS have demonstrated exaggerated innate and adaptive immune responses mediated though various cytokines. Over-expression of cytokines such as TNFα and IL-17 has provided a rationale for targeted biologic agents for suppressing the disease activity. Identifying the cellular sources of these cytokines is crucial to understand the pillars of inflammation in AS. Recently, mucosal associated invariant T (MAIT)-cells have been implicated in various autoimmune diseases. Their effectors phenotype and preferential localization to peripheral tissue makes them possible contributor in the pathogenesis of AS. Thus we hypothesized that MAIT cells may be increased in AS patients compared to normal controls.

Methods: Peripheral blood mononuclear cells (PBMC) and synovial fluid (SF) mononuclear cells (SMFC) from the AS patients (N=17) and controls (n=11) were isolated. Healthy controls were used for the MAIT cells in the PBMC while RA and OA were used as controls for the SF MAIT cells. Flow cytometry was used to identify MAIT cells, which were defined as CD3+CD161hiV.α 7.2+CCR6+, with the majority being CD8+. Cytokine production by respective cell populations was assessed indirectly by intra-cellular staining for IL-4, IL-17, TNFa, IFNg and granzyme B.

Results: The percentage of MAIT cells in PBMC of AS patients and control groups were similar. Whereas CD69+ (activation marker) and CCR6+ (homing marker) MAIT cells were comparable in AS and HC, CCR6+ MAIT showed a tendency to be higher in AS PBMC. It was noted that in PBMC, activated MAIT cells (CD69+) represented a small proportion of the total MAIT cells in. In contrast, almost all SF MAIT cells from AS patients were activated (CD69+). We also noticed that the percentage of CD4+CD161+MAIT to total MAIT cells in AS SF is higher than peripheral blood. Similar results were seen in paired patient blood-synovial fluid analysis. In this analysis, IL17 production was similar while an increased granzyme B production and reduction of IL4, IFNg and TNFα were detected in SF MAIT cells compared to MAIT cells in PBMC.

Conclusion: To our knowledge, this study is the first to look at MAIT cells in both blood and SF of AS patients. Interestingly MAIT cells in the inflamed joints in AS are predominantly activated. This suggests that examining the microenvironment of the joint to define the activating signals for local MAIT cells would be productive.

Disclosure: I. Almaghlouth, None; E. Gracey, None; Z. Qaiyum, None; R. D. Inman, Advisory board and grant, 5; A. Anton, None.

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Decreased Frequencies of Circulating Follicular Helper T Cell Counterparts and Plasmablasts in Ankylosing Spondylitis Patients Naive for TNF Blockers. M. Belén Bautista-Caro1, Irene Arroyo-Villa2, Concepcion Castillo-Gallego3, Eugenio de Miguel4, Diana Peiteado1, Chamaida Plasencia-Rodriguez1, Alejandro Villalba3, Paloma Sanchez-Mateos1, Amaya Puig-Kröger2, Emilio Martín-Mola1 and María Eugenia Miranda-Carús1. 1Hospital La Paz - Idipaz, Madrid, Spain, 2University Hospital La Paz - Idipaz, Madrid, Spain, 3Hospital Gregorio Marañón, Madrid, Spain, 4Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain.

Mean BASMI

3.8 ± 1.7

N/A

Mean BASDAI-CRP

3.0 ± 0.9

N/A

Median m SASSS score

6 (0-72)

N/A

Serum periostin (ng/mL)

43.8 ± 35.0

72.5 ± 50.0

0.001

Dkk-1 (ng/mL)

49.2 ± 35.1

68.6 ± 37.8

0.040

IL-8 (pg/mL)

103.7 ± 270.2

66.9 ± 60.1

0.390

hsCRP (µg/mL)

5.2 ± 8.4

0.7 ± 1.3

<0.001

Creatinine (mg/dL)

0.76 ± 0.15

0.82 ± 0.14

0.017
Background/Purpose: Follicular helper T cells (Tfh), localized in lymphoid organs, promote B cell differentiation and function. Circulating CD4 T cells expressing CXCR5, ICOS and/or PD-1 are counterparts of Tfh. Three subpopulations of circulating CD4+CXCR5+ cells have been described: CXCR3+CXCR6- (Tfh-Th1), CXCR3+CXCR6+ (Tfh-Th17) and CXCR3- (Tfh-Th2). Only Tfh-Th17 and Tfh-Th2 function as B cell helpers.

Our objective was to study the frequencies of circulating Tfh (cTfh), cTfh subsets and plasmablasts (CD19+CD20-CD27+CD38++/++) in patients with Ankylosing Spondylitis (AS).

Methods: Peripheral blood was drawn from healthy controls (HC) (n=50), AS patients naïve for TNF blockers (AS/naive) (n=25) and AS patients treated with TNF blockers (AS/treated) (n=25). The frequencies of cTfh and plasmablasts were determined by flow cytometry. Circulating and supernatant CXCR3-CCR6- T cells with autologous CD19+CD27- naïve B cells were established from 3 AS/naive patients and 3 HC, and concentrations of IgG, A and M were measured in supernatants.

Results: In all, 56 AS/naive patients, demonstrated decreased frequencies of circulating CD4+CXCR5+ICOS+PD-1+ T cells and plasmablasts together with a decreased (Tfh-Th17+Tfh-Th2)/Tfh-Th1 ratio. The amounts of IgG and IgA produced in cocultures of CD4+CXCR5+ T cells with CD19+CD27- B cells of AS/naive patients were significantly lower than observed in cocultures established from HC.

Conclusion: AS/naive but not AS/treated patients, demonstrated a decreased frequency of cTfh and plasmablasts, and an underrepresentation of cTfh subsets bearing a B helper phenotype. In addition, peripheral blood CD4+CXCR5+ T cells of AS/naive patients showed a decreased capacity to help B cells ex vivo.

Disclosure: M. B. Bautista-Caro, None; I. Arroyo-Villa, None; C. Castillo-Gallego, None; E. de Miguel, None; D. Peiteado, None; C. Plasencia-Rodriguez, None; A. Villalba, None; P. Sanchez-Mateos, None; A. Puig-Krüger, None; E. Martín-Mola, None; M. E. Miranda-Caruso, None.

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The Immunological Basis of the Sex-Bias in Ankylosing Spondylitis: Th17 Expansion Is Restricted to Male Patients and Correlates with Sex-Related Alteration in Vitamin D Metabolism. Eric Gracey1, Blerta Green1, Paul Yip1, Renise Ayearst1, Ammepa Anton1, Aifeng Lin1 and Robert D. Inman2. 1University of Toronto and Toronto Western Hospital, Toronto, ON, 2University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory arthritis of the spine, which has a major impact on function and quality of life. AS is known to have a sex-bias with a M:F ratio of 3:1. In addition, females have a delayed onset and reduced radiographic severity compared to males. Genetic and immunologic studies have implicated the Th17-axis in AS pathogenesis, and recent clinical trials suggest efficacy of anti-IL-17A therapy. Prior studies have demonstrated a suppressed effect of vitamin D3 on Th17 cells. In the present study we examined whether there is a sex-bias in the Th17-axis, and its possible relationship to vitamin D metabolism in AS.

Methods: Serum IL-6 and IL-17A were measured by ELISA and 25(OH) vitamin D3 by mass-spectrometry in a cohort of 39 male AS patients, 36 female AS patients and 30 age- and sex-matched healthy controls. Data was analyzed by Mann-Whitney tests and correlations with Spearman tests.

Results: AS patients had an elevated Th17-axis when compared to healthy controls as demonstrated elevated IL-6 (p<0.01), IL-17A (p=0.06) and Th17 cell levels (p=0.05). When stratified for sex, the elevated Th17-axis was restricted to male patients, as exemplified by higher Th17 cell levels in male AS vs female AS (Figure 1). A trend was seen for lower serum 25(OH) vitamin D3 in male AS patients and healthy controls relative to their respective female counterparts. Gene expression of VDR and CYP27B1 (vitamin D3 activating enzyme) were equivalent in male and female AS patients, whereas CYP24A1 (vitamin D3 degrading enzyme) expression was significantly elevated in male AS patients. This was not seen in male vs female healthy controls. In male AS patients, serum 25(OH) vitamin D3 was inversely proportional to whole blood IL23R expression (r=-0.43, p<0.05) and Th17 cell level (r=-0.014, p=0.085).

Conclusion: This is the first demonstration that elevated levels of Th17 cells in AS are restricted to male patients, which could inform targeted therapy with anti-IL17 agents. This may be due to a sex-related alteration in the biochemistry of vitamin D3, which functions as an important inhibitory factor to the Th17 axis. This work demonstrates a biological basis for the observed sex-bias in incidence and in disease expression in AS.

Figure 1: Male AS patients have higher circulating Th17 levels than female AS patients and healthy controls (HC). Results displayed as scatter plot with mean and analyzed by Mann-Whitney test.

Disclosure: E. Gracey, None; B. Green, None; P. Yip, None; R. Ayearst, None; A. Anton, None; A. Lin, None; R. D. Inman, None.

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The HLA-B27 Peptidome in Vivo in Transgenic Rats. Joel D. Taurog1, Yael Haimovich1, Eilon Barnea1, Michal Bassani-Sternberg1, Shiria Yair-Sabag1, Marthath L. Dorris2, Nimman Satumtra1, Mylinh Nguyen1, Robert E. Hammer1, Tri M. Tran3, Robert A. Colbert3 and Arie Admon2. 1UT Southwestern Medical Center, Dallas, TX, 2Technion-Israel Institute of Technology, Haifa, Israel, 3NIAMS/NIH, Bethesda, MD.

Background/Purpose. In all current hypotheses for the association of B27 with SpA, the B27 peptide repertoire (peptidome) is likely to play a key role. ERAPI directly influences the MHC-I peptide repertoire and has strong genetic association with AS. The B27 peptidome has previously been reported only in cell lines. We used mass spectrometry to characterize the in vivo B27 peptidome in spleen cells from rats transgenic (TG) for B27 and human beta-2-microglobulin (hb2m).

Methods. B27 TG rats that develop SpA (males only), the protective Dazl-knockdown (kd) transgene, and rats TG for a B27 C67S mutant have been described (A&R 54,1317, 2006; 64,2518, 2012). ERAPI knockout (ko) rats were produced by microinjection of LEW rat zygotes with a zinc finger nuclease targeting ERAPI. In ERAPI-ko spleen, absence of ERAPI protein was confirmed by immunoblotting, and ERAPI mRNA abundance was 18±3% of wild type. One B27hb2m/ERAPI-ko male was available for peptide analysis. Frozen spleens were solubilized with 1% octyl-glucoside, B27 molecules were immunoaffinity-purified, and peptides were dissociated in 0.1% TFA and isolated by capillary reverse–phase chromatography. Peptides were analyzed by Orbitrap tandem mass spectrometry and data analyzed for peptide identities and relative intensities by MaxQuant, Sequest and Mascot software.

Results. A total of 20,096 unique peptides fitting the B27 peptide motif were identified, of which 10,587 were shared by all genotypes. The data are summarized in the table. The C67S mutant rats showed fewer B27-motif peptides and had a higher proportion of unique peptides, compared with the groups with wild type B27. The Dazl-kd rats, which have no disease manifestations, carried fewer unique peptides than the other groups.
B27-bound peptides isolated from male rat spleens

<table>
<thead>
<tr>
<th>Group (all B27/hb2m TG)</th>
<th>Age (d)</th>
<th>Phenotype</th>
<th>No. spleens</th>
<th>No. B27 motif peptides</th>
<th>No. specific peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type B27, Dazl, ERAP1</td>
<td>72–109</td>
<td>EO</td>
<td>4</td>
<td>9,808</td>
<td>1,238</td>
</tr>
<tr>
<td>Dazl-knockdown</td>
<td>223–236</td>
<td>EO, SpA</td>
<td>4</td>
<td>10,029</td>
<td></td>
</tr>
<tr>
<td>Dazl-knockdown</td>
<td>72–109</td>
<td>healthy</td>
<td>4</td>
<td>9,911</td>
<td>360</td>
</tr>
<tr>
<td>Dazl-knockdown</td>
<td>223–236</td>
<td>healthy</td>
<td>4</td>
<td>9,994</td>
<td></td>
</tr>
<tr>
<td>B27 C67S mutant</td>
<td>163–218</td>
<td>EO</td>
<td>12</td>
<td>7,610</td>
<td>1,896</td>
</tr>
<tr>
<td>ERAP1 knockout</td>
<td>57</td>
<td>*</td>
<td>1</td>
<td>9,808</td>
<td>781</td>
</tr>
</tbody>
</table>

EO = epidiidymo-orchitis; *phenotype not yet known

The peptidome from the ERAP1 ko rat was skewed toward longer peptides, compared with the young wild type and Dazl-kd rats (Figure).

Conclusion. HLA-B27 in TG rat spleen carries large numbers of peptides conforming to the B27 peptide motif identified in human cell lines. Rats with disease show more unique B27-bound peptides than healthy rats, suggesting that disease itself alters the B27 peptidome. Whether either specific peptides or the peptidome as a whole play a role is disease initiation is not yet clear, but the data are consistent with alterations in the peptidome playing a role in disease perpetuation. ERAP1 deletion leads to binding of longer peptides, and the effect of the deletion on disease should be known soon.

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Identification of Novel Autoantibodies in Patients with Ankylosing Spondylitis Using Human Protein Microarray. Matthew Presby1, Mark J. Soloski1, John A. Flynn1, Clifton O. Bingham III1, Michael M. Ward2 and Grant H. Louie1. 1Johns Hopkins University, Baltimore, MD, 2NIAMS/NIH, Bethesda, MD.

Background/Purpose: Ankylosing spondylitis (AS) is an immune-mediated disease for which the search for autoantibodies has been elusive. Conventional immunoserological approaches are slow and limited to the analysis of several dozen proteins at a time. In this pilot study, we used large-scale, high-throughput, protein microarrays to identify potential autoantibodies in AS.

Methods: Sera from patients who fulfilled the 1984 modified New York criteria for AS (N=20) were profiled using a human protein array composed of ~17,000 human proteins (CDI Laboratories, MD) and compared with healthy controls (N=18). Proteins were purified from Saccharomyces cerevisiae, N-terminus tagged with GST-HisX6, spotted in duplicate on the array, imaged using a GenePix 4000B microarray scanner (Molecular Devices, CA), and analyzed using GenePix Pro software. Signal intensity, referred to as an A-score, was computed.

Results: AS patients were age (mean ± SD) 53.5 ± 12.1 years, 80% men, 100% HLA-B27 positive, with a disease duration (mean ± SD) of 28.6 ± 12.8 years. Healthy controls were age 55.7 ± 14.4 years and 50% men. Among 146 potential autoantigens detected in AS patients but not in healthy controls, we identified 6 with the highest frequency and signal intensity. These proteins were microtubule-associated serine/threonine-protein kinase 4 (MAST4), centriole, cilia and spindle-associated protein (CCSAP), SNF related kinase (SNFRK), calcium-binding protein 4 (CaBP4), protein MTG8 (MTG8), and eukaryotic elongation factor 2 kinase (EEF2K). The 3 most frequently targeted autoantigens were the serine/threonine kinases SNFRK, EEF2K, and MAST4. SNFRK and EEF2K were positive in 4/20 patients (20%). Three patients (15%) were positive for autoantibodies against MAST4. Two patients (10%) had antibodies to both MTG8 and CCSAP. The highest A-score observed was reactivity to CaBP4 by 1 patient (5%) (Figure 1). This was the lowest frequency autoantigen observed; however, CaBP4 reactivity was higher in the overall AS population compared to healthy controls. The images of each autoantigen were inspected and can be seen in Figure 2 for the patients with the five highest A-scores.

Conclusion: Using a high-throughput, protein microarray system, we have identified 6 novel autoantigens (SNFRK, EEF2K, MAST4, MTG8, CCSAP, and CaBP4) in AS patients, with an overall frequency of 5–20%. The detection of these AS-specific antibodies may allow for better understanding of disease pathogenesis and potential therapeutic targets. Further validation studies in larger numbers of patients are currently underway.

Disclosure: M. Presby, None; M. J. Soloski, None; J. A. Flynn, None; C. O. Bingham III, None; M. M. Ward, None; G. H. Louie, None.

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Induced Pluripotent Stem Cells (iPSCs) As a Tool for Unraveling the Role of Different Cell Types in the Disease Process of Spondyloarthritis Pathogenesis. Gerlinde Layh-Schmitt, Shjia Lu, Fatemeh Navid, Massimo Gadina and Robert A. Colbert. NIAMS/NIH, Bethesda, MD.

Background/Purpose: Many genetic factors and cell types contribute to the axial inflammation, trabecular bone loss, and aberrant bone formation that result in ankylosing spondylitis. The functional consequences of genetic variants may be manifest in specific cell types and in many cases affected cell types are not readily accessible for evaluation. In order to obtain these cell types we examined the feasibility of reprogramming fibroblasts from patients...
with axial spondyloarthritis (AxSpA) into induced pluripotent stem cells (iPSCs) and subsequent re-differentiating iPSCs into various lineages. **Materials and Methods:** Dermal fibroblasts from 7 AxSpA patients and 3 healthy controls (HC) were reprogrammed using a Sendai virus vector encoding Oci4, Sox2, KIf4 and Myc. One AxSpA and one HC fibroblast line were reprogrammed in two different labs to assess technical reproducibility. Virus-free iPSCs were differentiated into mesenchymal stem cells (MSCs) using a TGF-β inhibitor. MSCs were differentiated into osteoblasts, chondrocytes, and adipocytes; defined cytokine cocktails were used to differentiate iPSCs into monocytes. iPSC derived monocytes were treated with RANKL to induce osteoclastogenesis. IPSG gene expression patterns were established by RNaseq. Gene expression during MSC-osteoblast differentiation was monitored by Nanostring. Flow cytometry was conducted to evaluate the expression of iPSC, MSC and monocyte specific markers.

**Results:** All iPSC lines expressed pluripotency markers (OCT4, TRA-1, SSEA-4) and stem cell specific genes. IPSG derived MSCs proved positive for CD105, CD73, CD90 and CD44, but lacked CD45, CD34, CD11b, CD19, and HLA-DR. MSCs exhibited the capacity to induce differentiation of peripheral blood monocytes into osteoclasts in co-culture as demonstrated by tartrate resistant acid phosphatase staining. MSCs could be differentiated into mineralizing osteoblasts, as confirmed by expression of osteogenic genes and Alizarin Red staining, into chondrocytes (proteoglycan staining with AlcanBlue), and into adipocytes (lipid staining with Oil Red O). IPSG-derived monocytes/macrophages expressed HLA-DR, CD14, CD86, CD80 and CX3CR1 and CD45, and were capable of phagocytosing beads and differentiating into osteoclasts. Preliminary comparison of mineralization potential revealed that MSCs from AxSpA patients (n=3) exhibited 3-fold higher mineralization than the HC as determined by Alizarin Red staining. Independently-derived iPSC lines behaved similarly.

**Conclusion:** We have successfully derived iPSCs from AxSpA patient fibroblasts. The iPSCs can be differentiated into functional MSCs capable of differentiating into mature osteoblasts, chondrocytes, and adipocytes, as well as inducing monocytes to become osteoclasts. We have also successfully generated hematopoietic cells that can differentiate into monocytes, macrophages and osteoclasts. Notably, MSCs from AxSpA patients demonstrated greater mineralization capacity. This was observed repeatedly in independently IPSG derived MSCs from the same patient. These cells may provide a powerful system to examine the molecular functional consequences of genetic differences that predispose to SpA.

Disclosure: G. Layh-Schmitt, None; S. Lu, None; F. Navid, None; M. Gadina, None; R. A. Colbert, None.

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**Functional Implications of the Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) Association with Ankylosing Spondylitis and Crohn’s Disease: Impact on the Unfolded Protein Response.** Zhenbo Zhang1, Francisco Ciccia2, Kirby Yee3, Giuliana Guggino4, Hasan Abdullah5, Ricardo Alessandro6, Stefania Raimondo7, Giovanni Triolo7 and Nigil Haroon1.

**Methods:** A total of 40 B27-positive AS patients were typed for the rs2248374 polymorphism. Peripheral Blood Mononuclear Cells (PBMC) were isolated and stained with antibodies to CD19 (B cells) and CD14 (Monocytes). Staining with HC10 antibodies to assess MHC-I FHC expression and ME-1 antibody for intact HLA-B27 was performed. Mean Fluorescence Intensities (MFI) for FHC and B27 expression was assessed by flow cytometry.

**Results:** At B27, a human B lymphoblastoid cell line stably transfected with HLA-B27, were treated with 2 separate shRNAs to suppress endogenous ERAP2. Changes in UPR were assessed by PCR for BiP, CHOP and PERK. Expression of CHOP was assessed by western blot and semi-quantitative XBP-1 splicing assay was done by PCR.

**Conclusions:** AS patients with no ERAP2 expression (homozygous for the minor allele of rs2248374) had higher FHC expression on the surface of PBMCs (P=0.019). When corrected for ME1 expression there was significantly lower ratio of intact-B27:FHC ratio in PBMC as well as specifically on monocytes.

**PCR showed more than 20-fold increase in CHOP levels with ERAP2 suppression and between 1.2–1.5 fold increase in BiP and PERK. CHOP protein levels increased more than 3 fold while XBP1s increased 20-fold.**

**Conclusion:** This is the first study showing a functional relevance of the ERAP2 association with AS and Crohn’s Disease. ERAP2 deficiency in AS patients are associated with higher MHC-I FHC expression on PBMCs. Suppression of ERAP2 in an in vitro system led to significant increase in UPR markers. Changes in ERAP2 expression could influence the pathogenesis of AS and CD.

Disclosure: Z. Zhang, None; F. Ciccia, None; K. Yee, None; G. Guggino, None; H. Abdullah, None; R. Alessandro, None; S. Raimondo, None; G. Triolo, None; N. Haroon, None.

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**Autophagy and Unfolded Protein Response: A Fine Balance That Can Influence the Pathogenesis of Ankylosing Spondylitis and Inflammatory Bowel Disease.** Nigil Haroon1, Giuliana Guggino2, Zhenbo Zhang1, Kirby Yee3, Hasan Abdullah4, Ricardo Alessandro6, Stefania Raimondo7, Giovanni Triolo7 and Francesco Ciccia8.

**Conclusion:** We have shown an increase in the unfolded protein response (UPR) with decreased ERAP1 or ERAP2 function in an in vitro system. Similarly UPR has been demonstrated to correlate with onset of disease in the HLA-B27 rat model. UPR has been difficult to demonstrate in the gut of AS patients but autophagy is upregulated. ERAP2 is associated with both AS and inflammatory bowel disease (IBD). Here we explore the moderating effect of autophagy on UPR.

**Methods:** Laminin Propria Mononuclear cells (LPMC) were isolated from terminal ileal biopsies of 10 AS patients. Autophagy was suppressed with agents anisomycin and 3-MA. In parallel an in vitro system was established with C1R-B27 cells (B-lymphoblastoid cells with stable HLA-B27 expression) and the presence of autophagy in these cells was established by electron microscopy as well as by transfecting these cells with LC3-RFP followed by confocal microscopy. Autophagy was suppressed in C1R-B27 cells using 3-MA.

In both LPMC and C1R B27 cells, suppression of autophagy was demonstrated by RT-PCR of appropriate markers. Changes in MHC-I free heavy chain (FHC) expression were tested by HC10 staining and flow cytometry. Changes in UPR following inhibition were tested by XBP1 splicing assay and RT-PCR for BiP, CHOP, PERK, GADD34 and PDIA6.

**Results:** Electron and confocal microscopy demonstrated autophagy in C1R-B27 cells. Autophagy was in a dynamic state in the C1R cells as demonstrated by changes with rapamycin a stimulator of autophagy. Significant suppression of expression of UPR was noted in both LPMCs and C1R-B27 cells. Following autophagy suppression there was a significant increase in FHC expression in both C1R cells and LPMCs. In parallel we demonstrated increase in UPR markers in both LPMCs and C1R cells.

**Conclusion:** The inability to demonstrate UPR in some in vivo studies could be due to compensation by autophagy. Inhibition of autophagy led to significant increase in UPR in both LPMCs and C1R cells. Autophagy and UPR regulate each other and perturbations of this fine balance can influence the pathogenesis of AS and IBD.

Disclosure: N. Haroon, None; G. Guggino, None; Z. Zhang, None; K. Yee, None; H. Abdullah, None; R. Alessandro, None; S. Raimondo, None; G. Triolo, None; F. Ciccia, None.

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**Association of Platelet Endothelial Cell Adhesion Molecule-1 and beta Integrin Gene Polymorphisms with Uveitis Development in Ankylosing Spondylitis.** Seong-Wook Kang1, Seung-Taek Song1, Su-Jin Yoo1, Mi-Kyoung Lim2, Dong-Hyuk Sheen2, In-Seol Yoo1, Jinhyun Kim1 and Seung-Chol Shim1.

**Methods:** A total of 40 B27-positive AS patients were typed for the rs2248374 polymorphism. Peripheral Blood Mononuclear Cells (PBMC) were isolated and stained with antibodies to CD19 (B cells) and CD14 (Monocytes). Staining with HC10 antibodies to assess MHC-I FHC expression and ME-1 antibody for intact HLA-B27 was performed. Mean Fluorescence Intensities (MFI) for FHC and B27 expression was assessed by flow cytometry.

**Results:** At B27, a human B lymphoblastoid cell line stably transfected with HLA-B27, were treated with 2 separate shRNAs to suppress endogenous ERAP2. Changes in UPR were assessed by PCR for BiP, CHOP and PERK. Protein expression of CHOP was assessed by western blot and semiquantitative XBP-1 splicing assay was done by PCR.

**Conclusions:** Elevated values of UPR markers, CHOP and PERK, were associated with patients with the ERAP2 null allele. We further tested if ERAP2 suppression in an in vitro system results in changes in B27 misfolding and UPR.
Platelet-endothelial cell adhesion molecule 1 (PECAM1) is a member of the immunoglobulin superfamily which is expressed on endothelial cells. There is emerging evidence to suggest that PECAM1 may be an important regulator of antigen induced cell activation of lymphocytes. The β1 integrin (ITGB1) can associate with different membrane proteins and cause signal transduction by interactions in the extracellular and trans-membrane domain. Therefore, we examined the association of PECAM1 and ITGB1 gene polymorphisms with development of uveitis in patients with AS.

**Methods:** We conducted a case-control study where 223 AS patients who met the Modified New York criteria and 239 ethnically matched controls were genotyped for 9 single nucleotide polymorphisms (SNPs) in the PECAM-1 promoter and gene. Genomic DNA was isolated from peripheral mononuclear cells (PBMC) and the possible influence of ERAP1 allelic discrimination technique (Beakman Coulter, USA) according to standard procedure. Values were expressed as mean ± standard deviation. Differences between AS patients and healthy subjects were analyzed by Mann-Whitney U test.

**Results:** The association of PECAM1 and ITGB1 SNPs with development of uveitis in patients with AS, however, remains not fully understood.

**Conclusion:** This is the first analysis of the PECAM1 and ITGB1 gene polymorphisms in AS, demonstrating a clear association with uveitis in AS. Given the functional role of PECAM1 and ITGB1 variants in the immune system, larger studies are now warranted to elucidate the association of PECAM1 and ITGB1 in the pathogenesis of uveitis in AS.

**Table 1.** Logistic analysis of PECAM1 polymorphisms and the risk of uveitis among AS patients

<table>
<thead>
<tr>
<th>rs no.</th>
<th>Dominant Model Odds (95% CI)</th>
<th>P.Value</th>
<th>Recreasive Model Odds (95% CI)</th>
<th>P.Value</th>
<th>Co-dominant Model Odds (95% CI)</th>
<th>P.Value</th>
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<tr>
<td>rs109832</td>
<td>2.170 (1.116–4.210) 0.023 (0.627) 0.496 (0.129–1.611) 0.223 (0.262) 1.314 (0.828–2.059) 0.250 (0.094)</td>
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<tr>
<td>rs1075975</td>
<td>1.823 (0.748–3.937) 0.221 (0.261) 1.299 (0.560–2.920) 0.543 (0.371) 1.345 (0.621–2.280) 0.228 (0.297)</td>
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<tr>
<td>rs2812</td>
<td>2.191 (0.620–7.783) 0.210 (0.247) 0.434 (0.155–0.707) 0.031 (0.034) 0.752 (0.457–1.263) 0.195 (0.208)</td>
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<tr>
<td>rs496723</td>
<td>2.302 (1.675–4.543) 0.016 (0.022) 0.412 (0.117–1.446) 0.160 (0.127) 1.304 (0.402–2.079) 0.612 (0.298)</td>
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<tr>
<td>rs1187078</td>
<td>0.436 (0.226–0.839) 0.012 (0.019) 0.563 (0.249–1.272) 0.167 (0.245) 0.589 (0.377–0.918) 0.019 (0.030)</td>
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<tr>
<td>rs8065316</td>
<td>1.563 (0.998–2.453) 0.026 (0.031) 0.712 (0.325–1.578) 0.294 (0.341) 1.364 (0.492–2.920) 0.511 (0.632)</td>
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<tr>
<td>rs6809</td>
<td>2.354 (1.408–3.961) 0.012 (0.022) 0.509 (0.143–1.813) 0.297 (0.330) 1.414 (0.876–2.283) 0.155 (0.282)</td>
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<tr>
<td>rs9899806</td>
<td>2.354 (1.193–4.641) 0.013 (0.022) 0.456 (0.129–1.611) 0.223 (0.297) 1.364 (0.852–2.184) 0.195 (0.279)</td>
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**Table 2.** Logistic analysis of ITGB1 polymorphisms and the risk of uveitis among AS patients

<table>
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<tr>
<th>rs no.</th>
<th>Dominant Model Odds (95% CI)</th>
<th>P.Value</th>
<th>Recreasive Model Odds (95% CI)</th>
<th>P.Value</th>
<th>Co-dominant Model Odds (95% CI)</th>
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<tr>
<td>rs107078</td>
<td>1.563 (0.998–2.453) 0.026 (0.031) 0.563 (0.249–1.272) 0.167 (0.245) 0.589 (0.377–0.918) 0.019 (0.030)</td>
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<td>rs17468</td>
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<td>rs9913080</td>
<td>2.354 (1.408–3.961) 0.012 (0.022) 0.509 (0.143–1.813) 0.297 (0.330) 1.414 (0.876–2.283) 0.155 (0.282)</td>
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**Discussion:** S. W. Kang, None; S. T. Song, None; J. S. Yoo, None; M. K. Lim, None; D. H. Sheen, None; I. S. Yoo, None; J. Kim, None; S. C. Shim, None.

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**Background/Purpose:** Ankylosing Spondylitis (AS) is a chronic inflammatory disease of the spine strongly associated with the majority of HLA-B27 alleles, with the exception of B^2*2709 and B^2*2706. Genome wide association studies (GWAS) have revealed that besides HLA-B27, other genes are involved in AS pathogenesis, such as ERAP1, an ER aminopeptidase that is implicated in peptide trimming thus influencing B27-peptide-β2microglobulin (β2m) complex stability. Several theories have been proposed to explain the B27 association with AS. Among them, the unfolded protein response (UPR) theory suggests that the tendency of B27 trimeric complex to misfold determines free heavy chain (FHC) accumulation in the endoplasmic reticulum, leading to a stress response and activation of pro-inflammatory pathways. To our knowledge this is the first ex vivo study investigating the intracellular (ic) level of FHC and β2m in peripheral blood mononuclear cells (PBMC) and the possible influence of ERAPI allelic variance in HLA-B27 positive AS patients and healthy subjects (HSs) bearing the AS-associated (B^2*2705) and the non-AS-associated (B^2*2709) allele.

**Methods:** The ic amount of FHC and β2m in CD14+ cells from ex vivo PBMC was evaluated in 12 HLA-B^2*2705 patients with AS, 12 HLA-B^2*2705 and HSs by flow cytometry analysis. H101 (gift of Dr. Chella David) and TU99 clone (BD Biosciences, USA) monoclonal antibodies were used to detect FHC and β2m, respectively, and quantified by comparison with standard beads (antibody binding capacity ABC units, Dako Denmark). Cells were fixed and permeabilized by the Intrappep Permeabilization technique (Beakman Coulter, USA) according to standard procedure. Patients and controls were also genotyped for two ERAPI SNPs associated with AS (rs27044 CG and rs30187 CT). Optimized allelic discrimination assays were purchased from Applied Biosystem (Life Technologies, Italy). Values were expressed as mean ± standard deviation. Differences between AS patients and healthy subjects were analyzed by Mann-Whitney U test.

**Results:** FHC expression in AS patients was 37486 ± 30346 compared to B^2*2705 HSs 35673 ± 16723 and B^2*2709 HSs 26683 ± 10592 ABC units (p=ns), β2m quantity was also not significantly different in AS patients 74930 ± 90441 compared to B^2*2705 HSs 156471 ± 123855 and B^2*2709 HSs 153478 ± 42117 ABC units (p=ns). The majority of AS patients and HSs were heterozygous for both rs27044 (CG) and rs30187 (CT) SNPs; the intracellular amount of FHC and β2m in the PBMC of the analysed cohorts appeared not influenced by ERAPI allelic distribution, as shown in the figure below.

**Disclosure:** A. Cauì, None; G. Desole, None; G. Porru, None; M. Piga, None; A. Vacca, None; A. Mathieu, None.

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The Association of PPM1A with Inflammasome Activation in Ankylosing Spondylitis.

**Background/Purpose:** Ankylosing spondylitis (AS) is a chronic inflammatory disorder usually affecting axial skeleton and joints. The pathogenesis and mechanism of inflammatory response in AS, however, remains not fully under-
stood. Recently, it has been suggested that AS could be associated with autoinflammatory responses, which are driven by innate immunity through inflammasome activation. We have reported that immunity to protein phosphatase magnesium-dependent 1A (PPM1A), which regulate BMP and Wnt signaling, are associated with AS. In this study, we try to investigate the association of PPM1A with inflammatory response in AS and its role in the inflammasome activation.

Methods: The concentration of PPM1A was measured in the plasma from AS, rheumatoid arthritis (RA) and healthy control (HC) subjects by enzyme-linked immunosorbent assay (ELISA), and addressed the association with inflammatory burden including disease activity in AS patients. Next, the expression of intracellular PPM1A was evaluated in the synovia from patients with AS, RA and osteoarthritis and in peripheral blood mononuclear cells (PBMCs) from patients with AS, RA and HC. To know the role of PPM1A in the inflammasome activation, the production of IL-1β and expression of active caspase-1 were measured with or without PPM1A knockdown in the macrophage. The expression of PPM1A was evaluated after stimulation with various cytokines.

Results: The levels of PPM1A were significantly higher in the plasma of AS patients compared with RA or HC subjects. In addition, there was significant correlation between the levels of PPM1A in plasma and the values of BASDAI, ESR and CRP in AS patients (Figure 1). The expression of PPM1A in the synovia and PBMCs were elevated in AS. Further, IL-1β secretion and activation of caspase-1 was significantly decreased by knockdown of PPM1A. Finally, the expression of PPM1A was enhanced by stimulation with TGF-β in the macrophage.

Conclusion: Our present study suggested that inflammasome activation could be regulated by intracellular PPM1A, which contribute to the pathogenesis of inflammatory responses in AS.

Background/Purpose: Expression of HLA-B27 and human beta 2-microglobulin (β2m) in rats induces a spontaneous inflammatory disease resembling human spondyloarthropathy (SpA). SpA overlaps with IBD in genetic predisposition, pathogenic mechanisms and clinical manifestations. While key components of rat SpA have been studied in great detail, a complete understanding of the associated inflammatory bowel disease (IBD) has not been established. The goal of this project is to determine how HLA-B27 alters gut transcriptome in transgenic rats that develop SpA-like disease. HLA-B27 and β2m transgenic (TG) rats (33–3 transgene locus) on a Lewis (LEW), Fischer (F344), and Dark Agouti (DA) background from two different animal facilities are being studied along with strain-specific controls. TG LEW and F344 rats develop SpA beginning with colitis at about 8 weeks of age, while TG DA rats are disease free. Arthritis develops later in LEW and F344 TG animals, and is more variable.

Methods: To assess colitis, tissue samples from colon were assessed by H&E staining and scored for histological differences. Samples were also assessed for transcriptome differences using RNA-Seq. Total poly (A) enriched RNA was reverse transcribed into double stranded complementary DNA (dsDNA) and sequenced on Illumina HiSeq 2000. Raw reads were mapped to Rat m5 genome using Tophat (2.0.8). Transcript expression levels in Reads per Kilobase Million (RPKM) and ANOVA comparisons were calculated using Partek GS (6.6/6.14.0514). A minimum fold change of 50% (p value ≤ 0.05% and q value ≤0.2) with Max Mean ≥−3.3 was used as cutoff criteria for identifying differentially expressed genes between TG and WT animals on LEW, F344 and DA background at 2, 3 and 6 months. These genes were subjected to pathway exploration by Ingenuity Pathway Analysis (IPA) software.

Results: Inflammation in the colon was documented by histopathological analysis. Transcriptome analysis revealed that LEW and F344 TG animals exhibit up-regulation of the genes for IFN response (e.g. Tap1, Tap2, Irf1, Cxcl10, Oasl1 Gbp-2, Stat1). The Il17 pathway is highly up regulated at all age groups whereas Il123 up regulation became statistically significant at 6 months of age. Apoptotic signaling and iNos (Nos2) pathways as well as the oxidative stress (Gpx2, Nos1, Duox2) pathway in colon were up-regulated as compared to their age matched WT controls. Susceptibility genes (CBad9, Nod2) as well as IBD associated genes (Tnf, Ltb, Tnf, Reg3) as well as IBD associated genes (Tnf, Ltb, Reg3, Ccl2, Ccr7) were up regulated in TG F344 and LEW animals. DA background had a protective affect since TG DA did not exhibit significant gene expression changes consistent with the fact that they do not develop either SpA or IBD.

Conclusion: Transcriptome analysis of the TG inflamed colon depicts upregulation of interferon and Il23/I17 pathways suggesting a shift in the immune microenvironment in the colon. The interferon signature contrasts results recently obtained from isolated dendritic cells, and underscores the role of interferon in this disease process. These results increase our understanding of SpA associated IBD and may lead to the identification of potential biomarkers for use in diagnosis and treatment.

Disclosure: T. Gill None; M. Asquith None; S. Brooks None; J. T. Rosenbaum None; R. A. Colbert None.

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In Situ Analysis of Mechanisms of New Bone Formation in Zygapophysial Joints from Patients with Ankylosing Spondylitis. Janine Blei1, Joachim Steper1, Rene Maier2, Uwe Schlichting3, Axel Hempfing3, Heiner Appel4 and Uta Syrbe7. 1Charite ´ Medical University, Campus Benjamin Franklin, Berlin, Germany, 2Charite ´ Universitätsmedizin Berlin, Berlin, Germany, 3Deutsches Rheumafor- schungszentrum, Berlin, Germany, 4Charite, Berlin, Germany, 5Werner-Wicker-Klinik, Bad Wildungen, Germany, 6Rheumatology and Nephrology Practice, Hamm, Germany, 7Charité, Berlin, Germany.

Background/Purpose: Osteoproliferation leading to joint ankylosis is a characteristic feature of ankylosing spondylitis (AS). In general, there are two ways of bone formation: a) endochondral bone formation via generation of collagen X scaffolds requiring hypertrophic chondrocytes and b) membraneous or direct bone formation mediated by osteoblasts without primary cartilage synthesis.

Using zygopophysial joints of AS patients (and zygopophysial joints from autopsy controls and from OA patients for comparison), we determined whether chondrocytes acquire signs of chondrocyte hypertrophy upon joint remodeling or whether direct ossification by osteoblasts could be involved in the process of new bone formation in AS.

Methods: 17 zygapophysial, i.e. facet joints from 14 patients with AS fulfilling the modified New York Criteria, 22 zygopophysial joints from 12
patients with OA and 11 zygaphyseal joints of 10 non-AS control patients were included in the study.

The percentage of hypertrophic chondrocytes was determined by immunohistochemistry according to Runx2, MMP13 and collagen X expression in the cartilage of zygaphyseal joints. Activation of the wingless (wnt) pathway controlling chondrocyte hypertrophy was analyzed according to beta-catenin expression. Osteoblasts were identified according to CD56 staining.

**Results:** The percentage of hypertrophic chondrocytes expressing Runx2, COL10 and MMP13 was significantly increased in OA (mean ± SEM: Runx2 = 55.03 ± 11.83%, COL10 = 8.79 ± 8.88%, MMP13 = 14.55 ± 8.77%) but not in AS joints (Runx2 = 38.49 ± 22.84%, COL10 = 2.71 ± 3.05%, MMP13 = 1.80 ± 2.53%) compared to CO joints (Runx2 = 33.06 ± 17.27%, COL10 = 4.87 ± 4.66%, MMP13 = 1.43 ± 0.87%). Beta-catenin expression was low in AS (0% ± 1.0%) and CO (zygaphyseal joints (1.83 ± 2.85% of chondrocytes) while in OA joints the number of beta-catenin-positive chondrocytes was significantly increased (18.84 ± 18.31%).

Osteoblasts were observed at their typical location, i.e., within the bone marrow, lining the trabecular bone. However, CD56-positive cells were also found at the edges of fibrous tissue which is often observed at subchondral bone marrow sites in AS and OA joints and which invades the subchondral bone. Runx-2 and weak osteocalcin expression of these lining cells further supports their osteoblastic nature. Ossification of cartilage was predominantly in bone marrow, lining the trabecular bone. However, CD56-positive cells were also found at the edges of fibrous tissue which is often observed at subchondral bone marrow sites in AS and OA joints and which invades the subchondral bone.

**Conclusion:** The lack of chondrocyte hypertrophy as an indicator of endochondral bone formation but co-localization of osteoblasts with fibrous tissue and bony transformation at contact zones to cartilage in AS joints suggest that direct ossification is involved in joints ankylosis in AS.

**Disclosure:** J. Bleil: None; J. Sieper: None; R. Maier: None; U. Schlichting: None; A. Hempling: None; H. Appel: None; U. Szyrbe: None.

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**Shared HLA Class I and II Alleles in Susceptibility to Ankylosing Spondylitis Among Three Ethnic Groups.** Mark Hwang 1, Xiaodong Zhou 1, Michael H. Weissman 1, Michael M. Wolfe 1, Jucum Wang 2, Jianne S. Gensler 3, Heijian Zou 4, Dongyi He5, Matthew A. Brown 6, Paul Scheer 6 and John D. Reveille 1. 1University of Texas Health Science Center at Houston, Houston, Texas, 2Cedars-Sinai Medical Center, Los Angeles, CA, 3NIAMS/NIH, Bethesda, MD, 4Huashan Hospital, Shanghai, China, 5University of California, San Francisco, San Francisco, CA, 6Shanghai Guanghua Hospital, Shanghai, China, 7University of Queensland Diamantina Institute, Brisbane, Australia, 8MD Anderson Cancer Center, Houston, TX.

**Background/Purpose:** The purpose of this study is to examine associations of HLA class I and II alleles with AS in different patients’ populations of whites of European ancestry (EA) and African-American (AA) ethnicities, and with a Han Chinese (HC) Asian population.

**Methods:** HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 alleles were examined by DNA typing in unrelated patients from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort, the North American Spondylitis Consortium and Australo-Anglo-American Spondyloarthritis Consortium. For the HLA-B locus analyses, an additional 578 British and Australian AS patients from the Australo-Anglo-American Spondylitis Consortium and 360 HC AS patients were also analyzed. Included therefore in the study were 1829 EA, 62 AA patients and 360 HC who met modified New York criteria for AS. Controls were North American white and African American as well as Han Chinese subjects without history of rheumatic disease. To remove an associated effect of HLA-B*27 due to linkage disequilibrium, analyses were also conducted on HLA-B*27 non-carriers only. Statistically analysis was done by construction of 2x2 tables and testing the proportion of alleles in cases vs. controls with Fisher’s exact test. Other analyses included permutation-based omnibus testing and “relative predispositional effects” (RPE) analysis.

**Results:** HLA-B27 occurred in 88.7% of EA, 61% of AA, and 93% of HC patients compared to 7.5%, 2% and 7.6%, respectively, of ethnicity matched controls. HLA-B*07 was negatively associated with AS in all three ethnic groups (6.2% versus 14.9% in EA, p = 3.655 × 10^-26 3.2% versus 14% in AA(p = 0.002), and 1% versus 12% in HC (p = 0.0018). Among EA AS patients, HLA-B27 noncarriers showed positive associations with HLA-B*38 (OR = 2.94, p = 0.0008) and DRB1*04:04 (OR = 3.02 p = 0.0065) and negative associations with HLA-B*07 and HLA-DRB1*03, HLA-DRB1*15:01 and their respective linked alleles DQB1*02:01 and DQB1*06. Additional associations with HLA-B*14 (OR = 1.74, p < 0.0001) and HLA-B*40 (OR = 1.32, p = 0.02) were observed via RPE analysis, which excludes the HLA-B*27 alleles. No associations were seen with HLA-DRB1 alleles or with HLA-A*02 (the latter seen in a much larger study where HLA AS alleles were imputed but not directly genotyped). Among AA patients, positive associations were seen in HLA-B*27 (OR = 75.11, p = 0.0001), HLA-B*40 (OR = 8.33, p = 0.01) and HLA-DRB1*13:02 (OR = 2.43, p = 0.02). No statistically significant associations were seen in HLA-DRB1 alleles. In the HC, no association was seen with B*40:01 (B60) although an association was seen by a covariate via logistic regression analysis (p = 0.02, OR = 2.3) and by RPE analysis (p = 0.01, OR = 1.56). Negative associations were also demonstrated with HLA-B*13, B*15, B*46 and B*51.

**Conclusion:** This is the largest directly genotyped HLA study to date. These data, analyzing the largest number of AS patients in three patient populations examined to date, suggest other HLA alleles to be operative in AS predisposition in addition to HLA-B*27. The shared association of certain alleles in all three groups suggests a direct role in AS pathogenesis.

**Disclosure:** M. Hwang: None; X. Zhou: None; M. H. Weissman: None; M. M. Ward: None; J. Wang: None; L. S. Gensler: UCSF, 5, AbbVie, 5, Celgene Corporation; 9, H. Zou: None; D. He: None; M. A. Brown: None; P. Scheet: None; J. D. Reveille: None.

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**A Gender Bias in Gut Microbiota of SKG Mice Colonized with a Limited Bacterial Consortium Associated with Severity of Spondyloarthritides and Bacterial Control of SpA by TGF-β.** Linda Rehman-Curtin, Xiuling Amer, Kelly Adams, Michael J. Kraft, Alicia Kang, Helen Benham, Paraic O Cuiv, Mark Morrison and Ranjeny Thomas. University of Queensland Diamantina Institute, Brisbane, Australia.

**Background/Purpose:** Beta-glucan (curdlan)-treated BALB/c•ZAP-70^−/− (SKG) mutant mice develop IL-23-dependent spondyloarthritides, and curdlan promotes ileitis in SKG mice housed under specific pathogen-free (SPF) but not germ-free (GF) conditions. When GF SKG mice were recolonized with a defined bacterial consortium, known as altered Shaeudler microbiota (ASM), SKG mice developed spondyloarthritides and ileitis. Relative to GF conditions, ASM-SKG mice developed spondyloarthritides and ileitis with reduced severity, and incidence of ileitis was reduced. Relative to female mice, disease severity in male SKG mice was reduced. Our aim was to study SKG mice recolonized with ASM to understand the mechanisms by which certain gut micro-organisms drive SpA-like disease, and their relationship to gender and the curdlan inflammatory trigger.

**Methods:** GF SKG mice were recolonized at the Walter and Eliza Hall Institute of Medical Research with ASM (Eubacterium plexicaudatum, Lactobacillus murinus, Mucispirillum schaeieleri, 2 Clostridium sp., Lactobacillus sp., Parabacteroides sp., Firmicutes bacterium) then injected with curdlan or saline. Fecal samples were collected following recolonization and then serially cultured. The bacterial community profile was analyzed by next generation sequencing methods. Arthritis, spondylitis and ileitis were assessed histologically in ASM-SKG mice or SPF SKG-DTR mice depleting or not of regulatory T cells (Treg).

**Results:** After colonization and before injection, four bacterial strains were detectable in male ASM-SKG mice (Clostridium sp, Lactobacillus murinus, Mucispirillum schaeieleri, 2 Clostridium sp.), with Parabacteroides the dominant species. In female ASM-SKG mice before curdlan, this same bacterial profile was observed except that the Clostridium species was not detected. After injection, the Clostridium species increased in female mice treated with curdlan but not saline-treated mice, and was maintained at similar levels in male mice. Depletion of Treg from curdlan-treated SKG mice under SPF conditions resulted in rapid and severe disease development.

**Conclusion:** Similar to non-obese diabetic mice, microbiota of ASM-SKG mice show a gender bias. Furthermore, these preliminary data suggest that the absence of a Clostridium species in naive female mice and outgrowth of the same species associated with curdlan-induced inflammation correlate with greater disease severity in females. Clostridium species derived from mouse and human microbiota have been shown to induce Treg in mouse colon. Together our data suggest a link between gender, microbial environment, and disease severity, and that the presence of a species that is feminized in mouse gut microbiota is associated with phenotype.
Despite the strong association with MHC class I, CD8 T cells are not required for the direct recognition of HLA-B27 homodimers by NK cells suggest pathogenic mechanisms which may be independent of classical acquired immune responses. Therefore, we and others propose that SpA may be primarily driven by an innate immune response. Using the HLA-B27/huβ2m transgenic rat model, we investigated this hypothesis by studying the effect of innate immune stimulation on ex vivo cytokine expression and in vivo development of arthritis and spondylitis.

Methods: Splenocytes and bone marrow cells isolated from HLA-B27/huβ2m tg rats and controls were stimulated for 6 hours with 50 ng/ml LPS, 5 μg/ml zymosan or 5 μg/ml heat-inactivated Mycobacterium tuberculosis, TNF, IFN-γ, IL-6, IL-10 and IL-23p19 expression was measured by qPCR. In vivo, six week old male and female HLA-B27/huβ2m tg were immunized with a low dose of M. tuberculosis in incomplete Freund’s adjuvant. Rats were followed up for 60 days and scored clinically for arthritis and spondylitis. At day 60 hind limbs and tails were analysed for inflammation, destruction and new bone formation by histology.

Results: In vitro stimulation of splenocytes with zymosan and with M. tuberculosis, but not with LPS, strongly induced gene expression of pro-inflammatory cytokines such as TNF, IFN-γ, IL-1β and IL-6 in all 3 groups of rats. IL-1α and IL-1β, but not TNF or IL-6, were increased in the HLA-B27/huβ2m transgenic cells as compared to both HLA-B7/huβ2m tg and wild-type controls upon ex vivo stimulation. IL-10 and IL-23p19 expression could not be detected in any of the groups after stimulation. In vivo, non-immunized HLA-B27/huβ2m tg males spontaneously develop arthritis and spondylitis after 4–6 months of age with an incidence of 70% and 40%, respectively, whereas female rats do not develop disease. Immunization of male HLA-B27/huβ2m tg rats with 30 μg of M. tuberculosis was sufficient to induce arthritis and spondylitis within 2–3 weeks with an incidence of 80–100%. Moreover, HLA-B27/huβ2m tg females developed similar disease when immunized with 60 μg of M. tuberculosis. Control rats were less sensitive to low doses of M. tuberculosis. Histologically in both male and female HLA-B27/huβ2m tg rats inflammation, destruction and new bone formation was detected in both peripheral and axial joints.

Conclusions: The transgenic expression of HLA-B27/Huβ2m increases the sensitivity to innate immune stimulation as evidenced by increased IL-1α and IL-1β expression ex vivo and development of arthritis and spondylitis in vivo. These data suggest that the B27/Huβ2m expression lowers the threshold for innate immune activation of the IL-1 pathway, and this alone may be sufficient to trigger experimental SpA.

References:

Disclosure: T. M. Tran; None; S. Hong; None; J. H. Edwan; None; R. A. Colbert; None.

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a multifunctional enzyme involved in the processing of peptide cargo for major histocompatibility complex (MHC) class I complexes, and can have significant effects on peptide repertoire, and cell surface expression and stability of MHC class I molecules. ERAP1 variants are associated with several MHC class I-associated inflammatory diseases, such as ankylosing spondylitis (AS), Behcet’s disease, and psoriasis/psoriatic arthritis, with evidence for epistasis with MHC class I susceptibility alleles. Since peptide supply is a critical determinant of MHC class I folding and assembly, we asked whether ERAP1 knockdown would affect HLA-B27 misfolding and endoplasmic reticulum stress in HLA-B27 transgenic Rat Macrophages. Sohee Hong and Robert A. Colbert. NIAMS/NIH, Bethesda, MD.

Methods: Bone marrow derived macrophages from HLA-B27 Tg, HLA-B7 Tg and wild type (WT) rats were transduced with lentiviral ERAP1 shRNA or scrambled shRNA as a control. Protein expression including folded, unfolded, and misfolded forms of HLA-B27 was evaluated using immunoblotting of whole cell lysates and immunoprecipitates. To evaluate the effects of cytokines, macrophages were treated without or with IFNg (100 ng/ml) or IFN-γ and TNFa (30 ng/ml) for 24–48 hr. ER stress was assessed using real time PCR and XBP-1 splicing.

Results: ERAP1 protein expression was reduced 55–77% by ERAP1 shRNA as measured by immunoblotting blotting in several experiments, before and after treatment with cytokines. ERAP1 knockdown led to...
increased accumulation of aberrant disulfide-linked HLA-B27 complexes in whole cell lysates and HC10 immunoprecipitates. Interestingly, HLA-B7 heavy chains, which do not misfold under normal conditions, could be detected forming dimers with prolonged exposure in ERAP1 KD cells, although quantitatively much less than for HLA-B27. Expression of Bip and CHOP mRNA and XBP1 splicing were elevated in ERAP1 KD cells compared to sc shRNA. With cytokine stimulation, the there was increased UPR target gene expression and XBP1 splicing consistent with accumulation of aberrant HLA-B27 complexes.

Conclusion: In summary, these results suggest that ERAP1 loss-of-function impacts HLA-B27 misfolding and may affect the pathogenesis of AS via the aberrant biology of HLA-B27 and ER stress.

Disclosure: S. Hong, None; R. A. Colbert, None.

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Gut Microbiota Variations Correlate with Disease Activity in Spondyloarthritis (SpA) and Rheumatoid Arthritis (RA). Julien Tap, Jad Abou-Ghantous, Ariane Leboime, Roula Said Nahal, Philippe Langella, Henri-Jean Garchon, Gilles Chiocchia, Jean-Pierre Furet and Maxime Brelan. 1UMR INRA-AgroParisTech 1319, Equipe ProbiHote, MICALIS Institute, National Institute for Agronomical research (INRA), Jouy-en-Josas, France, 2Service de Rhumatologie, Hopital Ambroise Pare, Boulogne-Billancourt, France, 3INSERM U987, Faculté des Sciences de la Santé Simone Veil, Montigny-le-Bretonneux, France, 4INSERM U987, UFR des Sciences de la Santé, Montigny-le-Bretonneux, France.

Background/Purpose: Inflammatory bowel diseases (IBD) are associated with changes in microbiota which may be responsible for sustained gut inflammation and/or a consequence of it. Whether variations in microbiota also play a role during the course of inflammatory rheumatic disorders such as SpA or RA, remains to be addressed.

Methods: Targeted metagenomic profiles were established by deeply sequencing the 16S rRNA-encoding bacterial genes amplified by PCR in stools from 97 SpA and 33 RA patients, and 72 healthy controls (including 46 siblings of SpA patients). After pyrosequencing and a denoising step to remove artefactual reads, bacterial operational taxonomic units (OTUs) were attributed to the remaining sequences (>1.5M reads, 8,000 sequences per sample in average). Supervised analysis (between class co-inertia analysis and L1-regularized logistic machine learning procedure) was carried out to identify factors associated with OTUs variations. Age, gender, disease status and activity (SpA: BASDAI; RA: DAS28) and concomitant treatments (NSAIDs, corticosteroids, DMARDs, biotherapies) were the considered variables.

Results: Neither SpA nor RA status correlated with discrete OTUs variations. Using 600 OTUs represented in at least 1% of the reads mass per sample, disease activity was the main clinical factor explaining variations in OTUs composition, similarly in SpA and RA. Concomitant treatments, and particularly corticosteroids, had also significant impact but of lesser magnitude.

Conclusion: Variations in OTUs were found both in SpA and RA, as compared to healthy controls that primarily correlated with disease activity. Whether such variations are cause or consequence of chronic joint inflammation remains to be determined.

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Epigenetic Studies in Maternally Versus Paternally Transmitted Psoriatic Disease. Darren D. O’Rielly, Remy Pollock, Yuhua Zhang, Nayef Al Ghanim, Sean Hamilton, Dafna D. Gladman, Vinod Chandran, Rose Ardem, Guangju Zhai and Proton Rahman. 1Memorial University of Newfoundland, St. John’s, NF, 2University of Toronto, Toronto Western Hospital, Toronto, ON, 3Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John’s, NF.

Background/Purpose: Epidemiological studies have noted excess paternal transmission in psoriasis and psoriatic arthritis. To date, there has been no molecular explanation to account for this observation. Differential methylation patterns have long been implicated as a potential mechanism to account for excess paternal transmission. In this pilot study, we investigated the differential methylation pattern among paternally and maternally transmitted PsA.

Methods: Twenty-four (24) patients with maternally transmitted PsA were compared with 24 paternally transmitted PsA cases. For maternally transmitted PsA, the proband’s mother had either psoriasis or PsA, and for
paternally transmitted PsA, the proband’s father had either psoriasis or PsA. Genome-wide DNA methylation profiling was performed on all these 48 samples by using Illumina HumanMethylation450K Beadchip, which measures up to 480,000 different CpG sites per sample and covers 96% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

**Results:** Paternally transmitted PsA cases were predominantly females (19/24) with mean age of onset of PsA at 30.6 years. For paternally transmitted PsA, there were slightly more females (13/24) and age of onset of PsA was 22.2 years. Methylation data were normalized using BIMQ method and no batch effects were detected by PCA analysis. Methylation analysis was performed on 382,024 of the 485,512 CpG sites after filtering and revealed 90 significant CpG sites (p < 0.05). The three most significant CpG sites were hypermethylated regions located on chromosome 8 that did not reside on or adjacent to a gene, with p values ranging from 9 x 10^{-15} to 5 x 10^{-15}. Many genes of interest based on current understanding of psoriatic disease were identified, including hypermethylation of CpG sites on MICA (diff 15.2%; p = 0.014), IRF1 (diff 10.3%; p = 0.016), PSORS1C3 (diff 11.1%; p = 0.005), and TNFSF14 (diff 15.2%; p = 0.004). Excess hypomethylation at CpG sites was noted on PSORS1C1 (18.9% diff. p = 0.027).

**Conclusion:** These preliminary results demonstrate that the global DNA methylation pattern in paternally transmitted PsA differs from maternally transmitted PsA. High priority candidate regions and genes identified in this study need further validation.

**Disclosure:** V. Chandran, None; D. D. O'Reilly, None; R. Pollock, None; Y. Zhang, None; N. Al Ghaini, None; S. Hamilton, None; D. D. Gladman, Abbvie, Agenon, Celgine, Janssen, Pfizer, UCB; Z. Abbvie, Agenon, Celgine, Eli Lilly, Janssen, Novartis, Pfizer, UCB; V. Chandran, None; R. Arderin, None; G. Zhai, None; P. Rahman, None.

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**625 Fine-Mapping Major Histocompatibility Complex Associations Identified Contribution of Multiple Class I and II HLA Genes on Risk of Psoriasis and Its Clinical Subtypes.** Yukinori Okada1, Buhm Han2, Lam C. Tsoi3, Philip E. Stuart4, Eva Ellinghaus5, Trilokraj Tejasvi6, Vinod Chandran7, 8Fawnda Pellegrini7, Remi Pollock8, Anne M. O’Connor9, Gerald G. Krueger2, Michael Weichenhals2, John J. Voorhees2, Proton Rahman10, Peter K. Gregersen11, Andre Franke1, Rajan P. Nair4, Gonçalo R. Abecasis3, Dafna D. Gladman6, James T. Elder4, Paul IW. de Bakker12 and Soumya Raychaudhuri11. 1Tokyo Medical and Dental University, Tokyo, Japan, 2Broad Institute of MIT and Harvard, Cambridge, MA, 3University of Michigan, Ann Arbor, MI, 4University of Michigan Medical School, Ann Arbor, MI, 5Christians-Albrechts-University of Kiel, Kiel, Germany, 6University of Toronto, Toronto Western Hospital, Toronto, ON, 7University of Toronto, Toronto, ON, 8Imperial College, London, United Kingdom, 9University of Utah, Salt Lake City, UT, 10Memorial University of Newfoundland, St. John’s, NF, 11The Feinstein Institute for Medical Research, Manhasset, NY, 12University Medical Center, Utrecht, Netherlands, 13Bigham and Women’s Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** Psoriasis vulgaris (PsV) risk is strongly associated with genetic variation within the major histocompatibility complex (MHC) region, although its fine genetic architecture has not been elucidated.

**Methods:** To fully characterize and fine-map the MHC associations of PsV, we conducted a large-scale fine-mapping study of PsV risk in the MHC region in 9,247 PsV cases and 13,589 controls of European descent. We also evaluated risk of two major clinical subtypes of PsV, psoriatic arthritis (PsA; n = 3,038) and purely cutaneous psoriasis (PsC, defined as 10 years of psoriasis without developing PsA; n = 3,908). We imputed class I and II HLA gene variants by applying SNP2HLA software to the SNP genotype data. In addition, we newly constructed an imputation reference panel of sequence variants for MICA, an HLA-like gene within the MHC region that has been implicated for PsA risk. We applied MICA variant imputation to the SNP genotype data and evaluated their risk as well.

**Results:** As previously described, we observed that HLA-C*06:02 demonstrated the most significant impact on overall PsV risk (odds ratio [OR] = 3.38, 95% confidence interval [95%CI]: 3.18–3.60, P = 1.7x10^{-15}). Stepwise conditional analysis revealed multiple independent risk variants of both class I and class II HLA genes for PsV susceptibility independent of HLA-C*06:02 (HLA-C*12:03, HLA-B amino acid positions 67 and 9; HLA-A amino acid position 95, and HLA-DOQA1 amino acid position 53; P < 5.0x10^{-8}), but no apparent independent risk conferred by MICA. Strikingly, we found that risk heterogeneity between PsA and PsC may be driven by one amino acid position at HLA-B (Glu at HLA-B amino acid position 45; OR = 1.46, 95%CI: 1.31–1.62, P = 2.9x10^{-15}), which demonstrated much more significant association signals compared to classical HLA-B alleles including HLA-B*27 and HLA-B*57:01 (P > 1.0x10^{-15}).

**Conclusion:** These results indicate that multiple class I and II HLA genes (HLA-C, HLA-B, HLA-A, and HLA-DOQA1) contribute to development of PsV, and suggest that different genetic factors, most evident at HLA-B, underlie for the differential risk of specific PsV sub-phenotypes. Our study illustrates the value of high-resolution HLA and MICA imputation for fine-mapping causal variants in the MHC.

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**Background/Purpose:** Human Leukocyte Antigen (HLA) class I alleles and obesity are risk factors for psoriatic arthritis (PsA). We aimed to assess whether there is an interaction between HLA risk alleles for PsA and obesity in susceptibility to PsA.

**Methods:** The study comprised two parts: 1) a case-only design that included patients with early PsA (<2 years) from 2 PsA cohorts, 2) a case-control design in which patients with early PsA were compared to those with psoriasis alone (PsC). Body Mass Index (BMI) at the first visit was stratified to normal (<25), overweight (25<BMI<30) and obese (BMI≥30). HLA genotyping was performed by sequence-specific oligonucleotide probes. The following alleles that were independently associated with PsA were analyzed: HLA-B*08, B*18, B*27, B*38, B*39 and C*06. Due to low frequency and similar structure, the effect of HLA-B*08, B*18, B*39 and B*38 was assessed in conjunction (termed “combined HLA-B alleles”). The interaction between obesity and HLA alleles was assessed by comparing the distribution of the various alleles across the three BMI categories in patients with PsA using trend test (case-only design). The interaction between HLA alleles and obesity was further investigated (case-control design) by assessing a departure from multiplicative combined effect of risk using logistic regression analysis after adjusting for age and sex and by assessing a departure from additivity by calculating the attributable proportion (AP).

**Results:** 637 Caucasians patients were analyzed (262 PsA, 375 PsC). Obesity was more frequent in patients with PsA compared to those with PsC (p=0.005). In addition, HLA-B*27 (p=0.0001) and the combined HLA-B alleles (p=0.03) were associated with PsA vs. PsC. A differential distribution of HLA-B alleles was observed across the 3 BMI categories in patients with PsA (case-only design) suggesting an interaction. The frequency of B*27 was higher in patients with normal weight compared to those with higher BMI (p=0.005). In contrast, PsA patients who carried one of the combined HLA-B alleles tended to be heavier (p=0.03). Similar findings were observed in the case-control analysis. A multiplicative interaction was found for the combined effect of B*27 and obesity in logistic regression analysis (OR 0.1 p=0.01) as well as for the joint effect of combined HLA-B alleles and obesity (OR 2.7 p=0.03). A significant additive interaction of combined HLA-B alleles and obesity was found with the proportion of risk due to additive interaction (AP) of 0.62 (95% CI 0.38, 0.93, p=0.0001). No interaction was found between obesity and HLA-C*06 allele.

**Conclusion:** An interaction was found between HLA-B alleles and obesity in PsA risk thus the effect of obesity on PsA risk may depend on the presence of HLA-B alleles.
The Predictive Value of Cardiovascular and Metabolic Biomarkers for Progression of Atherosclerosis in Psoriatic Disease. Lihi Eder, Fatima Abji, Cheryl Rosen, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The pathophysiologic mechanisms underlying the accelerated atherosclerosis in patients with psoriatic disease (PsD) are unknown. We aimed to investigate candidate pathways involved in this process by identifying biomarkers that predicted progression of atherosclerotic plaques in patients with PsD.

Methods: A prospective cohort study was conducted in patients with psoriatic arthritis (PsA) and psoriasis alone (PsC) from 2010 to 2014. Patients with PsA met the CASPAP criteria. Patients with PsC were examined by a rheumatologist to exclude the presence of arthritis. Information about demographics, co-morbidities and disease manifestations was collected. The following serum cardiovascular and metabolic biomarkers were assessed at baseline by enzyme-linked immunosorbenct assay (ELISA): insulin, adiponectin, leptin, vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), plasminogen activator inhibitor 1 (PAI-1), myeloperoxidase (MPO) and lipoprotein-associated phospholipase A2 (Lp-PLA2). The homeostatic model assessment (HOMA) was calculated using insulin and glucose levels to estimate insulin resistance. Ultrasound assessment of the carotid arteries was performed and Total Plaque Area (TPA) was measured at baseline and after 3 years. This measure represented the extent of atherosclerosis and was considered the outcome of interest. TPA at baseline was classified to 4 categories (No plaques, mild, moderate and severe atherosclerosis). A significant progression in atherosclerosis was defined as an increase in TPA of > 0.1 cm² at 3 years (top quartile of TPA progression from baseline). The association between the log-transformed levels of the various biomarkers and TPA at baseline and atherosclerosis progression at 3 years was assessed using logistic regression models adjusted for age, sex and cardiovascular risk factors.

Results: A total of 235 patients with PsD (121 PsA, 114 PsC) were screened at baseline, 129 of them were re-scanned at 3 years. The mean age of the study population was 52.5 ± 11.9 years and 54% were males. Patients with more severe atherosclerosis at baseline had higher levels of VCAM-1 (p = 0.0002), ICAM-1 (p = 0.03), leptin (p = 0.03) and HOMA (p = 0.0002); however in the age- and sex-adjusted model only HOMA remained significantly associated with more severe atherosclerosis. A significant progression in atherosclerosis was defined as an increase in TPA of > 0.1 cm² at 3 years (top quartile of TPA progression from baseline). The association between the log-transformed levels of the various biomarkers and TPA at baseline and atherosclerosis progression at 3 years was assessed using logistic regression models adjusted for age, sex and cardiovascular risk factors. Patients with a higher level of leptin at baseline had a higher risk of progression of atherosclerosis (OR 1.6, 95% CI 1.2, 2.3, p = 0.006). 31 of 129 patients had a significant progression of atherosclerosis at 3 years. Higher levels of Lp-PLA2 (p = 0.03), PAI-1 (p = 0.05) and HOMA (p = 0.01) and lower levels of adiponectin (p = 0.04) predicted progression of atherosclerosis. In the multivariate regression model adjusted for age, sex and cardiovascular risk factors, Lp-PLA2 (OR 5.5, 95% CI 1.4, 22.5, p = 0.02), adiponectin (OR 0.3, 95% CI 0.8, 2.008) and HOMA (OR 2.2, 95% CI 1.1, 4.4, p = 0.03) predicted progression of atherosclerosis in patients with PsD. No interaction was found between disease status (PsA vs. PsC) and any of the biomarkers.

Conclusion: Biomarkers involved in lipid and glucose metabolism and other metabolic pathways play a role in progression of atherosclerosis in patients with PsD.

Disclosure: L. Eder, None; F. Abji, None; C. Rosen, None; V. Chandran, None; D. D. Gladman, None.

Biomarkers of Chondrocyte Activity Are Increased in Psoriasis Arthritis and Spondyloarthritis. Natasa Stehr Gudman1, Heidi Lausten Munk2, Anne Friesgaard Christensen3, Leif Ejstrup4, Grith Lykke Sørgensen5, Anne Gitte Loft5, Morten A. Karsdal1, Anne C. Bay-Jensen6, Y. He7, Anne Sofie Siebuh6 and Peter Junker6. 1. Nordic Bioscience, Biomarkers and Research, Herlev, Denmark. 2. Department of Rheumatology, Odense University Hospital, Odense, Denmark. 3. Department of Rheumatology, Vejle Hospital, Vejle, Denmark. 4. Department of Rheumatology, Esbjerg Hospital, Esbjerg, Denmark. 5. Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark. 6. Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark. 7. Nordic Bioscience, Herlev, Denmark.

Background/Purpose: Psoriasis arthritis (PsA) and spondyloarthritis (SpA) are both inflammatory joint diseases in which the pathogenesis is not fully understood. However, both pathologies are associated with extracellular matrix (ECM) remodeling favoring cartilage formation and calcification (type II and X collagen formation) in the affected joints. Treatment of the diseases has improved within recent years, but the therapeutic response at the level of the individual cannot be adequately predicted. Hence, there is an increasing interest in diagnostic and prognostic biomarkers to further characterize the patients to achieve personalized medicine. The biomarker ProC2 measures the level of propeptide type II collagen and C-Coll10 measures type X collagen. Collagen type X is exclusively expressed by hypertrophic chondrocytes and is a measure of hypertrophic cartilage. The aim of this study was to evaluate the level of two novel biomarkers of cartilage formation (ProC2) and hypertrophy (C-Coll10) in SpA, PsA and healthy controls, and to investigate whether these markers would have diagnostic potential.

Methods: 99 PsA patients, 94 SpA patients and 120 age-matched healthy controls were included in the study. Demographic and clinical disease measures were recorded. ProC2 and C-Coll10 were quantified in serum by newly developed and specific competitive ELISAs based on monoclonal antibodies. One way analysis of variance and Tukeys multiple comparison test were performed on log-transformed data. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the discriminative power of the biomarkers.

Results: The serum levels of P2BNP had a mean level of 0.59ng/ml for healthy controls, but were significantly increased in patients with either SpA (mean 1.25ng/ml) or PsA (mean 1.35) compared to controls (p < 0.001). When segregating between patients and healthy controls by mean of ROC curves the AUC was 0.78 for SpA (CI 0.95% 0.71 to 0.84) and 0.79 (CI 95% 0.73–0.85) for PsA as listed at the table below. Furthermore SpA had a slightly, but significantly increased level of type X collagen (mean 0.60ng/ml) compared the controls (mean 0.50ng/ml) (p = 0.05). None of the two markers correlated with age, sex, BMI and the markers did not correlate with each other.

Conclusion: These findings indicate that both SpA and PsA arthritis have enhanced cartilage formation reflected by increased levels of P2BNP levels in serum compared to healthy controls. In addition, an increased level of the hypertrophic chondrocyte collagen X marker was found in SpA only, indicating a difference in cartilage turnover between the two diseases. This difference could aid in the differentiation between SpA and PsA.

The AUC, sensitivity and specificity of each ROC-analysis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC (CI95%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2BNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy vs PsA</td>
<td>0.79 (0.73–0.85)</td>
<td>65.1</td>
<td>81.7</td>
</tr>
<tr>
<td>Healthy vs SpA</td>
<td>0.77 (0.71–0.84)</td>
<td>60.4</td>
<td>83.3</td>
</tr>
<tr>
<td>SpA vs PsA</td>
<td>0.55 (0.46–0.62)</td>
<td>40.4</td>
<td>60.4</td>
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<tr>
<td>CxX</td>
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<tr>
<td>Healthy vs PsA</td>
<td>0.60 (0.53–0.68)</td>
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<tr>
<td>Healthy vs SpA</td>
<td>0.58 (0.50–0.66)</td>
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<tr>
<td>SpA vs PsA</td>
<td>0.52 (0.45–0.60)</td>
<td>40.4</td>
<td>60.6</td>
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</table>

Disclosure: N. S. Gudman, Nordic Bioscience Diagnostic, 3; H. L. Munk, None; A. F. Christensen, None; L. Ejstrup, None; G. L. Sørgensen, None; A. G. Loft, None; M. A. Karsdal, Nordic Bioscience Holding, 1; A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 1; Y. He, Nordic Bioscience Diagnostic, 3; A. S. Siebuh, Nordic Bioscience A/S, 3; P. Junker, None.

Biomarkers of Bone Remodeling Are Elevated in Psoriatic Arthritis. Fatima Abji, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that develops in about a third of patients with cutaneous psoriasis (PsC). The identification of biomarkers to aid in the early diagnosis of PsA in patients with PsC may prevent disability and improve the quality of life for those affected. Inflammation in peripheral and/or axial joints in PsA is associated with abnormal bone metabolism, including erosions and bone formation. The goal of the current study was to determine if markers of bone remodeling are associated with PsA patients with active disease compared to patients with PsC only.

Methods: PsA patients with active disease (≥ 3 tender and swollen joints) and PsC patients were identified from the cohort of patients followed prospectively. Patients were matched for age, sex, PASI score and psoriasis duration and were not receiving treatment with biologic agents. PsA patients
satisfied CASPAR criteria and PsC patients were examined by a rheumatologist to exclude arthritis. Patients were not receiving treatment with methotrexate for a minimum of two years before the sampling date. Serum biomarkers measured included DKK1, FGF23, IL-6, IL-1β, leptin, osteocalcin, osteoprotegerin, osteopontin, sclerostin and TNFα. All proteins were measured simultaneously using the Millipore Milliplex MAP human bone magnetic bead panel, according to the manufacturer’s instructions. Data was acquired using the LumineX 200 system and analyzed with the Biorad Bio-Plex Manager software. Significant differences were determined by performing paired t-tests between the PsA and PsC cohorts (p<0.05).

Results: The levels of bone biomarkers were measured in 60 PsA patients (mean age 51 years, 50% males, psoriasis duration 18 years, PASI 4.24, 11.4 mean age 52 years, 50% males, psoriasis duration 20 years, PASI 3.7). DKK1, leptin, osteoprotegerin, osteopontin, and sclerostin were significantly elevated in PsA patients compared to PsC patients (Table 1, paired student’s t-test). TNFα levels were significantly reduced in PsA (3.7 pg/ml) patients compared to those with psoriasis (10.6 pg/ml). Elevation in markers of bone resorption (DKK1, OPN, SOST) and ossification (leptin, OPG) in PsA relative to PsC were found, reflecting the balance in both synthesis and degradation that is disrupted in PsA. Using a reduced conditional logistic regression model that included all markers tested, IL-6, osteopontin, sclerostin and TNFα were independently associated with PsA.

Conclusion: Serum markers of bone remodeling were elevated in PsA patients with active disease compared to patients with PsC only. Future studies will focus on validating these markers in a large, independent cohort, to determine whether these genes can serve as biomarkers of PsA susceptibility.

Table 1: Expression of bone biomarkers (p<0.05) in serum of PsA and PsC patients

<table>
<thead>
<tr>
<th>Protein</th>
<th>Description</th>
<th>Function</th>
<th>Mean (sd) levels (pg/ml)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKK1</td>
<td>Dickkopf-1 Wnt signaling pathway inhibitor F</td>
<td>Resorption</td>
<td>1940.7 (627.6) 1750.6 (403.7)</td>
<td>0.045</td>
</tr>
<tr>
<td>FGF23</td>
<td>Fibroblast growth factor 23</td>
<td>Resorption</td>
<td>113.7 (226.7) 76.5 (155.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
<td>Resorption</td>
<td>37.6 (183.5) 61.9 (397.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Interleukin-1 beta</td>
<td>Resorption</td>
<td>2.1 (0.7) 4.1 (1.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>LEP</td>
<td>Leptin</td>
<td>Ossification</td>
<td>2234.7 (2291.3) 1127.9 (1088.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>OC</td>
<td>Osseocalcin</td>
<td>Ossification</td>
<td>10532.0 (690.4) 1049.3 (485.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>OPG</td>
<td>Osteoprotegrin</td>
<td>Ossification</td>
<td>4046.0 (281.0) 3743.2 (161.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>OPN</td>
<td>Osteopontin</td>
<td>Ossification</td>
<td>11486.5 (6780.4) 7323.3 (4411.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>SOST</td>
<td>Sclerostin</td>
<td>Ossification</td>
<td>3665.5 (1890.6) 3653.4 (1840.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumor necrosis factor alpha</td>
<td>Recombinant</td>
<td>5.7 (5.6) 10.1 (16.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Disclosure: F. Ahji, None; A. Thavaneswaran, None; V. Chandran, None; D. D. Gladman, None.

631 Joint and Bone Related Pathways Discriminate Psoriatic Arthritis Lesional Skin from Psoriasis vulgaris Lesional Skin. Jennifer Belasco1, James S. Louie2, Nicholas Gulati3, Nathan Wei4, Kristine Noguera5, Hiroshi Mitsui6, Mayte Suarez-Farinas7 and James G. Krueger1. 1The Rockefeller University, New York, NY; 2UCLA School of Medicine, Los Angeles, CA; 3Arthritis & Osteoporosis Center of MD, Frederick, MD.

Background/Purpose: It is preferable to start therapy as early as possible in psoriatic arthritis because of the destructive nature of the arthritis. Starting treatment promptly is complicated because the arthritis component can occur years after the psoriatic skin disease (psoriasis vulgaris, PsV), and the arthritis may not be diagnosed until lesions are established. Many patients with PsV are seen in dermatology clinics where early arthritis symptoms may not be diagnosed. Given these issues, it would be useful to have a predictive model that would allow the identification of patients with PsV that will go on to have PsA, possibly even before clinical symptoms of arthritis are apparent. Since the psoriasis lesions of previously healthy patients with PsV samples were chosen after a histological phenotype similar to human Ps with elevated constitutive levels of cartilage oligomeric matrix protein (COMP), secreted frizzled-related protein 1 (SRP1), and proteoglycan 4 (PRG4). In addition, IPA showed differential expression of several pathways related to joint destruction and dysregulated bone metabolism. These include the "Role of Macrophages, Fibroblasts, and Endothelial Cells in Rheumatoid Arthritis", the "BMP Signaling Pathway", the "Wnt/β-Catenin Signaling Pathway" and "RANK Signaling in Osteoclasts". RT-PCR confirmed a significant difference in BMP2.

Conclusion: In this pilot study we show differences in gene expression of lesional skin from subjects with PsA and PsV. To our knowledge, this is the first study to show that markers linked to the joint and dysregulated bone metabolism could be identified in skin biopsies. This could be useful as both an early predictor of PsV patients who will go on to have PsA and help to guide therapies at a very early stage of disease diagnosis to prevent destructive arthritis. In addition, this could lead to the discovery of key pathogenic molecules in skin that may affect joints and/or enthuses, thus suggesting new therapeutic targets.

Disclosure: J. Belasco, None; J. S. Louie, Celgene, 5, Eli Lilly and Company, 5, Amgen, 5, Pfizer Inc, 5, Genentech and Biogen IDEC Inc., 5, N. Gulati, None; N. Wei, None; K. Noguera, None; H. Mitsui, None; M. Suarez-Farinas, None; J. G. Krueger, Abbvie, 5, Abbvie, 5, Akros, 2, Akros, 2, Amgen, 5, Astellas, 2, Astellas, 5, Boehringer Ingelheim, 5, Boehringer Ingelheim, 5, Biogen Idec, 2, Biogen Idec, 5, Centocor, Inc., 2, Centocor, Inc., 5, Dermira, 2, Dermira, 2, Eli Lilly and Company, 2, Eli Lilly and Company, 5, Genzyme Corporation, 2, Genzyme Corporation, 5, LEO Pharma, 2, LEO Pharma, 5, Merck Pharmaceuticals, 2, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 2, Pfizer Inc, 5.

632 IL-23 Mediates Psoriasis-like Inflammation in the SKG Mouse Model of Spondyloarthropathy. Helen Benham1, Linda Rehaune1, Athan Baille1, Zaied Bhuyan1, Jacy Bowyn1, Dimeng Pang1, Kristine Kilty1, Geoffrey Strutton1, Matthew Brown1 and Ranjeny Thomas1. 1University of Queensland Diamantina Institute, Brisbane, Australia; 2Biotechnology Discovery Research, Eli Lilly and Co, Indianapolis, IN; 3Department of Pathology, Princess Alexandra Hospital, Brisbane, Brisbane, Australia.

Background/Purpose: Psoriasis (Ps) is a common immune-mediated inflammatory skin disease and is a well recognized early-autoreactive manifestation of the spondyloarthopaties (SpA). Genetic studies implicate IL-23 signalling in the pathogenesis of both Ps and SpA. Spondyloarthritis and psoriasis-like disease develop in an IL-23-dependent fashion in ZAP70- mutant SKG mice, which have defective IL-23 receptor signaling. We characterized curdlan (1,3-D-β-glucan) induced psoriasis-like inflammation in SKG mice, investigating the role of IL-23, IL-22/IL-17, regulatory T cells (Tregs) and microbiota.

Methods: SKG mice, IL-17A-deficient SKG mice, Germ Free SKG mice and Foxp3-DTR SKG mice were injected intraperitoneally with curdlan (1,3-D-β-glucan) to induce disease. Anti-mouse IL-22, anti-IL-23 or isotype control antibodies were given i.p one day before curdlan, and weekly until sacrifice. Recombinant IL-23 or PBS was administered intra-durally into ear skin. Outcomes were measured by clinical and histological scoring; cytokines and by qRT-PCR and in supernatants of cultured tissue explants by ELISA and CBA.

Results: Curdian induced psoriasis-like inflammation in addition to spondyloarthritus in 100% of SKG mice. SKG skin lesions showed a histological phenotype similar to human Ps with elevated constitutive levels of IL-23(p819) and increased secretion of both IL-17 and IL-22, 7 days after curdian. Neutralisation of both IL-23 and IL-22 suppressed development of skin inflammation, in contrast IL-17A-deficient SKG mice were only partially spared. Germ Free (GF) SKG mice failed to develop significant skin inflammation after curdian, however colonization of GF-SKG mice with a limited microbiota induced mild psoriasis-like inflammation. Tregs modulated the severity of skin inflammation through the suppression of IL-23 secretion. Intradermal injection of IL-23 induced IL-22 mediated, microbiota dependent psoriasis-like inflammation in naive SKG mice.

Conclusion: In curdian-treated SKG mice IL-23-driven psoriasis-like inflammation is induced in the setting of spondyloarthritus. The skin inflammation recapitulates several features of human Ps and is dependent on the relative contributions of IL-17, IL-22, microbiota and the balance of Treg and T effector cells.
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Immunological and Clinical Relationships of Synovial IL-17+ T Cells in Psoriatic Arthritis. Bruce Kirkham1, Bina Menon2 and Leonie S. Taams3.


Background/Purpose: We recently reported elevated numbers of synovial fluid IL-17+ CD4+ T-cells (mainly CD8+ Tc17) cells in Psoriatic Arthritis (PsA), correlating with clinical, serological and imaging measures of disease activity (1). These relationships are not found with CD4+ IL-17+ (Th17) synovial cells. Here we report the relationship of synovial fluid T cell cytokine expression with PsA clinical patterns, and the relationships between synovial fluid cytokine-expressing T cells.

Methods: Mononuclear cells from synovial fluid (SF) and peripheral blood (PB) samples from 22 patients with PsA were isolated and stimulated for 3 hours in vitro with PMA and ionomycin in the presence of GolgiStop. CD3+ T-cells were investigated for cytokine expression (IL-17A, IFN-γ, TNF-α, IL-22, IL-21, IL-10) by flow cytometry. Clinical measures and Power Doppler Ultrasound (PDUS) of the affected joint were made at the time of joint aspiration.

Results: Of 22 subjects, 16 (73%) had an oligoarthritis (<5 involved joints) and 6 (27%) a polyarticular pattern of PsA, with 9 (41%) having disease activity at 5 joints. All clinical subgroup patients had elevated synovial IL-17+ CD4- and IL-17+ CD4+ T-cells compared to PB, which was significant in the oligo (p=0.001 and p=0.02 respectively) and axial groups (p=0.01 for both), with the polyarthritis group increase not statistically significant (p=0.06 for both), most likely due to low numbers.

TNF-α and IL-17 frequency positively correlated with DAS28 (r=0.51, p=0.02) with a trend for TNF-α+CD4+ T-cells and DAS28 (r=0.43, p=0.07). The Th17 cells were expressed co-expressed in IL-17+ CD4+ T-cells, with no correlation between TNF-α+ T-cells and ESR, CRP or PDUS. IL-22+ CD4+ T-cells correlated with PDUS. No other T cell cytokine expression pattern correlated with clinical measures.

Relationships of cytokine expressing T cells were assessed for the percentages of IL-17+ CD4- T-cells and IFN-γ+ TNF-α+ IL-22+, IL-21+ and IL-10+ CD4- T-cells in PsA SF. Only TNF-α+ cells positively correlated with IL-17+ cells in the CD4- T-cell compartment (r=0.55, p=0.01). This relationship may be partly explained by the finding that 60% of IL-17+ CD4- cells co-express TNF-α. IL-22 was co-expressed in 22% of IL-17+ CD4- T-cells.

Conclusion: These data suggest that IL-17 expressing CD4+ (CD8+) T-cells are found in all articular patterns of PsA. The correlation of IL-17+ and TNF-α+ CD4- cells suggests that IL-17 and TNF-α may be related in expression as well as synergy of function.

Ref

Disclosure: B. Kirkham, None; B. Menon, None; L. S. Taams, None.

ACR Poster Session A: Systemic Lupus Erythematosus - Animal Models

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Characterization of CD4+ T Cell Response and Effects of Regulatory T Cells in Pristane Induced Lupus (PIL). Harald Leiss, Barbara Schwarzecker, Irina Gessl, Antonia Puchner, Birgit Niederreiter, Carl-Walter Steiner, Josef Smolen and Georg H. Stammvoll. Medical University of Vienna, Vienna, Austria.

Background/Preconditions: CD4+ T cells and the Th1 and Th17 subsets in particular play a pivotal role in SLE. Regulatory T cells (Treg) are essential for maintaining peripheral tolerance, but their number and function in SLE is decreased. We herein characterize CD4+ T cell and Treg homeostasis and severity of organ involvement in a murine model of SLE and analyze the effects of in vitro –induced iTreg.

Methods: Mice were injected ip. with 0.5 ml of pristane or PBS as control and killed after 8 months. Naïve CD4+ thymocytes were cultured under specific conditions and tested for CD4+ Foxp3+ expression by FACS. Cell suspensions with >80% purity for CD4+ Foxp3+ iTreg were injected intravenously either once at start of experiments (iTreg-boost) or monthly (1x iTreg-repeated).

Animals were monitored for clinical signs of arthritis and, in order to analyze and compare disease severity, histological features of arthritis and pneumonitis were quantified by an image analysis system. Lungs were scored for the severity of perivascular inflammation by analyzing the numbers of affected vessels and the area of the inflammatory infiltrate.

Lymphocytes were isolated from granulomas (intraperitoneal ectopic lymphoid tissue), lymph nodes (LN) and spleens and were analyzed separately by FACS. For analyses of the Th1, 2 and 17 subsets, cells were restimulated in vivo plate bound with anti-CD3 and anti-CD28Ab.

Results: PIL mice presented with involvement of inner organs, most frequently affected were the lungs (100% pneumonitis); 52% of PIL developed arthritis, both clinically and histologically. Monthly iTreg-injection significantly decreased clinical signs of arthritis and histological lung and joint parameters. 66% of treated mice did not show any signs of arthritis at all. (Fig. 1A-F)

The iTreg-boost did not prevent joint manifestations or pneumonitis, but appeared to have a retarding effect (Fig. 1A-F) indicated by a delayed onset of clinical symptoms and by a significantly decreased erosive area at the end of observation (Fig 1B).

Intrapertitoneal granuloma typical for PIL appeared to be the hotspots of inflammation showing a significantly elevated Teff/Treg ratio of 1.3. Upon re-stimulation, CD4+ cells showed a pronounced Th1 response (27% IFN-γ producers) compared to cells from LN and spleens from both PIL and HC (with Th1 percentages ranging from 9–16%). In addition, frequencies of Th2 and Th17 cells were elevated in PIL, again with the highest yield in granuloma. The repeated application of iTreg reduced the Teff/Treg ratio in PIL granuloma to 0.7.

Conclusion: Repeated injections of iTregs reduce severity of pneumonitis and arthritis as well as the Teff/Treg ratio. A single injection of iTregs is not effective, but appears to retard onset of symptoms and progression of arthritis and pneumonitis. Thus, iTreg have significant effects on lupus symptoms, which may have consequence for future therapeutic considerations.
Disclosures: H. Leiss, None; B. Schwarzecker, None; I. Geiss, None; A. Puchner, None; B. Niederreiter, None; C. W. Steiner, None; J. Smolen, None; G. H. Stummvoll, None.

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Mir-663 Impairs the Effects of Bone Marrow-Derived Mesenchymal Stem Cells on MRL/lpr Mice. Liniu Geng, Xuебing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Previously we have shown that miR-663 was increased in bone marrow derived mesenchymal stem cells (BMSCs) from SLE patients and involved in the functional deficiency of BMSCs through inhibiting transforming growth factor β1 (TGF-β1) production. This study was undertaken to explore whether the modulation of miR-663 in BMSCs could affect their therapeutic effects on MRL/lpr mice.

Methods: Negative-control-miR-663 (miR-663-C), mimics-miR-663 (miR-663-M) and inhibitor-miR-663 (miR-663-I) eukaryotic expression vectors were artificially transfected into BMSCs and intravenously injected (1×10^6) into 20 weeks old male MRL/lpr mice. 8 weeks later, mice were sacrificed, with kidneys, lymph node harvested and spleen weighed. Their serum and urine samples were collected for the measurement of autoantibodies (including IgG, ds-DNA and ANA) and cytokines (TGF-β1, IL-4, IFN-α, IL-17A and so on) by ELISA, and proteinuria by coomassie blue staining assay. Immune complex deposition including IgG and complement 3 (C3) in kidney sections was performed by immunofluorescence staining. The percentages of Th1, Th2, Th17, regulatory T cells (Treg) and follicular T helper (Tfh) cells in splenic mononuclear cells were detected by flow cytometry.

Results: Compared to the miR-663-C and miR-663-M group, miR-663-I transfected BMSCs displayed enhanced therapeutic effects on MRL/lpr mice, as shown by significantly declined spleens and lymph nodes size as well as reduced serum IgG and anti-dsDNA levels. Compared to miR-663-C and miR-663-M group, mice treated with miR-663-M transfected BMSCs presented enlarged glomerulus with hypercellularity and meningo expansion, and greater amounts of immune complex deposition including IgG and C3 in the meningo and peripheral capillary loops. Meanwhile, Treg cell percentages were increased in miR-663-I group compared with those in miR-663-M and miR-663-C group (13±1.12% vs. 8.9±0.92% and 8.2±1.07%, overall p<0.05), while Th1 cell percentages were decreased (8.5±1.09% vs. 22.9±4.24% and 12.40±1.61%, overall p<0.05).

Conclusion: Inhibition of miR-663 in MSCs enhanced the therapeutic effects of MSC transplantation on MRL/lpr mice.

Disclosure: L. Geng, None; X. Feng, None; L. Sun, None.

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Background/ Purpose: Glucocorticoids (GCs) have been known for years to be the most effective therapy in SLE. Their use is however limited by the need of high doses due to the unfavorable pharmacokinetics and biodistribution of the drug. A possible approach to overcome this obstacle is to use liposomal formulation that has a different biodistribution than that of the free GCs. We have previously developed a new liposomal GC formulation and demonstrated its specific accumulation in inflamed tissues, as well as superior therapeutic efficacy over that of free GC in the autoimmune adjuvant arthritis model. In the present study we have tested the effect of the liposomal GC formulation in the murine SLE model of MRL/lpr/lpr.

Methods: We used 80 nm sterically stabilized nanoliposomes that were remote-loaded with an amphiathic weak acid GC methylprednisolone hemisuccinate (liposomal GC). Six-weeks old MRL/lpr/lpr mice were injected subcutaneously with either the liposomal GC 25 mg/kg weekly, or free MPS 5 mg/kg daily, or the appropriate solvent and their clinical course, kidney damage and serology, followed until the age of 24 weeks.

Results: No mortality was observed in mice treated with the liposomal GC up to 24 weeks, as compared to 20% and 30% mortality in the free MPS and the solvent-treated groups. Anti-dsDNA levels (OD) were 0.49±0.05 in the liposomal GC group, compared to 1.21±0.22 and 1.7±0.12 in the two other groups. Significant reduction of spleen size was observed in the liposomal GC-treated group, 1.09±0.43 cm^2, compared to 2.98±0.65 cm^2 and 2.82±0.51 cm^2 in the two other groups. A significant improvement in renal histopathology was achieved in the liposomal GC treatment, and mean urea levels were 8.8±1.05 mM/L in the liposomal GC group compared to 18.9±5.86 mM/L and 22.5±2.69 mM/L in the two other groups.

Conclusion: Liposomal GC has significant superiority over daily injections of free MPS in suppressing murine lupus. These results make our liposomal GC formulation a good candidate for the treatment of human SLE.

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Decreased Inflammatory Dendritic Cells in Lupus-Prone Estrogen Receptor Alpha Knockout (EsrKO) Mice Correlate with Increased Survival. Melissa A. Cunningham, Jena R. Wirth, Jackie G. Eudaly, Jennifer L. Scott, Osama S. Naga and Gary S. Gilkeson. 1Medical University of South Carolina, Charleston, SC, 2MUSC, Charleston, SC.

Background/ Purpose: SLE is a disease that disproportionately affects females. The etiology of the sex bias in this disease is unclear. We previously showed that a functional knockout of estrogen receptor alpha (EsrKO) resulted in significantly reduced renal disease and increased survival in murine lupus. Subsequently, we demonstrated a role for ERα in modulating Toll-like receptor (TLR)-induced inflammation, partially explaining the protected phenotype. The mechanism of this effect, however, is not known. Dendritic cell development, which requires both estrogen and ERα is impacted, as is activation status and cytokine production. Due to altered feedback loops, the hormonal milieu of ERα mutant mice is significantly different from WT. ERαKO mice have hypergonadism and partial endocrine sex reversal (elevated estrogen and testosterone levels), and decreased prolactin levels. These hormones may have immunomodulating effects in concert with other intact hormone receptors. Therefore, we investigated the phenotype of the NZM/ErαKO mouse following ovariectomy (OVX) and estrogen pellet (to preserve a physiologic hormonal state).

Methods: ErαKO and Ex3a (Era null) strains were backcrossed onto the NZM2410 lupus-prone background. Subsets of mice were ovariectomized (at 4 or 8 weeks). Urine and blood were collected at 2–4 week intervals starting at 10 weeks, and mice were sacrificed at 32 weeks, or earlier if they had high proteinuria and >10% weight loss. Bone marrow was isolated and cultured for 7 days with Flt3L to enrich for dendritic cells. Spleen and kidney cells were also isolated. Flow cytometry was utilized to determine number of cDC1 (CD11c+CD11b−) and activated cDCs (CD11c+CD11b+ MHCII+) from cultured BM-DCs, as well as from ex vivo spleen and kidney cells.

Results: Survival at 32 weeks: NZM/ErαKO – OVX + E2: 8/8 (100%) vs. NZM/ErαKO – OVX: 5/8 (63%) vs. NZM/WT – OVX: 8/14 (57%) vs. NZM/ErαKO – Ex3a: 7/7 (100%) vs. NZM/Ex3a – OVX: 3/6 (50%) vs. NZM/ErαKO – Ex3a + E2: 8/8 (63%). Proteinnemia (diopstick) correlated with survival as did total and activated cDCs (BM-DCs) which were significantly reduced in NZM/ErαKO – OVX + E2 vs. both NZM/WT – OVX (p<0.001) and NZM/ErαKO – OVX (p<0.05). To date, analyzed numbers of activated cDCs from both spleen and kidney of NZM/ErαKO mice were also significantly reduced.

Conclusion: Consistent with previous experiments, NZM/ErαKO mice were protected from lupus disease expression (no early deaths; no proteinuria at 32 weeks). This was only true if they were either unmanipulated, or both ovariectomized and E2-repleted. These mice had fewer inflammatory and activated cDCs from bone marrow, spleen and kidney, which correlated with increased survival in this group. The protective phenotype was lost after ovariectomy if no E2 pellet was administered, suggesting that the effect requires E2 in the system (despite the lack of a full length ERα). A protective effect was not observed in lupus-prone Ex3a mice (Erα−/−) that were OVX ed and E2-repleted, suggesting that the A/B domain mutant in ErαKO mice potentially modulates disease in the presence of estrogen, rather than ERα deficiency alone being protective.

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Commensal Microbiota Influence Systemic Autoimmune Responses. Jens Van Praet1, Erin Donovan2, Michael Drennan3, Fons Van de Loo4, Sylvie Rabot5, Jeroen Raes6, Tom Van De Wiele7, Carl Ware4 and Dirk Elewaut8, Ghent University Hospital, Ghent, Belgium, 2Ghent University Hospital, ghent, Belgium, 3Raboud University Medical Center, Utrecht, Netherlands, 4AgroParisTech, Micalis, Jouy-en-Josas, France, 5Rega Institute, KU Leuven, Leuven, Belgium, 6Sanford-Burnham Medical Research Institute, La Jolla, CA, 7Department of Rheumatology Ghent University Hospital, Ghent, Belgium.

**Background/Purpose:** Antibacterial antibodies are a hallmark feature of general, rheumatoid, and systemic lupus disease. They play a role in disease pathogenesis and systemic sclerosis. However, the processes underlying the loss of tolerance, particularly the role of lymphoid organs, against self-constituents remains largely unresolved.

**Methods:** We generated mice lacking all secondary lymphoid organs including spleen by crossing intercellular lymphocyte beta receptor deficient mice with Hox11 deficient animals. LtbR-Fc was administered intraperitoneally and postnatally at various stages of development. LtbR-Fc, T-LtbR-Fc, B-LtbR, and Rorγt-LtbR were generated by crossing LtbR-floxed mice with Cd4-cre, mхи-crd, Rorgt-crd mice respectively. Thymi were isolated from newborn LtbR-floxed mice and transplanted into the kidney capsule of adult nude mice. 16S rRNA profiling and analysis was conducted on mucosal, luminal and faecal samples. Germfree versus conventionalized mice were treated with LtbR-Fc intraperitoneally and postnatally. Germfree mice were monocloned with SFB or E. Coli species and treated with LtbR-Fc. We screened for antibodies using a validated immunoassay with a broad range of ANA, including anti-U1RNP, anti-Sm, anti-Scl70/Topoisomerase-I, anti-Centromere protein B, anti-SSA/Ro52 and anti-Jo1 (INNO-LIA ANA Update, Innogenetics NV).

**Results:** We found that approximately 25% of mice lacking secondary lymphoid organs spontaneously develop specific antibacterial antibodies. Interestingly, we find this phenotype is not caused by a defect in central tolerance. Rather, cell-specific deletion and in vivo lymphopenia in blockade link these autoimmune responses to the formation of gut associated lymphoid tissue in the neonatal period of life. We further demonstrate antibacterial antibody production is influenced by the presence of commensal gut flora, in particular increased colonisation with segmented filamentous bacteria, IL-17 receptor signalling, and IgA production, which appears to have a protective role against autoantibody formation.

**Conclusion:** Together, these data indicate that neonatal colonization of gut microbiota influences generalized autoimmunity in adult life.

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Lack of Response Gene to Complement-32 Impairs Th17 Differentiation and Attenuates Lupus-like Chronic Graft Versus Host Disease. Vinh Nguyen1, Cosmin Tegla1, Cornelia Cudrici2, Tudor Badea3, Horea Rus1 and Attenuates Lupus-like Chronic Graft Versus Host Disease. Vinh Nguyen1, Cosmin Tegla1, Cornelia Cudrici2, Tudor Badea3, Horea Rus1 and

Disclosures: V. Nguyen, None; C. Tegla, None; C. Cudrici, None; T. Badea, None; H. Rus, None; V. Rus, None.

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A Peptide Mimic Inhibits the Cross Reaction of Anti-DNA Antibodies with Glomerular Antigens. Yumin Xia, Ertan Eryilmaz, Rahul Pawar, David Cowburn and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY.

**Background/Purpose:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by high titers of multiple autoantibodies. Of those, anti-DNA antibodies play a key role in the pathogenesis of lupus nephritis by cross reacting with renal antigens. Previously, we generated a panel of anti-DNA antibodies from the murine PL9–11 anti-DNA mAb (IgG3), which share identical variable regions of both heavy and light chains but differ in their heavy chain constant region. We demonstrated that the binding affinity of the PL9–11 mAbs to self-antigens (including renal antigens) is isoform-dependent. The present study was designed to further investigate the cross reaction between anti-DNA mAbs and renal antigens, by identifying a peptide mimic that can bind to multiple anti-DNA isotypes.

**Methods:** A phage display library was used for peptide selection, and identified a 12-mer peptide, ALWPPNLHAWWP or “ALW”. The specificity and kinetics of binding affinity of ALW to anti-DNA isotypes were determined by ELISA and surface plasmon resonance. Inhibition and cell surface ELISAs, flow cytometry, and glomerular binding assays were performed to evaluate how well ALW inhibits murine and human anti-DNA antibodies in binding to glomerular antigens in vitro and ex vivo.

**Results:** The ALW peptide exhibits differential binding affinity to the PL9–11 anti-DNA antibodies in the order of IgG2b > IgG2a > IgG3 > IgG1. Pre-incubation with the ALW peptide significantly reduced the binding of anti-DNA IgGs to dsDNA, laminin, matrigel, mesangial cells, and isolated glomeruli. Moreover, the inhibition by ALW of anti-DNA binding was isoform-dependent. Alamine replacement studies and phage binding assays confirmed the specificity of the amino acid sequence in the binding of ALW to the PL9–11 panel. Finally, ALW significantly inhibited the binding of sera from MRL/lpr and B6.Sle1/3 mice and patients with active SLE to nuclear and glomerular antigens.

**Conclusion:** The ALW peptide significantly inhibits the binding of nephritogenic anti-DNA antibodies and human/mouse lupus sera to multiple self-antigens, presumably by mimicking their antigenic properties. The ALW peptide or its derivatives may potentially be a useful approach in the treatment of lupus nephritis and other autoantibody-mediated disease manifestations, by...
inhibiting the binding of polyclonal anti-DNA antibodies to their in vivo targets.

Disclosure: Y. Xia, None; E. Eryilmaz, None; R. Pawar, None; D. Cowburn, None; C. Puterman, None.

641 Peptidylarginine Deiminase Inhibition Mitigates NET Formation and Protects Against Kidney, Skin, and Vascular Disease in Lupus-Prone MRL/lpr Mice. Jason S. Knight1, Venkataraman Subramanian2, Alexander A. O’Dell3, Sri Lakshmi Yalavarthi4, Wenzhu Zhao5, Carolyne K. Smith6, Jeffrey B. Hodgkin7, Paul Ryan Thompson8 and Mariana J. Kaplan9, 1University of Michigan, Ann Arbor, MI; 2The Scripps Research Institute, Jupiter, FL; 3National Institutes of Health, Bethesda, MD.

Background/Purpose: An imbalance between neutrophil extracellular trap (NET) production and NET degradation has been observed in systemic lupus erythematosus (SLE), potentially contributing to autoantigen externalization, type I interferon production, and endothelial dysfunction. We have previously demonstrated that peptidylarginine deiminase (PAD) inhibition can mitigate NET formation and protect against vascular damage in the New Zealand Mixed model of lupus. However, another strategy for disrupting NET formation—knockout of NOX2—accelerates lupus in a different mouse model, MRL/lpr. Here, we tested PAD inhibition in MRL/lpr mice in an attempt to clarify whether some NET inhibitory pathways may be consistently therapeutic across different models of SLE.

Methods: NET formation, autoantibodies to NETs, interferon signature, and endothelial function were characterized at baseline in MRL/lpr mice. MRL/lpr mice were also treated for six weeks (daily, from 8 to 14 weeks of age) with two different PAD inhibitors, CI-amidine and the newly developed BB-Cl-amidine. NET formation, interferon signature, endothelial function, nephritis, and skin disease were examined in treated mice.

Results: Neutrophils from MRL/lpr mice demonstrate more NET formation than controls. MRL/lpr mice also form autoantibodies to NETs and have evidence of endothelial dysfunction. PAD inhibition with either CI-amidine or BB-Cl-amidine markedly improves endothelial function, while downregulating expression of type I interferon-regulated genes. PAD inhibition also protects against proteinuria, immune complex deposition in the kidneys, and skin disease.

Conclusion: Chemical PAD inhibition reduces NET formation, while protecting against damage to the endothelium, kidneys, and skin in various lupus models. The strategy by which NETs are targeted will have to be carefully considered if human studies are to be undertaken.

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642 Treatment with a Glycolipid Ameliorates Lupus Dermatitis and Expands Skin ãa T Cells That Promote the Migration of Langerhans Dendritic Cells. Ram Raj Singh, Anna Eriksson, Darshan Randhawa and Miguel-Angel Gutierrez. UCLA, Los Angeles, CA.

Background/Purpose: Self antigens are taken from tissues to local lymphoid organs to acquire ability to avoid self-reactivity. This important immune function is accomplished by dendritic cell (DC) populations that primarily reside in tissues. We posit that a defect in the migration of tissue-resident DCs may predispose to autoimmunity in a tissue-specific manner; and an improved migration of tissue-specific DC may ameliorate disease in the respective organ. We have previously reported that lupus dermatitis-prone MRL mice exhibit a profound defect in the migration of skin-resident DC. Here, we investigated the effect of improved skin-DC migration on lupus dermatitis and determined mechanisms that regulate the migration of tissue-resident DC from tissues to lymph nodes.

Methods: Skin and cutaneous lymph nodes from MRL-lpr mice and MHC-matched control mice and y6 T cell-deficient mice were analyzed for Langerhans DC and skin-resident invariant y6 T cells before and after treatment with a glycolipid GalCer that was previously shown to ameliorate lupus dermatitis, without affecting disease in other organs.

Results: MRL mice that exhibit reduced skin-DC migration had reduced skin-resident y6 T cells, whereas treatment with GalCer reduced the severity of lupus dermatitis and restored skin-y6 T cells and skin-DC migration. This effect of GalCer was independent of its effect on invariant natural killer T cells, but required the presence of lipid antigen presenting molecule CD1d. We further show that gd T cell-deficient mice had reduced skin-DC migration in vivo, and skin-gd T cells directly promoted the migration of skin-DC in vitro via CD40L-CD40 interaction.

Conclusion: Our data elucidate a new mechanism of regulation of skin-DC homeostasis whereby skin-gd T cells normally facilitate skin-DC migration from skin to cutaneous lymph node. Such ‘local’ control of migratory behavior of tissue-DC can regulate immune response in a tissue-specific manner. This mechanism of skin-DC homeostasis is disrupted in lupus dermatitis, but can be repaired by treatment with a glycolipid.

Disclosure: R. R. Singh, None; A. Eriksson, None; D. Randhawa, None; M. A. Gutierrez, None.

643 The Effect of TNF Inhibition on the Autoimmune B Cell Repertoire in SLE Prone Mice. Anne Davidson, Weiqing Huang and Ranjit Sahu. Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: TNF inhibitors are widely used for inflammatory diseases but often induce ANAs that sometimes progress to overt SLE. TNF deficient mice fail to generate germinal centers (GCs) but are still able to mount effective humoral responses to exogenous antigens. A similar loss of GCs occurs in the tonsils of RA patients treated chronically with TNF inhibitors. The goal of these studies was to analyze the mechanism of induction of ANAs by TNF inhibition and the nature of the checkpoint between ANA production and clinical SLE in a mouse model.

Methods: TNF deficient autoimmune prone SLE mice were generated and the 3H9 IgVH transgene that confers anti-DNA and anti-cardiolipin specificity was introduced. Mice were followed clinically and sacrificed at the age of 52 weeks. Spleen cells were analyzed by single cell PCR for the repertoire of Vk light chains associated with the 3H9 heavy chain. Selected 3H9/Vk combinations were transfected into 293 cells and supernatants were tested for autoantibody activity by ELISA.

Results: TNF deficient 3E1 mice did not spontaneously develop clinical SLE or proteinuria and survived until at least 52 weeks of age. Surprisingly, serum levels of both anti-chromatin and anti-dsDNA antibodies were decreased in TNF deficient mice compared with their TNF sufficient controls, with similar results in the 3H9 TNF deficient mice. By contrast, TNF deficient mice developed high titers of IgG anti-cardiolipin autoantibodies. Similar results were observed in 3E1.TNF1 deficient but not 3E1.TNF2R2 mice. Single cell analysis of the follicular B cell repertoire of 3H9.Sle1 TNF deficient mice revealed a loss of 3H9/Vk12–46/Jk2 encoded B cells that can bind to histones and chromatin.

We have previously shown a preferential selection of Vk5 light chains into the GCs of 3H9 SLE prone mice; these light chains confer anti-chromatin activity in their germline configuration and acquire high affinity anti-DNA and anti-cardiolipin activity as a result of somatic mutations. Since GCs are not present in TNF deficient mice we analyzed the light chain repertoire of splenic class switched B cells and plasma cells. 3H9.Sle1 mice had marked overrepresentation of Vk5 encoded light chains among their class switched B cells and plasma cells. By contrast, 3H9.Sle1 TNF deficient mice had few Vk5 encoded plasma cells and instead had a vast overrepresentation of Vk4–57–1. Co-transfection of this light chain with 3H9 into 293 cells revealed that this combination had anti-cardiolipin but not anti-DNA or anti-chromatin activity. Further analysis of the Vk4–57–1 encoded light chains from class switched B cells of TNF deficient mice revealed that they were germline encoded.

Conclusion: TNF deficiency has significant effects on the Ig repertoire of mature and antigen activated B cells. The loss of GCs in TNF deficient Sle1 mice alters the spontaneously autoreactive Ig repertoire and is associated with a decrease in somatic mutations in autoreactive B cells suggesting that these cells have matured in an environment that is not exposed to cognate T cell help. The data further suggest that a “second hit” that bypasses the germinal center defect is required for TNF inhibition to induce pathogenic autoimmunity.

Disclosure: A. Davidson, None; W. Huang, None; R. Sahu, None.

Background/Purpose: Syk is a key mediator of signaling events downstream of a wide array of receptors important for immune functions, including the B cell receptor, immunoglobulin receptors bearing the Fcg or Fce chain. Therefore, modulation of Syk could provide a novel therapeutic approach for autoimmune diseases and cancers. HM-0523, a highly potent and selective, orally available Syk inhibitor, is currently in Phase I clinical trials. The aim of this study is to evaluate the efficacy of HM-0523 in a systemic lupus erythematosus (SLE) model in lupus-prone (MRL/lpr) mice.

Methods: HM-0523 was orally administered to MRL/lpr mice before or after disease onset. Key lupus features, including skin lesions, proteinuria and blood urea nitrogen levels were examined periodically. Overall survival and renal pathologic parameters were also assessed during the study (8–25 weeks).

Results: Lupus-prone (MRL/lpr) mice, commonly used as a SLE model, spontaneously develop autoimmune disorders that reflect pathologies of human SLE, including enlargement of lymph nodes, elevation of IgG levels, anti-nuclear antibody production, proteinuria, and kidney failure caused by inflammation of the glomeruli.

In this study, in vivo efficacy of the orally active HM-0523 was evaluated in the lupus-prone (MRL/lpr) mice. The mice, at the age of 8 weeks, were prophylactically administered with HM-0523 at 0, 5 and 20 mg/kg (QD), respectively. HM-0523, at 20 mg/kg, significantly blocked skin lesions [skin lesion score: 1.0±0.3 (vehicle control) vs. 0.0±0.0 (HM-0523); p<0.05], delayed the onset of proteinuria and reduced the immune organs to body weight ratios [for example, spleen: 1.74±0.158 (vehicle control) vs. 0.426±0.034 (HM-0523); p<0.05]. HM-0523, at 20 mg/kg, also significantly suppressed production of anti-dsDNA antibodies [408.6±172.6 KU/ML (vehicle control) vs. 156.3±25.8 KU/ML (HM-0523); p<0.05]. Histopathological investigation demonstrated that HM-0523, at 20 mg/kg, greatly alleviated the pathological changes in renal, including glomerulonephritis, interstitial nephritis, and perivascular infiltration. HM-0523, at 20 mg/kg, also significantly increased the levels of serum BUN and creatinine.

Overall survival rate at week 25 in the HM-0523 treated mice was 100% (at 20 mg/kg and 5 mg/kg) compared to 70.0% in controls (p<0.01). These comprehensive data indicate that HM-0523 has significant activity against the development of lupus and could be developed as a novel therapeutic agent for the treatment of SLE.

Conclusion: Our data demonstrated that HM-0523, acting through selective inhibition of Syk activation, exhibited significant beneficial effects in a murine lupus model. HM-0523 is currently in Phase I clinical trials. These new data provided support that HM-0523 could potentially become a novel therapeutic agent for systemic lupus erythematosus.

Disclosure: Y. Cai, Hutchison Medipharma Limited, 3; Z. Wu, Hutchison Medipharma Limited, 3; P. Ren, Hutchison Medipharma Limited, 3; X. Dai, Hutchison Medipharma Limited, 3; J. He, Hutchison Medipharma Limited, 3; F. Yin, Hutchison Medipharma Limited, 3; W. Deng, Hutchison Medipharma Limited, 3; G. Dai, Hutchison Medipharma Limited, 3; W. Su, Hutchison Medipharma Limited, 3; X. Li, Hutchison Medipharma Limited, 3.

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The Combination of Metformin and 2-Deoxy-D-Glucose Normalizes CD4 T Cell Metabolism and Functions, and Reverse Disease in Murine Models of Lupus. Laurence Morel, Yiming Yin, Seung-Chul Choi, Eric S. Sobel and Byron Croker. University of Florida, Gainesville, FL.

Background/Purpose: Autoactive CD4 T cells are key effectors in Systemic Lupus Erythematosus (SLE). Cell metabolism is an important checkpoint for T cell activation and differentiation. Both anaerobic glycolysis and mitochondrial oxidative phosphorylation are necessary for effector CD4 T cell differentiation and inflammatory cytokine production. We hypothesized that 1) SLE T cells have metabolic defects that impair their functions; 2) Targeting CD4 T cell metabolism may abrogate CD4 T cell inflammatory functions and reduce disease symptoms in SLE mice; 3) The functions of CD4 T cells from SLE patients can be normalized by treatment with metabolic inhibitors.

Methods: CD4 T cells from lupus-prone mice and controls, as well as CD4 T cells obtained from SLE patients and healthy controls were treated with metformin or 2-DG, or a combination of the two. Metabolic analysis of lupus-prone mice were treated with these drugs, either before or after disease onset. Glycolysis (extracellular acidification rate; ECAR) and oxygen consumption rate (OCR) were measured in CD4 T cells with an Extracellular Flux Analyzer. CD4 T cell activation and effector subsets were analyzed by flow cytometry. Disease progression was assessed by measuring serum anti-dsDNA IgG and anti-nuclear autoantibodies by ELISA and immunofluorescence, as well as renal histopathology.

Results: CD4 T cells from lupus mice have a significantly higher metabolism with increase in both ECAR and OCR, as well as an enhanced mTOR activity as compared to control mice. To normalize T cell metabolism in these mice, we used metformin, which activates the AMPK pathway and inhibits mitochondrial oxygen consumption, and 2-DG, an inhibitor of glycolysis. In vivo, metformin blocked IFNγ production and enhanced Treg cell development while 2-DG also blocked CD4 T cell activation. In vivo, a combined treatment with metformin and 2-DG normalized T cell metabolism and reversed disease phenotypes, including T cell activation and effector functions, as well as autoantibody production in the B6.Sle1.Sle2.Sle3 and the NZB/WF1 spontaneous models, as well as the chronic graft-vs-host disease model. Renal pathology is pending. Neither treatment with metformin or 2-DG alone resulted in disease reversal. Further, CD4 T cells from SLE patients showed an enhanced metabolism as compared to healthy controls, and their excessive IFNγ production was significantly reduced by metformin.

Conclusion: The combination of a glucose inhibitor with metformin restores T cell functions and reverses disease in mouse models, while metformin treatment normalizes the function of T cells from lupus patients. We propose that T cell metabolism is a novel target for SLE treatment.

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex and heterogeneous autoimmune disease associated with the overproduction of high affinity autoantibodies, mainly raised against nuclear antigens and can be considered a B-cell disease. These autoantibodies mediate tissue injury affecting multiple organs such as skin and joints in mild forms of the disease or central nervous system (CNS) and kidney damage in severe forms that can be fatal. SLE is a chronic disease with a relapsing and remitting time-course of unknown etiology and the precise understanding of how these auto-antibodies contribute to the disease is still incomplete. However, over-activity of B-cell responsiveness to immune stimulation and direct activation of circulating FcR bearing cells are sufficient to initiate inflammatory responses, which may be an essential feature of SLE pathogenesis. ONO-4059 is a highly potent and dual oral Btk/Tec inhibitor with an IC50 in the sub-nmol/L range. We have previously shown that ONO-4059 strongly suppressed B-cell activation, FcγR-induced TNFα production in monocytes and FcγR-induced TNFα production in mast cells (ACR 2012). Given Btk/Tec play a critical role in B-cell development and function, we examined the potential efficacy of ONO-4059 using female NZB/WF1 mice in a model of spontaneous SLE.

Methods: Mice were randomized to two treatment groups and fed a diet containing 0.012% (equivalent to 20 mg/kg/day) and 0.0037% (6 mg/kg/day) ONO-4059 from 12 to 37 weeks. The mice were weighed weekly and the level of anti-dsDNA antibody was examined on weeks of 28, 32 and 37. The level of proteinuria and overall survival were recorded during the treatment period. A subset of mice was sacrificed at 37 weeks for histopathological analysis of the kidney and ELISPot assays for total Ig-secreting cells and anti-dsDNA-secreting B-cells were evaluated in spleens.

Results: The treatment with 0.012% and 0.0037% of ONO-4059 resulted in 100% and 90% survival respectively, while 60% survival was observed in untreated mice. The onset of proteinuria was markedly lower in ONO-4059 treated mice (untreated: 6570.2±3520.5 μg/mL vs. 0.012% and 0.0037% of ONO-4059 treated: 366.2±19.2 and 358.3±18.4 μg/mL). ONO-4059 dramatically inhibited the production of anti-dsDNA in serum by 76% (P<0.05, 0.0037% diet) and 98.6% (P<0.01, 0.012% diet), compared with untreated mice at week 37. Furthermore, the observed inhibition was much stronger at week 37 (95.5% and 98.9% respectively). Significant reductions in the numbers of total IgG and anti-dsDNA-secreting B-cells were apparent in spleens from ONO-4059-treated mice. Germinal center B-cells and plasma cells were also significantly lower in ONO-4059 treated mice.

Conclusion: Recent studies indicate that the pathogenesis of SLE is associated with B-cell activation and circulating FcR bearing cells, in which Btk/Tec may play an important role. Our results demonstrate that treatment
with ONO-4059 may simultaneously target autoantibody producing and effector cells to prevent the spontaneous disease development in NZB/WF1 mice. These data suggest that ONO-4059 may provide promising therapeutic benefit in human lupus and related disorders.


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Helminth Derivative for Treating Lupus and Colitis in Mice Models. Miri Blank1, Tomer Bashi2, Dana Ben-Ami Shor3, Mati Fridkin4, Iris Barshack5, Alexander Volkov6 and Yehuda Shoenfeld7. 1Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, 2Weizmann Institute for Sciences, Rehovot, Israel, 3Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, 4Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: In areas where helminthes infections are common, autoimmune diseases are rare. Treatment with ova from helminthes, improved clinical findings of inflammatory bowel disease and other auto-immune diseases. The tolerogenic properties of the helminthes and their ova were attributed to the phosphorylcholine (PC) molecule. We aimed to decipher the tolerogenic potential of Tuffsfin-PC (TPC) compound in experimental Lupus and Colitis models.

Methods: 1. Lupus prone NZBxWF1 mice received subcutaneuously TPC (5µg/ml), 3 times a week using preventive protocol. Autoantibodies were tested by ELISA, T-regulatory-cells by FACS, cytokines by RT-PCR and R&D ELISA DuoSet. Glomerulonephritis was addressed by the presence of proteinuria, PAS staining and immunoglobulin deposition in the mesangium by immunofluorescence. 2. Colitis was induced by Dextran-Sodium Sulfate (DSS) in drinking water. TPC was given by daily oral ingestion (500 µg/mouse or PBS) starting at day (~2). DAI score was followed daily and histology of the colon was performed by H&E staining.

Results: 1. Lupus mice treated with TPC attenuated the development of glomerulonephritis, illustrated by a significant diminished proteinuria (p<0.02), and reduced immunoglobulin deposits in the kidney mesangium. TPC enhanced expression of TGFbeta and IL-10 (p<0.001), and inhibited anti-inflammatory cytokines profile on the level of protein and RT-PCR. Significant enhancement of CD4+CD25+Foxp3+ T-regulatory cells phenotype was documented. 2. Chemically induced colitis mice, treated with TPC, developed a significant moderate colitis, in comparison to mice which received the vehicle. The DAI score of the TPC treated mice was 0.9, whereas DAI score of 2.6 was observed in colitis mice which received the vehicle, p<0.02. The reduced DAI score in the TPC group was associated with a significant colon shortening and prevention of colon destruction as observed by histological analyses.

Conclusion: TPC delayed lupus development in lupus prone mice and prevented a significant colitis induction in naïve mice.

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Influenza A (H1N1) Virus Infection Triggers Severe Pulmonary Inflammation in Lupus-Prone Mice Following Viral Clearance. Samantha Slight-Webb, Harini Bagavant, Sherry Crowe, Jourdan R. Anderson and Robert Faltus1, Joseph Eckman1, Kimberly Bettano1, Gain Robinson1, Raquel Sevilla1, Bindu Bennett2, Lisa LaFranco-Scheuch2, Franklin Vives1, Michael Judo1, Gulesi Ayanoglu1, Weisheng Zhang1 and Milenko Cimic1.

1Merck Research Laboratories, Boston, MA, 2Merck Research Laboratories, West Point, PA, 3Merck Research Laboratories, Palo Alto, CA.

Background/Purpose: Rodent models mimic some aspects of human lupus disease manifestations in various tissues, such as kidney, skin, joint, and CNS. NZB/NZW F1 and MRL/lpr/lpr models have been used extensively for gaining understanding of disease driving mechanism as well as pharmacological evaluation of new therapies. However, the translatability of therapeutic results from rodent lupus models to human lupus patients is limited. Here, we explored the feasibility of using a combination of clinically relevant methods, such as biochemistry analysis, terminal histology, and in vivo imaging modalities, to characterize and/or quantify specific inflammatory pathways/tissue damage and to evaluate treatment effect in MRL/lpr/lpr mice.

Methods: Female MRL/lpr mice were treated with cyclophosphamide (50 mg/kg i.p. iv) starting at 6–8 weeks of age. Disease development was monitored by gross skin lesion scoring, conventional blood (anti-dsDNA and blood urea nitrogen) and urine (proteinuria) biochemistry, and terminal skin and kidney H&E histology analyses. Disease phenotypes were also monitored longitudinally in vivo using multi-modality imaging. Changes in glomerular filtration rate (GFR) were tracked by contrast agent Omnipaque washout using micro-computed tomography (micro-CT). Myeloperoxidase-dependent reactive oxygen species (ROS) production by neutrophils/myeloid cells was quantified with luminol-bioluminescence imaging (luminol-BLI) to monitor skin and joint inflammation. Finally, changes in cerebral cortical thickness and ventricle size were measured by brain magnetic resonance imaging (MRI).

Results: MRL/lpr mice treated with cyclophosphamide had no detectable production of anti-nuclear antibodies and exhibited with minimal skin and kidney disease phenotype. Neutrophil activation and ROS production in the skin and hind limbs visualized by luminol-BLI was detectable at 12 weeks of age and preceded gross skin lesion observation at 14 weeks of age. MicroCT detected a GFR decrease as early as 14 weeks of age in MRL/lpr mice, compared to the blood urea nitrogen level increase at 16 weeks of age. Skin and kidney imaging
results correlated with the terminal tissue H&E histology evaluation. Furthermore, MRI of the brain detected cerebral cortical thinning as early as 10 weeks of age in MRL/lpr mice. Cyclophosphamide treatment resulted in reduced progression of the cerebral cortical thinning process in these mice.

Conclusion: Here for the first time we have successfully demonstrated that evaluation of disease progression and treatment effect can be achieved by a combination of in vivo imaging, blood biochemistry, and terminal histological analysis in MRL/lpr model. The novel non-invasive imaging approach in MRL/lpr model captured disease progression and treatment effect efficiently. This comprehensive approach of combined in-life and terminal inflammation pathway/tissue damage evaluation in a pre-clinical lupus model provides a potential platform for translatable biomarkers of lupus diagnosis and treatment evaluation in drug discovery.

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Decreased Severity of Pristane Induced Lupus in miR155 Deficient Mice.
Harald Leiss, Wilhelm Salzberger, irina Gessl, Barbara Schwarzzecker, Nicolas Kozakowski, Stephan Bluml, Antonia Puchner, Birgit Niederreiter, Carl-Walter Steiner, Josef Smolen and Georg H. Stummvoll. Medical University of Vienna, Vienna, Austria.

Background/Purpose: MicroRNAs (miRs) are an important class of regulators of gene expression that are associated with a variety of biological functions. Deregulation of endogenous miR155 was observed in many autoimmune conditions, including SLE. We herein examine the role of miR155 in the development of systemic manifestations in murine pristane induced lupus by evaluating the severity of organ involvement and assessing serum antibody-levels and T helper cell homeostasis.

Methods: MIR155-deficient (miR155-PIL) and C57/B16 (WT-PIL) mice were injected i.p. with 0.5ml of pristane or PBS as control (WT-PBS). In order to observe the effects of miR155 deficiency in fully developed SLE, we analyzed the mice 8 months after induction.

A blinded specialist appraised histological features of GN using the composite kidney biopsy score (KBS). Histological features of pneumonitis were quantified by an image analysis system: Lungs were stained for the area of the inflammatory infiltrate. In order to assess the composition of these infiltrates, specimens were stained with B220 (B), CD3 (T), Neu7/4 (neutrophils) and F4/80 (macrophages) and analyzed by cell-identification algorithms for nuclear segmentation (HistQuest®).

Lymphocytes were isolated from spleens and analyzed separately for each mouse by standard FACS procedures. For analysis of the Th1, 2 or 17 subsets, respectively, cells were re-stimulated in vivo with anti-CD3 and anti-CD28Abs.

Results: Lungs were affected in both pristane-treated groups, but not in controls. MiR155-PIL had reduced lupus severity as indicated by significantly decreased perivascular inflammatory area with B cells being the most prominent inflammatory cell type in the HistoQuest analysis (Fig. 1A). Without showing clinical abnormalities WT-PIL had a more severe renal involvement in the kidney biopsy score than miR-PIL (Fig. 1B). Corresponding with reduced severity in organ involvement, miR155-PIL had lower serum levels of anti-dsDNA-abs (Fig. 1C), decreased frequencies of CD4+ cells (14.24 ± 0.7587 vs. 18.04 ± 1.075, p = 0.01) and slightly lower frequencies of activated CD4+CD25+Foxp3+ cells (1.539 ± 0.1279 vs. 1.838 ± 0.2259, p = ns.). Interestingly, also frequencies of CD4+CD25+Foxp3+ regulatory T cells were lower in MiR155-PIL (1.689 ± 0.1388 vs. 2.375 ± 0.2320, p = 0.03). Upon restimulation, CD4+ cells showed a more pronounced Th2 and Th17 response in WT-PIL, but no significant differences in Th1 phenotype (Fig. 1D).

Conclusion: MiR155 deficiency in PIL mice did not prevent the development of disease, but was associated with less severe lung and kidney involvement, lower serum auto-abs levels and lower Th17 and Th2 frequencies when analyzed in fully established PIL after 8 months. Thus, antagonism of miR155 might be a beneficial future approach in treating SLE.

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Inhibiting Tweak (TNF-like weak inducer of apoptosis) Signaling Improves Blood Brain Barrier Integrity and Protects from Neuronal Damage in Murine Neuropsychiatric Lupus. Jing Wen1, Jessica Doemer1, Ariel Stock1, Jennifer Michaelson2, Linda Burkly3, Maria Gulinello1 and William Putterman1, 2Albert Einstein College of Medicine, Bronx, NY. 2Biogen Idec, Cambridge, MA.

Background/Purpose: While neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) is relatively common and appears early, the underlying mechanisms are not fully understood. The disruption of the blood brain barrier (BBB) is believed to be one key pathological feature in NPSLE, allowing the passage of neurotoxic autoantibodies into the brain. TWEAK is a cytokine member of the TNF superfamily; the TWEAK receptor, Fn14, is expressed in brain endothelial cells, astrocytes, microglia and neurons. We recently found that lupus prone MRL/lpr Fn14 knockout (KO) mice display a markedly attenuated neuropsychiatric phenotype, as revealed by a significant reduction in depressive-like behavior and improved cognitive function. Moreover, NPSLE patients demonstrate high levels of TWEAK in the cerebrospinal fluid (CSF). We undertook the current studies to determine the mechanisms by which TWEAK signaling is involved in the pathogenesis of NPSLE.

Methods:Brains from female MRL/lpr Fn14WT and MRL/lpr Fn14KO mice at 20 weeks of age were prepared for qRT-PCR, Western blot, and immunohistochemistry (IHC). Cellular infiltrates were quantified by hematoxylin and eosin staining. To assess BBB integrity, extravascular fibronectin and IgG deposition, VCAIMCAM, and iNos expression was evaluated by Western blot, IHC and qRT-PCR, respectively. Complement activation was assessed by measuring the expression of C3, C4a and C6 by qRT-PCR and Western blot. Fluoro Jade B and TUNEL staining were employed to analyze neuronal damage and apoptosis in the brain. Furthermore, gliosis, neuron loss, and neurogenesis were assessed by immunostaining with GFAP, NeuN and Ki-67, respectively.

Results: We found that MRL/lpr Fn14KO mice had significantly improved BBB integrity, as shown by a lower CSF albumin index, decreased fibronectin and IgG deposition, and reduced brain expression of VCAIMCAM and iNos. Furthermore, Fn14KO mice exhibited significantly fewer cellular infiltrates in the choroid plexus compared to the Fn14WT mice. At the same time, a significant reduction in C3, C4a and C6 expression was observed in brains of Fn14KO mice. Neuronal damage, an important pathological change present in lupus animal models, was also ameliorated by Fn14 deficiency. Fn14KO mice displayed reduced apoptosis in the cortex, as well as less neuron loss and less gliosis in the hippocampus. Interestingly, there were no differences in neurogenesis and in microglia activation between Fn14KO and Fn14WT mice.

Conclusion: Our studies indicate that TWEAK/Fn14 interactions can play a central role in the pathogenesis of NPSLE by improving BBB integrity.
Identification of EAT-2 As a Lupus Susceptibility Gene in New Zealand Black (NZB) Mice That Regulates Dendritic Cell Function. Nafiseh Talaei1 and Joan E. Wither2. 1Toronto Western Research Institute, Toronto, ON; 2Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: We have previously shown that B6 mice with an introgressed homozygous NZB chromosome (c) 1 interval (70 to 100 cM) develop high titres of antinuclear antibodies and severe glomerulonephritis (GN), with approximately 40% of the mice dying by 8 months age. Using subcongenic mice with shorter intervals in this region we found that Gc and dendritic cell (DC) defects, derived from several genetic loci, synergize to convert the preclinical disease in c1(96–100) mice to fatal GN in c1(70–100) mice through expansion of pro-inflammatory T cell subsets. EAT-2, an adapter molecule in the SLAM signaling pathway that is located in the 70–96 cM region, has a promoter polymorphism in NZB mice that is predicted to lead to decreased expression. In this study we examine whether altered expression of this molecule leads to the abnormal DC function observed in these mice.

Methods: Expression levels of EAT-2 were evaluated in bone marrow derived DC from c1 congenic and B6 mice using qRT-PCR and Western blots. siRNAs targeting EAT-2 gene were introduced into B6 and c1 congenic DC. Subsequently, naïve OVA-specific TCR transgenic (OTII) T cells from B6 and c1 congenic mice were isolated and co-cultured with EAT-2 silenced or scrambled control treated DC in the presence of OVA peptide. In parallel DC were stimulated with anti-CD40 before and after knock-down of EAT-2. Production of cytokines (IL-12, IL-6, IFN-g) by DC and T cells were analyzed by flow cytometry.

Results: Expression of EAT-2 was reduced by ~70% in DC from c1(70–100) mice as compared to c1(96–100) and B6 mice. Silencing of the EAT-2 gene in DC from B6 and congenic mice resulted in increased production of IL-12 as compared to scrambled control and was associated with increased differentiation of OVA-specific T cells from both B6 and c1 congenic mice to a Th1 phenotype. Knock-down of EAT-2 in DC from all strains of mice did not affect IL-6 production when co-cultured with B6,OTII T cells, however increased IL-6 production was seen for c1(96–100) and c1(70–100) DC when co-cultured with naïve T cells from c1 congenic mice. This was accompanied by somewhat enhanced production of IL-21, but not IL-17, by c1 congenic OTII T cells. SLAM/SLAM homotypic interactions inhibit production of IL-12 and IL-6 by CD40L-activated DCs. Consistent with a role for EAT-2 in this inhibition, knock-down of EAT-2 resulted in increased production of IL-12 by CD40-stimulated B6 and c1 (96–100) DC. This was recapitulated in c1(70–100) DC, which demonstrated increased production of IL-12, and a trend to increased production of IL-6, as compared to B6 or c1(96–100) DC following CD40 stimulation.

Conclusions: EAT-2 negatively regulates cytokine production in DC downstream of the SLAM molecules and a genetic polymorphism leading to low levels of EAT-2 in c1(70–100) mice may contribute to the increased production of IL-12 we have previously observed for their DC.

Disclosure: N. Talaei; None. J. E. Wither; None.

Dermal Injury Promotes Nephritis Flare in Lupus-Prone NZM2328 Mice. Kaitlyn Clark, Tamra J. Reed, Jeffrey B. Hodgin and J. Michelle Kahlenberg. University of Michigan, Ann Arbor, MI.

Background/Purpose: Systemic lupus erythematosus is an autoimmune disease with pleotropic manifestations, including severe skin disease, hematologic abnormalities and nephritis. Clinically, lupus is characterized by episodes of flare and remission, and exposures such as UV light or viral infections have been proposed as flare triggers. However, induction of flare has been difficult to emulate in murine models. Here, we describe a system in which cutaneous injury is able to trigger the development of a lupus nephritis flare in lupus-prone mice.

Methods: 20-week old NZM2328 (NZM) female mice were depleted in a 2x4 cm area on the dorsal skin followed by 25 applications of duct tape under isofluroane anesthesia. NZM mice lacking the type I interferon (IFN) receptor (iNZM) were used as a non-lupus prone control. Skin biopsies were taken prior to and following tape-stripping, and gene expression changes were evaluated via quantitative PCR. Serial blood draws and urine collection were obtained following tape stripping, and anti-double-stranded DNA titers, C3 levels and urine albumin/creatinine ratios were measured via commercially available kits. Inflammatory cells were isolated from whole kidneys and cell populations were measured via flow cytometry. Renal immune complex deposition was assessed via immunofluorescent staining for IgG and C3. Renal inflammation was assessed on Hematoxylin and Eosin stained sections by a blinded renal pathologist.

Results: NZM mice subjected to tape stripping had a rapid dermal upregulation of type I IFN-mediated and inflammatory gene expression. Importantly, tape-stripped NZM mice developed onset of proteinuria and death within 3 weeks of skin injury whereas non-taped stripped littermates remained free of proteinuria. This was coupled with a drop in serum C3. Proteinuria induction did not occur in tape-stripped iNZM mice, suggesting the rapid death was not secondary to skin injury itself. In NZM mice, renal immune complex deposition was enhanced within two weeks of tape stripping, as was renal expression of the B cell chemokine CXCL13. Evaluation of renal inflammatory cell populations revealed an increased infiltrate of B cells in the kidney prior to proteinuria onset.

Conclusion: Cutaneous injury via tape-stripping induces a rapid flare of lupus nephritis that is preceded by enhanced renal immune complex deposition and B cell recruitment. This novel model provides a mechanism to study the communication between the dermal and renal immune systems and how crosstalk between these systems can lead to lupus flare, thus providing potential targets for prevention of flares in human disease.

Disclosure: K. Clark; None. T. J. Reed; None. J. B. Hodgin; None. J. M. Kahlenberg; None.

Type I Interferon Induces the Depletion and Dysfunction of Endothelial Progenitor Cells in Gld. ApoE−/− C57BL/6 Mice. Linyu Geng, Shiyong Wang, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: To study whether the accelerated atherosclerosis in SLE is mediated by type I interferon (IFN-I) through the regulation of endothelial progenitor cells (EPCs) in gld. ApoE−/− C57BL/6 mice under normal chow diet.

Methods: The gld. ApoE−/− mice were generated through intercrossing of gld and ApoE−/− mice on C57BL/6 background. At 20 weeks of age, female gld. ApoE−/− mice were injected with either saline vehicle, synthetic CPG-oligodeoxynucleotides (CPG-ODN) IRS423 (TLR7/9 agonists) or IRS661 (TLR7 antagonists) twice a week. 4 weeks later, mice were euthanized. Quantitative PCR was applied to detect the mRNA expressions of these genes. The number of EPCs and the ability of EPC to differentiate into mature endothelial cells, to re-adherent and to ing IRF7, MX1, OAS1, OAS2 and IFIT-2), while IRS423 promoted the expressions of these genes. The number of EPCs and the ability of EPC to differentiate into mature endothelial cells, to re-adherent and to

Conclusions: Type I interferon could induce the depletion and dysfunction of both peripheral and BM EPCs in gld. ApoE−/− C57BL/6 mice, thus may contribute to the development of atherosclerosis.

Disclosure: L. Geng; None. S. Wang; None. X. Feng; None. L. Sun; None.
Hydroxychloroquine Is Cardioprotective in an In Vivo Rat Model of Myocardial Ischaemic Reperfusion Injury. Lauren Bourke1, Valerie Taylor2, James McCormick3, Charis Pericles4, John Franklin5, Daniel Stickey6, Mark Lythgoe7, Anastasis Stephanou8 and Yiannis Ioannou3.

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Background/Purpose: A significant amount of myocardial damage during a myocardial infarction (MI) occurs during the reperfusion stage which is known as ischaemic reperfusion (IR) injury and can account for up to 50% of cell death. Systemic lupus erythematosus (SLE) is associated with increased cardiovascular morbidity and mortality. Many of these patients are treated with the drug Hydroxychloroquine (HCQ) and whilst retrospective studies have suggested HCQ lowers the risk of suffering an MI, inevitably many still do. This study investigates the effects of HCQ on myocardial survival during reperfusion (IR) injury.

Methods: Male Sprague-Dawley rats (200–220g) were dosed by gavage with 200mg/kg of HCQ once a day for three days which yielded blood concentrations of HCQ in line with that seen in patients (1–2µg/ml). Rats underwent myocardial IR injury by occlusion of the left anterior descending (LAD) coronary artery, with reperfusion after 40 mins. Twenty-four hours later animals were sacrificed. Hearts were excised and hearts perfused in vitro with red blood cells and the hearts perfused with Evans Blue dye (to label perfused myocardium). Hearts were then cut into 1mm slices and stained with TTC to label viable myocardium. Infarct size (IS) was calculated as entire myocardium area - area of viable tissue. Area at risk (AAR) was then calculated from entire myocardium area - perfused myocardium from the area of viable myocardium. In vitro experiments were performed in neonatal rat cardiomyocytes isolated from 1–2 day old rat pups and exposed to simulated IR injury using a hypoxic chamber. Protein lysates were collected and processed for use in western blot.

Results: In vivo, HCQ resulted in a significant reduction in infarct size (IS) presented as a percentage of area at risk (AAR) (area supplied by the LAD). Control rats had an IS/AAR of 20.36% (n=5), which was significantly reduced in the presence of HCQ to 13.41% (n=5) (p=0.0159). When the hearts were probed for the protective kinase ERK, there was a significant increase in the phosphorylation of ERK in the presence of HCQ - control 0.11 for p-p42 and 0.14 for p-p44 versus HCQ 0.55 (p=0.029) for p-p42 and 0.52 (p=0.020) for p-p44. In vitro data has also shown that pre-treatment of neonatal rat cardiomyocytes with HCQ prior to simulated IR injury was protective, specifically reducing apoptosis. This was observed by a reduction of 43.74% (p value <0.0001) in the number of TUNEL positive cells during apoptosis.

Conclusion: HCQ is cardioprotective in this in vivo IR injury model and phosphorylation of the pro-survival kinase ERK is enhanced in the presence of HCQ. Mechanistic experiments in vitro demonstrate that HCQ protection is ERK dependent.

Disclosure: L. Bourke, None; V. Taylor, None; J. McCormick, None; C. Pericles, None; J. Franklin, None; D. Stickey, None; M. Lythgoe, None; A. Stephanou, None; Y. Ioannou, None.

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Breath of B Cell Tolerance in New Zealand Black Chromosome 1 Congenic Mice. Kieran Manion1, Nan-Hua Chang2, Yuriy Baglaenko3 and Joan Wither4.

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Background/Purpose: Mapping studies in the lupus-prone New Zealand Black (NZB) mouse strain identified an interval from 170.8–181 Mb on chromosome 1 sufficient to induce B cell-intrinsic increases in B cell activation, germinal center formation and anti-ssDNA autoantibody production when introgressed onto a non-autoimmune C57BL/6 background. It was previously shown that B cells from these mice (denoted c1) expressing a transgene for hen egg lysozyme (HEL)-specific immunoglobulin in the presence of soluble HEL were able to breach anergy. The purpose of the current study was to determine if the autoimmune phenotype in c1 mice similarly resulted from a breach of anergy in DNA-reactive B cells.

Methods: To generate mice with a homogeneous, anergic B cell repertoire, genes for heavy (3H9) and light (Vκx) chains specific for ssDNA were backcrossed onto the c1 strain (c1.Vκ8/3H9). Mice with both knock-in genes were aged to 8 months, at which time autoantibody production and B cell localization, activation and differentiation were assessed by ELISA and flow cytometry, respectively. Adoptive transfers were conducted by staining 10 million negatively isolated splenic B cells from 8–10 week old B6.Vκ8/3H9 or c1.Vκ8/3H9 mice with carboxyfluorescein succinimidyl ester (CFSE) and injecting them via tail vein into B6 or c1 mice. Splenic B cell subsets were analyzed by flow cytometry 7 days post-injection to assess survival, activation, plasma cell differentiation and germinal center recruitment. Germinal centers and plasma cells were further quantified by immunofluorescence microscopy.

Results: Surprisingly, analysis of autoantibody production and splenic B cell subsets in c1.Vκ8/3H9 mice revealed a reduced breach of tolerance to ssDNA as compared to c1 mice and a failure to recapitulate the cellular defects observed in the HEL model. To examine whether the preponderance of anergic B cells in the repertoire of c1.Vκ8/3H9 mice was suppressing the breach of tolerance that would otherwise occur, adoptive transfers of B6.Vκ8/3H9 and c1.Vκ8/3H9 B cells into recipients lacking the knock-in genes were performed. Supporting the previous observations of a breach of cell tolerance in the c1 HEL model, transferred c1.Vκ8/3H9 B cells showed significantly increased activation compared to their B6 counterparts. Furthermore, increased marginal zone localization and a corresponding decrease in the size of the mature follicular subset for transferred c1.Vκ8/3H9 B cells were observed. Despite this, preliminary data did not reveal a difference between transferred B6.Vκ8/3H9 B cells and transferred c1.Vκ8/3H9 B cells with respect to recruitment to germinal centers in either B6 or c1 recipients, suggesting that the activation of transferred c1.Vκ8/3H9 B cells may be extrinsic in nature.

Conclusion: The results reaffirm previous findings that c1 mice breach tolerance to nuclear self-antigen through an intrinsic B cell defect. There is also indication of an active role for anergic B cells in maintaining tolerance through immune suppression.

Disclosure: K. Manion, None; N. H. Chang, None; Y. Baglaenko, None; J. Wither, None.
Results: In 7 month old female B6.SLE1 mice, 10% of mice developed anti-dsDNA IgG. Neither C1q nor C3 deficiency alone changed the percentages of anti-dsDNA IgG+ mice. MFG-E8+/− SLE1 mice had a significantly higher number of germinal center B cells and 30% of females became anti-dsDNA IgG+. Combining MFG-E8+/− with either C1q+/− or C3+/− significantly accelerated the production of anti-dsDNA IgG and increased the percentage of anti-dsDNA IgG+ mice to 65% and 80%, respectively (Figure). Furthermore, 50% MFG-E8+/−C1q+/− but 0% FG-E8−/−C3−/− SLE1 mice showed early mortality due to spontaneous lupus nephritis. When exposed to UVB irradiation, 90% (8 out 9) MFG-E8−/−C3−/− developed either acute nephritis or persistent skin lesions. On the contrary, none of MFG-E8−/−C1q+/− mice (0 out 15) experienced similar symptoms.

Conclusion: Both C1q and C3 are essential in reducing the immunogenicity of apoptotic cells in lupus. The protective mechanisms they provide depend on availability of other opsonins and environmental factors such as sunlight exposure.

Disclosure: C. Sontheimer, None; Y. Nguyen, None; K. B. Elkon, None; Y. Peng, None.

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Background/Purpose: The immunomodulating roles of estrogens are not completely understood. Although 17β estradiol (E2) has been shown to promote systemic autoimmunity, it has also been shown to inhibit pro-inflammatory cytokine secretion. We showed previously that treatment of male mice with E2 led to improved survival in nephrotoxic serum induced nephritis (NTN). In this study we aimed at determining the effect of E2 on intrinsic renal cells and to understand the role of E2 in regulating inflammation in vivo in the kidney during nephritis. Vascular Cell Adhesion Molecule, VCAM-1, is an adhesion molecule for leukocytes that is upregulated in vivo in mice with autoimmune nephritis, and in vitro in tubular epithelial cells and mesangial cells (MCs) upon stimulation with tumor necrosis factor alpha (TNFα) and Interferon gamma (IFNγ). In this study we determined whether E2 regulates the extent of renal inflammation by regulating adhesion molecule expression by MCs.

Methods: We used nephrotoxic serum induced nephritis as a model of autoimmune nephritis. Mice were treated with E2 pellets prior to induction of nephritis. We determined the molecular mechanisms of VCAM-1 regulation by E2 using cell and molecular biology techniques such as flow cytometry, immunofluorescence, Chromatin immunoprecipitation (ChIP) assays, and quantitative PCRs in TNFα stimulated MCs.

Results: We show that E2 treatment inhibited VCAM-1 upregulation in kidneys in vivo during NTN in both male and female mice. E2 also inhibited upregulation of VCAM-1 in MC upon TNFα stimulation. The VCAM-1 upregulation in MCs was regulated by the transcription factor NFκB, since inhibition of NFκB blocked the upregulation. We further determined the molecular mechanism of regulation of VCAM-1 by E2. We show that E2 does not regulate the nuclear translocation of p65 subunit. ChIP assays showed that although E2 does not inhibit p65 binding to the VCAM-1 promoter, it inhibits the recruitment of RNA polymerase II to the promoter, suggesting that E2 may inhibit the formation of pre-initiation complex at the promoter. We showed previously that absence of Poly (ADP-Ribose) Polymerase-1 (PARP-1) inhibited TNFα stimulated VCAM-1 upregulation in mouse MCs. PARP-1 has been shown to interact with estrogen receptor and we showed that E2 inhibits PARP-1 activity in macrophages. PARP-1 has also been proposed as a co-factor for NFκB activation. We therefore determined whether E2 regulates VCAM-1 upregulation through PARP-1. Indeed our data show that PARP-1 interacts with p65 upon TNFα stimulation and this interaction is inhibited in the presence of E2.

Conclusion: Our data show that E2 inhibits upregulation of VCAM-1 in nephritic kidneys. Using mesangial cells we further showed that E2 inhibits VCAM-1 upregulation by inhibiting the formation of pre-initiation complex at the VCAM-1 promoter. E2 inhibits PARP-1 recruitment to p65, further inhibiting the recruitment of RNA polymerase II and transcription at the VCAM-1 promoter. We propose that E2 plays an important role in regulating renal inflammation locally, which may explain why nephritis in systemic autoimmunity tends to be worse in males.

Disclosure: N. Jog, None; R. Caricchio, None.

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Background/Purpose: Systemic autoimmune diseases such as lupus affect multiple organs including skin and kidneys, usually in a diverse fashion whereas only certain organs are affected in individual patients. It is unclear whether the breakdown in tolerance manifested by global immune dysregulation can account for the tissue specificity in relation to heterogeneity of disease, or if local factors also contribute. We hypothesized that the local immune environment may regulate tissue specificity and chose to study skin tolerance within a systemic lupus disease model. Here, we investigated whether a subset of skin-resident dendritic cells, namely Langerhans cells (LC), maintain immune tolerance in skin versus other target organs in a model of SLE.

Methods: We used genetically lupus-prone MRL/MpJ-Fas+/+ (MRL+/+) and MRL-lpr mice that develop lupus dermatitis, nephritis, arthritis, vasculitis, and dsDNA antibodies as models of systemic autoimmunity. To conditionally ablate LC in these mice, we introgressed the Langerin-DTR-EGFP knockin mutation from the stock B6 onto the MRL by back-crossing >10 generations, and injected diphtheria toxin in adult mice. Recombinant desmoglein 3 (Dsg3) was used as a skin autoantigen to assess tissue-specific tolerance using an epicutaneous tolerization assay. Thymidine uptake/Ki67 expression was used for cell proliferation and Western blot for measuring autoantibodies against skin lysate. Disease was assessed by clinical and histological scoring.

Results: We previously reported that MRL mice have reduced migration of langerin+ DC from the skin to the skin-draining lymph nodes (dLN), with a profound defect in the emigration of LC from their epidermis. This migration defect worsens with age and disease onset. We hypothesized that this impaired DC migration observed in MRL mice play a role in the loss of skin tolerance. Indeed, lymphocytes from dLN of MRL-lpr mice spontaneously proliferate to a skin autoantigen, desmoglein 3 (Dsg3), which can be reversed by the epicutaneous application of Dsg3. Such resumption of tolerance to skin antigen, however, is prevented upon a transient ablation of LC in these mice. We then asked that if reduced DC cell migration to the dLN contributes to lupus dermatitis, then the complete ablation of them would further exacerbate dermatitis. Indeed, an inducible LC ablation in adult MRL-lpr and MRL+/+, but not in B6 and B6-lpr mice, accelerated and exacerbated lupus dermatitis and increased circulating antibodies against skin antigens, along with reduced frequency of IL-10-producing CD4 T cells in dLN. However, LC ablation did not affect disease in other organs such as kidneys, lung, or liver, and serum levels of systemic autoantibodies such as anti-dsDNA.

Conclusion: These data indicate that LCs maintain skin tolerance in systemic lupus, and highlight the importance of the local immune milieu in regulating tissue-specific autoimmunity, without affecting systemic immunity. Such immune regulation at the local level may explain the heterogeneity of multorgan involvement in SLE. Our data have implications for therapy at the local organ level, providing a target for therapy to correct a local breakdown in tolerance rather than attempting correction at a systemic level.

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Microthrombotic Renal Vascular Lesions Are Associated to Increased Renal Inflammatory Infiltration in a Mouse Model of Lupus Nephritis.

Maria Galindo, Elena Gonzalo-Gil, Oscar Toldos, Carmen García-Herrero, Alicia Usategui, Sonia Pérez-Yagüe, Gabriel Criado, Domingo F. Barber and Jose L. Pablos. Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain, Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain.

Background/Purpose: In patients with lupus nephritis (LN), acute renal vascular and atherosclerotic lesions correlate with the degree of inflammation regarding the presence of antiphospholipid antibodies. The aim of this study was to confirm these results in MRL/lpr mice and to analyze the specific effect of blocking inflammatory factors and/or platelet aggregation.

Methods: The pattern of renal vascular disease, acute and chronic glomerular and tubulointerstitial lesions were specifically analyzed with histological staining (H&E, PAS) in 12–20 wk old female MRL/lpr mice with nephritis. Immunohistochemistry (IHC) techniques were used to detect CD41 (platelet aggregates), fibrinogen (FGN), periglomerular macrophagic F4/80 (quantified as the % of positive glomeruli), intraglomerular macrophage infiltration (Mac-2) and C3 deposition. Renal function was assessed by measuring proteinuria, serum creatinine and albumin (sCr, sAlb). Levels of a-dsDNA and anticardiolipin (aCL) antibodies were quantified by ELISA. The specific effect of treatment with steroids and antiaggregation (aspirin or clopidogrel) was analyzed. Association between categorical variables was tested by the Chi² test. For continuous variables, comparisons were carried out using t-test for two independent samples. A Spearman’s rank was used for correlations among different study parameters. P values < 0.05 were considered significant.

Results: In the descriptive phase, 41 mice were analyzed. Histological, IHC and clinical characteristics of lpr mice with lupus nephritis are described in table 1.

Mice with microthrombotic renal vascular lesions showed a greater degree of glomerular macrophage infiltration (r=0.002; all mice had detectable a-dsDNA or aCL IgG, irrespective of the presence of TMA or CD41+). Proteinuria positively correlated to the proportion of sclerotic glomeruli (r=0.4; p=0.01) and glomerular macrophage infiltration (r=0.46; p=0.004) and was higher in mice with diffuse proliferative glomerular lesions (340.8 vs 110.8; p=0.02).

After two weeks of treatment, the specific effect of 15 mg/d dexamethasone, 10 mg/d aspirin or 1.5 mg/d clopidogrel, or combined therapy dexamethasone and antiaggregation was compared to PBS treatment in 52 mice, and results are detailed in table 2.

Table 1

<table>
<thead>
<tr>
<th>Glomerulonephritis</th>
<th>Mice (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular lesions:</td>
<td></td>
</tr>
<tr>
<td>Focal and segmental proliferative</td>
<td>53.7%</td>
</tr>
<tr>
<td>Diffuse proliferative</td>
<td>46.3%</td>
</tr>
<tr>
<td>Intestinal fibrosis</td>
<td>5%</td>
</tr>
<tr>
<td>Intertstitial inflammation:</td>
<td></td>
</tr>
<tr>
<td>Medullar</td>
<td>7.30%</td>
</tr>
<tr>
<td>Cortical</td>
<td>29.30%</td>
</tr>
<tr>
<td>Both</td>
<td>36.60%</td>
</tr>
<tr>
<td>Mice with sclerotic glomeruli (number of glomeruli)</td>
<td>46% (1–11)</td>
</tr>
<tr>
<td>Microthrombotic renal vascular lesions (thrombotic microangiopathy (TMA) or CD41+ microthrombi)</td>
<td>34%</td>
</tr>
<tr>
<td>Glomerular/extraglomerular FGN (%)</td>
<td></td>
</tr>
<tr>
<td>Glomerular Mac-2 (%)</td>
<td>4.8 ± 3.6</td>
</tr>
<tr>
<td>Periglomerular F4/80 ( + glom %)</td>
<td>3.9 ± 2.3</td>
</tr>
<tr>
<td>Mean sCr (mg/dl)</td>
<td>41.9 ± 21.4</td>
</tr>
<tr>
<td>Proteinuria (&gt;300mg/dl)</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>PBS</th>
<th>dexamethasone (15 mg/d)</th>
<th>aspirin/ clopidogrel</th>
<th>dexamethasone and antiaggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp1</td>
<td>N=8</td>
<td>N=9</td>
<td>N=8</td>
</tr>
<tr>
<td>↓ proteinuria**</td>
<td>↓ proteinuria</td>
<td>↓ proteinuria**</td>
<td>↓ proteinuria</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.01; *** P<0.001; NS: no significant

Conclusion: Presence of microthrombotic renal vascular lesions is associated to a higher degree of macrophage infiltration in MRL/lpr model of LN. Both dexamethasone and blockers of platelet aggregation reduce glomerular damage and inflammatory response, suggesting platelets involvement in inflammatory damage.

Disclosure: M. Galindo, None; E. Gonzalo-Gil, None; O. Toldos, None; C. García-Herrero, None; A. Usategui, None; S. Pérez-Yagüe, None; G. Criado, None; D. F. Barber, None; J. L. Pablos, None.

661 Dysfuncion of Glycosphingolipid Metabolism in Lupus Nephritis.

Thirumagal Thiyagarajan, Leah Siskind, Jim Oates, Richard Drake and Tamara K. Nowling. 1Medical University of South Carolina, Charleston, SC, 2University of Louisville, Louisville, KY, 3Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC.

Background/Purpose: Lupus is a chronic autoimmune disease characterized by autoantibody production and aberrant activation and proliferation of lymphocytes. Subsequent deposition of immune complexes in target tissues leads to an inflammatory reaction and tissue damage. Glomerulonephritis (GN) is the most severe complication of lupus, lupus nephritis (LN) affecting up to two-thirds of lupus patients and is associated with high morbidity and mortality. LN is characterized by podocyte dysfunction, proteinuria and a decrease in renal function. Glycosphingolipids (GSLs) are a heterogeneous class of lipids in the sphingolipid family that play a role in the regulation of cellular processes. Highly abundant in the kidney, GSLs are present in most cells and are thought to play roles in signal transduction, cell-cell adhesion and immune responses. GSLs are enriched in the kidney. Loss of sialic acid residues from the surface of podocytes is linked to proteinuria in GN. Neuraminidases (NEUs) remove sialic acids from gangliosides to generate lactosylceramide (LacCer) and glucosylceramide, (GlcCer) ganglioside precursors.

Methods: Kidney homogenates, serum and urine samples were prepared from 11, 14 and 18 week-old MRL/lpr mice and human lupus patients and controls. GSL levels were measured by Supercritical Fluid Chromatography coupled with tandem mass spectrometry. NEU protein and activity were measured by western immunoblot and/or enzyme activity assays. Gene expression was analyzed by real-time RTPCR on RNA isolated from kidney cortex. Matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) and immunohistochemistry for LacCer was performed on frozen kidney sections.

Results: GlcCer and LacCer levels are significantly elevated 3–5-fold, NEU activity and Neul expression levels are significantly elevated 2-fold and...
12-fold, respectively, in the kidney of lupus mice with nephritis compared to lupus mice without nephritis and/or normal, healthy controls. Levels of ceramide and other enzymes in the GSL metabolic pathway are unchanged. Urine LacCer levels appear to be significantly elevated prior to significant increases in proteinuria. Using MALDI-IMS, we also observed a striking decrease in the levels of gangliosides GM1 and GM3 in the LN mice compared to controls. Of translational significance, human LN patients compared to controls have a 1) significant 25-fold increase in urine LacCer levels, 2) significant increase in urine Neu1 levels, and 3) observed increased LacCer levels in the mesangial regions in renal biopsy sections. No significant differences were observed in serum LacCer levels in LN patients compared to controls.

Conclusion: Our results demonstrate that elevated LacCer is likely due to an upregulation of the GSL catabolic pathway in the kidney of lupus mice and patients with nephritis. Furthermore, the elevated LacCer levels in the urine of patients may be largely due to kidney rather than systemic contributions and our mouse studies suggest it may be an earlier marker than proteinuria of nephritis.

Disclosure: T. Thiyagarajan, None; L. Siskind, None; J. Oates, None; R. Drake, None; T. K. Nowling, None.

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Interferon Regulatory Factor-5 Promotes Disease in the MRL/lpr Mouse Model of Lupus. Amanda Watkins, Ramon Bonegio, Guneet Kochar, Gabriella Wilson, Bari Laskow, Christophe Richez, Ian Rifkin and Kei Yasuda. Boston University School of Medicine, Boston, MA.

Background/Purpose: Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated with an increased risk of developing Systemic Lupus Erythematosus (SLE). SLE is caused, in part, by the survival of self-reactive B cells which produce autoantibodies that can deposit in tissues such as the kidney leading to tissue injury and significant morbidity.

In murine lupus models, IRF5-deficiency has been shown to reduce disease severity, in part, by ameliorating immune complex-mediated kidney disease. IRF5 is highly expressed in B cells where it is involved in isotype switching to IgG2a and TLR-mediated activation. However, whether IRF5 contributes to lupus pathogenesis by promoting B cell differentiation or plasma cell survival is not fully understood. We hypothesized that IRF5 may contribute to disease in the MRL/lpr lupus mouse model by promoting B cell survival through regulation of B lymphocyte stimulator (BLyS).

Methods: We evaluated the effect of IRF5-deficiency in the MRL/lpr mouse lupus model by measuring splenomegaly, lymphadenopathy, severity of kidney disease, as well as total serum IgG and anti-Sm/RNP and anti-nuclear autoantibodies. In addition we analyzed the splenic and bone marrow lymphocyte populations and measured serum BLyS levels over the course of disease.

Results: We found that IRF5-deficient (IRF5-/−) MRL/lpr mice developed much less severe disease compared to their IRF5-sufficient (IRF5+/+) littermates. Despite markedly lower serum levels of anti-nuclear autoantibodies and reduced total splenocyte and CD4+ T cell numbers, IRF5-/− MRL/lpr mice had similar numbers of all splenic B cell subsets compared to IRF5+/− MRL/lpr mice, suggesting that IRF5 is not involved in B cell development to the mature B cell stage. However, IRF5-/− MRL/lpr mice had greatly reduced numbers of splenic plasmablasts and bone marrow plasma cells. Despite the marked reduction in serum IgG and plasmablast numbers in IRF5-/− MRL/lpr mice, serum BLyS levels remained highly elevated with no difference observed between groups.

Conclusion: Overall our data demonstrate that IRF5 contributes to disease pathogenesis in the MRL/lpr lupus model and that this is due, at least in part, to the role of IRF5 in plasma cell formation and independently of BLyS production. Our data also suggest that combined therapy targeting both IRF5 and BLyS might be a particularly effective therapeutic approach in lupus.

Disclosure: A. Watkins, None; R. Bonegio, None; G. Kochar, None; G. Wilson, None; B. Laskow, None; C. Richez, None; I. Rifkin, None; K. Yasuda, None.

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STAT3 Inhibition Delays the Onset of Lupus Nephritis in MRL/lpr Mice. Lindsay Edwards1 and Vasileios C. Kyttarís2. 1Beth Israel Deaconess Medical Center, Boston, MA; 2Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: The transcription factor Signal transducer and activator of transcription (STAT) 3 is overexpressed and aberrantly activated in patients with SLE as well as lupus-prone mice. More specifically, STAT3 plays a central role in T cell differentiation into pathogenic Th17 as well as T follicular helper cells, two T cell subsets that are thought to orchestrate autoimmune responses in SLE. Our previous studies have shown that STAT3 is important in SLE T cell migration in response to chemokines. To better understand its role in SLE, we inhibited STAT3 in lupus-prone mice using the small molecule Stat3i.

Methods: MRL/lpr mice were treated 3 times per week with 10 mg/kg of the STAT3 inhibitor Stat3i or vehicle delivered intraperitoniely beginning at 6 weeks of age and continuing through 15 weeks of age. The kidney function was monitored weekly by urinalysis. Levels of anti-dsDNA antibodies, C3 and various cytokines were measured in the serum. At the conclusion of treatment, tissues were harvested for histology and phenotypic analysis. In vitro assessment of the effects of Stat3i treatment on T cell function was also performed.

Results: Stat3i treated mice exhibited a delay in the onset of proteinuria by approximately 3 weeks. Stat3i treated mice had lower levels of anti-dsDNA production (mean=1771 U/ml in treated vs. 32174 U/ml in control) and decreased autoantibody cytokine production (serum IL-17 levels approximately 2-fold higher in untreated mice). Inhibitor treatment reduced lymphadenopathy, and resulted in a decrease in the total number of T cells in treated mice. Absolute numbers of T cells were 3–4 fold higher in untreated mice. Furthermore, the numbers of T follicular helper cells were reduced in Stat3i treated mice by 4-fold. Complimentary in vitro experiments showed that T cells treated with Stat3i exhibited a dose dependent decrease in proliferation and an approximately 70% decrease in their ability to migrate in response to CXCL12 stimulation.

Conclusion: From the data generated in this study, we conclude that treatment of lupus prone mice with a STAT3 inhibitor delays the onset of autoimmunity and end-kidney damage. Our in vivo and in vitro findings suggest that STAT3 inhibition leads to the following: a. decreased T cell proliferation, b. decreased Tfh cells and decreased anti-dsDNA production, and c. decreased cell migration in response to chemokines. We propose that STAT3 inhibition represents a therapeutic target in SLE and in particular lupus nephritis.

Disclosure: L. Edwards, None; V. C. Kyttarís, None.

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The Pathogenesis of Neuropsychiatric Systemic Lupus Erythematosus Is Dependent on Brain Intrinsic Factors. Ariel Stock, Jing Wen, Jessica Doerner and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: Neuropsychiatric disease is a common manifestation of systemic lupus erythematosus (SLE). Frequent presentations include depression, anxiety, memory loss and cognitive decline. The pathogenesis of neuropsychiatric SLE (NPSLE), however, remains unclear; several potential mechanisms include thrombosis, complement deposition, brain reactive autoantibodies, and cytokine mediated inflammation. The MRL-fas/lpr (MRL/lpr) mouse has proven quite valuable to the study of SLE in general, including NPSLE. This is due to development of a disease profile similar to humans including renal and cutaneous manifestations, as well as an early neuropsychiatric phenotype characterized by depression and spatial memory deficit. However, it is not clear whether the neuropsychiatric manifestations of SLE are secondary to systemic disease or a primary pathogenic process.

Methods: In order to distinguish between the relative contributions of the central nervous system (CNS) vs hematopoietic compartments, we generated three groups of bone marrow chimeras between MRL/lpr mice and the congenic control MRL/+ mouse (Table 1). We monitored systemic disease progression through titers of autoantibodies and levels of proteinuria. The mice underwent extensive behavioral testing to characterize their motor, cognitive and emotional states, including open field, object placement, object recognition and the forced swim tests.

Results: MRL/lprMRL/lpr mice showed increasing autoantibody titers over time, consistent with untransplanted MRL/lpr mice. MRL/+uMRL/+
mice showed consistently low or undetectable levels of autoantibodies. MRL/+àMRL/lpr mice showed early increases in autoantibody titres that decreased over time, indicative of MRL/+ bone marrow engraftment and abrogation of the MRL/lpr systemic disease phenotype. Behaviorally, MRL/+àMRL/lpr mice displayed a phenotype remarkably consistent with MRL/lprMRL/lpr (as well as untransplanted MRL/lpr) mice, including depression like behavior (Fig 1) and increased spatial memory deficits. MRL/+àMRL/lpr mice displayed no behavioral deficits, consistent with untransplanted MRL/lpr mice.

Conclusion: Previous studies have shown that MRL/lpr mice develop neuropsychiatric disease similar to human lupus, though have not determined whether this is a primary CNS manifestation or secondary to peripheral immune abnormalities and systemic disease. The data presented herein indicate that the MRL/lpr CNS is responsible for NPSLE development, which can occur absent hematopoietic contributions.

Table 1. Bone marrow transplant scheme

<table>
<thead>
<tr>
<th>Donor</th>
<th>Host</th>
<th>Chimera</th>
<th>Source of CNS Cells</th>
<th>Source of Hematopoietic Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRL/+</td>
<td>MRL/+</td>
<td>MRL/+àMRL/lpr</td>
<td>MRL/+</td>
<td>MRL/+</td>
</tr>
<tr>
<td>MRL/lpr</td>
<td>MRL/lpr</td>
<td>MRL/lpràMRL/lpr</td>
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<tr>
<td>MRL/+</td>
<td>MRL/lpr</td>
<td>MRL/+àMRL/lpr</td>
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<td>MRL/+</td>
</tr>
</tbody>
</table>

Conclusion: Our results showed that low-dose IL-2 therapy in active SLE was safe and achieved satisfactory efficacy with increasing Treg and decreasing effector helper T cells.

Disclosure: A. Stock, None; J. Wen, None; J. Doerner, None; C. Puttermann, None.

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Approach to Discriminate Treatment Impact in Both Moderate and Severe SLE: The Atacicept Phase III Trial Design. Joan T. Merrill1, Yong Li2, Stephen D. Wax3 and Christopher Teihlirian4. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2R&D Global BioStatistics, EMD Serono, Billerica, MA, 3Global Clinical Development Center - Immunology, EMD Serono Inc, Rockland, MA, 4EMD Serono, Rockland, MA.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by loss of tolerance to nuclear self-antigens, production of pathogenic autoantibodies and damage to multiple organs. While corticosteroids and immunosuppressive agents have improved the outcome of patients, there remains a significant unmet need for safe and more effective treatments. Low-dose Interleukin-2 (IL-2) therapy has recently been shown effective to treat autoimmune disease. We aimed to assess the safety and efficacy of low-dose IL-2 therapy in active SLE.

Methods: We conducted a clinical trial on active SLE patients (NCT02084238). A total of 40 patients were enrolled. Patients with SLE Disease Activity Index (SLEDAI) scores ≥8 received three courses of low dose recombinant human IL-2 (1 million IU every second day for 2 weeks followed by a 2-week hiatus). The primary end point was the response rate at week 10. Both the safety and efficiency of IL-2 therapy were evaluated.

Results: Total 36 patients (36/40, 90%) achieved an SLE Responder Index (SRI) improvement at week 6. No patients demonstrated high grade adverse events; mild injection-site reaction was observed in 5 patients (5/40, 12.5%). Better response was seen in patients with skin involvement (erythema, photo sensitivity, Rynolds, vasculitis), hematologic abnormalities (leukopenia, Thrombocytopenia and anemia) and disease-related fever. Patients showed the improvement of major laboratory indicators, including reduced anti-dsDNA autoantibodies and 24-hour proteinuria, and increased levels of the complement proteins C3 and C4. Immunological analysis showed significant increase of Treg cells and decrease of effector helper T cells after the therapy.

Conclusion: Our results showed that low-dose IL-2 therapy in active SLE was safe and achieved satisfactory efficacy with increasing Treg and decreasing effector helper T cells.

Disclosure: J. He, None; X. Zhang, None; X. Sun, None; J. Guo, None; Y. Wei, None; Z. Hou, None; Y. Di, None; Z. Li, None.

Background/Purpose: Increases in background treatment in SLE trials lead to higher placebo group responses in patients with moderate but not those with high disease activity (1–3). The optimal allocation of background medication increase to ensure patient safety and still enable data interpretability over a range of disease severity remains unknown. Since even moderate lupus activity leads to organ damage, disability and poor quality of life (4–6), a goal of the ADDRESS II trial of atacicept (inhibitor of B cell stimulators BLyS and APRIL) is to discriminate treatment effects on both moderate and high SLE disease activity within one trial.

Methods: This 24 week study examines atacicept (75 or 150 mg/wk) versus placebo for the reduction of SLE disease activity. Similar to the Phase III belimumab (BLISS) program, study drug is added to standard of care. Unlike the BLISS design, which allowed temporary unlimited background steroids and permanent increases in immune suppressant doses, after the Week 4 study visit ADDRESS II restricts the corticosteroid dose to ≤30 mg prednisone (or equivalent), and immunosuppressives must be stable from 2 months before screening throughout the duration of the study. Additional treatment defines a non-responder.

Results: The primary endpoint is similar to the BLISS trials as defined by the SRI (≥4 point reduction in SLEDAI-2K, ≤<10% increase in PGA, no new BILAG A score and ≤1 new BILAG B score, at Week 24 compared to the Screening visit). A placebo response rate of 30% (lower than BLISS placebo rates due to more stringent background medication restriction) is predicted, enabling 80% power to detect a 20% absolute difference in proportion achieving an SRI response with 93 patients per arm and a 2-sided α=0.05 with a randomization ratio of 1:1:1. A steroid reduction endpoint, which includes a provision for lack of flare, will also be examined. Patients are stratified by level of disease activity (SLEDAI < 10 vs. ≥ 10), race, and use of mycophenolate at screening, enabling analysis of response in these subpopulations. A 2 year extension study will give all completers patients the option to receive active treatment (placebo patients will be switched to 150 mg atacicept), but the dose will be blinded, allowing longer term evaluation of responses.

Conclusion: Interpretation of SLE trials is hampered by confusing data in patients with moderate disease activity. The ADDRESS II study was
designed to discern treatment impact in both severe and moderate disease patients, who represent a large, underserved population with poor quality of life and progressive damage despite high response rates to increased standard of care in trials.

References

2. Thanou A. Nat Rev Rheumatol 2014;10:23-34

Disclosure: J. T. Merrill, EMD Serono, 5, GSK, 5, Lilly, 5; Y. Li, EMD Serono, 3; S. D. Wax, EMD Serono, 3; C. Tehilian, EMD Serono, 3.

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24-Month Outcomes Associated with Belimumab in Patients with Systemic Lupus Erythematosus in Clinical Practice Settings. Christopher E. Collins1, Hong Kan2, Maria Dall’era3, Cynthia Macalihig4, Ramesh Pappu5, Charles T. Molta6 and Volker Kosciely7. 1MedStar Washington Hospital Center, Washington, DC, 2GlaxoSmithKline, Research Triangle Park, NC, 3UCSF, San Francisco, CA, 4Medical Data Analytics, Parsippany, NJ, 5GlaxoSmithKline, Philadelphia, PA, 6GlaxoSmithKline, Brentford, United Kingdom.

Background/Purpose: The clinical efficacy of belimumab in patients with systemic lupus erythematosus (SLE) has been demonstrated in large randomized clinical trials. We examined clinical outcomes following belimumab treatment in clinical practice settings in the US.

Methods: OBSERVE US (evaluation of use of Belimumab in clinical practice settings in the US; GSK Study: BLM117295) was a multicenter, retrospective, medical chart review study. Rheumatologists from non-academic centers were randomly recruited from a national physician database. Physicians reported prospective data from medical charts of randomly identified adult SLE patients in their care who had received ≥8 belimumab infusions as part of usual care. Data were reported for 6 months prior to index date (date of first belimumab infusion), and every 6 months thereafter for up to 24 months. The primary outcome measure was physician impression of change in SLE disease manifestations, relative to the previous time point. Here we report the final analyses of patients who had outcomes reported at Month 24.

Results: At index date, 501 patient charts were analyzed. By Month 24, 112 patients were lost to follow-up and 112 patients had discontinued. Most common reasons for discontinuation included patient request (n=112, 40.2%), medication not effective (n=33, 29.5%), disease progression (n=15, 13.4%), loss of insurance or reimbursement (n=14, 12.5%) and lack of patient compliance (n=11, 9.8%). The Month 24 complete analysis included 277 patients: female, 90.6%; mean age, 42.9 (standard deviation [SD]: 12.0) years; Caucasian, 52.7%; African-American, 24.9%; Hispanic, 15.5%; Other, 6.9%.

Of the 277 patients, 134 (48.4%) had ≥50% improvement in overall clinical response between index date and Month 6 according to the physicians’ impression (Figure 1). Further improvements were observed during Months 6-12 and 12-18. At Month 24, 78 (28.2%) patients had improved by ≥50% since Month 18.

Figure 1. Clinical responses in completers (n=277), according to physicians’ impression of overall change in SLE manifestations relative to the previous timepoint.

At index date, 218/277 (78.7%) patients received concomitant steroids (mean [SD] dose: 18.0 [12.2] mg/day); by Month 24, the mean (SD) dose among these patients was 2.9 (3.4) mg/day and 95 (43.6%) patients had discontinued steroids. During the 24-month period six patients initiated steroid treatment.

Of the 277 patients who completed to Month 24, 69 (24.9%) had SELENA-SLEDAI scores available at index date and Month 24; the mean (SD) score at index date was 12.5 (3.0), with a reduction of 8.2 (3.8), to 4.4 (3.1) by Month 24.

Conclusion: Overall, physicians reported continued improvements in clinical outcomes throughout the study, among patients who had completed 24 months of treatment with belimumab 10 mg/kg plus usual care (≥8 belimumab infusions). Over 24 months, mean steroid dose among baseline users was reduced by 84%.

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Disclosure: C. E. Collins, GlaxoSmithKline, 5, GlaxoSmithKline, 8, Abbvie, 8; H. Kan, GlaxoSmithKline, 3, GlaxoSmithKline, 1; M. Dall’era, None; C. Macalihig, Medical Data Analytics, 9; R. Pappu, GlaxoSmithKline, 3, GlaxoSmithKline, 1; C. T. Molta, GlaxoSmithKline, 3, GlaxoSmithKline, 1; V. Kosciely, GlaxoSmithKline, 3, GlaxoSmithKline, 1.

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Evolution of Patients with Systemic Lupus Erythematosus Treated with Belimumab in Clinical Practice Settings. Josefnia Cortes1, Carlos Marras2, Jose Luis Andreu1, Jaime Calvo-Alen3, Angel M. Garcia-Aparicio4, Elvira Fernandez5, Carlos Coronado6, Elena Morejon7, Alessandra Perna8, Volker Kosciely9 and Josep Ordi-Ros1. 1Vall d’Hebron Hospital, Barcelona, Spain, 2Virgen de la Arrixaca Hospital, Murcia, Spain, 3Puerta de Hierro University Hospital, Madrid, Spain, 4Sierallana Hospital, Torrelavega, Spain, 5Virgen de la Salud Hospital, Toledo, Spain, 6Leon Hospital, Leon, Spain, 7GlaxoSmithKline, Madrid, Spain, 8GlaxoSmithKline, Brentford, United Kingdom.

Background/Purpose: After the approval of belimumab for patients with systemic lupus erythematosus (SLE), the objective of this study is to describe the clinical outcomes associated with 6 months of belimumab treatment in clinical practice settings in Spain.

Methods: OBSERVE (GSK 200883) is a multi-center and retrospective study from community-based rheumatology practices with high experience in SLE treatment. All adult SLE patients in their practices who had received belimumab (10 mg/kg) as part of routine care were identified for chart abstraction. Baseline date is the date of belimumab initiation. The activity of the disease was classified as mild, moderate and severe according the perception of the disease manifestations by the physician or based on SELENA-SLEDAI index. The primary clinical outcome measure is the overall clinical response, reported as change from baseline in SLE disease manifestations, 6 months after belimumab initiation based on physician subjective assessment. Reasons for premature treatment discontinuation were collected as secondary variable of safety, and information about steroid use and dosage within the first 6 months of belimumab therapy was collected as secondary variables of efficacy.

Results: 64 eligible patient charts were included. The mean patient age was 42.7 years ± 12; 89% were female; 23% were diagnosed with SLE <5 years ago; 6%, 61% and 33% had mild, moderate and severe SLE respectively at baseline; 70% of patients had low C3 or C4, and 69% high anti-dsDNA at baseline. The most frequent reasons for initiating belimumab were an ineffective previous treatment regimen (78%), the intent to decrease steroid use (58%), and worsening patient condition (55%). The most frequent manifestation of SLE in these patients were musculoskeletal arthritis (56.2%), Immunologic (low complement [C3, C4, or CH50]=53.13), Increased anti-ds-DNA antibody levels=48.44%, and Mucocutaneous Rash=26.56%. In general, belimumab appeared to be well-tolerated; two patients (3%) had discontinued belimumab within the first 6 months of therapy: one due to lack of efficacy, the other due to Pelvic inflammatory disease. After 6 months of belimumab therapy 72%, 52% and 27% of patients had an overall clinical improvement of >20%, >50% and >80% respectively. For the most frequent SLE manifestations, such as in arthritis (69%), low complements (47%), high anti-ds-DNA levels (48%), and fatigue (60%) ≥50% improvement was observed. Additionally, the mean score of the SELENA-SLEDAI index decreased from 10.1 to 4.5 (p<0.0001) in the first 6 months. In 88% of the patients (n=57), a decrease SELENA-SLEDAI index was observed.

Oral steroids were used concomitantly in 95% of SLE patients at baseline. Patients had a mean reduction in steroid dose of 6.8mg/day from 14.8mg/day.

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at baseline after 6 months of treatment with belimumab (p<0.0001). 75% of patients (n=57) experienced a reduction in steroid use during the 6 months.

Conclusion: Among SLE patients treated with belimumab, clinical and serological improvement was observed in a majority of SLE patients over their first 6 months of routine treatment in a sample of clinical practices in Spain.

Disclosure: J. Cortes, GlaxoSmithKline; 5; C. Marras, GlaxoSmithKline; 5; J. L. Andreu, GlaxoSmithKline; Eli Lilly; 5; J. Calvo-Alen, GlaxoSmithKline; Eli Lilly; 5; A. M. Garcia-Aparicio, None; E. Diez Alvarez, None; C. Cornrell, GlaxoSmithKline; 1, GlaxoSmithKline; 3; E. Morejon, GlaxoSmithKline; 1, GlaxoSmithKline; 3; A. Perna, GlaxoSmithKline; 1, GlaxoSmithKline; 3; V. Kosciuch, GlaxoSmithKline; 3; J. Ordí-Ros, GlaxoSmithKline; 3.

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Predicted Chronic Exposure and Dose Selection for Belimumab Administered Subcutaneously to SLE Patients. Herbert Struempfer1, David Roth2 and Angela Tincani2. 1GlaxoSmithKline, Research Triangle Park, NC; 2Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, 2AlbaNova, Stockholm University, Stockholm, Sweden.

Background/Purpose: Monthly (q4w) intravenously (IV) administered belimumab 10 mg/kg is approved for the treatment of adults with active, autoantibody-positive SLE receiving standard therapy. The present analysis was conducted to predict a safe and efficacious weekly (qw) belimumab subcutaneous (SC) dose to be evaluated in a SC Phase 3 trial in adult SLE patients.

Methods: The belimumab IV Phase 3 clinical trials BLISS-52 and BLISS-76 indicated better efficacy with comparable safety for the 10 mg/kg versus the 1 mg/kg dose. A Phase 1 study (BEL114448: NCT01583530) evaluated the pharmacokinetics (PK) of SC belimumab in healthy subjects as a single or multiple doses up to 240 mg. IV and SC PK parameters were estimated using linear, 2-compartment PK models with NONMEM and Pharsight Phoenix modeling platforms, respectively, and chronic exposure profiles were simulated. The target steady-state SC exposure was set to an exposure level approximating the steady-state average belimumab serum concentration (Cavg) for 10 mg/kg IV q4w. Body-size dependent individual clearance values from the population PK analysis of the IV Phase 3 trials were used to predict the range of Cavg for the SC regimen.

Results: Simulation predicted that belimumab Cavg for 200 mg SC qw closely matched the corresponding Cavg for 10 mg/kg IV q4w. The simulated SC profile showed smaller fluctuations compared to the IV regimen, due to the slow absorption and more frequent dosing. At the end of the first month the trough concentration (Cmin) for 200 mg SC dosing is expected to exceed the steady-state Cmin for the 10 mg/kg IV regimen and therefore a loading dose was not deemed necessary.

The predicted body-size dependent steady-state Cavg values for the SC regimen, demonstrated that the Cavg ranges are similar between 10 mg/kg IV q4w and 200 mg SC qw dosing. While for the IV regimen patients with large BMI experienced higher exposure, for the SC regimen higher weight patients are predicted to experience lower exposures.

Conclusion: 200 mg SC qw belimumab is predicted to result in a steady-state belimumab Cavg comparable to the Cavg for 10 mg/kg IV q4w dosing. The fixed SC dose is predicted to result in a similar range of Cavg values as compared to the weight-proportional 10 mg/kg IV dose, albeit with an inverse relationship between body size and exposure. This analysis supported the choice of the belimumab dose tested in the BLISS-SC Phase 3 trial.

Disclosure: H. Struempfer, GlaxoSmithKline; 1, GlaxoSmithKline; 3; D. Roth, GlaxoSmithKline; 3, GlaxoSmithKline; 1; D. Gordon, GlaxoSmithKline; 1, GlaxoSmithKline; 3.

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Decreased Disease Activity and Corticosteroid Usage and No Renal Flares during Belimumab Treatment in Patients with Systemic Lupus Erythematosus. Ioannis Parodis1, Elisabet Svenungsson1, Magnus Axelsson2 and Iva Gunnarsson1. 1Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, 2AlbaNova, Stockholm University, Stockholm, Sweden.

Background/Purpose: B cells have a central role in Systemic Lupus Erythematosus (SLE) and autoantibody production. B-Lymphocyte Stimulator (BLyS) is important for the activation and maintenance of B cells. Belimumab is a recombinant monoclonal antibody that specifically binds to soluble BLyS, and the only biologic agent approved for treatment of SLE. Its effects in patients with lupus nephritis (LN) are poorly known.

The aim of this study was to investigate the effects of belimumab given as an add-on to patients with active SLE despite standard-of-care therapy, with focus on patients with renal involvement.

Methods: Twenty-three patients (mean age 39.5 years) have been treated with belimumab at Karolinska University Hospital and have been included in this prospective observational study. Clinical data were acquired at baseline and at week 12, 26, 52 and 104. Disease activity was assessed using SLE Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus Activity Measure (SLAM). C3 and C4 levels were determined by nephelometry. The predominant organ manifestations to motivate treatment with belimumab were mucocutaneous (n=14) and musculoskeletal (n=14). Thirteen patients with history of LN, five of them having signs for nephritis and low-grade proteinuria, were included.

Results: At baseline, all but 2 patients received oral prednisolone (mean dose 9.1 mg/d, range 0–20 mg/d), 17 patients received antimalarials, 6 received azathioprine, 4 mycophenolate mofetil, 1 methotrexate, and 1 cyclosporine. The median SLEDAI and SLAM scores were 9 (range 2–24) and 12 (range 5–26), respectively.

Significant decreases of both SLEDAI-2K and SLAM were seen at week 12 (p=0.018 and p=0.003, respectively; n=18), 26 (p=0.008 and p=0.002, respectively; n=15), 52 (p=0.003 and p=0.044, respectively; n=12) and 104 (p=0.042 and p=0.042, respectively; n=5), as compared to baseline. Prednisolone dosages were significantly decreased compared to baseline at week 12 (p=0.012, n=18), 26 (p=0.002, n=16), 52 (p=0.005, n=12) and 104 (p=0.043, n=5). Eighteen patients had low complement at baseline. We observed no significant increase in C3 or C4 levels, with the exception of a significant increase of C4 levels at week 12 (p=0.047, n=18).

The patients with history of nephritis had at baseline a mean 24-h albuminuria of 0.25 g/d (range 0.01–1.16 g/d). No renal flare was observed during the study. The grade of proteinuria remained unchanged compared to baseline at all follow-up occasions.

Conclusion: Belimumab treatment decreased SLE disease activity and reduced corticosteroid usage. Despite the limited number of patients, our observations indicate that belimumab may prevent renal flares and may be used in patients with renal involvement and persistent low-grade proteinuria.

Disclosure: I. Parodis, None; E. Svenungsson, None; M. Axelsson, None; I. Gunnarsson, None.

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Belimumab Reduces the Frequency of Flares in Patients with Refractory SLE: DATA from Clinical Practice Setting. Andrea Doria1, Luca Iacca-Parolin1, Silvana Bettio1, Mauro Frassi1, Laura Andreoli2, Rossella Reggia3, Margherita Zen1, Linda Nalotto1, Mariele Gatto1, Lara Pia1, Leonardo Punzi1 and Angela Tincani2. 1University of Padova, Padova, Italy, 2Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Conclusion: Among SLE patients treated with belimumab, clinical and serological improvement was observed in a majority of SLE patients over their first 6 months of routine treatment in a sample of clinical practices in Spain.
Background/Purpose: To investigate the efficacy and safety of belimumab in patients affected with active systemic lupus erythematosus (SLE) refractory to standard therapy in the clinical practice setting.

Methods: Forty-one patients affected with active SLE (1997 ACR criteria), with low complement and high anti-double stranded DNA (dsDNA) antibody levels, unresponsive to corticosteroids, antimalarials and/or immunosuppressant were treated with belimumab (10 mg/kg at day 0, 14 and 28 and then every 28 days) for a median follow-up of 8.9 months (range 13.1–2.0). A total of 426 infusions of belimumab were performed. The median age of patients was 38.9 years (range 21–62) and mean disease duration 12.2 years (range 1–32). SLE Disease Activity Index 2000 (SLEDAI-2K), anti-dsDNA (tested by ELISA or Farr method), C3 and C4 serum levels, and corticoid daily dose were recorded at baseline and every 3 months thereafter. Disease flare was defined according to SLE flare index. Disease flare rate was evaluated in 23 patients prior and during treatment. Adverse events were carefully recorded at each clinical evaluation and were defined severe when hospitalization was required and/or death and/or life-threatening manifestations occurred.

Results: Refractory manifestations requiring belimumab were renal (41.4%), musculoskeletal (36.5%), mucocutaneous (36.5%), hematologic (21.9%), and serositis (4.8%). In the efficacy analysis we considered 34 patients followed for at least 6 months. Decrease in median SLEDAI-2K, anti-dsDNA, and corticoid daily dose and increase in C3 and C4 serum levels at baseline, 3, and 6 months of follow-up are reported in Table 1. Notably, a reduction in the frequency of flares was observed: 70 flare/100 patients in the 6 months before the start of belimumab and 18 flares/100 patients during the 6-month belimumab treatment (p = 0.02).

Adverse events were analyzed in 23 patients. A total of 70 adverse events were observed. Most frequent non infectious adverse events were fatigue (15%), hypertension (7%), and mild hair loss (5%). Infectious adverse events were 38 (54.2%), 34 were mild and 4 were moderate. Mild infusion reactions was observed in 2 patients (8.7%). No severe adverse events were observed.

Conclusion: These preliminary data confirm the efficacy and tolerability of belimumab in the treatment of patients with active SLE refractory to standard treatment in the clinical practice setting. Belimumab seem to reduce the number of disease flares and this suggest that it might be useful especially in those patients with relapsing remitting pattern of disease.

Table 1. SLEDAI-2K, anti-dsDNA antibody, C3, C4 and corticoid daily dose at baseline, 3, and 6 months of follow-up

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3 months</th>
<th>P</th>
<th>6 months</th>
<th>P</th>
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<tr>
<td>SLEDAI-2K</td>
<td>8.9</td>
<td>5.4</td>
<td>0.002</td>
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<td>Anti-dsDNA</td>
<td>459.8</td>
<td>142.6</td>
<td>0.001</td>
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<td>- ELISA, KIU/L in 23 pts</td>
<td>76.0</td>
<td>37.3</td>
<td>n.s.</td>
<td>27.5</td>
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<td>- Farr method, IU/mL in 18 pts</td>
<td>0.67</td>
<td>0.73</td>
<td>&lt;0.0001</td>
<td>0.74</td>
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<td>C3 (g/l)</td>
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<td>0.14</td>
<td>&lt;0.0001</td>
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<td>C4 (g/l)</td>
<td>12.1</td>
<td>8.2</td>
<td>0.015</td>
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</table>

Disclosure: A. Doria, GlaxoSmithKline, 8; L. Iacarino, None; S. Betto, None; M. Frassi, None; L. Andreoli, None; R. Furie, None; M. Zenni, None; L. Nalotto, None; M. Gatto, None; L. Pea, None; L. Punti, None; A. Tincani, None.

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Background/Purpose: Recent SLE RCTs were examined and compared to rheumatoid arthritis (RA) RCT to suggest modifications to SLE RCTs that could improve the future success of SLE trials.

Methods: RA and SLE biologics RCTs published between 2005 and July 2013 were identified using PubMed. Inclusion criteria, study design, outcome measures, sample size calculations, baseline characteristics, steroid use and results were compared.

Results: Twenty-two RA RCTs and eight SLE RCTs were included. RA RCTs used composite scores (ACR response or DAS28). SLE RCTs used SLEDAI, BILAG, SLAM, SRI and BICLA. RA trials were larger (543 vs. 376 participants). RA measurements of response included patient reported outcomes. SLE trials did not. Concomitant corticosteroid use was stable in 100% of RA trials while all SLE RCTs allowed tapering. RA trials were mostly in methotrexate or DMARD inadequate responders whereas SLE trials allowed for the presence or absence immunosuppressors within all trials. Positive trials were found in 100% of RA RCTs and 25% of SLE RCTs. Table shows suggestions to improve SLE trials.

Conclusion: The potential insensitivity of SLE disease activity index (SLEDAI) to partial improvements may result in type II errors in SLE RCTs, whereas many BILAG flares were recorded with a significant number not considered as important flares by the physician (nonspecificity). Varying concomitant pharmacotherapy, especially corticosteroid use, in SLE may blunt observed treatment effects. Steroid dose must be accounted for within
SLE trials. Sample size calculations in SLE may be unrealistic in some SLE trials. Moving forward, clinical relevance in treatment could be considered by proportional responses similar to ACR20 such as in SLE inflammatory arthritis trials or per cent improvement for skin studies in SLE and/or time to improvement of active urinary sediment in nephritis studies and/or reduction of steroids. SLE trial experts may need to reassess what outcomes and what minimal degree of change should be necessary to consider a treatment effective.

Suggestions of Outcomes in SLE trials: Points to Consider

Organ specific trials in SLE

Inflammatory arthritis

If arthritis is being studied, the SJC and TJC should be the primary outcome and patients with fibromyalgia may need to be excluded.

Rash

If rash is the being studied, MD and patient global assessment of SLE rash and the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) may be considered as outcomes.

Renal

In renal SLE, head to head comparisons of standard of care vs. the new treatment or add on to standard of care can be done with active urinary sediment (red blood cell [RBC] casts, total protein/24h) and creatinine as the outcomes as well as time to normalizing urinary sediment. WBCs in the urine are not part of lupus nephritis and should not be included as an outcome (unless interstitial nephritis is being studied).

Likewise, urinary RBCs may not be due to lupus nephritis.

Many patients will do well on standard of care treatment so longer outcomes such as creatinine, 24h proteinuria at one and two years may be needed.

Time to achieving a certain renal outcome, steroid sparing effect and safety may be the important outcomes.

Flares as an outcome

Flares in SLE patients within trials are frequent and a minimally important flare should be defined as relevant to the drug under study. A flare may need different definitions with a sensitivity analysis – such as MD reported major flare, a major increase in prednisone or a change in SLEDAI by at least 2 or 4 points.

A primary outcome could be a steroid sparing effect of a drug where steroids are not strictly mandated in their use and tapering but a suggested protocol of steroid tapering is given and only those with a certain minimum dose of steroids are allowed into the trial.

The speed of improvement, ability to taper steroids and/or safety may be the primary outcomes or a non-inferiority design.

Steroid sparing effects of treatment

Head to head trial with active new comparator

Disclosure: A. Miles, None; J. E. Pope, None.

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Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience, Renata Aguiar, 1 Ana Carolina Araújo, 2 Ana Luisa Pappola, 1 Marta Alves and David Isenberg 1, 2 Centro Hospitalar do Baixo Vouga, 3 Centro Hospitalar Lisboa Central, Lisbon, Portugal, 1 Centro Hospitalar Lisboa Central, Lisbon, Portugal, 2 Centro Hospitalar Lisboa Central, Lisbon, Portugal, 3 Centre for Rheumatology Research, University College Hospital London, London, United Kingdom.

Background/Purpose: Rituximab (RTX), an anti-CD20 chimerical monoclonal antibody, has been used as an off-label in patients with systemic lupus erythematosus (SLE) refractory to standard treatment. Although some small, open label and retrospective studies suggest that RTX might be beneficial in SLE treatment, the two randomized controlled trials of RTX in SLE did not meet the primary endpoints.

The purpose of this work was to assess clinical efficacy and safety of RTX in a cohort of SLE patients treated at a single centre for a long period.

Methods: The authors undertook a retrospective in-depth analysis of all patients (>100) with SLE treated with RTX at a single center between June 2000 and December 2013 and followed for up to 14 years. Data collected included BILAG scores AT and 6, 12, 18 and 24 months after RTX treatment; anti dsDNA antibody and C3 levels before and 6 months after RTX infusions; adverse events, including allergic/anaphylactic reactions, hypogammaglobulinemia, infections, cardiovascular and cerebrovascular events, and death.

Statistical analysis was performed using Wilcoxon and McNemar non-parametric tests.

Results: A total of 115 patients were reviewed; 93.9% female; 43.5% were Caucasian, 32.2% African and 17.4% South Asian; mean age at diagnosis was 26.39±11.90 years and mean disease duration at first RTX treatment was 91.96±84.80 months. The most frequent indications for RTX treatment were refractory musculoskeletal, renal and mucocutaneous involvement. Mean BILAG score before first RTX treatment was 18.29±10.62; after 6 months, 40% of patients had a complete response (loss of all A’s and B’s) and no new A’s or B’s, and 27% had partial response (partial loss of some A’s and B’s, no new ones). At 6 months, there was a significant reduction in the BILAG score (p<0.001). Also, 6 months after the first treatment, 36.5% of patients had an increase in C3 levels of 25% and 25.5% had a decrease of over 50% from anti dsDNA antibody baseline level. Depletion of CD19+ cells was successfully achieved in 94% of patients. Hypogammaglobulinemia was detected in 14.9%, however, this reduction was only significant for IgM (p<0.001) and IgG (p<0.001); severe infections, infusion-related and hypersensitivity reactions occurred in 7%, 3.5% and 2.6% of patients, respectively. Of the 115 patients initially treated with RTX, 62 patients had further RTX treatments, maximum of 6, with an average number of 1.95±1.17 cycles per patient and a mean interval between infusions of 21.44±20.11 months. The reason that led to the second RTX treatment was different from the reason leading to the first one in 16 patients, and 25 of the 40 patients who had had partial or complete response at first administration remained partial or complete responders.

At the end of follow-up, 11 patients had died and 6 had cardiovascular events (2 deaths).
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Response to Rituximab in Patients with Refractory Systemic Lupus Erythematosus (SLE): Results from a National Multicentre Register

Emily Sutton1, Kath D. Watson2, David A. Isenberg3, Anisur Rahman4, David Jayne5, Caroline Gordon6, Ben Parker7, David P. D’Cruz8, Munther A. Khamashita9, Pamela Lutalo10, Peter Lanyon11, Benjamin Rhodes12, Bridget Griffiths13, Edward M. Vital14, Chee-Seng Yee15, Christine Edwards16, Mohammed Akil17, Nicola Erb18, Althea Prabu19, Azad A. Zoma20, Neil McHugh21, Hazem Youssef22, Lee-Su San Teh23, Michael W. Beresford24 and Ian N. Bruce25

1 Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, 2 Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, 3 Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, 4 Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, 5 Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, 6 Queen Elizabeth Hospital, Birmingham, United Kingdom, 7 Freeman Hospital, Newcastle Upon Tyne, United Kingdom, 8 Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom, 9 College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, 10 King’s College London School of Medicine, London, United Kingdom, 11 Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, 12 Queen Elizabeth Hospital, Birmingham, United Kingdom, 13 Royal Hospital, Newcastle upon Tyne, United Kingdom, 14 University Hospital, Bath, United Kingdom, 15 Nuffield Department of Clinical Medicine, Oxford, United Kingdom, 16 University College London, London, United Kingdom, 17 Rheumatology Department, Sheffield South Yorkshire, United Kingdom, 18 Russell’s Hall Hospital, Dudley, United Kingdom, 19 Department of Rheumatology, Worcestershire Acute Hospitals NHS Trust, Worcester, United Kingdom, 20 Hairmyres Hospital, East Kilbride, United Kingdom, 21 Royal National Hospital, Bath, United Kingdom, 22 NHS Grampian, Aberdeen, United Kingdom, 23 Royal Blackburn Hospital, Blackburn, United Kingdom, 24 Institute of Translational Medicine (Child Health), University of Liverpool, Liverpool, United Kingdom, 25 Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Published efficacy data for rituximab in SLE are complex with positive single-centre case series and negative randomised controlled trials. This may be due to heterogeneity of SLE or the populations, design and endpoints of trials. The BILAG Biologic Registry (BILAG BR) is a national, multicentre, prospective study of safety and efficacy of biologics in SLE patients refractory to standard immunosuppressive therapy. The objective of the present analysis was to describe clinical response to rituximab at three and six-months post therapy.

Methods: Patients with SLE (≥ 4 ACR 1997 criteria), ≥ 5 years old, refractory to conventional therapy and newly starting treatment with rituximab, from centres across the UK, were recruited into the BILAG BR. A comprehensive questionnaire collected information on concomitant medications, risk factors for infection, co-morbidities and disease duration. Disease activity was monitored using the BILAG 2004 index and the SLEDAI2K at treatment initiation, 3 and 6 months post therapy.

Results: Baseline, 3 and 6 month disease activity were collected for 80 patients (92.5% women) starting therapy with rituximab. The cohort included 44 (60.3%) white British patients. The median (interquartile range [IQR]) age and disease duration at baseline were 39.5 years (IQR 30.0, 47.3) and 5.7 years (IQR 2.5, 11.6) respectively. The most commonly involved BILAG 2004 index systems were mucocutaneous (53 [41.25%]), renal (28 [35.0%]) and musculoskeletal (25 [31.0%]). The baseline SLEDAI2K was 8 (IQR 4-13.5). At 3 months follow-up, 47 (58.7%) patients showed an improvement in their overall BILAG 2004 index, 16 (20.0%) had persisting active disease and 12 (15.0%) had deteriorating disease. The majority of patients (11/12 [91.7%]) who deteriorated, did so in one system only. In the same follow-up period, 56 (70.0%) had an improved SLEDAI2K, 15 (18.75%) had no change and 9 (11.25%) worsened. Data at 6 months showed 39 (48.75%) with improvement, 18 (22.5%) with persistent disease and 16 (20.0%) deteriorating. In addition, there was a trend towards steroid dose being reduced over the 6 month period (Table 1).

Conclusion: There was variability in the degree of response to rituximab with respect to both the magnitude and duration of response, in this cohort of SLE patients refractory to standard immunosuppression. Although nearly half of the cohort demonstrated significant reduction in disease activity across all systems at 6 months, there was a sub-group that worsened in either the original system involved, or developed activity in a new system. This may be explained some patients who initially responded to rituximab at 3 months, beginning to flare by 6 months post therapy. Further analysis will attempt to identify predictors of response in this cohort.

Table 1:

<table>
<thead>
<tr>
<th>N = 80 unless otherwise stated</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>74 (92.5)</td>
</tr>
<tr>
<td><strong>Ethnicity (n = 73)</strong></td>
<td></td>
</tr>
<tr>
<td>White British/other white</td>
<td>44 (60.3)</td>
</tr>
<tr>
<td>Indian/Pakistani/Bangladeshi</td>
<td>10 (13.7)</td>
</tr>
<tr>
<td>African Ancestry</td>
<td>10 (13.7)</td>
</tr>
<tr>
<td>Mixed (white/Caribbean/other mixed)</td>
<td>9 (12.3)</td>
</tr>
<tr>
<td><strong>BILAG 2004 Index score at baseline (n = 80)</strong></td>
<td></td>
</tr>
<tr>
<td>≥1 A score and/or ≥2 B score</td>
<td>55 (68.8)</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>30.0 (18.4, 40.2)</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>39.5 (30.0, 47.3)</td>
</tr>
<tr>
<td>Disease duration at baseline (years)</td>
<td>5.7 (2.5, 11.6)</td>
</tr>
<tr>
<td>Prednisolone dose at baseline (mg/day) (n = 70)</td>
<td>10 (8.0, 22.5)</td>
</tr>
<tr>
<td>Number of previous immunosuppressant therapies at baseline (n = 78)</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>Baseline SLEDAI2K score</td>
<td>8 (4, 13.5)</td>
</tr>
<tr>
<td>Baseline SLE/ACR Damage Index</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td><strong>Patient Follow-up</strong></td>
<td></td>
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<tr>
<td>BILAG 2004 Index</td>
<td></td>
</tr>
<tr>
<td>3M: N (%)</td>
<td>47 (58.75)</td>
</tr>
<tr>
<td>6M: N (%)</td>
<td>39 (48.75)</td>
</tr>
<tr>
<td>Improvement [All As to B/C/D; all Bs to CD (allowing for 1≤B persisting)]</td>
<td>16 (20.0)</td>
</tr>
<tr>
<td>Persistent active disease [Any system still A or 2Bs as per previous time point]</td>
<td>12 (15.0)</td>
</tr>
<tr>
<td>Deterioration [Any system to A from C/D or to B from CD]</td>
<td>5 (6.25)</td>
</tr>
<tr>
<td>No Change/Inactive [Stable C/D/E with no new A or B]</td>
<td>7 (8.75)</td>
</tr>
<tr>
<td><strong>SLEDAI2K (n = 80)</strong></td>
<td></td>
</tr>
<tr>
<td>3M Score at follow-up (median [IQR])</td>
<td>4 (2, 6.5)</td>
</tr>
<tr>
<td>6M Score at follow-up (median [IQR])</td>
<td>4 (2, 7)</td>
</tr>
<tr>
<td>Improve: N (%)</td>
<td>56 (70.0)</td>
</tr>
<tr>
<td>worsen: N (%)</td>
<td>15 (18.75)</td>
</tr>
<tr>
<td>Prednisolone dose at follow-up (mg/day) (median [IQR])</td>
<td>10 (5, 13.75)</td>
</tr>
</tbody>
</table>

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Pharmacokinetics, Safety, and Biological Activity of Intravenously or Subcutaneously Administered Tabalumab in Subjects with Rheumatoid Arthritis or Systemic Lupus Erythematosus

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**Background/Purpose:** B-cell activating factor (BAFF) promotes B-cell survival and maturation, and increased serum levels are associated with autoimmune disease and disease activity in systemic lupus erythematosus (SLE). Tabalumab is a human anti-BAFF monoclonal antibody that neutralizes both soluble and membrane-bound BAFF. The objectives of 2 Phase 1 studies were to evaluate the pharmacokinetics (PK), safety, and biological activity of tabalumab administered intravenously (IV) or subcutaneously (SC) in subjects with rheumatoid arthritis (RA) or SLE.

**Methods:** In Study A, subjects with stable RA (n = 23) received a single dose of tabalumab ranging from 0.01 to 8.0 mg/kg (0.01, 0.04, 0.125, 0.5, 2.0, and 8.0 mg/kg) or placebo, and subjects with stable SLE (n = 6) received 1 of 2 tabalumab doses (0.125 or 2.0 mg/kg) or placebo by IV infusion. In Study B, subjects with RA received a single tabalumab dose SC (20 mg) (n = 12) or IV (10 mg infused over 30 min) (n = 12). Serum tabalumab and peripheral CD20+ B-lymphocyte levels were evaluated for 56 weeks in Study A and 12 weeks in Study B with optional follow up to monitor B-lymphocyte recovery, if required. Safety was assessed throughout both studies.

**Results:** Tabalumab PK were nonlinear across the 0.01 to 8.0 mg/kg dose range (Figure A), with a slower clearance (CL) and longer half-life (t1/2) at higher doses. The CL decreased from 2.9 to 0.1 L/day over the dose range, resulting in greater than dose-proportional increases in exposure. The terminal t1/2 increased from 1.6 to 25 days over the dose range. PK parameters were similar between RA and SLE subjects. SC dosing had a slow absorption phase with time to maximal concentration (tmax) of approximately 5.5 days. The estimated bioavailability (F) for the 20-mg SC dose was 62%. Single-dose tabalumab was well tolerated, and the majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity in both studies. The rate of TEAEs was similar for IV and SC groups in Study B. TEAEs considered related to study drug included headache (n = 1), back pain (n = 1), dry mouth (n = 1), dysgeusia (n = 1) dysphagia (n = 1), and nausea (n = 3) in study A, and injection-site pain (n = 1) and flushing (n = 1) in the 20-mg SC group in Study B. In general, a tabalumab-dependent transient increase from baseline in CD20+ B-lymphocytes followed by a progressive decrease below baseline levels was observed in both studies, with the decrease being significant (P<0.05; overall F-test) for the 2-mg/kg and 8-mg/kg doses. No increases in anti-tabalumab antibodies were detected post-treatment.

**Conclusion:** A single tabalumab dose administered IV or SC was well tolerated and had non-linear CL over the dose range investigated in subjects with RA and SLE. The non-linearity likely reflects target-mediated CL due to binding to BAFF. Tabalumab showed biological activity based on changes in peripheral CD20+ lymphocyte numbers in both subjects with RA and SLE.

**Disclosure:** J. Wada, Astellas, 2; Boehringer Ingelheim, 2; Novartis Pharmaceutical Corporation, 2; Novo Nordisk, 2; Pfizer Inc, 2; Takeda, 2; Tanabe Mitsubishi, 2; Astellas, 2; Boehringer Ingelheim, 2; Novartis Pharmaceutical Corporation, 2; Novo Nordisk, 2; Pfizer Inc, 2; Takeda, 2; Tanabe Mitsubishi, 2; Astellas, 2.

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**Background/Purpose:** Treatment with hydroxychloroquine (HCQ) is recommended for all patients with lupus nephritis to prevent further damage and reduce disease manifestations. Some studies suggest that drug levels may be important in medication efficacy. In view of reports of an increased risk of ocular toxicity with HCQ, however, the American Academy of Ophthalmology (AAO) recommends more stringent screening for damage as well as changes in dosing. Specifically, the AAO recommends dosing by ideal and not actual weight, which would decrease the dose of HCQ for many patients. To assess the impact of these dosing recommendations, we explored the patterns of HCQ use in a large patient cohort and the effect of dose levels on the trajectory of disease activity. For this purpose, we analyzed data from the Lupus Clinical Trials Consortium, Inc. (LCTC) Lupus Data Registry, a prospective registry of 1506 patients with SLE from 16 lupus centers in the US and Canada.

**Methods:** Patients were consecutively enrolled into the Registry and followed at outpatient visits by participating rheumatologists. Medication use, disease activity, and patient global assessment were recorded at each visit. Baseline dose of HCQ was recorded as mg per kg and was analyzed as <4 mg/kg, 4–4.99 mg/kg, 5–5.99 mg/kg and 6 mg/kg.

**Results:** There were 14 eligible patients in the TAC group and 20 eligible patients in the GC group. Although SLEDAI at the flare was higher in the TAC group than the GC group (8.2 vs. 6.2, p=0.05), other baseline characteristics (sex, age, serological markers, and the dose of GC) were comparable between the two groups. The initial dose of TAC for the flare was 1.6 mg/day in the TAC group, while the dose of GC for the flare was 13.7 mg/day in the GC group. The proportion of responders was 79% in the TAC group and 75% in the GC group (p=0.92). In the responders, 2 of 11 (18%) patients in the TAC group and 4 of 16 (25%) patients in the GC group developed the second flare (p=0.68). The dose of GC was higher in the GC group than in the TAC group at 12 months (9.7 mg/day vs. 7.1 mg/day, p<0.05). Only 1 patient withdrew TAC because of fatigue after three months.

**Conclusion:** Adding TAC without increased dose of glucocorticoids may be an effective treatment option for minor flares of patients with SLE.
681 Hydroxychloroquine Use Is Associated Independently with Improved Quality of Life in Systemic Lupus Erythematosus. Meenakshi Jolly1, Winston Sequeira2, Sarfraz Hasni3, Zulfiqar Ali4, Ana M. Bertoli5, Ivana Blazevic6, Luis M. Vila7, Ioana Moldovan8, Karina D’Torralba9, Bema Goker10, Josiane Bournier-Tessier11, S. Navaara12, Daniel Wallace13, Michael H. Weinblatt14, None; UCB Pharma, 5; NIH, Bethesda, MD, 4NIH, Bethesda, MD, 5Hospital San Juan Bautista, San Fernando del Valle de Catamarca, Argentina, 6Instituto Reumatológico Strusburg, Cordoba, Cordoba, Argentina, 7University of Buenos Aires, Buenos Aires, Argentina, 8University of Puerto Rico Medical Sciences Campus, San Juan, PR, 9Bethesda Medical Group, Redlands, CA, 10University of Southern California, LA, CA, 11Gazi University School of Medicine, Ankara, Turkey, 12Division of Rheumatology, Centre Hospitalier de l’Université de Montréal, Montréal, QC, 13University of Santo Tomas Hospital, Manila, Philippines, 14UCCLA, LA, CA, 15Cedar-Sinai Medical Center, Los Angeles, CA, 16University of Calgary, Calgary, AB, 17Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: Hydroxychloroquine (HCQ) has been shown to be beneficial to patients with Systemic Lupus Erythematosus (SLE), however, its effects on the quality of life (QOL) of patients with SLE has not been evaluated. Interestingly, there is not a clear concordance between pharmacological amelioration of visceral organ damage in SLE and QOL, as reported by patients themselves. LupusPRO is a disease targeted QOL tool that is well validated in English and various other languages, and has two construct: logical amelioration of visceral organ damage in SLE and QOL, as reported by patients themselves. LupusPRO domains using nonparametric independent sample t tests, using damage was assessed using SLICC-ACR/SDI. We compared the QOL on the LupusPRO domains using nonparametric independent sample t tests, using

Methods: Cross sectional data from 1,037 SLE patients (USA, Canada, Argentina, Mexico, Philippines, Turkey, and China) was accumulated, after obtaining informed consent and IRB approval. Age, gender, LupusPRO scores, disease activity, and disease damage were analyzed. Disease activity was measured by SLEDAI (physician global assessment and Total), while damage was assessed using SLICC-ACR/SDI. We compared the QOL on the LupusPRO domains using nonparametric independent sample t tests, using two sided p values of ≤ 0.05 as significant. T tests were also used to compare disease and disease damage in patients where the data were available. Multivariate linear regression analysis for satisfaction with treatment domain of LupusPRO was performed as the dependent variable, and HCQ use, age, gender, disease activity (SLEDAI), damage (SLICC-ACR/SDI) and current steroid use as independent variables.

Results: 253 patients were included (91.3% women), with a mean age at SLE onset of 30 ± 13 years. Globally, 74.3% of patients developed hematological involvement (HI): 37.2% TP (21% moderate, 21% severe); 26.1% AHA, 75% leukopenia, 68% lymphopenia and 11.2% neutropenia. Evans syndrome was present in 13 patients and secondary antiphospholipid syndrome (APS) was diagnosed in 19.4%. Among patients with severe haematological disease, aggressive treatments (bolus of methylprednisolone, cyclophosphamide, rituximab, intravenous immunoglobulin or splenectomy) were needed in 9% of patients with TP and in 18% of AHA. Only 20% of the patients had received AM prior to the development of HI. In 5.5% of cases life-threatening complications appeared because of HI. Relapses occurred in TP (9.1%) and in AHA (2.8%). In 3 cases of neutropenia colony stimulating factor was needed, all relapsed cases. TP was significantly associated with having positive aDNA (p<0.035), antiB2GP1IgG, lupus anticoagulant AL +, with APS and venous thrombosis secondary to APS (all p<0.01). AHA was associated with malar rash and discoid lupus, and AL+, ACL IgG +, antiB2GP1IgG and IgM (all p<0.05) but not with APS. AHA was associated with exitus as a result of hematologic involvement (p<0.039). Neutropenia was associated with arthritis (p 0.024). Hypocomplementemia (C3, C4) was associated with TP, AHA (p<0.005). Treatment with hydroxychloroquine was associated with a tendency of complete response to therapy in AHA and a partial response in TP.

Conclusion: Up to 41% of patients had some kind of severe cytopenia. Only AHA was associated with increased mortality from this cause. All cytopenias were associated with hypocomplementemia except neutropenia. AM treatment tended with favorable therapeutic response in AHA and thrombocytopenia. In our series, treatment with antimalarial drugs not proved to be a protective factor for developing severe cytopenias LES related neither for prevent severe complications or to prevent recurrences, although further studies are needed.

Disclosure: E. Enriquez Merayo, None; M. Galindo Izquierdo, None; E. Rodriguez-Almaraz, None; M. Martin Lopez, None; O. M. Olivas Vergara, None; P. E. Carreira, None; I. Mateo, None.

680 Influence of Antimalarial doesn’t Modify the Outcome of Cytopenias in Systemic Lupus Erythematosus. Eugenia Enriquez Merayo1, Maria Galindo Izquierdo2, Esther Rodriguez-Almaraz4, Maria Martin Lopez2, Otto Martin Olivas Vergara, Patricia E. Carreira and Isabel Mateo1. 12 DE OCTUBRE, MADRID, Spain, 2HOSPITAL 12 DE OCTUBRE, MADRID, Spain, 3Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, 4Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, 5Servicio De Reumatología, Hospital 12 De Octubre, Madrid, Spain.

Background/Purpose: To analyze the effect of antimalariales (AM) as preventive factor for the development of severe cytopenias and in their outcome after treatment in a large series of patients with systemic lupus erythematosus (SLE).

Methods: 253 SLE patients followed in rheumatology department (12 de Octubre hospital) between 1976–2014 were included. Demographic, clinical data and patients outcome were obtained from pre-existing databases and from the charts. SLE related cytopenias were defined as: autoimmune haemolytic anaemia (AHA): hematocrit<35%, reticulocytes >5% or spherocytosis in peripheral blood smear; leucopenia:WBC<4000/106/l; neutropenia: neutrophils<1000/106/l; thrombocytopenia (TP): normal 50–100x109/l and severe <50x109/l. The associations between categorical variables were tested using the chi-square or Fisher’s exact test, where appropriate. The odds ratios with the corresponding 95% CIs were calculated. For continuous variables, the comparisons were carried out using the t-test for two independent samples. P-values<0.05 were considered significant. The analysis was performed using advanced SPSS software version 11.

Results: 253 patients were included (91.3% women), with a mean age at SLE onset of 30 ± 13 years. Globally, 74.3% of patients developed hematological involvement (HI): 37.2% TP (21% moderate, 21% severe); 26.1% AHA, 75% leukopenia, 68% lymphopenia and 11.2% neutropenia. Evans syndrome was present in 13 patients and secondary antiphospholipid syndrome (APS) was diagnosed in 19.4%. Among patients with severe haematological disease, aggressive treatments (b...
Results: 1,037 SLE patients (727 HCQ users and 310 non-HCQ users) data were analyzed. HCQ users and non-users were similar in age and gender (Mean age (SD) 40.1 (13.0 vs. 42.5 (12.9) yrs). SLICC-ACR/SDI was lower, while non-HRQOL was higher among HCQ users as compared to non-HCQ users (Table 1). Specifically non-HRQOL domain of satisfaction with treatment was significantly better among HCQ users than non-HCQ users. On multivariate analysis, HCQ use remained an independent predictor of satisfaction with treatment (non-HRQOL LupusPRO domain), even after adjusting for age, gender, disease activity, damage and current steroid use.

Conclusion: Hydroxychloroquine use in SLE has clearly beneficial effects on QOL. This is in addition to the well-recognized ameliorative effects on cumulative damage. The QOL improvement appears to be related to non-HRQOL (satisfaction with treatment) independently. Longitudinal studies with disease targeted QOL tools with use of HCQ are indicated.

<table>
<thead>
<tr>
<th>HCQ (n=310)</th>
<th>No HCQ (n=727)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) Mean (SD)</td>
<td>40.1 (13.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender (Female %)</td>
<td>93.6</td>
<td>0.75</td>
</tr>
<tr>
<td>SLEDAI (Mean, SD)</td>
<td>3.4, 4.3</td>
<td>0.92</td>
</tr>
<tr>
<td>SLICC-ACR/SDI (Mean, SD)</td>
<td>0.7, 1.1</td>
<td>0.003</td>
</tr>
<tr>
<td>LupusPRO HRQOL (Median, IQR)</td>
<td>77.5, 23.7</td>
<td>0.14</td>
</tr>
<tr>
<td>LupusPRO non HRQOL (Median, IQR)</td>
<td>68.2, 27.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Satisfaction with Treatment (Median, IQR)</td>
<td>75.0, 56.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate Analysis for Satisfaction with Treatment non-HRQOL LupusPRO domain</td>
<td>B co-efficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>HCQ use</td>
<td>7.2</td>
<td>2.7 to 11.7</td>
</tr>
<tr>
<td>Age</td>
<td>−0.2</td>
<td>−0.4 to −0.01</td>
</tr>
<tr>
<td>Disease Activity (SLEDAI)</td>
<td>−3.1</td>
<td>−11.8 to 5.7</td>
</tr>
<tr>
<td>Damage Index (SLICC-ACR/SDI)</td>
<td>0.7</td>
<td>0.2 to 1.2</td>
</tr>
<tr>
<td>Current Steroid use</td>
<td>1.8</td>
<td>−0.05 to 3.6</td>
</tr>
<tr>
<td>Steroid use</td>
<td>4.2</td>
<td>−0.2 to 8.6</td>
</tr>
</tbody>
</table>

Disclosure: M. Jolly, None; W. Sequeira, None; S. Hasni, None; Z. Ali, None; S. Toloza, None; A. M. Bertoli, None; L. Blazevic, None; L. M. Vila, None; L. Moldovan, None; K. D. Torralba, None; B. Goker, None; I. Bourré-Tessier, None; S. Navarra, Pfizer, GSK, 8; D. Wallace, None; M. H. Weismman, None; A. E. Clarke, None; C. C. Mok, None.

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Background/Purpose: Systemic Lupus Erythematosus (SLE) greatly reduces the quality of life (QoL) and satisfaction with life of affected patients. SLE patients can have numerous unmet needs and may feel misunderstood by their health care providers. The aim of this study was to explore what is important to SLE patients when it comes to their care.

Methods: Participants were adults satisfying the ACR classification for SLE, and were recruited by phone, letter or directly by their respective rheumatologist. A qualitative approach based on audio-recorded focus groups was used to collect data. Interview guides were prepared prior to the meetings by an expert panel including: a resident in internal medicine, a psychologist, a rheumatologist, and nurse. The open-ended questions covered SLE patient priorities, their means of conveying these priorities to their medical team, and the impact of these priorities on their disease management. The transcriptions were independently coded by 2 analysts using 2 techniques: 1) a qualitative data analysis software (NVivo 10) and 2) manual analysis. The analytic approach was based on grounded theory.

Results: Nineteen female participants attended 3 focus groups in 2 sites (university and community-based). Participants’ ages ranged from 18 to 70 with the majority between 30 and 59 years of age. The average disease duration was 8.8 ± 7.7 years, ranging from 1 to 23 years. 68% were married/cohabitating with a partner and 63% were employed. Five priorities (Figure 1) were identified: 1) management of disability, in particular, loss of energy that prevents full engagement in daily activities, relationships, and social roles; 2) management of the unpredictable nature of SLE including, preventing flares and worsening of their condition, employment and financial issues associated with chronicity; 3) management of side effects; 4) access to information about lupus and support resources, in particular, support groups; 5) access to health care (improved communication between physicians, shorter wait times and longer consultations with physicians).

Conclusion: SLE patients have multiple complex priorities and may have difficulty articulating them. Health care providers need to develop strategies and communication tools to help SLE patients identify their priorities and support them in the self-management of their disease.
impacts caregivers and patients will help healthcare professionals and policymakers expand their outreach to consider the well-being of caregivers.

Reference:


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Successful Withdrawal and Discontinuation of Immunosuppressants in Lupus Patients: Outcomes and Predictors. Zahi Touma, Murray B. Urowitz, Dominique Ibáñez and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Physicians and patients (Pts) are hesitant to withdraw immunosuppressant (IS) in Pts in clinical remission as the consequences of this approach are unknown.

We aimed to determine the number of successful withdrawals of IS and their predictors in a large observational cohort study.

Methods: Analysis was conducted on all Pts seen in The Lupus Clinic, from 1987–2012, in whom IS was tapered and stopped. Pts who were in clinical remission and on prednisone (P) ≤7.5 mg/day were included. Tapering start was defined as the date of the visit with a decrease ≥25% in IS dose. IS Stop was the day of IS discontinuation. Study end was the date of flare or last clinic visit following IS stop.

Flare was defined as the introduction of new IS or increase of P dose for active disease. Flare was evaluated within the first 2 years from IS stop and at any time after IS stop.

Kaplan-Meier curve was used to evaluate the time to flare after IS stop. Pts who flared after IS stop were compared to Pts who did not flare (t-test and χ² test) at the time of IS tapering start and IS stop.

Covariates evaluated in the univariate analysis were: sex, ethnicity, IS, DNA antibody level and DNA antibody [yes/no], C3/C4 level and low C3/C4 [yes/no], lupus duration, age at IS taper, length of time on IS, disease activity [SLEDAI-2K, AMS year 1 before IS taper] and steroids at IS stop [yes/no]. Forced and stepwise regression models were fitted with covariates with p<0.1 in addition to age, sex and ethnicity to predict flare in Pts who discontinued IS.

Results: Of the 1678 lupus Pts, 973 were ever on IS, 179 had tapering attempts and 99 Pts stopped IS. 91% were female and at tapering start age was 40.4±13.1 and disease duration was 11.4±9.4 years.

Of the 99 Pts, 25 flared within 2 years (16 AZA; 7 MTX and 2 MMF; p=0.31). The length of time from tapering to IS stop was 1.8±2.1 years in the flare and 0.9±0.9 years in the flare group; p=0.002.

46 of the 74 Pts who had not flared by 2 years had follow-up available beyond 2 years; 32 were followed beyond 3 years and 24 beyond 5 years. 17 Pts experienced a flared after year 2. Using Kaplan-Meier curve for time to flare showed that at 1, 2, 3, 4 and 5 years, the percent of Pts who flared was 17%, 30%, 46%, 49% and 51% respectively; Figure 1.

The percentage of Pts on P at the time of IS stop was greater among those who flared, 52% compared to 30%; p=0.04. At the time of IS tapering the mod-flares were not statistically significant for all studied covariates. At the time of IS stop, the results from the logistic regression showed that Pts off P are more likely not to flare; OR 2.99; 95% CI: 1.13, 7.89; p=0.03.

Conclusion: Within 2 years, successful stopping of IS was possible in about 75% of clinically stable Pts. Half were successful within 3 year and this proportion was stable up to 5 years. At the time of IS stop, Pts who discontinued IS slowly and who were off P were less likely to flare.

Disclosure: Z. Touma, None; M. B. Urowitz, None; D. Ibáñez, None; D. D. Gladman, None.
Clinicians Approaches to the Management of Background Therapy in SLE Patients in Clinical Remission: Results of an International Survey

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Background/Purpose: At present there is no consensus on what constitutes a remission in SLE. In particular it is not clear how background therapy should be interpreted in remission studies. We aimed to survey clinicians involved in the care of SLE patients to determine how background therapy is managed in patients in clinical remission and in particular to assess how previous severity, duration of remission and serological parameters influence therapy alterations.

Methods: We undertook an internet-based survey of clinicians involved in the management of SLE. Case scenarios were constructed to reflect different states of clinical remission: previous organ involvement, current serological abnormalities, duration of remission (1, 3 and 5 years) and current therapy (HCQ, steroids and/or immunosuppressives[ISS]). The survey link was sent to (1) the corresponding authors from Lupus Journal published between January 2013 and December 2013 (2) Lupus working groups e.g. BILAG, SLICC. Percentage of responses in each scenario was described and compared between different factors.

Results: 130 clinicians from 30 countries (Europe 54 [41.5%], Asia 53 [40.8%], North America 16 [12.3%]) responded including 113 (86.9%) rheumatologists. The median (range) duration of practice and number of SLE patients seen per month was 13 (2, 42) years and 30 (2, 200) respectively. There was variation in management decisions across all scenarios with increasing caution on therapy reduction with shorter duration of remission, extent of serological abnormalities and previous disease severity. Even with mild disease, normal serology and a 5 year clinical remission 104 (86.7%) clinicians would still continue HCQ, with only 16 (13.3%) stopping the drug. Similarly, when low dose steroid are co-prescribed in this scenario 78 (64.5%) would continue these and 116 (96.7%) would continue HCQ. When MTX is added to this scenario 85 (70.2%), 79 (67.8%), and 116 (96.7%) would continue all therapies. Of interest, persistent abnormal serology in the above scenario led to a higher proportion of respondents continuing HCQ 113 (96.6%). Similarly, 106 (89.1%) would continue steroid and 119 (100%) would continue HCQ when patients were prescribed both. Prescribing in remission scenarios varied geographically, particularly with regard to steroids. For example, in the scenario describing stable, mild disease for 5 years, steroids would be withdrawn by 24 (48%) European respondents, 4 (28.6%) North American respondents and 10 (19.6%) Asian physicians.

Conclusion: Clinicians approach to withdrawing or reducing therapy in patients with SLE in clinical remission varies substantially. Serological abnormalities, previous disease severity and duration of remission all influence a clinician’s decision to reduce treatments and anti-malarials are not usually withdrawn. It is unusual for clinicians to withdraw all therapies, even after a very prolonged period of clinical remission and therefore any definition of remission needs to include the continued use of some background maintenance therapies.

Disclosure: P. Ngamjanyaporn, None; I. Bruce, None; B. Parker, None; J. Sergeant, None.

Effect of Corticosteroid Use By Dose on the Risk of Developing Organ Damage over Time in Systemic Lupus Erythematosus—the Hopkins Lupus Cohort.
Sarah Al Sawah1, Xiang Zhang2, Baojin Zhu1, Laurence S. Magder1, Shonda A Foster1, Noriko Iikuni1 and Michelle Petri2.
1Eli Lilly and Company, Indianapolis, IN, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Reduction of corticosteroid dose remains an important goal in the management of systemic lupus erythematosus (SLE). Current standard of care in SLE relies heavily on corticosteroids, despite what is known about the side effects of corticosteroids and their role in the development of new organ damage.

Methods: We used data from a longitudinal lupus cohort to understand the impact of different levels of exposure to corticosteroids on the risk of developing new irreversible organ damage, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Cox proportional hazard models were used to estimate the impact of predictors, including mean prednisone dose, on the risk of developing any new organ damage or any new organ damage by organ system (e.g., ocular, musculoskeletal, cardiovascular, and renal damage) over time.

Results: At cohort entry, the average age of SLE patients was 38 years and the average disease duration was 5.1 years. Patients were followed for an average of 6.2 years. The most frequent types of organ damage, occurring over time, were ocular damage (cataract) and musculoskeletal damage (osteoarthritis fractures). Mean prednisone dose, disease activity score, and immunosuppressant use during the follow-up period, as well as SDI score at cohort entry, were significant predictors of the risk of developing any new organ damage. There was a dose-response relationship between mean prednisone dose during the follow-up period and the risk of developing any new organ damage (Models 1 and 2; Table 1). A 1-mg/day increase in prednisone dose increased the risk of developing any new organ damage by 2.8% (p<0.001). The risk more than doubled when patients were exposed to a prednisone dose during follow-up of ≥20 mg/day versus <7.5 mg/day (HR=2.51, 95% CI 1.98, 3.20; p<0.001). For individual organ systems, exposure to a mean prednisone dose during follow-up of ≥7.5mg/day versus <7.5 mg/day significantly increased the risk of developing cataracts (HR=2.41, p<0.001), osteoporotic fractures (HR=2.16, p<0.001), and cardiovascular damage (HR=1.54, p=0.041), but showed no significant difference for renal damage (HR=1.14, p=0.163).

Conclusion: Organ damage in SLE is multifactorial, with both corticosteroid treatment and disease activity playing a role. However, even a minimal change in corticosteroid dose (1 mg/day of prednisone) significantly affects the accrual of organ damage over time. These findings may be offset, to some degree, by the impact that prednisone has on damage through the reduction in disease activity.

Table 1. Time-dependent Cox proportional hazard model showing the effect of mean prednisone dose on the risk of any new organ damage in systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>p-Value</th>
<th>Model 2</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELENA-SLEDAI score during follow-up (≥6 vs. &lt;6)</td>
<td>1.40 (1.17–1.67)</td>
<td>&lt;0.001</td>
<td>1.37 (1.15–1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean prednisone dose, mg/day:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥7.5 vs. &lt;7.5)</td>
<td>1.74 (1.49–2.04)</td>
<td>&lt;0.001</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>(≥7.5–15 vs. &lt;7.5)</td>
<td>NA</td>
<td>1.54 (1.28–1.84)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>(≥15–20 vs. &lt;7.5)</td>
<td>NA</td>
<td>1.80 (1.35–2.40)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>(≥20 vs. &lt;7.5)</td>
<td>NA</td>
<td>2.51 (1.98–3.20)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index.

Disclosures: S. Al Sawah, Eli Lilly and Company, 3; X. Zhang, Eli Lilly and Company, 3; B. Zhu, Eli Lilly and Company, 3; L. S. Magder, None; S. A. Foster, Eli Lilly and Company, 3; N. Iikuni, Eli Lilly and Company, 3; M. Petri, None.

Corticosteroids in Early Treatment Pathways in SLE.
John G. Hunly1, Amyn Sayani1, Steve Doucette2, Sandra Iczkovitz3 and Jorge Alfonso Ross.
1Dalhousie University and Capital Health, Halifax, NS, 2Medical Affairs, GlaxoSmithKline, Mississauga, ON.

Background/Purpose: The treatment algorithm for patients with new onset systemic lupus erythematosus (SLE) is more variable than that for other rheumatic diseases (e.g. rheumatoid arthritis). We examined the treatment...
patterns, with a particular emphasis on corticosteroids (CS), in an inception cohort of SLE patients over the first 3 years of disease.

Methods: The study was conducted at a single academic center with a longitudinal lupus database. All patients fulfilled the ACR classification criteria for SLE within 12 months preceding their enrollment and completed at least 3 subsequent annual followup visits during which data since the previous assessment were recorded. Information was collected per protocol at each visit and included patient demographics, SLE manifestations, medications, SLE disease activity index-2K (SLEDAI-2K), SLICC/ACR damage index (SDI) and SF-36 for assessment of health related quality of life (HRQoL). Analysis included descriptive statistics and repeated measures mixed models.

Results: Seventy-nine patients, 86.1% female and 91.1% Caucasian were studied. At baseline the mean ± SD age was 39.8 ± 16.1 years, disease duration was 0.36 ± 0.28 years and SLEDAI-2K was 5.7 ± 4.6. Over 3 years the cumulative exposure to CS, antimalarials (AM) and immunosuppressive (IM) drugs was 53.2%, 77.2% and 40.5% respectively, and CS were virtually always used in combination with AM and/or IM. The use of CS fell between baseline and final assessments (44.3% vs. 15.2%) in contrast to the use of AM (55.7% vs. 70.9%) and IM (26.6% vs. 24.2%). Of the 44/79 (55.7%) patients who were not receiving CS at baseline 84.1% remained off CS for the duration of the study, Thirty-seven of 79 (46.8%) patients never received CS and only 5/79 (6.3%) of patients were taking corticosteroids at all 4 assessments. Patients exposed to CS at baseline had higher mean ± SD daily dose and cumulative dose of CS over 3 years compared to patients not on CS at baseline (9.0 ± 6.8 vs. 0.3 ± 1.3 mg; 10.8 ± 8.5 vs. 0.3 ± 1.2 gr.) The adjusted mean SLEDAI-2K over 3 years was higher in patients exposed to CS regardless of whether group assignment was determined by cumulative dose (none vs > 10 gr: 3.7 ± 1.9 vs 6.5 ± 3.5; p=0.0001), CS at baseline visit (none vs present: 2.9 ± 2.1 vs 5.1 ± 3.9; p=0.006) or CS exposure at any time during the study (2.7 ± 1.9 vs 3.8 ± 0.6; p=0.002).Using the same group assignments CS exposure over the next 3 years was associated with a significant fall in SLEDAI-2K scores (p<0.05) compared to patients not exposed to CS. There was no consistent association with baseline SDI or HRQoL or change over time.

Conclusion: Exposure to CS occurred in approximately half of the patients with new onset SLE, usually in association with AM and/or IM. It was associated with both higher disease activity, especially at baseline, and a subsequent fall in disease activity over time. In SLE patients who do not receive CS at disease presentation, the introduction of CS is very unlikely over the next 3 years.

Disclosure: J. G. Hanly, None; A. Sayani, GlaxoSmithKline, 3; S. Doucette, None; S. Iezkovitz, GlaxoSmithKline, 3; J. A. Ross, GlaxoSmithKline, 3.

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Prednisone, Disease Activity and Hypertension Independently Predict Cataracts in Systemic Lupus Erythematosus (SLE). Khaled Alderaan1, Vuk Sekicki2, Laurence S. Magder3 and Michelle Petri4. 1King Fahad Specialist Hospital, Dammam, Saudi Arabia, 2Saint Agnes Hospital, Baltimore, MD, 3University of Maryland, Baltimore, MD, 4Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Cataract is the most common ocular damage in SLE. It is the second most frequent item in the SLICC/ACR Damage Index. Apart from cumulative corticosteroid doses, there are virtually no reports on other risk factors for cataract in SLE population. We report on a large prospective study of cataract risk factors in SLE.

Methods: The analysis was based on the follow-up experience prior to age 60 of 2109 SLE patients who had not had a cataract prior to cohort entry. Patients saw their ophthalmologist every 6 months. Cataract was defined by the SLICC/ACR Damage Index. The rate of incident cataract was calculated from the first 3 years of follow-up, with median follow up time of 4.1 years per patient. During this follow-up we observed 157 new cases of cataract, for an incidence of 13.2 per 1000 persons-years. We estimated that the risk of being diagnosed with a cataract by age 60 was 58%. Table 1 shows the results of a multivariate regression model. Adjusting for other predictors, a cumulative prednisone dose equivalent to 10 mg/day for 10 years was a strong predictor of cataract (RR=3.1, p=0.0005). Disease activity measured by SLEDAI (P =0.0005) and higher systolic blood pressure (P =0.0006) were associated with cataract. Duration of SLE, diabetes mellitus, smoking, cholesterol, renal involvement, immunological profile and medication history, other than prednisone, were not associated with cataract.

Conclusion: Cataract development in SLE patients is multifactorial with cumulative prednisone doses, systolic blood pressure and disease activity all playing an independent role.

Table 1: Independent Predictors of Cataract Based on a Multivariable Model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Comparisons</th>
<th>Rate Ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per 10 year increase</td>
<td>2.0 (1.7, 2.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Systolic BP during prior cohort visits &gt; 140 mmHg</td>
<td>Yes vs. no</td>
<td>2.2 (1.4, 3.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean total cholesterol</td>
<td>Per 50 mg/dl increase</td>
<td>1.1 (1.0, 1.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes/no</td>
<td>1.3 (0.9, 2.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean SELENA-SLEDAI</td>
<td>Per 2 point increase</td>
<td>1.3 (1.1, 1.5)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cumulative Corticosteroid Exposurea</td>
<td>&lt;3650mg vs. none</td>
<td>1.1 (0.5, 2.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>None</td>
<td>3650–10,949mg vs. none</td>
<td>1.1 (0.5, 2.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>None</td>
<td>10,950–36,499mg vs. none</td>
<td>2.3 (1.3, 4.3)</td>
<td>0.0065</td>
</tr>
<tr>
<td>36,500g vs. none</td>
<td>3.1 (1.6, 5.7)</td>
<td>0.0005</td>
<td></td>
</tr>
</tbody>
</table>

1 Includes prednisone history prior to cohort entry
2 Exposure equivalent to <10 mg/day for 1 year
3 Exposure equivalent to 10 mg/day for 1–3 years
4 Exposure equivalent to 10 mg/day for 3–10 years
5 Exposure equivalent to 10 mg/day for >10 years

Disclosure: K. Alderaan, None; V. Sekicki, None; L. S. Magder, None; M. Petri, None.

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Lupus Patients Requiring First Corticosteroid Intervention Late in Disease Course - a Phenotypic Description. Barry J. Sheane, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/ Purpose: The University of Toronto Lupus Clinic (UTLC) recently described the phenotype of a group of inception patients with SLE who remained naïve of corticosteroid (CS-naïve) for the entire duration of follow-up at the Clinic. One third of those CS-naïve SLE patients accrued damage over time, yet developed less damage and at a slower rate than those exposed to CS.

We have identified a group of patients who remained CS-naïve for at least 3 years but who later required CS intervention. Below we describe the clinical features of this subset of patients.

Methods: Patients with SLE attending the UTLC satisfying the following criteria were included in the study: 3 years or more of follow-up from inception, no exposure to CS for the first 3 years from inception, no organ damage (as per the SLICC Damage Index (SDI)=0) from inception and at least 5 follow-up visits. Two groups were identified from this cohort: those who remained entirely CS-naïve up to their last visit (CS-naïve) and those exposed to CS at some point after 3 years during follow-up (CS-late). Differences between the 2 groups were examined: in disease activity at inception (SLEDAI-2K) and over time (adjusted mean SLEDAI (AMS)), in the time to first incidence of organ damage (SDI ≥ 1), and the effect of exposure to anti-malarial (AM) medication on organ damage accrual (SDI ≥ 1).

Results: In the CS-late group, 31 patients were identified and 59 in the CS-naïve. The mean time to first CS exposure in the CS-late group was 9.0 ± 5.6 years.

Comparing the CS-late vs. CS-naïve groups, sex distribution (93.6% vs. 94.9% female), mean age at diagnosis (33.3 ± 11.9 vs. 37.8 ± 14.5 years; p = 0.15), years of follow-up (9.1 ± 5.6 vs. 11.0 ± 6.4 years; p = 0.15), mean SLEDAI at first visit (5.68 ± 3.31 vs. 5.25 ± 3.69; p = 0.59), AMS for the first 3 years, time to first damage (3.7 ± 3.9 vs. 4.8 ± 5.1 years; p = 0.36), damage scores over 10 years of follow-up, and the proportion eventually developing damage (11 (35.5%) vs. 23 (39%); p = 0.74) were similar between groups.

73.3% of the CS-late and 50.9% of the CS-naïve received a score on the SLEDAI for immunological activity (p = 0.04), with a mean immunological score of 2.00 ± 1.49 and 1.25 ± 1.38, respectively (p = 0.02). The CS-late had a lesser number with musculoskeletal (MSK) activity (16.1%) at first
Clinical and subclinical cardiac involvement is a frequent and important finding in patients with systemic lupus erythematosus (SLE), often preceding the development of overt organ damage. The recognition of subclinical cardiac involvement is of potential clinical importance, as early detection may allow the initiation of timely interventions to prevent or delay organ damage. Our purpose was to determine the prevalence of subclinical echocardiographic abnormalities in patients with SLE.

Methods: One hundred patients fulfilling the American College of Rheumatology (ACR) classification criteria for SLE were enrolled. Demographic and clinical data were collected and patients underwent transthoracic echocardiography (TTE). Serologic data, and a history of smoking and cardiovascular disease were also recorded. TTE data were evaluated by experienced cardiologists. Non-parametric tests were used for statistical analysis. The significance level was set at 0.05.

Results: The mean age of patients (75 women) was 50.6 ± 14.3 years, and the median disease duration was 14.5 years (range, 0.1–40). The main findings were: 1) Systolic dysfunction in 11.1% (9/91) of patients. 2) Diastolic dysfunction in 5.5% (5/91) of patients; all had arterial hypertension and two had positive antiphospholipid antibodies (aPL). 3) Segmental wall motion abnormalities suggestive of ischemic heart disease and pulmonary arterial hypertension (PAH) defined as a systolic pulmonary artery pressure (PAP) of 40 mmHg and tricuspid regurgitation velocity (TRV) greater than 2.5 m/s. 4) Pulmonary arterial hypertension: 7.7% (7/91) of patients. Mean PAP was 46.8 ± 4 mmHg (range, 40–56) and mean TRV was 3 ± 0.3 m/s (range, 2.7–3.4). Pulmonale was observed in two patients; neither had dilated inferior vena cava or pericardial effusion. Six out of seven patients (86%) of patients with PAH also had some kind of valve disease.

Conclusion: The prevalence of subclinical echocardiographic abnormalities in patients with SLE was high, with a significant proportion of patients having moderate to severe subclinical cardiac involvement. The identification of patients at risk for the development of overt organ damage may benefit from early intervention.

Disclosure: V. Higuera, None; C. Hübbe, None; L. M. Amezquita-Guerra, None.

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Circulating Anti-Ro/SSA Antibodies Are Associated with the Presence of Severe Mitral Regurgitation in Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder involving multiple organ systems. The frequency of symptomatic heart disease ranges from 5 to 10%, but noninvasive imaging methods such as transthoracic echocardiography (TTE) may demonstrate subclinical cardiac involvement in up to 95% of SLE patients. In spite of this, intrinsic SLE factors conferring risk to develop cardiac valve involvement have not been adequately defined. Indeed, almost all available information about cardiac valve disease in SLE is related to both circulating antiphospholipid antibodies and the antiphospholipid syndrome.

A recent short study described that anti-Ro/SSA antibodies, one of the most commonly autotubodies found in SLE (40–50%), could be associated with the presence of valvulopathy.

Objectives: To evaluate the association between anti-Ro/SSA and other antibodies and cardiac valve disease in SLE.

Methods: One hundred patients fulfilling the ACR classification criteria for SLE were enrolled. Demographics and clinical data were collected and patients underwent to TTE. Serum antibodies against nuclear antigens, dsDNA, Sm, Ro/SSA, La/SSB, RNP, cardiolipin, and β2GPI were measured. Patients were grouped according to the presence or absence of anti-Ro/SSA antibodies, and clinical, serological and TTE data were compared by chi-square or Mann-Whitney tests as correspond.

Results: Eleven patients were eliminated because rheumatic valve disease or congenital heart disorder. Eighty-nine patients were included for analyses, 36 patients (35 female, mean age 37.3±14 years) were positive and 53 negative (43 female, 40.1±15 years) for circulating anti-Ro/SSA antibodies. There were no differences in age, disease duration or co-morbidities between groups. A difference was noted in the presence of anti-dsDNA (67% vs 45%; P=0.04) and anti-La/SSB (19% vs 2%; P=0.004) antibodies. In the cardiac abnormalities detected by TTE, there was a significant relationship between positive anti-Ro/SSA antibodies and severe mitral regurgitation (27% vs 5%; P=0.02). Indeed, anti-Ro/SSA antibodies confer an OR 6.5 (P=0.03) for the presence of severe mitral regurgitation. No other differences in the TTE findings were found.

Conclusion: In SLE, circulating anti-Ro/SSA antibodies are associated with the presence of severe mitral regurgitation.

Disclosure: V. Higuera, None; C. Hübbe, None; L. M. Amezquita-Guerra, None.

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Acute Myocarditis in Patients with Systemic Lupus Erythematosus: Experience from Affiliated Hospitals of Catholic University of Korea. Joon-in Baek1, Ji-Jo Kim1, Yune-Jung Park2, Chong-Hyeon Yoon3, Wan-Uk Kim4 and Chul-Soo Cho5. 1Yeouido St. Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea, 2St. Vincent’s Hospital, The Catholic University of Korea, Suwon, South Korea, 3St. Vincent’s Hospital, The Catholic University of Korea, Suwon, South Korea, 4Uijeongbu St. Mary’s Hospital, The Catholic University of Korea, Uijeongbu, South Korea, 5Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: To determine the factors associated with occurrence of acute myocarditis (AM) and its outcomes in patients with systemic lupus erythematosus (SLE).

Methods: This was a retrospective study of hospitalized SLE patients with AMC from 2002 to 2014 at Catholic University affiliated hospitals. A diagnosis of AMC was made on the basis of clinical findings, electrocardiographic changes, elevated cardiac enzymes levels and echocardiographic abnormalities. Eighty-six SLE patients who showed no echocardiographic evidence of myocarditis were enrolled as a control group. The clinical and laboratory data from each patient were collected from the charts and compared between 2 groups.

Results: During these periods, 22 SLE patients were identified to have AMC (male 3, female 19). Patients with AMC, as compared with those without, were found to be associated with shorter disease duration and higher frequency of smoking (P<0.005, P<0.005, respectively). Moreover, they showed significantly higher SLE disease activity index score (P<0.001) and
C-reactive protein levels ($P<0.001$), but lower complement levels (C3, C4 and CH50, all $P<0.005$). Interestingly, antiphospholipid syndrome (APS) was more prevalent in patients with AMC compared with those without ($P<0.01$). In multivariate analysis, shorter disease duration, smoking and presence of APS were independent factors associated with AMC in SLE patients. All patients with AMC received high-dose corticosteroid and 2 of them received intravenous cyclophosphamide; 17 patients completely recovered, 1 died.

**Conclusion:** AMC patients are more likely to have high disease activity and its occurrence is associated with shorter disease duration, smoking, and presence of APS.

Disclosure: I. W. Baek, None; K. J. Kim, None; Y. J. Park, None; C. H. Yoon, None; W. U. Kim, None; C. S. Cho, None.

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**Lupus Myocarditis: Clinical, Echocardiographic and Magnetic Resonance Characteristics.** Marı́a del Carmen Zamora Medina1, Hilda Fraguoso-Loyo2, Martha Morelos3, Juan Jakez-Ocampo1, Luis Llorente4, Juan Rosas Saucedo1 and Yemel Atisha-Fregoso1.

1. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 2. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, 3. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, 4. Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico, 5. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

**Background/Purpose:** Myocarditis is an uncommon manifestation with important morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). There are scant information about this manifestation that comes from case series, which include no more than 24 patients. Also, there are not a uniform definition about the criteria for the diagnosis of this manifestation in SLE, and only in few reports the diagnosis was supported by cardiac magnetic resonance (CMR).

**Methods:** Retrospective study of all cases of myocarditis seen in a single center between 2005 and 2014. Patients with diagnosis of SLE according to the updated 1982 ACR criteria, who met the expanded criteria for myocarditis and had CMR compatible with the diagnosis were included.

The objective of the study was to describe the clinical and laboratorial manifestations, and echocardiographic, echocardiographic and CMR findings of these patients.

**Results:** Twenty five patients (24 women, 96%), with a mean age of 29.38 ± 11.36 years, and who presented 26 episodes of myocarditis were included. The mean time to development of myocarditis after SLE diagnosis was 11.5 months (IQR 0–31.2%). The main clinical and imaging findings are shown in tables 1 and 2.

During the episode of myocarditis the activity of SLE at diagnosis measured by SLEDAI was of 8.77 (IQR 4–12). Patients had a SLICC Damage Index at diagnosis of 1.43 ± 1.6. Nine of 26 patients (35%) required admission to the ICU and 6 of 26 (23%) patients were treated with inotropic. There were no deaths during the acute episode, but 4 patients died during the follow-up, three of them secondary to infections. All patients were treated with prednisone, mean dose 50 ± 12 mg/day.

Follow-up MRI was performed on 10 patients, the mean initial LVEF was 49.2% ± 9.2 vs 61% ± 8.1 (p=0.007). The SLEDAI score at follow-up was of 2 points (IQR 0–6), and the SLICC Damage Index at follow-up was of 1.71 ± 1.82.

**Conclusion:** Myocarditis is a severe manifestation of SLE. CMR is a useful study in the diagnosis of myocarditis that can evaluate some parameters that are not detectable in echocardiography e.g., valvulitis, edema, hyperemia and myocardial fibrosis. Further studies are needed to determine the role of CMR and currently follow-up studies are undergoing at our Institute in SLE patients with myocarditis.

Disclosure: M. D. C. Zamora Medina, None; H. Fraguoso-Loyo, None; M. Morelos, None; J. Jakez-Ocampo, None; L. Llorente, None; J. Rosas Saucedo, None; Y. Atisha-Fregoso, None.

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**Osteonecrosis in Patients with Systemic Lupus Erythematosus: Risk Factors and Clinical Outcome.** Andrea Zacarias1, Javier Narváez2, Sergi Heredia1, Helena Borrell1, Paula Estrada1, Alex Roset1, Nestor Arce Gonzalez1, Carmen Gomez Vaquero1, Olga Capdevila1 and Joan Miquel Nolla1.

1. Hospital Universitario de Bellvitge, Barcelona, Spain, 2. Hospital Universitas rio de Bellvitge, Barcelona, Spain, 3. Hospital Universitaria de Bellvitge, Barcelona, Spain, 4. Hospital Universita rio de Bellvitge, Barcelona, Spain, 5. Hospital Universita rio de Bellvitge, Barcelona, Spain.

**Background/Purpose:** To study the prevalence of osteonecrosis (ON) in patients with systemic lupus erythematosus (SLE) and to identify the risk factors for development of this complication and predictors of total hip/knee arthroplasty.

**Methods:** The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Patients with ON were selected for analysis. The diagnosis was confirmed in all cases with imaging techniques (conventional radiography and bone scan, CT scan or MRI). The variables associated with the occurrence of this complication were analyzed using a backward logistic regression model.

**Results:** During the follow-up period, 11 patients (4.5%) had 12 episodes of ON (one patient developed two). The mean age of the patients (nine women) was 52 ± 15 years and median time to progression of SLE at the time of diagnosis of ON was 149 months (range: 24–323). Three out of 11 cases of ON (27%) occurred within the first five years of the course of the disease.

The condition was monoarticular in eight episodes (66%) and multifocal in four (34%); in the latter case it simultaneously affected two or more joints (range 2–4). The most common site was the femoral head (75% of episodes), followed by the knee (33%) and the humeral head (8%). In 90% of the affected joints, ON presented with pain and functional impairment (the asymptomatic joints were detected in the scintigraphic study).

The mean dose of prednisone at the time of diagnosis of ON was 11.2 ± 8.2 mg/day and the total cumulative dose was 30.4 ± 16.7 g. Seven patients (64%) had received a prednisone dose of at least 0.5 mg/kg/day at some point of the disease; 5 (45%) of these had received a dose of 1 mg/kg/day for serious complications. However, at the time of ON diagnosis, disease was inactive or mild in all patients according to the SLEDAI score (mean 1.3, range 0–4).

Antiphospholipid antibodies were positive in two patients (18%); both were on antplatelet therapy. We did not identify any other risk factors that have been associated with the development of ON in SLE.

Outcome was unfavorable in seven patients (64%), who required total hip/knee replacement. There was no increase in mortality.

Both in the comparisons between groups using univariate analysis and in the multivariate analysis, the only predictor of risk for development of this complication was the total cumulative prednisone dose (OR = 19.07 [95% CI: 2.7 – 133.7], p = 0.0002). No associations were found with the presence of antiphospholipid antibodies, immunosuppressive therapy, presence of arthritis or degree of disease activity according to the SLEDAI score. In the Cox proportional hazards model, advanced radiological stage was the only statistically significant predictor for arthroplasty.

**Conclusion:** ON is a rare complication in patients with SLE (4.5%). In the majority of the cases it is symptomatic and occurs in advanced stages of the disease; the major risk factor associated with the development of this complication is the cumulative dose of glucocorticoids. ON was not associated with increased mortality, but it was associated with physical disability.

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**Clinical Characteristics and Outcome of Intestinal Pseudo-Obstruction in Patients with Systemic Lupus Erythematosus.** Lingling Zhang, Meng-tao Li, Dong Xu, Na Gao, Li Zhang, Yong Hou, Qian Wang and Xiaofeng Zeng. Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China.

**Background/Purpose:** Intestinal pseudo-obstruction (IPO) is a rare clinical syndrome characterized by ineffective intestinal motility. IPO has been recently recognized as an uncommon complication of systemic lupus erythematosus (SLE). Though case series of patients with SLE-related IPO (SLE-IPO) have been reported, the epidemiology, characteristics, risk factors and prognosis for SLE-related IPO remain poorly understood.

**Methods:** To analyze the clinical characteristics and outcome of SLE-IPO, we retrospectively enrolled 68 SLE patients with IPO syndrome as the case group and 323 randomly matched SLE patients without any gastrointestinal manifestations as controls out of 397 inpatients at Peking Union Medical College Hospital (PUMCH) from 2003 to 2013. IPO was diagnosed according to gastrointestinal symptoms, gaseous small bowel distension with air-fluid levels showed by radiographic signs or thickened gastric wall and dilated small or large bowels showed by CT scan, otherwise, patients were...
thrombosis, age over 60 yrs, male gender, African-American ethnicity, SLEDAI greater than 3, and prednisone greater than 0 were risk factors.

Results: In general, rates of venous thrombosis were fairly constant, while rates of arterial thrombosis increased with age. The figure below shows that initially the venous thrombosis rate is higher (including before diagnosis) and later the arterial thrombosis rate is higher.

Conclusion: Prevention of venous thrombosis remains important throughout the course of SLE. Prevention of arterial thrombosis becomes more important later in the disease course. Disease activity is a risk factor for arterial thrombosis while prednisone is a risk factor for both venous and arterial thrombosis.

Disclosure: K. Hickman, None; L. S. Magder, None; M. Petri, None.

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Background/Purpose: Muscle weakness is common and contributes to physical disability in women with systemic lupus erythematosus (SLE). Recently, the Foundation for the National Institutes of Health Sarcopenia Project reported grip strength cutpoints that identified weakness associated

Table 1: Incidence rates (per 1000 patient-years) of thromboses

<table>
<thead>
<tr>
<th>Characteristic of Person-Month</th>
<th>All Thromboses</th>
<th>Arterial Thromboses</th>
<th>Venous Thromboses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate Ratios (95% CI)</td>
<td>P-values</td>
<td>Rate Ratios (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td>Male</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td>African American</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td>Other</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td>SLEDAI greater than 3</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
<tr>
<td>Prednisone greater than 0</td>
<td>1.0 (Ref. Group)</td>
<td>0.0001</td>
<td>1.0 (Ref. Group)</td>
</tr>
</tbody>
</table>

Conclusion: Prevention of venous thrombosis remains important throughout the course of SLE. Prevention of arterial thrombosis becomes more important later in the disease course. Disease activity is a risk factor for arterial thrombosis while prednisone is a risk factor for both venous and arterial thrombosis.

Disclosure: K. Hickman, None; L. S. Magder, None; M. Petri, None.

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Venous and Arterial Thrombosis in SLE: Differences in Natural History. Katharine Hickman1, Laurence S. Magder2 and Michelle Petri1. 1University College London, London, United Kingdom, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Thrombosis is increased in SLE due to disease activity and co-morbid factors including antiphospholipid antibodies. We separately investigated the natural history of venous vs. arterial thrombosis.

Methods: 2250 patients were enrolled in a prospective cohort; 334 had a thrombotic event before cohort entry or diagnosis of SLE. For ALL

Table 1: A comparison of demographics, clinical manifestations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n, (%)</td>
<td>66/68(97.1)</td>
<td>221/232(95.3)</td>
<td>0.739</td>
</tr>
<tr>
<td>Age, yrs, mean±SE</td>
<td>32.3±11.4</td>
<td>32.3±8.03</td>
<td>0.975</td>
</tr>
<tr>
<td>Fracture, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flare age, years, mean±SE</td>
<td>29.7±1.4</td>
<td>32.4±2.7</td>
<td>0.594</td>
</tr>
<tr>
<td>Disease duration, months, mean±SE</td>
<td>30.8±5.5</td>
<td>56.2±4.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatality, n(%)</td>
<td>6/68(8.8)</td>
<td>13/232(5.6)</td>
<td>0.398</td>
</tr>
<tr>
<td>Acute or subacute skin lupus</td>
<td>23/66(34.8)</td>
<td>85/232(36.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mucosal Ulcers</td>
<td>15/67(22.4)</td>
<td>40/232(17.2)</td>
<td>0.207</td>
</tr>
<tr>
<td>Hematological disturbance, n(%)</td>
<td>41/67(61.2)</td>
<td>99/232(42.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Urinary system disturbance</td>
<td>41/67(61.2)</td>
<td>10/232(4.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Elevated ESR, n(%)</td>
<td>41/60/63(66.8)</td>
<td>15/226(68.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Elevated CRP, n(%)</td>
<td>32/60/53(53)</td>
<td>63/202(29.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypocomplementemia, n(%)</td>
<td>61/68(89.7)</td>
<td>146/210(66.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ANA, n(%)</td>
<td>63/68(92.6)</td>
<td>183/232(78.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Anti-dsDNA Antibody, n(%)</td>
<td>21/68(30.9)</td>
<td>113/224(48.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>Anti-smartibody, n(%)</td>
<td>20/61(32.8)</td>
<td>56/230(24.3)</td>
<td>0.182</td>
</tr>
<tr>
<td>Anti-RNP antibody, n(%)</td>
<td>27/67(40.3)</td>
<td>81/230(35.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Anti-SSA antibody, n(%)</td>
<td>38/68(55.9)</td>
<td>124/230(53.9)</td>
<td>0.775</td>
</tr>
<tr>
<td>Anti-SSB antibody, n(%)</td>
<td>14/68(20.6)</td>
<td>27/220(11.7)</td>
<td>0.063</td>
</tr>
<tr>
<td>Ro-52, n(%)</td>
<td>9/67(13.4)</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td>Anti-RNP antibody, n(%)</td>
<td>60/68(88)</td>
<td>33/180(18.3)</td>
<td>0.066</td>
</tr>
<tr>
<td>ANCA, n(%)</td>
<td>1/60 (1.7)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>ACL antibody, n(%)</td>
<td>7/59(11.9)</td>
<td>3/160(15.8)</td>
<td>0.455</td>
</tr>
<tr>
<td>LA antibody, n(%)</td>
<td>5/54(11.1)</td>
<td>2/171(12.3)</td>
<td>0.843</td>
</tr>
<tr>
<td>SLEDAI, mean±SE</td>
<td>13.15±0.827</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: L. Zhang, None; M. Li, None; D. Xu, None; N. Gao, None; L. Zhang, None; Y. Hou, None; Q. Wang, None; X. Zeng, None.

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Venous and Arterial Thrombosis in SLE: Differences in Natural History. Katharine Hickman1, Laurence S. Magder1 and Michelle Petri1. 1University College London, London, United Kingdom, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Thrombosis is increased in SLE due to disease activity and co-morbid factors including antiphospholipid antibodies. We separately investigated the natural history of venous vs. arterial thrombosis.

Methods: 2250 patients were enrolled in a prospective cohort; 334 had a thrombotic event before cohort entry or diagnosis of SLE. For ALL

Excluded. The case-control study was conducted to compare the clinical and laboratory data. The outcome of SLE-IPO was also investigated.

Results: Within the last 10 years at PUMCH, the prevalence of IPO in SLE patients was 1.73% and the in-hospital fatality rate was 8.8%. 58.8% of the SLE-IPO manifested as the initial presentation of SLE. Ureterohydronephrosis was the most common complication (60.3%) in SLE patients with IPO and the incidence of biliary tract dilatation was 7.9%. SLE patients with IPO were always diagnosed at earlier stage of SLE with higher frequency of hematological disturbance, polyserositis and hypocomplementemia than control patients. Ureterohydronephrosis (OR = 90.32, 95% CI 21.283–383.32, p = 0.000), hypocomplementemia (OR = 10.437, 95% CI 1.341–81.217, p = 0.025) and elevated CRP level in serum (OR = 5.143, 95% CI 1.401–18.876, p = 0.014) were independent risk factors for IPO in SLE disease. However, the positivity of anti-dsDNA antibody was a protective factor for SLE with IPO (OR = 0.222, 95% CI 0.061–0.8, p = 0.021). SLE-IPO patients with long IPO duration, diagnosed at late stage of SLE had unfavorable outcome.

Conclusion: IPO can manifest as a complication of SLE and more commonly, as the initial presentation. SLE-IPO always occurs concomitantly with ureterohydronephrosis and biliary dilatation, and these three complications combined indicate a severe situation of SLE. SLE-IPO patients without systemic smooth muscular involvement could achieve better prognosis with early diagnosis and aggressive treatment.
with impaired mobility among women aged ≥ 65 years. However, the ability of grip strength to identify SLE patients at increased risk of physical disability is unknown. This study aims to test whether grip strength is associated with increased physical disability in women with SLE.

Methods: Subjects were women in a longitudinal cohort with physician-documented SLE. All measures were collected during an in-person research visit among a subset of the cohort. Grip strength was measured with a handheld dynamometer. Grip strength was classified as “weak” (<16kg), “intermediate” (16–20kg), and “normal” (>20kg). Self-reported physical functioning was assessed using the SF-36 Physical Functioning subscale (range 0–100, mean 50, SD 10) and Valued Life Activities (VLA) Disability (range 0–3) surveys. Higher SF-36 and lower VLA scores indicate higher functioning. Regression analyses controlling for age, SLE duration, prednisone use, SLE disease activity measured with the Systemic Lupus Activity Questionnaire (SLAQ), physical activity level measured by the International Physical Activity Questionnaire (IPAQ), and depressive symptoms measured by the Center for Epidemiological Studies Depression Scale (CES-D) modeled the effects of grip strength on SF-36 and VLA scores.

Results: Of the 146 women, mean age was 48 (±12) years; duration of SLE was 16 (±9) years; SF-36 score was 40.9 (±11.4); VLA disability score was 0.80 (±0.55). Fifteen women (10%) had “weak” grip strength, 31 (21%) “intermediate”, 78 (53%) “normal”; and 22 (15%) were missing grip strength data. In both unadjusted and adjusted models, having “weak” compared to “normal” grip strength was associated with significantly worse SF-36 and VLA scores (see Table 1). In sensitivity analyses examining the effects of missing grip strength data and of excluding women aged ≥ 65 years (n=11), the overall trends were unchanged.

Conclusion: Grip weakness was common in our cohort of women with SLE. With a prevalence comparable to that of geriatric populations, grip weakness successfully identified women with increased physical disability even when adjusting for potential confounders such as disease activity and depression. These findings underscore the high burden of muscle weakness among women with SLE, and they may suggest a clinical role for grip strength testing in identifying women with SLE at greatest risk of physical disability. Further studies will need to examine the ability of grip strength to predict incident disability in SLE.

Table 1. Association between Grip Strength and Disability Scores

<table>
<thead>
<tr>
<th>Grip Strength</th>
<th>SF-36 Physical Functioning</th>
<th>VLA Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak (&lt;16kg)</td>
<td>-11.8 (-17.6, -6.1)**</td>
<td>-4.4 (-8.7, -0.1)**</td>
</tr>
<tr>
<td>Intermediate (16–20kg)</td>
<td>-3.3 (-6.3, -0.3)**</td>
<td>0.29 (0.05, 0.5)***</td>
</tr>
<tr>
<td>Normal (&gt;20kg)</td>
<td>ref.</td>
<td>ref.</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001

Disclosure: J. S. Andrews, None; M. Margareten, None; J. Barton, None; J. Yazdany, None; E. Yelin, None; P. P. Katz, None.

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Osteonecrosis in Systemic Lupus Erythematosus: Prevalence, Patterns and Outcomes

Nimrit Dhillon, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Osteonecrosis is a serious comorbidity of systemic lupus erythematosus (SLE). The reported frequency of symptomatic osteonecrosis in SLE is variable, ranging from 4% to 15%.

The aim of this study is to provide an update of the prevalence, patterns and outcomes of symptomatic osteonecrosis in SLE.

Methods: SLE patients with osteonecrosis were identified from the Lupus Clinic Database containing patients with 4 ACR criteria of SLE or 3 criteria and a biopsy diagnostic of lupus. Osteonecrosis was defined as those patients with clinical symptoms and confirmed osteonecrosis by imaging (x-ray, bone scan, CT, MR). Demographic and clinical data of affected patients were collected prospectively, stored in an Oracle database and analyzed using descriptive statistics.

Results: Of the 1729 patients with SLE registered in the database as of 1970, 235 patients (13.6%) developed symptomatic osteonecrosis. 86.0% were female, with a mean age of 34.8 ± 12.8 years at first osteonecrosis diagnosis. This involved a total of 542 joints, 383 joints of which were identified at the time of first osteonecrosis occurrence. The mean time from diagnosis of SLE to diagnosis of first osteonecrosis was 8.2 ± 8.1 years, and the time from first osteonecrosis diagnosis to second osteonecrosis diagnosis was 3.4 ± 4.8 years.

111 out of 235 (47%) patients had multiple site involvement at first osteonecrosis occurrence, affecting from 2 to 6 sites. At the time of first diagnosis affected sites included the hip (245), knee (86), shoulder (28), ankle (15), wrist (3), other joints (3) and elbow (2). Those that progressed to surgical intervention included: hip 131/245 (53.5%), knee 18/86 (19.8%), wrist 1/3 (33.3%), shoulder 1/28 (3.6%), ankle 0/15 (0%), elbow 0/2 (0%), and other joints 1/3 (33%). The mean time from osteonecrosis diagnosis to surgery of the hip was 3.8 ± 5.5 years, while the mean time from osteonecrosis diagnosis to surgery of the knee was 5.5 ± 6.2 years.

Conclusion: To our knowledge, this is the largest cohort of SLE patients with symptomatic osteonecrosis. Osteonecrosis continues to be a significant comorbidity of SLE as 13.6% of patients developed symptomatic osteonecrosis. In patients developing osteonecrosis, the presentation occurred after 8.2 ± 8.1 years of SLE disease duration. 47.2% of patients had multiple site involvement at first ON diagnosis. Large weight-bearing joints, including the hip and knee, were most frequently involved. The majority of hips required surgical intervention. Better strategies to prevent this serious complication are needed.

Disclosure: N. Dhillon, None; D. Ibanez, None; D. D. Gladman, None; M. B. Urowitz, None.

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Decreased Lung Diffusion Capacity in Asymptomatic Patients with Systemic Lupus Erythematosus Does Not Predict Future Lung Disease

Ofr Elalouf, Elizabeth Fireman, David Levartovsky, Ilana Kaufman, Ori Rogovski, Ori Elkayam, Dan Caspi and Daphna Paran. Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background/Purpose: In a previous study, performed 9±3.6 years ago 74 asymptomatic patients with systemic lupus erythematosus (SLE) and or antiphospholipid syndrome (APS) who fulfilled the ACR criteria for diagnosis, underwent lung function testing. A significantly low diffusion capacity (DLCO) ranging from 45% to 70% was recorded in 28 of the 74 (37.8%) patients who were all free of respiratory symptoms. This study aims to assess the clinical importance and predictive value of a low diffusion capacity in asymptomatic patients with SLE or APS.

Methods: Asymptomatic patients with SLE and/or APS who were found to have a low DLCO in the previous study were contacted. Of the 28 patients, 15 were recruited and reevaluated in the current study [SLE with APS (n=7), SLE without APS (n=7); primary APS (n=1)]. A detailed history, physical examination, nail bed capillaroscopy, current laboratory tests and lung function tests including DLCO were obtained.

Results: During a surveillance period of 9±3.6 years none of the patients developed lung disease. Diffusion capacity corrected for alveolar volume (DLCO/VA) improved in the study group during this period from 61.3% ±6.3 to 77% ±12.7% (p=0.006). Lung function tests including total lung capacity (TLC) and forced expiratory volume in 1s (FEV1) remained within normal limits. Capillaroscopy studies did not reveal changes compatible with skin phenomena in any of the patients.

Conclusion: Low diffusion capacity findings on lung function testing does not have a positive predictive value for the development of future lung disease in patients with SLE who are free of respiratory symptoms. Our results suggest that a finding of low diffusion capacity in asymptomatic patients with SLE does not necessarily require further evaluation and imaging and may improve spontaneously over time. Further studies in a larger group of patients are needed to validate these findings.

Disclosure: O. Elalouf, None; E. Fireman, None; D. Levartovsky, None; I. Kaufman, None; O. Rogovski, None; O. Elkayam, None; D. Caspi, None; D. Paran, None.

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How Important Is Physical Activity for Patients with Systemic Lupus Erythematoses? -Results of Lula-Study.

Isabelle Kloubert1, Gamal Chehab1, Jutta Richter2, Rebecca Fischer-Bete3, Ralph Brinks2 and Matthias Schneider3. 1Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, 2Heinrich-Heine-University, Duesseldorf, Germany, 3University of Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Physical activity (PA) plays a decisive role in primary and secondary prevention in various domains of medicine. Our examination aimed to determine association PA and on outcomes in systemic lupus erythematoses (SLE).

Students included 111 SLE patients, 53 females (75%), mean age 43±11 years, mean disease duration 12.8±8.1 years, 111 out of 235 (47%) patients had multiple site involvement at first osteonecrosis occurrence, affecting from 2 to 6 sites. At the time of first diagnosis affected sites included the hip (245), knee (86), shoulder (28), ankle (15), wrist (3), other joints (3) and elbow (2). Those that progressed to surgical intervention included: hip 131/245 (53.5%), knee 18/86 (19.8%), wrist 1/3 (33.3%), shoulder 1/28 (3.6%), ankle 0/15 (0%), elbow 0/2 (0%), and other joints 1/3 (33%). The mean time from osteonecrosis diagnosis to surgery of the hip was 3.8±5.5 years, while the mean time from osteonecrosis diagnosis to surgery of the knee was 5.5±6.2 years.

Conclusion: To our knowledge, this is the largest cohort of SLE patients with symptomatic osteonecrosis. Osteonecrosis continues to be a significant comorbidity of SLE as 13.6% of patients developed symptomatic osteonecrosis. In patients developing osteonecrosis, the presentation occurred after 8.2±8.1 years of SLE disease duration. 47.2% of patients had multiple site involvement at first ON diagnosis. Large weight-bearing joints, including the hip and knee, were most frequently involved. The majority of hips required surgical intervention. Better strategies to prevent this serious complication are needed.
Methods: The LuLa-Study is a prospective long-term study since 2001, which systematically collects patients’ reported outcomes among members of the German SLE Self-Help Organization. In 2006 and 2009 we analysed data of 750 patients (94.4% female, age 52.3 ± 12.9 years (mean ± SD), duration of disease 15.9 years in 2009) with regard to their PA applying the “Freiburger Questionnaire on physical activity”. We calculated the Metabolic Equivalent of Task (MET) for every patient. In the univariate analysis we compared 422 patients with low/intermediate PA (<50 MET, n = 259) to those with high/very high activity (>50 MET, n = 163) in both years. Furthermore, we examined the association of PA to disease activity, HRQoL, (SF-12) and clinical symptoms in a multivariate regression analysis with age, sex, BMI and number of comorbidities.

Results: The mean MET of the group with low/intermediate PA was 13.4 ± 7.6 respectively, 73.9 ± 31.5 with high/very high PA. A high PA in 2006 and 2009 was associated with less cephalgia (p < 0.01) and muscle weakness (p < 0.001) and with lower disease activity in 2009 (determined with SLE Activity Questionnaire (SLAQ) and VAS; p < 0.001). No statistically significant relation between PA and myalgia or arthralgia could be found. Patients with high MET in 2006 and 2009 showed a better HRQoL (Physical Component Summary (p < 0.001) and Mental Component Summary (p < 0.014) determined with SF 12) in 2009. Both groups of activity improved their emotional HRQoL between 2006 and 2009, whereas the physical HRQoL stagnated in both groups. A higher PA in 2006 and 2009 was connected to a lower damage (determined by System Lupus International Collaborating Clinics/ACR Damage Index for SLE (SLICC-) Score; p < 0.012) as well as to an improved fatigue (Vanderbilt Fatigue Score (VFS); p < 0.001) and a different cognition of pain (FSS-Score; p < 0.001) in 2009. The multivariate analysis included all 750 patients (medium MET in 2006 28.5 ± 26.1, in 2009 34.5 ± 37.7) and affirmed the influence of higher MET to the above outlined scores. It could be shown, that a higher PA of 10 MET is related to a decreasing SLAQ (−0.43 points) three years later (p < 0.001). This effect remained after adjusting for the covariates. The same activity of 10 MET in 2009 is only associated with a decreasing SLAQ (−0.30 points) (p < 0.001). A similar observation could be depicted for emotional and physical HRQoL.

Conclusion: PA of SLE patients does have an impact on clinical manifestations and is related to a higher HRQoL. As increased PA has an impact on HRQoL and SLAQ three years later, a recommendation of more PA seems reasonable.

Disclosure: I. Kloubert, GlaxoSmithKline, 9, UCB; G. Chehab, GlaxoSmithKline, 9, UCB; J. Richter, GlaxoSmithKline, 9, UCB; R. Fischer-Betz, GlaxoSmithKline, 9, UCB; R. Brinks, GlaxoSmithKline, 9, UCB; M. Schneider, GlaxoSmithKline, 9, UCB, 9.

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Protein Losing Enteropathy in Systemic Lupus Erythematosus. Doo-Ho Lim, Seung-Hyon Bae, Soo Min Ahn, Seokchan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: Protein losing enteropathy (PLE), characterized by severe hypoalbuminemia and edema, is rare manifestation of systemic lupus erythematosus (SLE). The study was proposed to identify the distinct features of lupus PLE and to evaluate the factors related with treatment response or outcome of lupus PLE.

Methods: From Mar. 1998 to Mar. 2014, the clinical data of 14 patients with lupus related PLE (lupus PLE) and 7 patients with idiopathic PLE in tertiary center were reviewed. PLE was defined as demonstration of protein leakage from gastrointestinal tract by either technetium 99m-labelled human albumin scan or fecal 11C-antitrypsin clearance with no evidence of protein loss from other sources and impaired protein synthesis. Positive steroid response (PSR) was defined as return of serum albumin to ≥ 3.0 g/dl within 4 weeks after initial steroid monotherapy and remission as maintenance of serum albumin ≥ 3.0 g/dl for at least 3 months. High total cholesterol means the serum total cholesterol level of ≥ 240 mg/dl.

Results: The mean age of lupus PLE was 37.0 ± 19.8 years (range: 16 – 72) and 11 patients (78.6%) had PLE as initial manifestation of SLE. The mean follow-up duration was 55.8 ± 16.0 months (range: 6 – 172). There were significant increases in ESR and total cholesterol level in lupus PLE compared with idiopathic PLE. Among 14 patients with lupus PLE, 8 patients experienced PSR. Total cholesterol level was significantly higher in PSR group (Table 1). PSR was associated with initial high total cholesterol (OR = 7.0, 95% CI = 1.14 – 42.97) and with achievement of remission in 6 months (OR = 3.0, 95% CI = 0.97 – 9.30). Among 14 patients with lupus PLE, 10 patients who achieved remission in 6 months showed higher total cholesterol level (283.3 ± 79.3 mg/dL) compared to 4 patients who did not (165.3 ± 63.9 mg/dL).

Conclusion: In lupus PLE, high total cholesterol level could be a predictive factor to initial steroid response, expecting good response to steroid therapy alone. Furthermore, we suggest that initial high level of total cholesterol could predict a favorable outcome in patient with lupus PLE.

Table 1 Characteristics of lupus related PLE patients according to steroid response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive steroid response (n=10)</th>
<th>Negative steroid response (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.0 ± 19.8</td>
<td>48.3 ± 7.7</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>4 (50)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Symptom duration before treatment, weeks</td>
<td>6.1 ± 4.5</td>
<td>16.0 ± 11.5</td>
</tr>
<tr>
<td>White blood cells, x10^9/nl</td>
<td>7.7 ± 3.3</td>
<td>7.0 ± 1.9</td>
</tr>
<tr>
<td>Lympocytose, x10^9/nl</td>
<td>1.9 ± 0.7</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.5 ± 1.1</td>
<td>11.5 ± 1.5</td>
</tr>
<tr>
<td>Platelets, x10^9/nl</td>
<td>202.8 ± 119.9</td>
<td>260.1 ± 107.2</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>68.3 ± 23.9</td>
<td>70.7 ± 51.2</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>0.9 ± 1.9</td>
<td>1.1 ± 1.0</td>
</tr>
<tr>
<td>C3, mg/dl</td>
<td>52.8 ± 24.6</td>
<td>44.3 ± 19.4</td>
</tr>
<tr>
<td>C4, mg/dl</td>
<td>113.5 ± 5.7</td>
<td>13.2 ± 3.2</td>
</tr>
<tr>
<td>Anti-nuclear antibody, IU/ml</td>
<td>16.6 ± 19.8</td>
<td>20.4 ± 41.5</td>
</tr>
<tr>
<td>SLEDAl score</td>
<td>6.5 ± 3.3</td>
<td>7.67 ± 3.7</td>
</tr>
<tr>
<td>Protein, g/dl</td>
<td>4.2 ± 1.6</td>
<td>4.23 ± 0.9</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.35</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dl</td>
<td>304.6 ± 74.0</td>
<td>176.6 ± 52.3</td>
</tr>
<tr>
<td>High total cholesterol, (%)</td>
<td>7 (87.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Remission within 6 months (%)</td>
<td>8 (100)</td>
<td>2 (33.3)</td>
</tr>
</tbody>
</table>

* p < 0.05

Disclosure: D. H. Lim, None; S. H. Bae, None; S. M. Ahn, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

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Autoimmune Hepatitis in Systemic Lupus Erythematosus. Doo-Ho Lim, Seung-Hyon Bae, Soo Min Ahn, Seokchan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: Autoimmune Hepatitis (AIH) is a chronic progressive liver disease of unknown cause, characterized by circulating auto-antibodies and hyperglobulinemia. Patients with AIH often have other autoimmune diseases such as autoimmune thyroiditis and ulcerative colitis. However, AIH accompanied by SLE (AIH-SLE overlap) is comparatively rare condition. The aims of our study were to identify the distinct features of AIH-SLE overlap compared with primary AIH (PAIH) and to evaluate the factors related with outcome of AIH-SLE overlap.

Methods: From May, 1995 to Feb. 2014, the clinical data of 164 patients with PAIH and 23 patients with AIH-SLE overlap in a tertiary referral center were reviewed retrospectively. AIH was diagnosed if pretreatment or posttreatment score was above 9 or 11, according to AIH diagnostic scoring system of American Association for the Study of Liver Disease in 2002. Liver biopsy was performed in all AIH patients. SLE patients fulfilled at least 4 of the 1997 revised American College of Rheumatology criteria. Progression was defined as occurrence of liver cirrhosis (LC), hepatocellular carcinoma (HCC), liver transplantation (LT) or death from hepatic failure.

Results: The mean follow-up duration of AIH-SLE overlap and PAIH were 7.62 ± 4.13 years (range: 1.5 – 16) and 6.23 ± 4.0 (0.5 – 17.5), respectively (Table 1). The age at AIH diagnosis was younger and initial serum IgG level was higher in AIH-SLE overlap (P < 0.005). There were no significant differences of histological findings and treatment strategy. Although proportion of overall progression was not different, severe progression such as HCC, LT or death only happened in PAIH patients. Among 23 patients of AIH-SLE overlap, 8 patients with progression showed higher serum IgG level (4077.38 ± 1641.02 mg/dl) compared to 15 patients without progression (2560.71 ± 932.24 mg/dl) (p = 0.017). Furthermore, progression in AIH-SLE overlap was associated with serum IgG level of above 2 folds upper limit of normal (OR = 11.00, 95% CI = 1.420 – 85.201, P = 0.026).
Conclusion: The clinical course of AIH might be expected less aggressively in AIH-SLE overlap than PAIH. In addition, we could suggest that initial high level of serum IgG is a poor prognostic factor in patients with AIH-SLE overlap.

Table 1. Characteristics of AIH-SLE overlap and PAIH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AIH-SLE overlap (n = 23)</th>
<th>PAIH (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at AIH diagnosis, years*</td>
<td>37.35 ± 12.55</td>
<td>49.98 ± 12.365</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>23 (100)</td>
<td>149 (90.9)</td>
</tr>
<tr>
<td>Follow up, year</td>
<td>7.62 ± 4.13 (1.5 - 16)</td>
<td>6.23 ± 4.21 (0.5 - 17.5)</td>
</tr>
<tr>
<td>Other autoimmune disease (%)</td>
<td>4 (17.4)</td>
<td>21 (12.8)</td>
</tr>
<tr>
<td>Arthritis (%)*</td>
<td>9 (39.1)</td>
<td>27 (16.6)</td>
</tr>
<tr>
<td>Leukopenia (%)</td>
<td>3 (13.1)</td>
<td>25 (15.2)</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>11 (47.8)</td>
<td>44 (26.8)</td>
</tr>
<tr>
<td>Protein, g/dl</td>
<td>8.40 ± 1.10</td>
<td>8.02 ± 4.07</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>3.42 ± 0.70</td>
<td>3.53 ± 0.2</td>
</tr>
<tr>
<td>AST, IU/l</td>
<td>402.43 ± 444.87</td>
<td>432.40 ± 552.15</td>
</tr>
<tr>
<td>ALT, IU/l</td>
<td>372.70 ± 514.39</td>
<td>355.34 ± 468.92</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/l</td>
<td>235.39 ± 176.12</td>
<td>165.20 ± 116.71</td>
</tr>
<tr>
<td>GGT, IU/l</td>
<td>168.24 ± 190.10</td>
<td>162.44 ± 250.23</td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>5.99 ± 10.60</td>
<td>5.57 ± 6.83</td>
</tr>
<tr>
<td>Serum IgG, mg/dl*</td>
<td>3112.23 ± 1411.84</td>
<td>2419.23 ± 899.64</td>
</tr>
<tr>
<td>Autoantibody</td>
<td>23/23 (100)</td>
<td>141/162 (87)</td>
</tr>
<tr>
<td>anti nuclear antibody (%)</td>
<td>8/21 (38.1)</td>
<td>42/161 (26.1)</td>
</tr>
<tr>
<td>anti smooth muscle antibody (%)</td>
<td>1/17 (4.3)</td>
<td>0/136 (0)</td>
</tr>
<tr>
<td>anti LKMI (%)</td>
<td>0/22 (0)</td>
<td>6/160 (3.8)</td>
</tr>
<tr>
<td>anti mitochondrial antibody (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>interface hepatitis (%)</td>
<td>16 (69.6)</td>
<td>93 (56.7)</td>
</tr>
<tr>
<td>plasma cell infiltration (%)</td>
<td>5 (21.7)</td>
<td>35 (21.3)</td>
</tr>
<tr>
<td>rosette (%)</td>
<td>2 (8.7)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>biliary change (%)</td>
<td>6 (26.1)</td>
<td>23 (14)</td>
</tr>
<tr>
<td>Progression at AIH diagnosis (%)</td>
<td>4/23 (17.4)</td>
<td>37/164 (22.5)</td>
</tr>
<tr>
<td>Progression after AIH diagnosis (%)</td>
<td>4/19 (21.1)</td>
<td>45/127 (35.4)</td>
</tr>
<tr>
<td>liver cirrhosis (%)</td>
<td>4 (21.1)</td>
<td>38 (29.9)</td>
</tr>
<tr>
<td>hepatocellular carcinoma (%)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>liver transplantation (%)</td>
<td>0 (0)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>death from hepatic failure (%)</td>
<td>0 (0)</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

*; p < 0.05

AST, Aspartate aminotransferase; ALT, Alanine transaminase; GGT, Gamma glutamyltransferase; anti LKMI, anti Liver-Kidney-Microsomes antibody

Disclosure: D. H. Lim, None; S. H. Bae, None; S. M. Ahn, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. You, None.

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Utility and Associated Risk of Pulmonary Embolism CT Scans in the Michigan Lupus Cohort. Ruba Kado1, Emily Siegwald2, Emily Lewis3, Mitch Goodsit4, Emmanuel Christodoulou2, Ella Kazerooni2 and W. Joseph McCune2. 1University of Michigan, Ann Arbor, MI, 2University of Michigan, Ann Arbor, MI.

Background/Purpose: Ionizing radiation from CT scanning can increase cancer risk. Lupus patients are frequently evaluated for chest pain and may have multiple pulmonary embolism CT (PE-CT) scans in addition to other exposures to diagnostic or therapeutic radiation.

The objective of this study is twofold i) Determine the incidence of PE in University of Michigan Lupus Cohort patients who have undergone PE -CT scans ii) Estimate associated breast and lung cancer incidence.

Methods: We reviewed records of patients in the Michigan Lupus Cohort (N=856), and for each patient determined the number and outcome of PE-CT scans. All patients gave informed consent for review of their records. Based on estimated x-ray exposure from a state of the art GE Discovery CT750 HD CT scanner for an arterial chest scan, we estimated radiation dosage to the breast and lung in an average sized adult woman, utilizing CT-Expo software package. [1] We used the dose information and the patient’s age at the time of the CT scan and tabulated risks according to the BEIR VII report to estimate the increased lifetime incidence risks of breast and lung cancer. Risks from multiple CT scans were summed.

Results: 183/856 (21%) patients underwent a total of 358 PE CT scans. The overall rate of positivity was 7.5%. The likelihood of a positive scan decreased in proportion to the number of scans that had been previously performed. (Figure 1) For patients undergoing their first through third CT scans the rate of positivity for PE was 9.2 %, whereas patients undergoing their fourth through tenth CT scans had 1.6% positivity.

We estimated radiation doses to the breast and lung in female patients from a PE CT arterial scan, as 20mGy and 22mGy respectively. Separating patients based on age and number of CT scans, the estimated lifetime increase incidence risk of breast and lung cancer was calculated. In this simplified model the range of added risk for breast and lung cancer respectively per 100,000 female patients was 0–100 in 72% and 72%; 100– 500 in 25% and 28% and 500– 1000 in 4% and 1%.

Image/graph:

Conclusion: Patients with multiple previous PE CT scans had lower likelihood of a positive result on subsequent scans and higher risks of malignancy. Our conservative estimates of radiation exposure, that do not account for higher radiation doses from older CT scanners, indicate sufficient risk to warrant more precise characterization of radiation exposure in this population; and encourage development of guidelines for PE screening for patients with systemic lupus erythematosus and recurrent chest pain. The magnitude of risk should not discourage performance of PE CT when clinically indicated.

References:

Disclosure: R. Kado, None; E. Siegwald, None; E. Lewis, None; M. Goodsit, None; E. Christodoulou, None; E. Kazerooni, None; W. J. McCoy, None.

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Lupus Chest Pain in the Emergency Department: a Common Diagnostic Dilemma. Masoom Mod1, Mariko L. Ishimori1, Daniel J. Wallace2 and Michael Weisman1. 1 Cedars-Sinai Medical Center, Los Angeles, CA, 2 Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background/Purpose: Chest pain (CP) is a common symptom reported by SLE patients often leading to presentation to Emergency Departments (ED). The origin of CP can be attributed to many causes, which may or may not be cardiac in nature. It is important to understand the prevalence of CP in SLE, with ED visits being a window of opportunity for early detection of SLE heart disease.

Methods: Billing records of patients who presented to Cedars-Sinai Medical Center ED with ICD-9 codes for CP between 3/2009–10/2013 were reviewed; this data was then examined for secondary ICD-9 codes for CP performed. (Figure 1) For patients undergoing their first through third CT scans the rate of positivity for PE was 9.2 %, whereas patients undergoing their fourth through tenth CT scans had 1.6% positivity.

We estimated radiation doses to the breast and lung in female patients from a PE CT arterial scan, as 20mGy and 22mGy respectively. Separating patients based on age and number of CT scans, the estimated lifetime increase incidence risk of breast and lung cancer was calculated. In this simplified model the range of added risk for breast and lung cancer respectively per 100,000 female patients was 0–100 in 72% and 72%; 100– 500 in 25% and 28% and 500– 1000 in 4% and 1%.

Image/graph:

Conclusion: Patients with multiple previous PE CT scans had lower likelihood of a positive result on subsequent scans and higher risks of malignancy. Our conservative estimates of radiation exposure, that do not account for higher radiation doses from older CT scanners, indicate sufficient risk to warrant more precise characterization of radiation exposure in this population; and encourage development of guidelines for PE screening for patients with systemic lupus erythematosus and recurrent chest pain. The magnitude of risk should not discourage performance of PE CT when clinically indicated.

References:

Disclosure: R. Kado, None; E. Siegwald, None; E. Lewis, None; M. Goodsit, None; E. Christodoulou, None; E. Kazerooni, None; W. J. McCoy, None.
diagnoses. Continuous variables were analyzed by paired t test, and categorical data by chi squared test.

Results: Of 2675 ED visits with ICD-9 codes for SLE; 397 had secondary codes for CP (15%). Of the 397 SLE and CP visits, 173 visits were discharged directly from the ED and 224 visits became hospital admissions.

The ED discharged group was significantly younger (p<0.0005) compared with the hospital admitted group.

ED discharge group: The 173 ED visits were accounted for by 127 unique patients. 77% of these visits received a basic cardiac work up. While most patients had just 1 visit, a small number (7%) were frequent users of the ED, with an estimated one fourth of all visits.

Hospital Admitted Group: The 224 admissions were accounted for by 161 unique patients. 92% of admitted patients received a basic cardiac work up.

CP in the hospitalized group: The most commonly listed discharge diagnoses based upon primary physician’s work up and opinion, and the listed diagnoses for CP in the discharge summary are shown in Table 1. Rule out of Acute Coronary Syndrome (28.6%) was the most common diagnosis. Over 50% of CP at discharge was attributed to non-cardiac causes.

Conclusion: Of all SLE coded patients presenting to the CSMC ED over a 4.5 year period, 15% had complaints of CP, which is higher than the national average for CP in non-SLE patients (10%). Frequent ED users (3 or more visits) made up only 7% of the total sample, but accounted for 24% of all the ED visits. Over 90% of admitted patients had a basic cardiac work up performed. However, only a small percentage had a discharge diagnosis that was related to cardiovascular disease (7.2%). There is a high percentage of a negative cardiac work up with a majority of non-cardiac diagnoses in SLE patients, strengthening the need for more research into improved biomarkers or more specific imaging techniques to assess the etiology of CP. This study was a first step in revealing the high prevalence of CP in SLE patients presenting to the ED, while examining the limited diagnostic capabilities of a traditional cardiac work up.

Table 1: Chest Pain in the Hospitalized Group

<table>
<thead>
<tr>
<th>Discharge Diagnosis</th>
<th>Percentage of Admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease (CAD, MI, Unstable</td>
<td>7.2%</td>
</tr>
<tr>
<td>Angina, Microvascular Disease)</td>
<td></td>
</tr>
<tr>
<td>Pericarditis (SLE related)</td>
<td>3.1%</td>
</tr>
<tr>
<td>Other Cardiac NOS (CHF, Arrhythmia, PVD)</td>
<td>4%</td>
</tr>
<tr>
<td>Rule out of Acute Coronary Syndrome</td>
<td>28.6%</td>
</tr>
<tr>
<td>Musculoskeletal/ Costochondritis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (Pulmonary Embolism, Pneumonia, COPD)</td>
<td>13.8%</td>
</tr>
<tr>
<td>Gastro-Intestinal</td>
<td>8.9%</td>
</tr>
<tr>
<td>Multi-Factorial</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Disclosure: M. Modri; None; M. L. Ishimori; None; D. J. Wallace; None; M. Weisman. None.

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Humoral Immunodeficiency in Patients Presenting with Clinical Features of Systemic Lupus Erythematosus. W. Winn Chatham1, Duncan Harmon2 and Harry W. Schroeder Jr.* 1University of Alabama at Birmingham, Birmingham, AL; 2University of Alabama-Birmingham, Birmingham, AL.

Background/Purpose: Humoral immunodeficiency syndromes including common variable immune deficiency (CVID) are not uncommonly associated with autoimmunity. The spectrum of autoimmune disorders encountered in CVID patients may include features seen in systemic lupus erythematosus (SLE). Studies were undertaken at an academic center managing both disorders to determine the relative prevalence, clinical features, and outcomes of immunodeficiency associated SLE.

Methods: A retrospective review of records of patients seen between 2011 and 2014 with suspected humoral immunodeficiency and SLE was undertaken. Records for review were identified using an electronic medical record search of diagnosis codes for SLE and hypogammaglobulinemia. The clinical and immunologic profile was determined for patients with confirmed or suspected SLE who also had undergone evaluation for humoral immunodeficiency.

Results: We identified 36 patients meeting ACR criteria for SLE with inadequate response to pneumococcal vaccine challenge (failure to generate protective antibody titer to ≥ 5/14 pneumococcal vaccine antigens) and/or low serum IgG levels (< 700 mg/dl) not attributable to antecedent immunosuppressive therapy. This comprised 5.5% of our SLE patients meeting ACR SLE criteria in active follow-up. An additional 30 patients with SLE clinical features but not meeting SLE ACR criteria were identified with low serum IgG and/or inadequate vaccine responses. Among the 36 identified patients meeting ACR SLE criteria, serum immunoglobulin levels ranged from 459–744 mg/dl; 33 (92%) had serum IgG levels <700 mg/dl, while 19 (53%) had inadequate response to pneumococcal vaccine challenge, including the three patients with serum IgG > 700 mg/dl. Frequent upper/lower respiratory infections requiring antibiotic treatment (≥3 episodes/year) were reported in 24/36 (67%) patients. SLE features developed 2–26 years (mean = 8.9 years) prior to the recognition of low serum IgG in 25 (69%) patients, whereas initial SLE features were noted concurrently with or 3–4 years following first confirmed low IgG levels in 11 (31%). Arthritis (75%), photosensitivity (81%), malar rash (61%) and mucosal ulcers (56%) were the most prevalent SLE features. Only 9 (25%) of patients had low complement C3 or C4 levels, 6 (17%) had cytopenias, and 2 (6%) had elevated levels of anti-dsDNA. The majority of patients were managed with antimarialdrugs (86%), with 8/36 (22%) also using methotrexate; 18/36(50%) were on treatment with IVIG. Disease activity was low (SLEDAI score ≤2) in 32/36 (89%) at the last noted follow-up assessment.

Conclusion: SLE may be a presenting feature of patients with humoral immunodeficiency. Serum immunoglobulin levels and assessment of the response to pneumococcal vaccination for patients with low or low normal serum IgG levels should be included as part of the evaluation for suspected SLE, particularly in the context of frequent respiratory infections. Favorable outcomes are seen in the context of standard of care treatment for SLE combined with immunoglobulin replacement therapy.

Disclosure: W. W. Chatham; None; D. Harmon; None; H. W. Schroeder Jr., None.

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Characteristics of Lupus Patients with Interstitial Lung Disease and Relationship with Jo-1 Antibody. Samera Vasee1, Judith A. James2, Aikaterini Thanou3 and Joan T. Merrill4. 1University Of Oklahoma, Oklahoma City, OK; 2Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Pulmonary involvement is frequent in systemic lupus erythematosus (SLE) and can affect the pleura, pulmonary vasculature, and parenchyma. The prevalence of ILD is lower in SLE than in the other CTDs (3–15%). While ILD in SLE is usually mild, it can be progressive or severe in some patients. We aimed to determine clinical and serological characteristics of SLE patients with symptomatic ILD in an outpatient longitudinal lupus cohort.

Methods: The Oklahoma Lupus Cohort consists of a longitudinal cohort of patients who meet 1997 ACR criteria for SLE. Patients are enrolled after informed consent and their clinical and serological data are collected at routine clinic visits. Patients with pulmonary fibrosis or interstitial lung disease were identified using the database, and matched with 5–6 age and gender. Data were collected SLE controls without ILD. Data was collected using retrospective chart review. All patients included (n = 110) fulfilled 1997 ACR criteria for SLE.

Results: Fifteen SLE patients with a concurrent diagnosis of pulmonary fibrosis or ILD were identified among 517 in SLE cohort giving a prevalence of 2.9%. Fourteen of 15 patients had imaging reports available for review and all patients had radiographic evidence of parenchymal lung involvement. Most commonly reported abnormalities were ground glass opacities and interstitial thickening or fibrosis mostly involving basilar regions followed by traction bronchiectasis, reticular pattern and fibrotic NSIP. Subpleural honeycomb and UIP were least common.

American Indians were 27% of those with ILD and 13% of controls. African Americans were evenly divided (37% cases, 37% controls). 53% of ILD patients had a diagnosis of anti-phospholipid syndrome vs. 32% of controls. Cases had a high rate of serositis history (78% vs. 38% controls, P value 0.006), anti-dsDNA (53% vs 23% p =0.02) and lymphopenia (47% cases vs. 17% controls, P value 0.016). There was a trend to increased frequency of anti-La (43%), anti-Sm (43%), RNP (53%) and lupus anticoagulant (33%) in ILD vs non-ILD (18%, 24%, 37% and 13% respectively, p = 0.07, 0.2, 0.2 and 0.06).

There were only 2 patients positive for anti-Jo1 among 517 SLE patients (0.4%); one by laser immunobead assay and immunodiffusion (patient A), the other by immunobead assay only (patient B). Both were among the cases with significant ILD. Both were African American females; had cytoplasmic ANA
Impact of Sleep Disorders in Quality of Life, Pain and Disease Activity Using Actigraphy and Pittsburgh Sleep Quality Index (PSQI) in Female with Systemic Lupus Erythematosis (SLE).

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex heterogeneous disease which can be associated with significant morbidity and mortality. Hospitalization and readmissions have garnered significant attention in recent years through Medicare reimbursement adjustments. The aim of this study was to determine what factors may increase the risk of hospitalization in patients with SLE. The goal of this project is to develop a lupus risk model with the goal of helping to reduce hospitalization with an increase in missed appointments and higher creatinine.

Methods: Between 2006–2011, patients with an ICD-9 code of SLE were included. Additional information that could be relevant to risk profiling were extracted, including: laboratory results, medications, appointments (scheduled and/or kept), and hospitalizations. Patients were divided into two groups: hospitalized and non-hospitalized. Hospitalized patients selected for chart review and inclusion in the cohort, included any with an ICD-9 diagnosis of lupus as the primary reason for admission to the hospital. The non-hospitalized patients included any with an ICD-9 code for lupus who were seen by rheumatology. Patients were selected randomly from among all who met inclusion criteria. The risks associated with hypothesized risk factors, including proportion of missed appointments and creatinine levels, were estimated through weighted Cox regression models to account for patient selection into the study.

Results: Twenty-nine patients were selected who met the above lupus hospitalization criteria and 37 patients were randomly selected as non-hospitalized lupus controls. Patients were categorized into three groups based on the percentage of missed appointments (0% missed, >0%-33% missed, 33%-100% missed). Of the 60 patients with appointment data, 12 had no missed appointments, 27 (0–33%), 21 (33–100%). There was a trend toward an elevated risk of hospitalization for those with missed appointments and an elevated creatinine at their last appointment. In a multivariable model accounting for age and last creatinine measurement, patients who missed up to 33% of appointments, were estimated to have 2.92 (95% CI: 0.54–15.76) times the risk of patients who did not miss any appointments. Patients who missed between 33% and 100% of their appointments, the risk was 3.30 (95% CI: 0.52–20.96) times. The estimated risk of hospitalization associated with creatinine measure over 1.25 ml/dl at their last appointment was 4.72 (95% CI: 1.22–18.27) times the risk of those with lower creatinine.

Conclusion: Patients with SLE appear to have an elevated risk of hospitalization with an increase in missed appointments and higher creatinine. Data about proportion of missed appointments or elevated creatinine might be used to trigger electronic health record-based decision support alerts about such risk that could lead to clinical interventions to help avoid hospitalizations. Further study with larger cohort samples is needed to confirm these findings and potentially identify other risk factors.

Disclosure: None.

Table 1. Comparison between SF-36 domains and PSQI categorical groups:

<table>
<thead>
<tr>
<th>SF-36 domain</th>
<th>&lt; 10 points</th>
<th>&gt; 10 points</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>67.9 (4.4)</td>
<td>64.4 (5.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Role physical</td>
<td>47.1 (9.8)</td>
<td>27.9 (8.0)</td>
<td>0.131</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>52.8 (3.2)</td>
<td>35.5 (4.9)</td>
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<tr>
<td>General health</td>
<td>40.7 (3.5)</td>
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</tr>
<tr>
<td>Social functioning</td>
<td>60.6 (3.2)</td>
<td>54.1 (4.4)</td>
<td>0.219</td>
</tr>
<tr>
<td>Role emotional</td>
<td>70.6 (4.8)</td>
<td>63.3 (4.8)</td>
<td>0.187</td>
</tr>
<tr>
<td>Mental health</td>
<td>74.5 (7.8)</td>
<td>47.1 (10.3)</td>
<td>0.056</td>
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</tbody>
</table>

Table 2. Comparison between actigraphy results and PSQI categorical groups:

<table>
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<tr>
<td>SMIN_MEAN</td>
<td>372.7 (13.2)</td>
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<tr>
<td>SLEEP_MEAN</td>
<td>91.5 (1.3)</td>
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<td>0.396</td>
</tr>
<tr>
<td>WASO_MEAN</td>
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Disclosure: None.

Table 3. Comparison between SF-36 domains and PSQI categorical groups:

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Table 4. Comparison between actigraphy results and PSQI categorical groups:

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Disclosure: None.

Table 5. Comparison between SF-36 domains and PSQI categorical groups:

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<td>Mental health</td>
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<table>
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Splenectomy in Systemic LUPUS Erythematosus and AUTOIMMUNE Hematological Diseases. a Comparative Analysis. Luis J. Jara1, Nahim Barron2, Jesús Arenas-Osuna3, Arturo Vélez-García4, Arturo González-Zúñiga5, Miguel A Saavedra6 and Pilar Cruz-Domínguez7. 1Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico; 2Hospital de Especialidades Centro Médico La Raza, México, Mexico; 3Hospital de Especialidades Centro Médico La Raza, Mexico, Mexico; 4Hospital de Especialidades Centro Médico La Raza, Mexico, Mexico.

Background/Purpose: Acute presentation of severe autoimmune thrombocytopenia, and hemolytic anemia in systemic lupus erythematosus (SLE) is associated with high mortality. Splenectomy is the second line of treatment. The aim of this study is to investigate the efficacy and safety of splenectomy in refractory thrombocytopenia and hemolytic anemia associated or not with SLE.

Methods: From January 2004 to April 2014, 34 patients underwent splenectomy due to severe autoimmune thrombocytopenia and/or hemolytic anemia. The mean age of patients were 34.6 years old (range 18–62 y.o.) and twenty eight patients were female (82.35%). The patients were divided into two groups: Group 1: 18 patients with thrombocytopenia associated with SLE (9), SLE plus antiphospholipid syndrome, APS, (6), and primary APS (3). Group 2: 16 patients without SLE: Fisher-Evans Syndrome (2), and hemolytic anemia (14). All patients had refractory hematological manifestations, which were defined according to Mayo Clinic Criteria as: 1. If patients did not maintain platelets≥ 50,000 per ml for 2 weeks on medical therapy; 2. Medically dependent. 3. Medically intolerant. Patients with hemolytic anemia were submitted to surgery when they developed 2 hemolytic crisis (fever, jaundice, pallor, abdominal pain, and hemoglobin ≤ 6 grams per ml, desire to convert to platelet transfusion in a 6 months period. The response to splenectomy was considered for thrombocytopenia as follows: 1. Complete response ≥150,000 platelets per ml. 2. Partial response: 50,000 to 149,000 per ml or 3. No response: < 50,000 per ml. The complete response for hemolytic anemia as hemoglobin ≥ 9 gr per ml. The immediate response were evaluated after 7 days. The mean of follow up was 28.5 months (range3–96 months). Statistical Analysis: descriptive statistics and Chi square Test.

Results: Open splenectomy was performed in 15/34 patients (44.11%) and laparoscopy in 19/34 patients, 3 converted to open surgery. The complete response were observed in 15/34, (44.11%).Group 1, 14/8 (22.2%) and Group 2, 11/16, (68.8%) (p = .006). After 30 days of surgery a complete response were observed in 11/18, (61.1%) for Group 1 and 13/16, (81.2%) Group 2 (p = NS). The complications in the immediate post-operative period were observed in 6/34, 5 of Group 2 vs 1 in Group 1 (p = 0.05). Infections in 3/34, one patient had bleeding and 1 had more than one complication respectively. In Group 1, the mean of period between hematologic manifestations and surgery was 17.8 months and in Group 2, 16.5 months. After follow up, in Group 1, the relapse were observed in 7/18 patients, and in Group 2, 3/16. In Group 1, steroids were reduced in 13/18 patients, and 14/16 one patient had bleeding and 2 had mesenteric and portal vein thrombosis respectively.

Conclusion: This study suggest that patients with SLE, SLE plus APS and primary APS have a similar response to splenectomy compared with organ-specific autoimmune diseases despite a partial response in the immediate period. Patients with organ-specific autoimmune diseases had a significant increase of complications. The splenectomy is safety and effective in severe and refractory hematologic manifestations. The surgery approach has no influence in the prognosis of splenecomy.

Disclosure: L. J. Jara, None; N. Barron, None; J. Arenas-Osuna, None; A. Vélez-García, None; A. González-Zúñiga, None; M. A. Saavedra, None; P. Cruz-Domínguez, None.

Is the Disease-Specific LupusQoL Sensitive to Changes of Disease Activity in SLE Patients after Treatment of a Flare? Kathleen McElhone1, Jane Burnell2, Chris Sutton2, Janice Abbott2, Peter Lanyon3, Anisur Rahman4, Chee-Seng Yee5, Mohammed Akil6, Yasmeen Ahmad7, Ian Bruce8, Caroline Gordon9 and Lee-Suan Teh1. 1Royal Blackburn Hospital, Blackburn, United Kingdom; 2University of Central Lancashire, Preston, United Kingdom; 3Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; 4University of Reading, Reading, United Kingdom; 5Barts Health NHS Trust, London, London, United Kingdom; 6Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, United Kingdom; 7Sheffield Children Rheumatic Dis, Sheffield South Yorkshire, United Kingdom; 8Peter Maddison Research Centre, Bangor, United Kingdom; 9Arthritis Research UK Epidemiology Unit, Institution of Inflammation and Repair, University of Manchester, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; 10Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: With improving survival in SLE patients, patient-reported health-related quality of life (HRQoL) has become an important outcome. The LupusQol is a disease-specific patient-derived HRQoL measure with good psychometric properties. The aim of the UK centre in the LupusQol Sensitivity Study is to assess whether the LupusQol is sensitive to change when disease activity improves or deteriorates.

Methods: Patients with SLE (≥ 4 1997 ACR criteria), experiencing a flare (new A or B by BILAG-2004 Index) & requiring an increase in treatment (either prednisolone ≥ 20mg daily, introduction of methotrexate, parenteral steroids, cyclophosphamide &/or biologics) were recruited from 9 UK centres. Assessments were undertaken at baseline & monthly for 9 months after initiation of therapy & included BILAG-2004 disease activity index & the LupusQol with 8 domains - physical health, pain, planning, intimate relationships, burden to others, emotional health, body image, fatigue) and scores ranging from 0 (worst) to 100 (best HRQoL). Changes in disease activity are defined (see Table – first column) as deterioration: major & minor and improvement: major & minor. Changes in LupusQol domain scores when disease activity improved, deteriorated or was unchanged between consecutive time-points are reported as mean changes, with 95% confidence intervals (CI) constructed using robust standard errors to account for repeated patient assessments.

Results: Mean (SD) age was 40.9 (12.8) & duration since diagnosis was 9.3 (8.1) years for the 101 patients recruited; 94% females, 62.6% white Europeans, 15.2% south Asians, 8.1% black Caribbean, 4% black Africans, 9.3 (8.1) years for the 101 patients recruited; 94% females, 62.6% white Europeans, 15.2% south Asians, 8.1% black Caribbean, 4% black Africans, 5% mixed, 1% Chinese. At baseline mean (SD) BILAG2004 score was 16.4 (8.1); all mean LupusQol domain scores were < 52. LupusQol physical health, pain & fatigue domain scores increased when BILAG improved (overall, major & minor). Physical health and pain domain scores decreased when there was a major BILAG deterioration but changes with a minor BILAG deterioration were small and non-significant. The effects of improvements & deterioration in BILAG on the LupusQol domain scores were smaller or not present (Table).

Conclusion: Improvement and deterioration of LupusQol domain scores for physical health, pain & fatigue domain scores was seen in patients with significant changes in disease activity over 1 month. Sensitivity to change of other LupusQol domains in relation to changes of disease activity may need to be evaluated over a longer interval as the more emotive type of response to the disease & its consequences may be latent and therefore not evident at monthly intervals.

Disclosure: K. McElhone, None; J. Burnell, None; C. Sutton, None; J. Abbott, None; P. Lanyon, None; A. Rahman, None; C. S. Yee, None; M. Akil, None; Y. Ahmad, None; I. Bruce, None; C. Gordon, GlaxoSmithKline, MedImmune, Merck Serono, Paraxel and UCB Pharma, 5; L. S. Teh, Roche Pharmaceuticals, 8.

Mapping the Disease-Specific LupusQol to the SF-6D. Rachel Meacock1, Mark Harrison2, Kathleen McElhone3, Janice Abbott4, Sahena Haque5, Ian N. Bruce6 and Lee- Suu Teh7. 1The University of Manchester, Manchester, United Kingdom; 2University of British Columbia, Vancouver, BC, 3Royal Blackburn Hospital, Blackburn, United Kingdom; 4University of Central Lancashire, Preston, United Kingdom; 5University Hospital of South Manchester, Manchester, United Kingdom; 6NIHR Manchester Musculoskeletal Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom.

Results: The LupusQol is a disease-specific patient-derived HRQoL measure with good psychometric properties. The aim of the UK centre in the LupusQol Sensitivity Study is to assess whether the LupusQol is sensitive to change when disease activity improves or deteriorates.
Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom.

**Background/Purpose:** The LupusQoL is a measure of health-related quality of life (HRQoL) developed specifically to assess the impact of systemic lupus erythematosus (SLE) and its treatment. Whilst producing a profile of scores, it is not preference-based, and therefore does not provide utility values. Such utility estimates are necessary to calculate quality-adjusted life years (QALYs) evaluations, which are increasingly needed to guide decisions on how best to allocate health care resources.

The SF-6D (derived from the SF-36/SF-12) is a generic preference-based HRQoL measure which does provide utility scores. Despite evidence to support the validity of the SF-6D in SLE, and growing need for utility data, many trials fail to include a preference-based measure. One solution is empirical mapping; estimating a statistical relationship between a non-preference based and a preference-based measure using a dataset in which both measures have been administered to the same patients.

We aim to derive and test a mapping algorithm to predict SF-6D utility scores from the LupusQoL.

**Methods:** LupusQoL and SF-6D data were collected from 320 people with SLE at rheumatology outpatient clinics at 7 UK centres. Ordinary least squares regression was used to estimate models of increasing complexity to predict individuals’ SF-6D scores from their LupusQoL responses. Model performance was judged on predictive ability through the size and pattern of prediction errors generated, using mean absolute error (MAE) and root mean squared error (RMSE) statistics. Performance of the selected model was externally validated on an independent data set of 113 females with SLE who had completed both the LupusQoL and SF-36. All patients met 4 or more of the ACR criteria for SLE.

**Results:** Mean age and disease duration of the estimation sample was 44.8 (SD 13.6) and 10.5 (SD 8.7) years respectively. The sample cover the full range of SF-6D scores, mean 0.615 (range 0.296–1.00). Figure 1 shows mean LupusQoL domain scores. Four LupusQoL domains (physical health, pain, emotional health, fatigue) were selected in the final model. The validation dataset were slightly older (mean age 48.6 (SD 9.3) years) with longer disease duration (mean 12.6 (SD 9.7) years), but had comparable range of SF-6D (0.327 – 1.00) and mean LupusQoL scores (Figure 1). Model fit was good in both the estimation data (R2 0.7219, MAE 0.0557, RMSE 0.0706) and when applied to the validation sample (R2 0.7431, MAE 0.0528, RMSE 0.0663). The model predicts mean SF-6D utility in the validation sample extremely well (observed mean 0.624; predicted 0.617).

**Conclusion:** We provide a method by which utility values can be estimated from patient responses to the non-preference based LupusQoL, generalizable beyond the sample upon which it was estimated. Prediction errors, upon which mapping functions are primarily judged, were lower than those of published studies to date.

**Disclosure:** R. Meacock, None; H. Devilliers, None; N. Annapureddy, None; J. A. Block, None; M. Jolly, None.

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**The Validity of Patient and Physician Global Disease Activity Assessments of Systemic Lupus Erythematosus: Results from the Lupus Activity Scoring Tool (LAST) As Compared to the Selena Sledai (SS) Modification Multicentre Study.** Majed Khraishi1, Rana Aslanov2, Sanjay Dixit1, Ramin Yazdani3, Vandana Ahiwala4 and Sarah Khraishi5. 1Nexus Clinical Research, St John’s, NF, 2Memorial University of Newfoundland, StJohn’s, NF, 3McMaster University, Hamilton, ON, 4St. Clare’s Mercy Hospital, St. John’s, NF, 5William Osler Health Center, Brampton, ON, 6NL Research Technologies (NLRT), St. John’s, NF.

**Background/Purpose:** Patient reported outcome (PRO) tools are important to understand, educate, manage, and follow patients with systemic lupus erythematosus (SLE). Disease targeted PRO for SLE (LupusPRO) has good reliability and has been validated in several languages and cultural contexts. LupusPRO could be better integrated into routine clinical care and clinical trials in SLE if it was also found to be responsive to physician assessed changes in disease activity. We sought to test the responsiveness of LupusPRO domains to changes in physician disease activity assessments in the routine clinical care setting.

**Methods:** Longitudinal data on LupusPRO and disease activity assessments were collected in the Rush Lupus Data Repository during routine clinical care visits. We tested only the responsiveness of the health related quality of life domains (HRQOL) as we expect these to change over short periods of time in response to disease activity. Disease activity assessments used as anchors for testing responsiveness included the SELENA physician global assessments (PGA), Total SLEDAI, SLEDAI and the SELENA-Flare Index (SFI). Cut-offs used to determine change in disease activity were PGA (change of 0.3), SELENA-SLEDAI (change of 4), and SFI (remitting, stable and flaring). Non-parametric analysis of variance was used to compare changes in LupusPRO HRQOL domains against disease activity anchors.

**Results:** There were 658 visit data available for 185 patients. Consecutive visits were 2-5 months apart with a median number of visits per patient of 7. PGA was available for 651 visits; Total SLEDAI was available for 269 visits; SFI was available for 614 visits. Mean (SD) age and SELENA-SLEDAI were 43.5 (13.2) years and 6.4 (7.3), respectively. PGA changed significantly for 281 visit data (increased in 132, decreased in 142), while 377 visit data had unchanged PGA. LupusPRO HRQOL domains that changed significantly in the appropriate direction included Lupus Symptoms (p<0.001), Procreation (p=0.003), Pain-Vitality (p=0.002), Emotional Health (p=0.06), and Body Image (p=0.03). SELENA-SLEDAI changed significantly among 73 visits (32 increased, 41 decreased), and remained stable among 196 visits. LupusPRO HRQOL domains of Lupus symptoms (p=0.0004) and Pain-Vitality (p=0.02) responded significantly and in the appropriate direction. Significant changes in SFI were observed in 151 visit data (79 remitting, 72 flaring), while 463 visit data were unchanged. LupusPRO HRQOL domains that responded significantly in the appropriate direction in response to changes in SELENA-SLEDAI were Lupus symptoms (p<0.001), Procreation (p=0.005), Physical Health (p=0.0006) and Pain-Vitality (p<0.0001). Mixed model analysis supported similar results.

**Conclusion:** Most HRQOL domains of LupusPRO are responsive to physician-assessed changes in disease activity in the routine patient care setting. LupusPRO is an appropriate tool to be used not only in clinical trials but also in the clinical care setting.

**Disclosure:** D. Giangreco, None; H. Devilliers, None; N. Annapureddy, None; J. A. Block, None; M. Jolly, None.
were prospectively followed and evaluated by the same tools at each visit. The SS was also calculated for each visit.

**Results:** Fifty-eight patients (84.5% females) with 98 assessments from five study centers were included in this analysis. The median age was 49.0 (Q1-Q3=33.8–60.3) years with the mean (SD) disease duration 12.1 (6.5) years. Scores from the LAST/C-LAST were obtained at each visit in addition to the SLEDAI scores. The mean (SD) SLEDAI score was 8.2 (5.2). The mean (SD) LAST (with C5, C4 and Anti-ds Anti-DNA) score was 30.3 (17.3) and C-LAST – 32.2 (20.1). The SS scores were consistent and strongly correlated with the LAST and C-LAST scores (r = 0.430, p<0.001 & r = 0.215, p = 0.034, respectively) at the baseline and follow-up visits: SS scores 0–4 corresponded to the LAST scores of 0–30 while SS scores of 8 or higher corresponded to 50 and higher, respectively. Both SS and LAST scores were significantly correlated with current treatment with Prednisone (r = 0.305, p = 0.002 & r = 0.430, p<0.001, respectively); LAST score was also correlated with Mycophenolate mofetil (r = 0.205, p = 0.043) and Azathioprine (r = 0.286, p = 0.003) treatments. Patient’s (PGA) and Physician’s (PHGA) Global Assessments of SLE activity were strongly correlated with each other (r = 0.759, p<0.001) and with the LAST score (r = 0.781, p<0.001 & r = 0.826, p<0.001, respectively); PHGA was also significantly correlated with SELENA SLEDAI score (r = 0.324, p = 0.001). The LAST and C-LAST scores correlated in 90% of the assessments with r = 0.898 and p<0.001. We utilized an electronic application of the LAST which was easy to use and no errors were found with its results as compared to the manually obtained scores with the Pearson’s correlation coefficient r = 0.995 & p<0.001.

**Conclusion:** The Lupus Activity Scoring Tool (LAST) and C-LAST are new disease activity indices that correlate well with the SELENA SLEDAI modification. The use of simple clinical variables as a measure of SLE activity seems to be valid under different clinical settings with different assessors. The inclusion of patient’s global assessment and the current use of steroids and immunomodulators can be utilized effectively in assessing disease activity.

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**Simple Disease Assessment for People with Lupus Erythematosus.** Meenakshi Jolly1, Winston Sequera, Sergio Troa2, Ana M. Bertol3, Luis Mejia1,4, Ivan Blazevic5, Kiana Movlovian,6, Karina Torralba5, Berna Goker5, Josiane Bourré-Tessier5, Sandra V. Navarra1, 6, Daniel Wallace12, Michael H. Weisman13, Ann E. Clarke14, Chi Chiu Mok6, and Joel A. Block1.

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**Background/Purpose:** Community rheumatologists treating patients with Systemic Lupus Erythematosus (SLE) typically lack user-friendly tools to effectively track SLE disease activity. Current disease activity tools in SLE are resource and effort intensive, require special training and practice, take time, are difficult to implement in busy clinical practices and are of use almost exclusively to SLE researchers. Nonetheless, patient reported outcomes are recognized as important for patient care, and physician reimbursement (quality initiatives) and resource allocation are becoming tied to these outcomes. Here we report a novel user-friendly tool intended for daily clinical use.

**Methods:** Using our dataset of approximately 1,150 SLE patients from multiple countries and ethnicities that was accrued during the development of the LupusPRO, a disease targeted health outcome measurement, we created multiple models with self reported SLE health survey items (LupusPRO), clinical variables (medications) and laboratory values that would correlate best with physician disease activity assessments (Physician Global Assessment and SLEDAI). Using stepwise regression methods, we parsed our model to keep it simple, included few and easily accessible laboratory values so it can be performed in most locations, and expected minimal real-time physician involvement. “SIMPLE” index equation was derived from the regression model with the best fit (Simple disease assessment for People with LE). We then prospectively tested the correlation between SIMPLE Index and Total SLEDAI in an independent dataset (n = 150) of SLE patients.

**Results:** SIMPLE index has two parts (i) patient self-report 16 items and (ii) two laboratory values obtained within 10 days before/after the visit. Requisite physician input pertains to (1) interpretation of one blood and one urine lab result in the context of SLE diagnosis, and (2) addition of weighted scores using a mobile application on a smart phone/computer by health personnel. The SIMPLE equation is as follows: SI = 2.4(BL) + 0.28(DHS) + 0.95(CSU) + 0.04(CSD) + 5.6(UL) + 2.4(BL), where Simple Index: SI, LupusPRO Lupus Symptom domain: 3 items (LSX), Lupus Impact Tracker: 10 items (LIT), Change in Health Status: 1 item (DHS), Self Report of Current use of corticosteroid: 1 item (CSU), Self Report of current daily corticosteroid dose (Prednisone

tively refined, and finally, tested in tandem with the LFA-REAL™ ClinRO, through a pilot study and large scale validation trial.

**Results:** Our initial data confirm that, in addition to physical indicators of wellbeing, such as physical functioning, pain, fatigue, and acute and chronic symptoms, mental and emotional indicators of wellbeing are also important to people with lupus. Disease-related factors that cause anxiety or interfere with activities of daily living may be perceived as equally or more limiting than symptoms that indicate severe disease to an MD. Additionally, study subjects indicated that the ideal PRO should be able to track and rate resources with visual aids, assess symptoms over time and should also encourage open communication with their healthcare providers.

**Conclusion:** Findings show that patients view factors that cause anxiety and interfere with daily living as equally or more limiting than symptoms of severe disease. A two part system that addresses both physicians’ and patients’ views is likely to contribute to reconciling the discordance between physician and patient assessments of disease, improving short and long term outcomes in lupus.

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equivalent in mg): 1 item (CSD), Urine Laboratory-Proteinuria (SLEDAI definition) (UL) and Blood Laboratory-Low complement C3/C4 (BL).

The SIMPLE index explained 55% variance of total SLEDAI score. In the second dataset, correlation of SIMPLE index with Total SLEDAI was strong (0.74, p=0.0001).

**Conclusion:** SIMPLE Index appears to correlate well with disease activity. It is easy, requires minimal physician training and involvement, and has the potential for quick integration into practice with minimal personnel resources. It also allows active patient engagement in care. Longitudinal studies are ongoing to confirm its utility and acceptability.

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Comparison of Responsiveness of Lupus Impact Tracker with Lupus Quality of Life to Selena Responder Index. Hervé Devilliers1, Narender Annapureddy2, Winston Sequeira3, Joel A Block4 and Meenakshi Jolly5.

1Department of internal medicine and systemic diseases, Dijon, France; 2Rush University Medical Center, Chicago, IL; 3rush university, chicago, IL; 4Rush University, Chicago, IL.

**Background/Purpose:** Lupus Impact Tracker (LIT) is a 10-item patient reported outcome tool to measure the impact of Systemic Lupus Erythematosus (SLE) or its treatment on patients' daily lives. The transformed scores range from 0–100, where higher scores denote greater impact. The tool is responsive to self-reported changes in SLE health status over time. Herein, we compare the responsiveness of the LIT and LupusQol (34 items) to changes in disease activity as judged by SLE responder index (SRI).

**Methods:** Adult SLE patients were prospectively recruited from 20 North American Rheumatology clinics for the LIT study- an observational, non-interventional prospective multi-center study conducted across the US and Canada. Data (Demographics, LIT, LupusQol, BILAG, SELENA-SLEDAI) were obtained three months apart. Modified SRI was defined as (1) a decrease in SELENA-SLEDAI (4 points), (2) No new BILAG A and not more than 1 new B and (3) No increase in Physician Global Assessment (PGA). Litter definition was used as our PGA variable was categorical (0/1/2/3). Standardized response mean (SRM) and effect size (ES) for LIT and LupusQol domains were calculated among SRI responders and non-responders by taking the average difference divided by the standard deviation of the differences between the paired measurements at baseline and 3 month visit LIT scores. Kruskall Wallis test was used to compare the SRM among SRI responders (R) and non responders (NR).

**Results:** 325 patients participated (90% Female); 53% Whites, 33% Black and 17% Hispanic. Mean (SD) age and SELENA-SLEDAI at baseline were 42.3 (16.2) yrs and 4.3 (3.8), respectively. Mean (SD) LIT score at baseline was 39.4 (22.9). SRI data was available for 295 (40% R and 255 NR) at the 3 month timepoint. LIT SRM (ES) was −0.69 (−0.36) and −0.20 (−0.12) among SRI responders and non-responders respectively, (p=0.02).

For LupusQol, SRM (ES) for physical health and Pain domains were 0.42 (0.23) and 0.65 (0.44) respectively.

**Conclusion:** 10 item LIT was modestly responsive to changes in disease activity as assessed by SRI in patients with SLE in this study Two domains (16 and 18) and genital warts (types 6 and 11), and has been shown to be protective against these HPV-related diseases.

**Disclosure:** J. P. Dhar, Merck, Inc, 2, L. Essenmacher, None; R. Dhar, None; A. Magee, Merck, Inc, 9; H. Sugar, None; M. Venkatram, None; R. Sokol, None.
Methods: Two phase 2 randomized, open-label, dose-escalation studies were conducted in adult Chinese patients with SLE. AZD2800C (sifalimumab; N=30) and AZD3461C (anifrolumab; N=17). Patients enrolled in both studies satisfied ACR classification criteria. AZD2800C included dose cohorts of 1, 3, and 10 mg/kg (mpk) administered intravenously (IV) every 4 weeks; 100 mg subcutaneously every 2 weeks; and 600 and 1200 mg IV every 4 weeks. AZD3461C included dose cohorts of 100, 300, and 1000 mg administered IV every 4 weeks. In both studies, blood specimens were collected for PK and PD assessment at multiple time points between predose and 169 days (anifrolumab) or 365 days (sifalimumab) after initial administration. Sifalimumab and anifrolumab concentrations were measured using a validated electrochemiluminescence assay and PK parameters were determined by noncompartmental analysis. Transcription profiling was conducted with qRT-PCR on a 21 IFN gene signature (IFNGS).

Results: Sifalimumab exhibited linear pharmacokinetics with a half-life of about 20 days while, anifrolumab exhibited nonlinear pharmacokinetics. Though concentrations of both sifalimumab and anifrolumab reached steady state by Day 84. In AZD2800C and AZD3461C, 97% and 88% of patients had elevated IFNGS at baseline, respectively. In AZD2800C, maximum median suppression of the IFNGS was 63% with 1 mpk, 48% with 3 mpk, 67% with 10 mpk, 37% with 100 mg SC, 76% with 300 mg, and 61% with 1200 mg and was observed within 1 to 3 days of dosing with sifalimumab. In AZD3461C, maximum median suppression of the IFNGS by anifrolumab was 6% in the 100 mg (day 85), 85% (day 169) in the 300 mg, and 97% (day 85) in the 1000 mg cohort, with sustained suppression (>70% and >95%) in the 300 and 1000 mg cohorts after days 141 and 29, respectively. The level of suppression correlated well with increased anifrolumab concentrations. There were no major safety issues in the small sifalimumab and anifrolumab Japanese open-label trials (AZD2800C and AZD3461C, respectively) at the dose regimens studied but there is inadequate data to fully characterize the safety profile adequately and overall safety needs to be confirmed in larger double-blind controlled studies.

Conclusion: Both sifalimumab and anifrolumab showed expected mechan-anism of action in SLE, with anifrolumab having increased and more sustained target suppression of the IFNGS in Japanese SLE patients compared to sifalimumab.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Clinical and Therapeutics: Systemic Sclerosis Measures and Outcomes

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Measures of Disease Status in Systemic Sclerosis: Systematic Review. Tien Tay1, Nava Ferdowsi1, Wendy Stevens1, Marie Hudson2, Murray Baron3, Candice Rabusa4, David Prior5, Susanna Proudman6 and Mandana Nikpour1.1The University of Melbourne at St Vincent’s Hospital, Melbourne, Australia, 2Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC, 3Royal Adelaide Hospital, Rheumatology Unit and University of Adelaide, Discipline of Medicine, Adelaide, Australia.

Background/Purpose: To identify the measures of disease status in systemic sclerosis (SSc) using a systematic review.

Methods: A systematic review of Medline (1966–2014), EMBASE (1974–2014), and Cochrane Library (inception-2014) was undertaken to identify indices of disease status in systemic sclerosis. We focussed on objective measures and excluded non-English articles, animal-only studies and those relating to morphea, localized scleroderma or juvenile systemic sclerosis.

Results: Of the 5687 articles identified through the search, we identified 45 articles for review. We found a further 22 articles through a search of the bibliography of relevant articles. We identified 10 ‘composite’ (multi-organ) indices: two disease activity indices, six disease severity scales, and two combined response indices (Tables 1 and 2). There was no disease damage index for SSc. Furthermore, we found no objective organ-specific index for the gastrointestinal system.

Conclusion: We identified a number of composite and organ-specific indices in SSc, incorporating subjective and/or objective measures, developed to quantify disease activity, severity and response in clinical trials. Most of the existing indices require further evaluation according to the OMERACT filter. None of the existing indices measures organ damage per se, highlighting this as an area for future research.

Table 1: Features of existing composite measures of disease status in systemic sclerosis

<table>
<thead>
<tr>
<th>Disease activity indices</th>
<th>Disease severity indices</th>
<th>Outcome measures</th>
</tr>
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<tbody>
<tr>
<td>Features</td>
<td>Valvaritis</td>
<td>Malar</td>
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<tr>
<td>CRSS</td>
<td>EPOS</td>
<td></td>
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<tr>
<td>Methodology</td>
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<td></td>
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<tr>
<td>Composite-based</td>
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<td>Y</td>
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<tr>
<td>Number of experts</td>
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<td>9</td>
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<tr>
<td>Data-driven</td>
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<td>Y</td>
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<td>Variables</td>
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<tr>
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<tr>
<td>Weighted score</td>
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<tr>
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<tr>
<td>Patient-reported outcomes</td>
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<tr>
<td>Discrimination capacity</td>
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Disclosure: T. Tay, None; N. Ferdowsi, None; W. Stevens, None; M. Hudson, None; M. Baron, None; C. Rabusa, None; D. Prior, None; S. Proudman, None; M. Nikpour, None.

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Muscle Disease in Systemic Sclerosis Is Associated with an Increased Risk for Cardiac Involvement. Jison Hong1, Antonia Valenzuela1, David Fiorentino2 and Lorinda Chung1.1Stanford University School of Medicine, Palo Alto, CA, 3Stanford University, Redwood City, CA.

Background/Purpose: Patients with systemic sclerosis (SSc) and muscle involvement (myopathy/mysositis) have more severe disease and worse outcomes. We sought to determine the prevalence of muscle disease in our cohort of SSc patients and to compare these patients to those without muscle disease.

Methods: We conducted a retrospective medical record review of patients with SSc according to 2013 ACR classification criteria, evaluated at Stanford from 2006–2013. We collected demographics, clinical features if ever present, Manual Muscle Test (MMT), laboratory data (available autoimmune results and muscle enzymes: CKP, aldolase, LDH, AST and ALT). Muscle involvement was defined by the presence of any of the following criteria: elevation in muscle enzyme(s), physician reported history of myopathy/mysositis, and if performed, electromyogram, MRI, and/or muscle biopsy results consistent with myopathy/mysositis. Comparisons between SSc patients with and without muscle disease
were made with Student’s t-test for continuous variables and chi-square or Fisher’s exact test for categorical variables.

Results: The study included 273 patients (mean age 57.3 years, 88.7% female, 54.6% Caucasian, 37.4% diffuse, and 62.6% limited). Muscle disease was present in 80 patients (29.3%). The most common findings of muscle disease at presentation were elevated muscle enzymes (42.5%) and proximal muscle weakness (42.5%). The first manifestation of muscle disease occurred at a mean time of 7.1±1.1 years after the first non-Raynaud symptom of SSc. As expected, patients with muscle disease were more likely to have diffuse disease, arthralgias, myalgias, muscle weakness, dysphonia, mechanic hands, greater maximum modified Rodnan skin score, lower MMT-8 scores, and positive PM-1 antibody (p<0.03). They had less vascular manifestations such as Raynaud’s phenomenon (73.8% vs 87.1%; p=0.008) and telangiec-tastias (7.5% vs 21.8%; p=0.005) and were less likely to be centromere positive (21.3% vs 36.3%, p=0.02). Cardiac disease was more common in patients with muscle disease (13.8% vs 5.7%, p=0.03).

Conclusion: 30% of our SSc cohort had muscle disease, which was associated with a higher likelihood of cardiac disease. Obtaining baseline and routine monitoring of muscle enzymes and performing strength exams at every visit may help to identify patients with SSc with muscle involvement associated with a higher likelihood of cardiac disease. Obtaining baseline and routine monitoring of muscle enzymes and performing strength exams at every visit may help to identify patients with SSc with muscle involvement associated with a higher likelihood of cardiac disease.

**Any combination of MRI, EMG, muscle biopsy and muscle enzymes

Table 1. Baseline characteristics of 80 patients with muscle disease

| Patients n (%) |  
|----------------|----------------|
| Disease duration from first Raynaud’s symptom to muscle disease diagnosis (years ± SD)* | 8.26 ± 10.9 |
| Disease duration from first non-Raynaud’s symptom to muscle disease diagnosis (years ± SD)* | 7.1 ± 11.1 |
| Symptom at presentation of muscle disease: | |
| High muscle enzymes | 34 (42.5) |
| Myalgias | 34 (42.5) |
| Proximal muscle weakness | |
| Symptom at any time of muscle disease: | |
| Myalgias | 13 (16.25) |
| Subjective muscle weakness | 21 (26.25) |
| Muscle weakness on physical exam | 13 (16.25) |
| Dysphonia | 3 (3.75) |
| Dysphagia related to muscle weakness | 24 (30) |
| MRI performed | 6 (7.5) |
| Normal | 3 (3.75) |
| Abnormal | 2 (2.5) |
| Non-specific | 1 (1.25) |
| EMG performed | 10 (12.5) |
| Normal | 4 (5) |
| Neuropathy | 1 (1.25) |
| Myopathy | 1 (1.25) |
| Non-specific | 1 (1.25) |
| Inflammatory myositis | 3 (3.75) |
| Muscle biopsy performed | 8 (10) |
| Normal | 1 (1.25) |
| Abnormal | 7 (8.75) |
| Elevated muscle enzymes | 64 (82.5) |
| Peak CK (Units/Liter) | 1577.7 ± 3116.6 |
| Peak aldolase (Units/Liter) | 20.1 ± 26.5 |
| Peak AST (Units/Liter) | 264.8 ± 846.4 |
| Peak ALT (Units/Liter) | 215.1 ± 240.3 |
| Peak LDH (Units/Liter) | 544 ± 316.4 |
| More than one test positive** | 12 (15) |
| Normal muscle enzymes | 14 (17.95) |
| MMT-8 | 66.38 ± 15.5951 |

*Information available in 46 patients

**Any combination of MRI, EMG, muscle biopsy and muscle enzymes

Disclosure: J. Hung, None; A. Valenzuela, None; D. Fiorentino, None; L. Chung, None.

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Prediction of Improvement in Skin Fibrosis in Diffuse Cutaneous Systemic Sclerosis. Rucsandra Dobrota1, Britta Maurer2, Nicole Graf3, Carina Mihi3, Otylia Kowal-Bielecka4, Yannick Allanore5 and Oliver Distler on behalf of the EUSTAR investigators and co-authors. 1Department of Internal Medicine and Rheumatology, Dr. I.Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, 2Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, 3graf biostatistics, Winterthur, Switzerland, 4Department of Rheumatology and Internal Medicine, Medical University of Białystok, Białystok, Poland, 5Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France.

Background/Purpose: Improvement of skin fibrosis over time is part of the “natural history” of patients with diffuse cutaneous systemic sclerosis (dcSSc). However, in the individual patient, the pattern of change in skin fibrosis varies widely. The extent of skin fibrosis measured by the modified Rodnan skin score (mRSS) is the major outcome measure in clinical trials (CT) in dcSSc. Understanding the factors behind the improvement of skin fibrosis in dcSSc is important to avoid unnecessary use of therapy and medical resources. Moreover, it could improve cohort selection in CT using skin fibrosis as a major outcome.

Methods: A longitudinal analysis including 704 patients with dcSSc from the EUSTAR registry was performed. The inclusion criteria were diagnosis of dcSSc, fulfillment of ACR criteria, mRSS>7 at baseline and available data for mRSS at 12±2 months follow-up. First entry into the database was defined as baseline. Skin improvement was defined as a decrease in mRSS of >5 points AND ≥25 % within 1 year. Variables with p<0.02 in univariate analysis were selected for multivariate analysis through a nominal group technique. To compensate for missing data, a multiple imputation followed by a pooled logistic regression was run. Based on a likelihood ratio test, the full model was compared to a reduced model. The model with the best fit was evaluated in the available data set.

Results: A total of 155/704 patients showed skin improvement. On univariate analysis, cardiac involvement, immunosuppression and ESR<25 mm/h were associated with skin improvement. High baseline mRSS was the strongest parameter (p<0.001; Figure 1), with the best sensitivity and specificity for prediction of skin regression at a cut-off of 17.5 points (area under the curve 0.708). In addition, a high skin fibrosis progression rate at baseline was also strongly associated with regression of skin fibrosis at 12-months follow-up. A multivariate pooled logistic regression with 13 variables was run. The likelihood ratio test was in favor of a reduced model: baseline mRSS (Estimate 0.087, p<0.001) and ESR >25 mm/h (Estimate —0.526, p 0.030). When tested on the available data set, this latter model showed good performance in predicting regression of mRSS (area under the curve 0.726, 95%CI 0.64–0.80). Figure 1. Baseline mRSS in patients with and without skin regression: there is a clear trend towards the predominance of regression (black bars) over no regression (grey bars) in patients with high mRSS.

Conclusion: These results show that, opposite to current practice, patients with already advanced skin fibrosis are more likely to regress under standard of care in the next 12 months than patients with milder skin fibrosis. Thus, focus for treatment intervention and recruitment in CT aiming at skin fibrosis should shift from these patients with high baseline mRSS to at risk patients characterized by low to moderate skin fibrosis and high ESR at baseline.

Disclosure: R. Dobrota, Pfizer Inc, 2; B. Maurer, None; N. Graf, None; C. Mihi, None; O. Kowal-Bielecka, Abbvie, Actelion, Pfizer, 5, Abbvie, Actelion, Pfizer, 8; Y. Allanore, Bayer Pharma, Actelion, Pfizer, Sanofi-Aventis, CSL Behring, Roche, 5, Bayer Pharma, Actelion, Pfizer, Sanofi-Aventis, CSL Behring, Roche, 2; O. Distler on behalf of the EUSTAR investigators and co-authors, Actelion, Pfizer, Ergonex, BMS, Bayer, United BioSource Corporation, Roche/Genentech, medac, Biovitrum, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotics, Sinoxa, Sanofi-Aventis, Serodapharm, GSK, Epipharm, 5, Actelion, Pfizer, Ergonex, Sanofi-Aventis, 2.
**Early Mortality in Australian, Canadian and Spanish Scleroderma Patients: Rationale for Establishing a Multi-National Inception Cohort of Patients with Systemic Sclerosis.**

Yanjie Hao1, Marie Hudson2, Patricia Carreira3, Wendy Stevens3, Candice Rabusa3, Solene Tatibouet4, Loreto Carmona5, Beatriz E Joven6, Susanna Proudm1, Murray Baron3 and Mandana Nikpour3.

1St. Vincent’s Hospital Melbourne, Melbourne, Australia, 2McGill University, Montreal, QC, 3Hospital Universitario 12 de Octubre, Madrid, Spain, 4The University of Melbourne at St Vincent’s Hospital, Melbourne, Australia, 5Lady David Research Institute, Montreal, QC, 6Instituto de Salud Musculoesqueletica, Madrid, Spain, 7Hospital Universitario, Madrid, Spain, 8University of Adelaide, Adelaide, Australia, The University of Melbourne at St Vincent’s Hospital, Melbourne, Australia.

**Background/Purpose:** Studies of ‘prevalent’ cohorts wherein most patients have longstanding disease at recruitment may underestimate mortality in systemic sclerosis (SSc) due to survivor bias. The aim of this study was to quantify mortality in Australian, Canadian and Spanish patients with SSc and to compare patients with prevalent and incident disease.

**Methods:** We quantified mortality as Standardized Mortality Ratio (SMR) and Years of Life Lost (YLL) in each of the cohorts based on Australian Bureau of Statistics, Statistics Canada and Spain National Statistics Institute data for the general population, and percentage survival in the first decade of disease in the whole combined ‘prevalent’ cohort and a subset of patients recruited within 4 years of onset of disease (the combined ‘incident’ cohort). We determined a single primary cause of death (SSc or non-SSc related) and all other SSc organ involvement that contributed to death.

**Results:** In the combined prevalent cohort of 3218 patients (1411 Australian, 1465 Canadian and 342 Spanish), 53% of the primary causes of 440 deaths (157 Australian, 213 Canadian and 70 Spanish) recorded were SSc related; the most common cause of SSc-related death was heart-lung disease (Table 1). Malignancy, atherosclerotic vascular disease and sepsis were the most common causes of mortality in non-SSc related causes. SSc organ involvement contributed to 31% of these non-SSc related deaths. In multivariable regression, the predictors of mortality were male sex, older age at disease onset, diffuse subtype and presence of PAH, ILD, myocardial involvement, or renal crisis. The SMR and YLL were higher (Table 2) in Australian and Canadian incident cohorts compared with the respective prevalent cohorts. Survival was lower (Figure 1) in the combined incident cohort than the prevalent cohort.

Conclusions: Mortality in Canadian, Spanish and Australian SSc patients is substantial. Our results suggest that prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in diffuse disease. These findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

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**Table 1 Causes of SSc-related death**

<table>
<thead>
<tr>
<th>SSc Subtype</th>
<th>Australian Cohort</th>
<th>Canadian Cohort</th>
<th>Spanish Cohort</th>
<th>Combined cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart and Lung</td>
<td>74 (75%)</td>
<td>44 (29%)</td>
<td>57 (49%)</td>
<td>55 (52%)</td>
</tr>
<tr>
<td>PAH</td>
<td>41 (67%)</td>
<td>24 (15%)</td>
<td>30 (31%)</td>
<td>22 (24%)</td>
</tr>
<tr>
<td>ILD</td>
<td>18 (28%)</td>
<td>20 (13%)</td>
<td>17 (18%)</td>
<td>31 (34%)</td>
</tr>
<tr>
<td>P-AH and ILD</td>
<td>14 (11%)</td>
<td>10 (10%)</td>
<td>11 (11%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Myocardial involvement</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Pericardial involvement</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Renal crisis</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**Table 2** A comparison of mortality in ‘prevalent’ and ‘incident’ cohorts

<table>
<thead>
<tr>
<th>SSc Subtype</th>
<th>Australian Patients</th>
<th>Canadian Patients</th>
<th>Spanish Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited onset</td>
<td>110</td>
<td>27</td>
<td>151</td>
</tr>
<tr>
<td>Established onset</td>
<td>53</td>
<td>58</td>
<td>32</td>
</tr>
</tbody>
</table>

**Figure 1** Survival curves in combined cohorts

**Disclosure:** Y. Hao; M. Hudson; P. Carreira; W. Stevens; C. Rabusa; S. Tatibouet; L. Carmona; B. E. Joven; S. Proudm; M. Baron; M. Nikpour.

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**Moderate Decline in Forced Vital Capacity is Associated with a Poor Outcome in Systemic Sclerosis Patients.**

Anna-Maria Hoffmann-Vold1, Oyvind Midveldt2, Torkild Garen3, May Brit Lund1, T. Mogens Aalokken4, Jan Tore Gran5 and Oyvind Mølberg6.

1Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway, 2Department of Respiratory Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway, 3Department of Radiology, Oslo University Hospital Rikshospitalet, Oslo, Norway, 4Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway.

**Background/Purpose:** Interstitial lung disease (ILD) is a common manifestation in systemic sclerosis (SSc) and the leading cause of morbidity and mortality. Serial pulmonary function tests are useful for monitoring SSc-ILD, and total decline in forced vital capacity (FVC) above 10% predicts mortality. Moderate FVC decline (5–10%) was recently shown to predict poor outcome in idiopathic pulmonary fibrosis, but it is not known if moderate FVC decline has any impact on the outcome of SSc-ILD.

**Methods:** The study cohort included 305 SSc patients enrolled in the prospective SSc cohort (Norwegian Systemic Connective Tissue Disease and Vasculitis Registry [NOSVAR]) at the Department of Rheumatology, Oslo University Hospital (OUH). Serial pulmonary function test (PFT), lung fibrosis measured on high resolution computed tomography (HRCT) and clinical data were registered at baseline and then prospectively at annual follow-up visits. Patients were segregated in three groups according to annual FVC decline rates; (A) stable or minimal decline (<5%), (B) moderate decline (5–10%) and (C) major decline (>10%). Mortality and disease progression (fibrosis progression, DLCO and total FVC decline) quantified from baseline data were defined as poor outcome. Descriptive statistics and t-tests were applied; Kaplan-Meyer and Cox proportional hazard models were used to analyse survival.

**Results:** 305 SSc patients were followed for mean 3.8 years (range 1–9) from the baseline FVC. Altogether, 241 patients (79%) had stable FVC, 43 (14%) had moderate FVC decline and 21 (7%) had major decline (Table 1). Sixty-seven deaths occurred during the observation period. Moderate decline in FVC was significantly associated with mortality (HR 2.5 (95% CI 1.4, 4.6, p-value 0.003). The 1-year survival rates for the three FVC groups were 100%, 100%, 86%, 5-year survival rates were 97%, 85% and 76% and 10-year survival rates were 85%, 66% and 54%, respectively. Compared to the stable FVC group, the moderate FVC decline group were older at disease onset, had more lung fibrosis at baseline and at follow up, higher total decline in DLCO and lower FVC% at follow up (Table 1).

**Conclusion:** In this prospective SSc cohort, annual moderate FVC decline was associated with high total DLCO decline, high lung fibrosis scores and increased mortality. These results highlight the importance of regular PFT measurements in daily clinical practice.
Table 1: Clinical and lung characteristics of 305 SSc patients stratified by FVC decline

<table>
<thead>
<tr>
<th>Demographics</th>
<th>&lt;5%</th>
<th>5–10%</th>
<th>&gt;10%</th>
<th>p-val*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>241 (79)</td>
<td>43 (14)</td>
<td>21 (7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age at diagnosis, yrs (SD)</td>
<td>46.6 (13.1)</td>
<td>53.2 (13.6)</td>
<td>53.3 (13.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>Disease duration, yrs (SD)</td>
<td>3.2 (6.9)</td>
<td>4.9 (7.1)</td>
<td>6.0 (8.6)</td>
<td>0.062</td>
</tr>
<tr>
<td>Decreased, n (%)</td>
<td>41 (17)</td>
<td>14 (33)</td>
<td>12 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to death, yrs (SD)</td>
<td>9.6 (9.3)</td>
<td>10.6 (7.4)</td>
<td>9.1 (8.7)</td>
<td>0.328</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>49 (20)</td>
<td>11 (26)</td>
<td>3 (14)</td>
<td>0.473</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>100 (42)</td>
<td>14 (33)</td>
<td>10 (48)</td>
<td>0.436</td>
</tr>
<tr>
<td>deSSc, n (%)</td>
<td>60 (25)</td>
<td>17 (40)</td>
<td>9 (45)</td>
<td>0.056</td>
</tr>
<tr>
<td>ATA positive, n (%)</td>
<td>36 (15)</td>
<td>11 (26)</td>
<td>52 (17)</td>
<td>0.161</td>
</tr>
</tbody>
</table>

Lung function and imaging

| Baseline FVC, % (SD) | 91.0 (23.4) | 91.7 (21.0) | 91.4 (22.5) | 0.712 |
| FVC at follow up, % (SD) | 91.7 (22.9) | 77.0 (24.8) | 66.9 (19.9) | <0.001 |
| Baseline DLCO, % (SD) | 67.1 (20.0) | 68.4 (19.7) | 52.9 (17.4) | 0.179 |
| DLCO at follow up, % (SD) | 60.2 (20.2) | 55.4 (19.9) | 42.5 (18.5) | 0.154 |
| Total DLCO decline, % (SD) | 6.9 (13.4) | 13.0 (12.8) | 10.0 (15.4) | 0.006 |
| Baseline lung fibrosis, % (SD) | 6.0 (12.9) | 13.3 (18.5) | 6.4 (10.8) | 0.015 |
| Fibrosis at follow up, % (SD) | 7.6 (13.9) | 13.1 (19.2) | 7.8 (13.3) | 0.026 |
| >20% fibrosis, follow up, n (%) | 36 (15) | 11 (26) | 5 (49) | 0.084 |

Yrs: years; n: number; deSSc: diffuse cutaneous systemic sclerosis; ATA: anti-topoisomerase antibody; FVC: forced vital capacity; DLCO: diffusing factor for carbon monoxide; *p-value between <5% and 5–10% decline in FVC; 1 time from first non-Raynaud symptom to baseline FVC, 2 time from disease onset to death

Disclosure: A. M. Hoffmann-Vold; None; O. Midtvedt; None; T. Garen; None; M. B. Lund; None; T. M. Aalokken; None; J. T. Gran; None; O. Molberg; None.

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Reduced Diffusing Capacity of Carbon Monoxide Is Independently Associated with Worse Subclinical Left Ventricular Function on Speckle-Tracking Echocardiography in Systemic Sclerosis. Monique Hinchcliff, Vastasp Daruwalla, Lauren Beussink-Nelson, Sofia Podluskly, Mary A. Carns, John Varga, Michael Cuttica and Sanjiv J. Shah. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Reduced diffusing capacity of carbon monoxide (DLCO) is a predictor of worse outcomes in patients with systemic sclerosis (SSc). Traditionally, the association between low DLCO and mortality in SSc has been attributed to either interstitial lung disease (ILD) or pulmonary vascular disease due to pulmonary arterial hypertension (PAH). However, patients with primary cardiac involvement in SSc may have reduced DLCO due to pulmonary venous hypertension and/or generalized vascular disease in SSc. We sought to determine the association between DLCO and cardiac mechanics (speckle-tracking strain parameters) in patients with SSc.

Methods: We studied 195 patients with SSc who were enrolled in the Northwestern Scleroderma Program. All patients underwent comprehensive echocardiography using a standardized protocol for image acquisition and interpretation. Indices of cardiac mechanics (LV, RV, and left atrial [LA] strain parameters) were measured using speckle-tracking analysis. We used multivariable-adjusted linear regression analyses to determine the association between DLCO and indices of cardiac mechanics.

Results: The mean ± SD age was 51 ± 13 years, 84% were female, 59% had limited cutaneous SSc, 31% had diffuse cutaneous SSc, and 10% had other forms of SSc (e.g., overlap syndromes). Prevalence of SSc complications were as follows: PAH in 10%, significant iLD in 18.5%, and LV systolic dysfunction (EF<50%) in 3.6%. DLCO was not associated with global LVEF, but it was associated with LV, RV, and LA strain parameters, and early LV diastolic (e') tissue velocities, on univariate analysis (P=0.001) (Figure). Reduced DLCO remained associated with reduced absolute global longitudinal systolic strain (GLS, a marker of longitudinal LV systolic function) after adjusting for age, sex, SSc subtype, SSc disease duration, PAH, ILD, e' velocity (a marker of LV diastolic dysfunction), and tricuspid annular plane systolic excursion (a marker of RF function): β-coefficient = −0.9 (95% CI −1.5 to −0.2); % units, P=0.009. The association between DLCO and GLS persisted in the subset of patients with normal LVEF (>50%), no PAH, and FVC > 60% of predicted (multi-variate-adjusted P=0.014).

Conclusion: In patients with SSc, reduced DLCO is associated with subclinical abnormalities in LV mechanics even in patients without evidence of ILD, PAH, or global LV systolic dysfunction. DLCO may be a marker of SSc cardiac disease.

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Risk of Ischemic Stroke in Patients with Systemic Sclerosis: A Systematic Review and Meta-Analysis. Patompong Ungprasert1, Praveen Ratanasimetha2, Charat Thonggrrayoon3, Wisit Cheungpasitporn3 and Prompong Suksaunjit4. 1Bassett medical center, Cooperstown, NY, 2Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 3Mayo clinic, Rochester, MN, 4University of Utah School of Medicine, Salt Lake City, UT.

Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase risk of ischemic stroke secondary to accelerated atherosclerosis. However, the data on systemic sclerosis (SSc), another chronic inflammatory disease, remain unclear due to conflicting epidemiological studies. Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of ischemic stroke in patients with SSc versus participants without it.

Methods: Two investigators (P.U. and P.C.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2014 using the terms “systemic sclerosis” and “scleroderma” combined with the terms for cerebrovascular disease. A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between SSc and ischemic stroke and (2) odds ratios (OR’s), relative risk (RR’s) or hazard ratio (HR’s) or standardized incidence ratio (SIR’s) with 95% confidence intervals (CI’s) were provided. Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by consensus with the senior investigator. The quality of each study was, again, independently assessed by the two investigators using Newcastle-Ottawa scale.

RevMan 5.2 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran’s Q test.

Results: Out of 370 potentially relevant articles, three studies (all were retrospective cohort studies) with 3,861 cases of SSc were identified and included in our data analysis. The pooled risk ratio of ischemic in patients with SSc was 1.58 (95% CI, 1.12 to 2.25). The statistical heterogeneity of this meta-analysis was moderate with an I2 of 70%.

Conclusion: Our study demonstrated a statistically significant increased ischemic stroke risk among patients with SSc.
Disclosure: P. Ungprasert, None; P. Ratanasimetha, None; C. Thongprayoon, None; W. Cheungpasitporn, None; P. Suksraranjit, None.

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International Classification of Functioning, Disability, and Health (ICF) Core Sets for Connective Tissue Disease Interstitial Lung Disease (CTD-ILD) and Idiopathic Pulmonary Fibrosis (IPF) – a Necessary Map to Health Care Provision in the Era of ICD-11. Reuben Escorpizo, Kevin J. Keen, Kim Fligelstone, Matthew R. Lammi, Daphne LeSage, Anne-Marie Russell, Surinder Songr, Catherine Sarver, Janos Varga, Oliver Distler, and Lesley Ann Saketkoo 1. ICF Research Branch in cooperation with the WHO Collaborating Centre for the Family of International Classifications in Germany (DIMDI), Nottwil, Switzerland, 2Health Research Institute, Prince George, BC, 3Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, 4Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, 5Center for CCH at State of Louisiana, New Orleans, LA, 6Royal Brompton Hospital London, United Kingdom, 7King’s College Hospital NHS Foundation Trust, London, United Kingdom, 8Johns Hopkins, Baltimore, MD, 9National Koranyi Institute for TB and Pulmonology, Budapest, Hungary, 10University Hospital Zurich, Zurich, Switzerland, 11Louisiana State University Health Sciences Center, New Orleans, LA.

Background/Purpose: A recent consensus project (Saketkoo et al, Thorax 2014) recommended a minimum core set of outcome measures for use in future clinical trials of CTD-ILD and IPF. The World Health Organization (WHO) introduced the International Classification of Functioning, Disability, and Health (ICF) as a scientific method of disability data collection and a universal framework of ICF Core Sets for Connective Tissue Disease Interstitial Lung Disease (CTD-ILD) and Idiopathic Pulmonary Fibrosis (IPF) – a Necessary Map to Health Care Provision in the Era of ICD-11. Reuben Escorpizo, Kevin J. Keen, Kim Fligelstone, Matthew R. Lammi, Daphne LeSage, Anne-Marie Russell, Surinder Songr, Catherine Sarver, Janos Varga, Oliver Distler, and Lesley Ann Saketkoo 1. ICF Research Branch in cooperation with the WHO Collaborating Centre for the Family of International Classifications in Germany (DIMDI), Nottwil, Switzerland, 2Health Research Institute, Prince George, BC, 3Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, 4Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, 5Center for CCH at State of Louisiana, New Orleans, LA, 6Royal Brompton Hospital London, United Kingdom, 7King’s College Hospital NHS Foundation Trust, London, United Kingdom, 8Johns Hopkins, Baltimore, MD, 9National Koranyi Institute for TB and Pulmonology, Budapest, Hungary, 10University Hospital Zurich, Zurich, Switzerland, 11Louisiana State University Health Sciences Center, New Orleans, LA.

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Table 1. Instruments from published CTD-ILD and IPF minimum core sets for clinical trials; with Instrument Comparison and Inter-Reviewer Agreement.

<table>
<thead>
<tr>
<th>Minimum Core Set Instruments</th>
<th>Number of Items Linked</th>
<th>Number of Categories Identified</th>
<th>Agreement (%)</th>
<th>Agreement 95% Confidence Interval</th>
<th>ICF Domain Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council (MRC) Dypnea Scale</td>
<td>27</td>
<td>34</td>
<td>79</td>
<td>(62, 91)</td>
<td>Body Function include physical, mental and emotional functions</td>
</tr>
<tr>
<td>University of California San Diego-Behavior of Breath Questionnaire (UCSD-BBQ)</td>
<td>68</td>
<td>83</td>
<td>82</td>
<td>(76, 90)</td>
<td>Body Function include physical, mental and emotional functions</td>
</tr>
<tr>
<td>Leicester Cough Questionnaire</td>
<td>44</td>
<td>56</td>
<td>79</td>
<td>(66, 88)</td>
<td>Activities of Daily Living include participation and involvement in a life situation</td>
</tr>
<tr>
<td>St George’s Respiratory Questionnaire</td>
<td>126</td>
<td>138</td>
<td>91</td>
<td>(85, 95)</td>
<td>Activities of Daily Living include participation and involvement in a life situation</td>
</tr>
<tr>
<td>Medical Outcomes Study Short Form 36 (SF-36)</td>
<td>26</td>
<td>Based on previously linked version</td>
<td></td>
<td></td>
<td>Activities of Daily Living include participation and involvement in a life situation</td>
</tr>
<tr>
<td>Visual Analogue Scale Patient</td>
<td>Not defined by ICF (two breath)</td>
<td></td>
<td></td>
<td></td>
<td>Activities of Daily Living include participation and involvement in a life situation</td>
</tr>
<tr>
<td>Global Health and Functioning</td>
<td>2</td>
<td>2*</td>
<td>100</td>
<td>Not done</td>
<td>Body Structure relates to involvement of anatomical structures</td>
</tr>
</tbody>
</table>

Conclusion: This is the first effort to map CTD-ILD and IPF outcome measures to the ICF. A composite of these ICF linkages will be available to clinicians and researchers with validation studies to follow. ICF Core Sets are intended to be stream-lined disease-specific languages that support global, regional and personal health-related parity across cultures, age and socioeconomic status. ICF Core Sets enable fair assessment that may be utilized in policy making and service provision and funding. Familiarity with ICF Core Sets in CTD-ILD and IPF will enable clinicians to experience a smoother transition to ICD-11 which is under development and will meld diagnostic coding with the ICF.

Disclosure: R. Escorpizo, None; K. J. Keen, None; K. Fligelstone, None; M. R. Lammi, None; D. LeSage, None; A. M. Russell, None; S. Birting, None; C. Sarver, None; J. Varga, None; O. Distler, Actelion, Pfizer, Ergonex, BMS, Bayer, United BioSource Corporation, Roche/Genetech, medai, Biowintum, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotec, Sinoxa, Sanofi-Aventis, GSK, Epipharm, 5, Acelion, Pfizer, Ergonex, Sanofi-Aventis, 2 L. A. Saketkoo, None.

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Prediction and Impact of Attacks of Raynaud’s Phenomenon, As Judged By Patient perception. Michael Hughes 1, Amir Snapir 2, Jack Wilkinson 3, Daniel Snapir 4, Fredrick M. Wigley 4 and Ariane Herrick 5. 1The University of Manchester, Manchester, United Kingdom, 2Orion Corporation Orion Pharma, Turku, Finland, 3Salford Royal NHS Foundation Trust, Salford, United Kingdom, 4Johns Hopkins University School of Medicine, Baltimore, MD.

Background/ Purpose: Our aim was to evaluate (a) whether subjects with Raynaud’s phenomenon (RP) can predict RP attacks because if so, then this could have implications for new treatment approaches and (b) the impact of RP attacks on quality of life (QOL).

Methods: Subjects with RP were approached through international patient associations to participate in an online survey. The survey comprised 19 questions including demographic information and details of the RP. Subjects were asked to report their ability to predict (all on an ordinal scale) the occurrence of RP attacks (<20%, 21–50%, 51–70% and >70% of times), severity of attacks (very poorly, poorly, fairly well, well, and very well), and their ability to prevent/control RP attacks (very poor, poorly, fairly well, well and very well). Other questions related to medications, how well subjects felt they could control their RP, and the impact of RP on QOL.

Results: A total of 443 responses from subjects with self-reported RP (mean age 41 years, 91% female), from 15 countries were evaluable. 187 subjects (43%) had primary RP (PRP, as judged by self-report), 149 (34%) secondary RP (SRP) and 100 (23%) were not aware of the cause of their RP. 252 (58%) of subjects reported that they could predict at least 51% of RP attacks (66% of subjects with SRP vs. 56% PRP, p = 0.03), 248 (57%) subjects reported that they could predict attack severity either ‘fairly well’ or better (64% of subjects with SRP vs. 58% PRP, p = 0.16), with 43% predicting severity only poorly (30%) or very poorly (13%).
64% of all subjects reported either a ‘poor’ or ‘very poor’ ability to prevent or control RP attacks. 182 subjects (41%) reported current or previous use of medications for RP: 82% reported at least one currently used medication being ‘effective’. Most subjects (78%) reported making at least one life adjustment due to RP, more so in subjects with SRP compared with PRP (87% vs.71%, [P<0.001]). Patients reported the impact of their RP on QOL on a 0–10 scale, where 10 was the best imaginable: the mean QOL for all patients was 6.0 (SD 2.1 [range = 1–10]). PRP subjects’ current QOL was higher than SRP subjects (mean QOL 6.5 and 5.2 respectively, difference in means 95% CI: 1.21 (0.76 to 1.66) [P < 0.001]). When asked to imagine their QOL, without RP, SRP subjects imagined a greater absolute improvement from their current QOL (2.3 vs. 3.3, difference in means −0.9 (−1.4 to −0.4) [P=0.0002]).

**Conclusion:** 1. Subjects ability to predict both the occurrence and severity of RP attacks is limited (almost half of patients could predict neither attacks nor their severity), and this must be taken into account when designing clinical trials of future novel, ‘PRN’ (as required) treatments.

2. Only 16% of subjects currently on medication for RP reported that at least one current medication was ‘effective’, and most subjects reported a poor ability to prevent/control RP attacks, confirming an unmet need to develop new treatments.

3. RP significantly impacts on QOL, especially in subjects with SRP but also in PRP.

**Disclosure:** M. Hughes, None; A. Snapir, None; J. Wilkinson, None; D. Snapir, None; F. M. Wigley, None; A. Herrick, None.

### 729

**A Dilated Esophagus Is an Independent Risk Factor for Interstitial Lung Disease in SSc**

Carrie Richardson1, Rishta Agrawal2, Jungwha Lee3, Oriol Almagor3, John Varga2, Rowland W. Chang2 and Monique E. Hinchcliff4.

1McGaw Medical Center of Northwestern University, Chicago, IL, 2Northwestern University Feinberg School of Medicine, Chicago, IL, 3Northwestern University, Chicago, IL, 4Northwestern University, Feinberg School of Medicine, Chicago, IL.

**Background/Purpose:** High-resolution computed tomography of the chest (HRCT) performed for assessment of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc) frequently reveals a patulous esophageal diameter. While this finding may be incidental, it may be directly related to the magnitude of esophageal dilatation, we hypothesized that a greater HRCT esophageal diameter is associated with worse pulmonary outcomes.

**Methods:** A cross-sectional study of NorthWestern Scleroderma Registry patients with HRCT was conducted. Subjects met the ACR 1980 SSc or three out of five CREST (Calcinosis cutis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia) criteria. The esophageal diameter was measured at three levels: above the aortic arch, between the aortic arch and the right inferior pulmonary vein, and between the right inferior pulmonary vein and the diaphragmatic hiatus. Widest esophageal diameter (WED) was used as the predictor variable. A modified Likert scale (0 = none, 1 = < 3%, 2 = 6–25%, 3 for 26–50%, 4 = 51–75%, 5 = >75%) was used to score fibrosis and ground glass opacities. Total ILD (outcome variable) was assessed during a planned 3-year follow-up by a composite index defined by the occurrence of at least one of the following events: (1) a one or more new ischemic digital ulcer (DU), (2) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, (3) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF) <50% (Table)

**Results:** Three hundred eleven subjects had HRCT. Eight subjects without available HRCT images and one subject who had undergone esophagectomy were excluded. Twenty-eight patients who had mixed connective tissue disease, SSc sine scleroderma, or overlap syndromes were excluded, leaving 275 subjects for analysis. Adjusted standardized regression demonstrated positive associations between WED and total ILD score (β=0.33, p<0.0001), fibrosis (β=0.32, p<0.0001), and ground glass opacities (β=0.28, p<0.0001) (Table). There were negative associations between WED and TLC % predicted (β=−0.24, p=0.0002), FVC % predicted (β=−0.23, p=0.0004), and adjusted DLCO % predicted (β=−0.23, p=0.005).

**Conclusion:** Increasing esophageal diameter on HRCT in patients with SSc is associated with more severe radiographic ILD, lower lung volumes, and lower DLCO % predicted. Longitudinal studies should be done to elucidate the temporal relationship between esophageal disease and ILD in persons with SSc. Future trials of aggressive management of esophageal disease to prevent ILD may be warranted in persons with SSc.

**Table**

**Association between widest esophageal diameter and HRCT findings and pulmonary function test parameters**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted β coefficient (SE)</th>
<th>P value</th>
<th>*Adjusted β coefficient (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ILD score</td>
<td>0.36 (0.07)</td>
<td>0.0001</td>
<td>0.33 (0.08)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total fibrosis score</td>
<td>0.32 (0.04)</td>
<td>0.0001</td>
<td>0.32 (0.04)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total ground glass score</td>
<td>0.32 (0.04)</td>
<td>0.0001</td>
<td>0.28 (0.04)</td>
<td>0.0001</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>−0.34 (0.12)</td>
<td>0.0001</td>
<td>−0.34 (0.12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>−0.31 (0.12)</td>
<td>0.0001</td>
<td>−0.31 (0.12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adjusted DLCO % predicted</td>
<td>−0.29 (0.14)</td>
<td>0.0001</td>
<td>−0.29 (0.14)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ILD=interstitial lung disease, TLC=total lung capacity, FVC=forced vital capacity, DLCO=diffusion capacity for carbon monoxide.

**Disclosure:** C. Richardson, None; R. Agrawal, None; J. Lee, None; O. Almagor, None; J. Varga, None; R. W. Chang, None; M. E. Hinchcliff, None.

### 730

**Prediction of Cardiac and Vascular Events in Systemic Sclerosis: Input from Endothelin-1 Type A Receptor Antibodies.**

Jerome Avouac1, Gabriela Riemekasten2, Christophe Meune3, Barbara Ruiz2 and Yannick Allanore2.

1Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France; 2Charite´ University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany; 3Paris 13 University, University Hospital of Paris-Seine-Saint-Denis, Cardiology Department, Bobigny, France; 4Paris Descartes University, INSERM U1016, Institut Cochin, Sorbonne Paris Cite, Paris, France.

**Background/Purpose:** Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc). We have previously reported that angiogenic markers can predict the cardiovascular outcomes in SSc (1). In parallel, a cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ET1R) (2).

**Methods:** Serum levels of anti-AT1R and anti-ET1R autoantibodies, placenta growth factor (PIGF) and soluble vascular adhesion molecule (sVCAM) were measured with sandwich ELISA in a prospective cohort of 75 SSc patients. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting. The occurrence of at least one cardiac/vascular event was assessed during a planned 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: (1) a one or more new ischemic digital ulcer (DU), (2) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, (3) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50%, (4) scleroderma renal crisis (SRC) (1).

**Results:** The mean age of SSc patients (64 women) was 55±12 years old and the mean disease duration was 9±8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and a single patient). By univariate analysis, high baseline serum levels of anti-ET1R were predictive of the occurrence of cardiac/vascular events (p=0.002), together with low EPC counts (p=0.003) and increased levels of PIGF (p=0.0005) and sVCAM (p=0.009). No predictive value of anti-AT1R antibodies was identified. Multivariate analysis confirmed high serum levels of anti-ET1R antibodies (hazard ratio, HR: 3.71, 95%CI 1.44–9.52, p=0.03) and PIGF (HR: 5.22, 95%CI 1.96–15.87) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ET1R antibodies and PIGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95%CI 2.49–23.51, P=0.0002).

**Conclusion:** This study identifies for the first time anti-ET1R antibodies as an independent predictor of cardiac and vascular events in SSc. This
functional antibody, together with other angiogenic markers and in particular PGF2α, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.

Reference:

Disclosure: J. Avouac, None; G. Riemekasten, None; C. Meune, None; B. Ruiz, None; Y. Alarcon, None.

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Performance of the Old ACR and the New ACR-EULAR Systemic Sclerosis Classification Criteria in Patients with Limited Cutaneous Disease: Effect on the Ascertainment of Severe Pulmonary Arterial Hypertension. Beatriz E. Joven1, M Jesus Garcia de Yebenes2, Pilar Escribano3, Estibaliz Lopez4, M Jose Ruiz-Cano5, Carmen Jimenez Lopez-Guarch4, Loreto Carmona3 y Patricia E. Carreña1.1. Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, 2Instituto de Salud Musculoesqueletica, Madrid, Spain, 3Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, 4Institut, Madrid, Spain, 5Instituto de Salud Musculoesqueletica, Madrid, Spain.

Background/Purpose: To analyze the performance of the old ACR1980 and the new ACR-EULAR2013 classification criteria for systemic sclerosis (SSc) in patients with limited disease in clinical practice, and to compare the characteristics of patients with severe pulmonary arterial hypertension (PAH) who fulfilled or did not fulfill the 1980 criteria.

Methods: All patients with clinical diagnosis of limited cutaneous SSc followed in a single center from Jan1990 to May2014 were included. Descriptive analysis and comparisons between groups, according to their performance in new and old criteria, were carried out by parametric or non-parametric tests based on the distribution of the variables.

Results: From 321 patients, 202 (63%) fulfilled the 1980 and 297 (93%) fulfilled the 2013 criteria. Compared to those fulfilling 2013 criteria only, patients fulfilling 1980 criteria also were younger at diagnosis (48 vs 52 y), presented higher mRSS (8.5 vs 2.7) and had significantly more telangiectasia, esophageal involvement, lung fibrosis, ischaemic lesions, calcinosis and telangiectasia. In contrast, patients not fulfilling 1980 criteria had more ACA (61 vs 44%) and severe PAH (17 vs 9%) (Table 1).

Within the group of patients with severe PAH (n = 38), all fulfilled the 2013 but only 18 (47%) fulfilled the 1980 criteria. Clinical characteristics between those who fulfilled and did not fulfill 1980 criteria were similar, except for higher frequency of calcinosis (85 vs 22%) and ischaemic lesions (83% vs 0%) in the former group. In hemodynamics, patients not fulfilling 1980 criteria had higher pulmonary vascular resistance (16 vs 7) and lower cardiac index (2.2 vs 3.2). Mortality was high in both groups (72 vs 65%;Table 2).

Conclusion: The new SSc ACR-EULAR2013 criteria perform better than the old ACR1980 criteria in clinical practice. Patients with mild symptoms, not fulfilling 1980 criteria, are at higher risk of developing severe PAH, with increased mortality. Our study points out: 1) the need to apply the new criteria to all patients with SSc suspicion; and 2) since SSc-PAH has better prognosis and improved survival, testing can be performed to screen for SSc-PAH.

Table 1 Characteristics of the limited cutaneous SSc patients according to the fulfillment of the ACR1980 criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not fulfilling ACR1980</th>
<th>Fulfilling ACR1980</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 321)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative variables, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (yr) (n = 321)</td>
<td>49.3 (16.4)</td>
<td>52.0 (16.7)</td>
<td>47.8 (16.0)</td>
</tr>
<tr>
<td>Maximum mRSS (n = 314)</td>
<td>6.4 (5.7)</td>
<td>2.7 (1.6)</td>
<td>8.5 (6.2)</td>
</tr>
<tr>
<td>Categorical variables, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (women) (n = 321)</td>
<td>287 (89.4)</td>
<td>110 (92.4)</td>
<td>177 (87.6)</td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scl70 (n = 315)</td>
<td>51 (16.2)</td>
<td>10 (8.5)</td>
<td>41 (20.8)</td>
</tr>
<tr>
<td>ACA (n = 314)</td>
<td>159 (50.6)</td>
<td>72 (61.0)</td>
<td>87 (44.4)</td>
</tr>
<tr>
<td>Esophageal involvement (n = 321)</td>
<td>213 (66.4)</td>
<td>66 (55.5)</td>
<td>147 (72.8)</td>
</tr>
<tr>
<td>Lung fibrosis (n = 320)</td>
<td>59 (18.4)</td>
<td>2 (1.7)</td>
<td>57 (28.4)</td>
</tr>
<tr>
<td>PAH (confirmed by RHC) (n = 321)</td>
<td>38 (11.8)</td>
<td>20 (16.8)</td>
<td>18 (8.9)</td>
</tr>
</tbody>
</table>

Table 2 Clinical and hemodynamic characteristics of limited cutaneous SSc patients with severe pulmonary hypertension by their fulfillment of 1980 ACR criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe PAH (n = 38)</th>
<th>Not fulfilling ACR1980 (n = 20)</th>
<th>Fulfilling ACR1980 (n = 18)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative variables, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PAP, mmHg (n = 32)</td>
<td>54.6 (10.5)</td>
<td>57.4 (11.9)</td>
<td>51.5 (47.2)</td>
<td>0.112</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mmHg (n = 32)</td>
<td>9.5 (8.2)</td>
<td>9.3 (7.4)</td>
<td>9.6 (7.9)</td>
<td>0.850</td>
</tr>
<tr>
<td>PVR, Woods Units (n = 29)</td>
<td>12.9 (10.4)</td>
<td>15.7 (11.9)</td>
<td>9.6 (7.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.3 (1.7)</td>
<td>3.7 (1.5)</td>
<td>4.9 (1.9)</td>
<td>0.078</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.6 (1.1)</td>
<td>2.2 (0.8)</td>
<td>3.2 (1.3)</td>
<td>0.029</td>
</tr>
<tr>
<td>Categorical variables, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA (n = 36)</td>
<td>26 (72.2)</td>
<td>13 (68.4)</td>
<td>13 (76.5)</td>
<td>0.590</td>
</tr>
<tr>
<td>Hand edema (n = 38)</td>
<td>17 (44.7)</td>
<td>10 (50.0)</td>
<td>7 (38.9)</td>
<td>0.492</td>
</tr>
<tr>
<td>Raynaud’s phenomenon (n = 38)</td>
<td>15 (39.5)</td>
<td>2 (15.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sclerodactyly (n = 38)</td>
<td>36 (96.7)</td>
<td>18 (90.0)</td>
<td>18 (100)</td>
<td>0.168</td>
</tr>
<tr>
<td>Telangiectasia (n = 38)</td>
<td>25 (65.8)</td>
<td>11 (55.0)</td>
<td>14 (77.8)</td>
<td>0.139</td>
</tr>
<tr>
<td>Death (June 2014) (n = 38)</td>
<td>26 (68.4)</td>
<td>13 (65.0)</td>
<td>13 (72.2)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

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Predictors of Inpatient Mortality in Patients with Systemic Sclerosis: A Case Control Study. Shiv Tej Sehra1, Chris T. Derk2, Andrew Kelly2 and Joshua Baker1. 1University of Pennsylvania, Pennsylvania, PA, 2Pennsylvania Hospital, Pennsylvania, PA, 3University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: There are few published studies on predictors of inpatient mortality in patients with systemic sclerosis (SSc). Knowledge of these predictors is important for early identification of patients at high-risk of inpatient death and recognition of potential modifiable factors. Currently available data are mostly from large databases which lack a granular view. The aim of this study was to define factors associated with inpatient mortality in SSc.

Methods: All admissions coded for SSc (ICD-9 710.1) at the Hospital of University of Pennsylvania, between Jan 1, 2001 and Dec 31, 2011 were reviewed. The diagnosis of SSc was confirmed, and deaths were identified by chart review. For each death, an age (< 5 years), sex and gender matched five years), site of SSc and recognition of potential modifiable factors. Currently available data are mostly from large databases which lack a granular view. The aim of this study was to define factors associated with inpatient mortality in SSc.

Results: A total of 593 admissions and 30 deaths were identified. Data was not available on 1 death. A significant difference in non–SSc lung disease (p = 0.031), aspiration events (p < 0.001), WBC count (p = 0.048), Blood Urea Nitrogen (BUN) (p <0.001) and hemoglobin (Hb) (p = 0.025) was noted between subjects that died compared to matched controls. Odds of death were higher in patients with a higher BUN (OR = 1.06, CI = 1.02–1.11), non–SSc lung disease (OR = 3.87, CI = 1.26–11.88) and
Background/Purpose: Digital ulcers (DU) and Raynaud’s phenomenon (RP) are a frequent complication in patients with Systemic Sclerosis (SSc). The present study aimed to evaluate the frequency and severity of RP and DU in patients with SSc in four distinct geographic regions of Brazil in order to evaluate the influence of geographic variation on the risk of DU development.

Methods: One hundred and forty-one patients with SSc according to the ACR/EULAR classification criteria of 2013, from centers located in four regions of Brazil (Northeast, Midwest, Southeast and South), were evaluated from January to March 2012. Demographic, clinical, and nailfold capillaroscopy data were collected. The daily mean temperature and the mean temperature in the week before evaluation were also recorded. In order to evaluate a possible association between DUs and climate, the group of patients from the South region (Subtropical climate zone, with lower temperatures), was compared to those from the other regions (Tropical climate zone). Comparisons between groups were made using t-test or chi-square test. Simple and multiple logistic regression models were applied to determine the association between DUs and clinical and demographic variables.

Results: A total of 43 active DUs were observed in 23 (16%) of the 141 patients included. Eighty-six percent were women, with a mean age of 47.8 years, a mean duration of RP of 10.1 years and a mean duration of disease of 5.8 years. Forty-three percent had limited cutaneous SSc. 61.7% had digital pitting scars and 12.1% had a previous history of gangrene or amputation. Twenty-six (18.4%) patients were from the Subtropical climate zone and 115 (81.6%) from the Tropical climate zone, with no difference on age, gender, RP and disease duration between groups. By simple logistic regression model, the presence of DU was associated with a higher modified Rodnan skin score (P = 0.023), presence of necrosis or amputation (P = 0.008), presence of flexion contracture of the fingers (P = 0.002), active smoking (P = 0.038), higher avascular score on nailfold capillaroscopy (P = 0.019), higher severity of RP in the last week (P = 0.007), a higher sHAQ score (P = 0.001), and with the Subtropical climate zone patient group (P = 0.011). The presence of DU was not significantly associated with the mean daily temperature or the temperature in the week before the evaluation. Using multiple logistic regression model including the significant associations observed in univariate analysis, presence of DU was significantly associated with patients living in the Subtropical climate zone (odds ratio [OR] 95%CI = 3.5, 95%CI = 1.00–11.28, P = 0.034), with a previous history of necrosis or amputation (OR = 4.7, 95%CI = 1.20–19.10, P = 0.026) and with a higher sHAQ (OR = 4.7, 95%CI = 1.81–12.5, P = 0.002).

Conclusion: This was the first study to evaluate the influence of temperature and geographic variation on DU prevalence in SSc patients. In this multicenter study in a continental country with different climates, patients with SSc living in a colder region (Subtropical climate zone) have a 3.5 times higher risk of developing DU than those patients living in a warmer region (Tropical zone).

Disclosure: E. J. do Rosário e Souza, None; C. de Souza Muller, None; A. T. Dantas, None; H. A. Mariz, None; A. M. Coelho Horimoto, None; R. Alvarenga Rezende, None; I. Guimarães, None; I. Pereira da Costa, None; G. R. Leonardo Bertazzi, None; L. Païola, None; E. Andrade Medeiros Freire, None; R. Ismael, None; A. P. Toledo Del-Rio, None; J. Sekiyama, None; C. Barros Kahwage, None; C. Kayser, None.

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Lower Socioeconomic Status, Male Gender and Diffuse Scleroderma Are Associated with Worse Survival in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort. Jessica K. Gordon, Wei Zhang, Lorinda Chung, Yan Ma, Virginia D. Steen, PHAROS Investigators. 1Hospital for Special Surgery, New York, NY; 2Stanford University School of Medicine, Palo Alto, CA; 3Georgetown University Medical Center, Washington, DC.

Background/Purpose: Lower socioeconomic status (SES) and male gender have been associated with worse survival in idiopathic pulmonary arterial hypertension (PAH). Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a multicenter, prospective registry of systemic sclerosis (SSc) patients with pulmonary hypertension (PH) or at high risk for the development of PH. In this study we examined whether survival in patients with SSc-PH varied with gender, SES, or race.

Methods: 276 patients with SSc and newly diagnosed PH were enrolled in the PHAROS registry between 2006 and 2014. We used level of education and employment status as surrogates for SES, although more than half of our
patients were retired or medically disabled at the time of PH diagnosis. For employment status we analyzed working versus all other. For level of education, we analyzed 12th grade or less versus some college or more. Statistical analysis was performed using chi-square, univariate and multivariate Cox proportional hazard models.

**Results:** Baseline characteristics of the patients are described in Table 1. The following variables were examined as prognostic factors for survival: age, scleroderma subtype, disease duration, World Health Organization (WHO) PH Group classification, baseline mean pulmonary artery pressure (mPAP), gender, level of education, and employment status. The univariate and multivariate Cox Proportional Hazard Models are reported in Table 2. Male gender, diffuse subtype, and unemployment were associated with an increased risk of death. WHO group was not a significant predictor. Race was not found to be a significant prognostic factor. Lower level of education was a significant prognostic factor when evaluating the entire group; however, if the analysis is limited to WHO Group 1 PH subtype only, then lower level of education is associated with an increased risk of death with HR 2.1 (95% CI 1.2, 3.6), p < 0.01 when corrected for age, SSc subtype and mPAP.

**Conclusion:** Male gender, lower SES, and diffuse SSc are associated with a higher risk of death in the PHAROS cohort. Lower level of education was a risk factor for death only in WHO Group 1 (PAH). Worse survival in males is seen also in idiopathic PAH despite the fact that PAH is more prevalent in females, and the explanation for this is a topic for additional study. Addressing health disparities associated with lower SES may improve the outcomes of patients with SSc-PH.

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-mean ± S.D.</td>
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<td>Mean Pulmonary Artery Pressure at Baseline-mean ± S.D.</td>
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**Discussion:** J. K. Gordon, None; W. Zhang, None; L. Chung, Gilead Science, 9; Y. Ma, None; V. D. Steen, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berth, 2, Intermune, 2, Bayer, 5.

**735**

**Sarcopenia in Systemic Sclerosis: Prevalence and Association with Functional Parameters and Quality of Life.** Elise Siegert1, Kristina Norman2, Emilie Preis2, Alexander Makowka2, Gerd Burmester2 and Gabriela Riemekasten1. 1Charité – University Hospital, Berlin, Germany, 2Charité – University Medicine Berlin, Berlin, Germany.

**Background/Purpose:** Systemic Sclerosis (SSc) is an autoimmune disease that characterized by endothelial dysfunction, inflammation and fibrosis. It is associated with high mortality and physical impairment. We assessed the prevalence of sarcopenia in SSc patients and correlated sarcopenia with muscle strength and quality of life, also taking other clinical parameters into account.

**Methods:** Patients meeting the ACR/EULAR 2013 criteria for SSc were included in this study. Body composition was assessed using bioelectrical impedance analysis. Fat free mass (FFM) was estimated using the equation of Kyle and was normalized to patients’ height using the square of body size (FFM/m² = FFM). Sarcopenia was defined as a FFM value below 17.4 kg/m² for men and < 15 kg/m² for women. Maximal grip strength was measured using the Jamar Dynamometer, maximal knee extension strength using the Digitax and expiratory peak flow using a peak flow meter. Quality of life was assessed using the SF-36, while C-reactive protein (CRP), hemoglobin (Hb) and other clinical parameters were quantified by routine laboratory testing or by history taking.

**Results:** 111 patients were included in this study (101 women and 10 men; age 59.7 ± 13.8 years, BMI 24.5 ± 5 kg/m²). 53 (47.7%) patients were diagnosed with sarcopenia. Patients with sarcopenia differed significantly from patients without sarcopenia with respect to maximal grip strength, knee extension strength, peak flow and CRP. They did not differ in age and select clinical parameters such as gastrointestinal involvement, total number of organs involved, number of comorbidities and number of medical therapies. Absolute FFM correlated significantly with maximal grip, knee extension strength and peak flow (r = 0.64, r = 0.366 and r = 0.48, respectively, p < 0.0001). With respect to quality of life there was no significant difference between patients with and those without sarcopenia.

**Conclusion:** There was a high prevalence of sarcopenia among SSc patients in our study. Sarcopenia was associated with an impairment of muscle strength, low hemoglobin and high inflammatory activity.

**Disclosure:** E. Siegert, None; K. Norman, None; E. Preis, None; A. Makowka, None; G. Burmester, None; G. Riemekasten, None.

**736**

**Serum Galectin-3 Levels in Early Diffuse Systemic Sclerosis and the Relationship to Skin Score and Skin Score Change.** Siamak Moghadam-Kia, Thomas A. Medsger Jr. and Robin T. Domisc. University of Pittsburgh, Pittsburgh, PA.

**Background/Purpose:** Galectin-3 is a β-galactoside-binding animal lecin which is associated with inflammation, angiogenesis and fibrosis. Galectin-3 is upregulated in hepatic fibrosis, idiopathic pulmonary fibrosis and in the myocardium of heart failure patients. In heart failure it is a useful biomarker to predict mortality. In systemic sclerosis (SSc), one report (Koca...
2013) suggests higher levels compared to healthy controls (HC). In a second study (Taniguchi 2012) suggested down-regulation in diffuse SSc and on subset analysis, the 6 early diffuse SSc patients had the greatest reduction in galectin-3 levels. They also reported a modest correlation between galectin-3 (r = 0.45) and skin score. The objective of this study was to assess galectin-3 levels in very early diffuse SSc patients and the relationship to skin score and skin score change.

Methods: We identified patients with very early diffuse SSc who were seen for the first time in a dedicated Scleroderma Center between 1990 and 2010 and met the following criteria: (1) seen within 9 months of the first SSc symptom, (2) skin thickening proximal to the elbows and knees (or skin thickening with tendon friction rubs) and (3) had clinical follow-up with repeat skin scores at either 3 months, 6 month or both. HC were also identified. All SSc and HC first visit serum samples underwent ELISA testing (BGMedicine, Waltham, MA). Differences in galectin-3 levels between SSc and HC were assessed by nonparametric tests. Correlations with skin score at first visit, skin thickness progression rate (STPR) and absolute change in skin score at 3 and 6 months were assessed.

Results: We identified 114 SSc patients who met all inclusion criteria. Of these, 94 had available samples taken at the same time as the initial skin assessment. The 37 HC were collected on the same day. All SSc patients and HC were Caucasian and 70% female. Mean age was 51 in SSc and 47 in the HC. Of the SSc patients, 50 had f/u at both 3 and 6 months, 20 at 3 months only and 22 at 6 months only. There was no significant difference in serum galectin-3 level between SSc patients and HC (p = 0.92), as shown in Figure 1. Baseline serum galectin-3 levels were not correlated with the skin scores taken at the same time (p = 0.29) or STPR (p = 0.71). Skin scores at 3 or 6 months follow-up also showed no correlation (p = 0.43 and 0.76, respectively). There was a weak correlation with baseline galectin-3 levels and absolute skin score change at 3 months (r = 0.26, p = 0.02), but not at 6 month follow-up (p = 0.78).

Conclusion: Contrary to smaller pilot studies suggesting galectin-3 is significantly different in SSc compared to HC, and may modestly correlate with skin score, our study did not confirm this. We used very early patients not on medications, and it may be that the previously reported differences in galectin-3 occur later in disease and represent fibrotic burden, or may be affected by medications.

Disclosure: S. Moghadam-Kia. None; T. A. Medsger Jr. None; R. T. Domis. None.

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Reliability of Nailfold Capillary Density Measurement As a Possible Outcome Measure for Systemic Sclerosis-Related Microangiopathy. Graham Dinsdale1, Tonia Moore2, Joanne Manning3, Andrea Murray4, Michael Berks1, Philip Tresadern5, Chris Taylor2, Neil O’Leary6, Chris Roberts7, John Allen8, Marina Anderson9, Maurizio Cutolo10, Roger Hesselstrand11, Kevin Howell12, Paula Pyrkotsch13, Francesca Ravera14, Vanessa Smith15, Alberto Sulli16, Marie Wildt17 and Ariane Herrick18. 1Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; 2Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom; 3Centre for Imaging Sciences, University of Manchester, Institute of Population Health, Manchester, United Kingdom; 4Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, United Kingdom; 5Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne, United Kingdom; 6Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom; 7Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy; 8Lund University, Lund, Sweden; 9Institute of Immunity and Transplantation, University College London, Royal Free Campus, London, United Kingdom; 10Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Nailfold videocapillaroscopy allows non-invasive assessment of the microcirculation. Image annotation software allows tracking of changes over time; a potential outcome measure for systemic sclerosis (SSc) related microangiopathy. Our objective was to assess the reliability of capillary density measurement, known to be reduced in SSc.

Methods: 124 patients (102 SSc, 22 primary Raynaud’s phenomenon [PRP]), and 50 healthy controls (HC), underwent high-magnification (300x) videocapillaroscopy mosaic imaging of all 10 digits (1740 images).

Image subsets, sampled across disease categories, were randomly allocated to each of 10 capillaroscopy experts. These ‘raters’ used custom software to assess images. Each image used in this analysis was assigned to at least 2 raters. To assess intra-rater reliability, each rater performed repeat evaluations on an image subgroup. At least 6 images were assessed from each subject.

Raters marked distal vessel locations in an image. Vessel density was calculated as the total number of distal vessels divided by the Euclidean distance between the vessels at the horizontal extremities.

We examined: (1) the probability of raters marking sufficient (2 or more) distal vessels in an image (logistic mixed-effects model). Conditional on an image evaluation having sufficient distal vessels marked (2) distal vessel density (linear mixed-effects model).

Intra and inter-rater reliability was estimated with intra-class correlation coefficients from fitted model variance components.

Results: 3463 images were evaluated. Each rater assessed a median (range) of 112 (87, 140) unique images from 14 (9, 174) subjects. Same-rater repeat evaluations were performed on (median) 17% of images, and 904 images from 116 patients were evaluated by at least 2 raters.

Raters marked sufficient distal vessels in 79% of evaluations. Compared to HC, SSc and PRP images had odds ratios [95% CI] of sufficient distal vessels marked of 0.23 [0.14, 1.41] and 3.80 [0.37, 5.23] respectively. The mean vessel density in HC was 9.84 vessels/mm. Compared to HC, vessel density was lower in SSc (6.62) but not significantly different in PRP (9.58); respective differences [95% CI] were −3.22 [−3.88, −2.63] and −0.26 [−1.12, 0.63] vessels/mm.

Estimates of intra-rater reliability [95% CI] were 0.91 [0.89, 0.92] for vessel mark-up and 0.89 [0.87, 0.91] for vessel density. Corresponding estimates of inter-rater reliability were 0.51 [0.39, 0.76] and 0.56 [0.47, 0.64] respectively.

Conclusion: Mark-up rate differences between-groups are most likely due to differences in capillary architecture (capillary loss/damage in SSc patients). Density was unmeasurable in a sizable minority (21%) of image evaluations with potential implications for the representativeness of this measure. The high intra-(compared to inter-) rater reliability suggests that density could serve as outcome measure in prospective studies if the same rater examines images. Research on the impact of training on inter-rater reliability, and into more objective (automated) analysis methods is required to further develop this promising outcome measure.


Disclosure: G. Dinsdale. None; T. Moore. None; J. Manning. None; A. Murray. None; M. Berks. None; P. Tresadern. None; C. Taylor. None; N. O’Leary. None; C. Roberts. None; J. Allen. None; M. Anderson. None; M. Cutolo. None; R. Hesselstrand. None; K. Howell. None; P. Pyrkotsch. None; F. Ravera. None; V. Smith. None; A. Sulli. None; M. Wildt. None; A. Herrick. None.

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Troponin T as a Diagnostic and Prognostic Biomarker of Primary Cardiac Involvement in Systemic Sclerosis. Silvia Laura Bosello, Giacomo De Luca, Federico Parisi, Giorgia Berardi, Manuela Rucco, Giovanni Canestrari and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose: Heart involvement is common in Systemic Sclerosis (SSc), even if often clinically silent, and represents one of the leading
cause of death in these patients. The aim of our study was to define the role of cardiac troponin T (cTnT) and NT-proBNP to identify a cardiac involvement.

**Methods:** cTnT and NT-proBNP levels were evaluated in 200 consecutive SSc patients (mean age: 58.7 ± 13.9 years; mean disease duration: 11.1 ± 9.0 years; diffuse disease: 42.0%; anti-Scl70 positivity: 45.5%) from 2008 and 2013. Data regarding disease subtype and organ involvement were available for the entire cohort and all patients underwent: electrocardiogram (EKG), echocardiography and pulmonary function test (PFTs). All SSc-related deaths were registered during a mean follow-up of 40.8 ± 18.7 months.

**Results:** cTnT levels were above the normal limit in 79 (39.5%) SSc patients (mean levels in positive patients: 0.06 ± 0.08 ng/ml). NT-proBNP levels were above the cut-off limit of 125 ng/ml, recommended by the manufacturer, in 79 patients (39.5%) and 51 of these patients presented also increased levels of cTnT. The increased cTnT levels were associated with diffuse skin involvement and skeletal myositis (p < 0.0001; p = 0.06 respectively) and directly correlated with skin score (R = 0.27; p < 0.0001). Patients with high cTnT levels presented a lower left ventricular ejection fraction (LV-EF) (59.5 ± 9.3%) and higher pulmonary arterial systolic pressure on echocardiography (37.7 ± 16.8 mmHg). Compared to patients with normal cTnT values (63.1 ± 4.9%), p = 0.04; 28.3 ± 6.8 mmHg, p < 0.0001). These patients, furthermore, presented more frequently a right bundle branch block on EKG with respect to patients without increasing of cTnT (19.7% vs 7.0%; p = 0.008). In our cohort 28 patients (14%) presented a LV-EF < 55% and the sensitivity of increased cTnT levels (> 0.014 ng/ml) in the detection of depressed myocardial contractility was 67.8% and its specificity was 66.8%. It is also noteworthy that its negative predictive value in the assessment of depressed LV-EF was 92%. During the follow-up, 18 SSc-related deaths occurred; 10 of these were directly related to cardiac involvement (sudden cardiac death or heart failure) and all occurred in patients with increased cTnT levels. Cumulative survival estimated by Kaplan-Mayer curve was worse in patients with increased baseline levels of cTnT (X² = 21.2, p < 0.0001). Died patients presented higher levels of cTnT (0.11 ± 0.03 ng/ml) and of NT-proBNP (7193.3 ± 5691.3 pg/ml) and lower LV-EF (52.5 ± 11.9%) with respect to survivors (cTnT: 0.02 ± 0.05 ng/ml; NT-proBNP: 585.8 ± 2517.3 pg/ml; LV-EF: 61.9 ± 66.6%; p = 0.001 for all comparisons).

**Conclusion:** The cTnT levels were increased in up to 40% of the SSc patients, revealing that myocardial involvement is more relevant in scleroderma disease than appreciated previously. cTnT may provide an opportunity to screen non-invasively SSc patients for subclinical heart involvement. The more impaired systolic function and more frequent EKG abnormalities in SSc patients with increased TnT levels, suggest that cTnT may be a novel biomarker of cardiac damage. Our data on survival suggest it as a possible prognostic biomarker of SSc-related death.

**Disclosure:** S. L. Bosello, None; G. De Luca, None; F. Parisi, None; G. Berardi, None; M. Rucco, None; G. Canestrari, None; G. Ferraccioli, None.

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**739**

**Lack of Association Between Esophageal Symptoms and Abnormal Findings in High-Resolution Manometry in a Mexican Mestizo Cohort with Systemic Sclerosis (SSc).** Ana Arana-Guajardo1, Miguel Villarreal-Alarcón2, Gustavo Torres-Barrera1, David Vega-Morales3, Hector Maldonado-Garza2 and Mario Garza-Elizondo2. 1Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico. 2Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico. 3Servicio de Gastroenterología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico. 4Servicio de Gastroenterología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico. 5Hospital Universitario UANL, Monterrey, Mexico.

**Background/Purpose:** Esophageal involvement is present in 50–70% of SSc patients and it is the most common visceral organ complication. The impact of the esophageal involvement is related with high morbidity and included the association with interstitial lung disease, weight loss and malnutrition, Barretts esophagus and adenocarcinoma degeneration. Our objectives were characterize motor esophageal impairment in patients with SSc with or without esophageal symptoms using high-resolution manometry (HRM).

**Methods:** Observational, descriptive, cross-sectional study. We included SSc patients according to American College of Rheumatology classification criteria of the 1980 and patients with Sclerosis variants with esophageal symptoms; with an age ≥ 18 years old, from a clinic of a tertiary hospital. The demographic data, skin manifestations, esophageal symptoms and drugs used were recorded. The Carlsson-Dent questionnaire (CDQ) was used to evaluate gastroesophageal reflux disease and dysphagia was graded on a five-point scale according to Mellow and Pinkas. The modified Rodnan skin score (mRSS) was used in the skin evaluation. A standard HRM was performed and the results were classified according to Chicago Classification. In the analysis we categorized the grade of dysphagia, the mRSS and HRM results. We used 2x2 contingency tables and chi-square or Fisher’s exact test of their distribution to establish an association between each variable and HRM result. A p value < 0.05 was classified as statistically significant.

**Results:** We included 19 SSc patients, 1 with morphea and 1 with Scleroderma sine scleroderma. Clinical and demographic variables are shown in Table 1. Most of the patients were on normal BMI, had been classified in limited disease, and had used proton-pump inhibitors. The most common symptoms were dysphagia and heartburn. We found an abnormal HRM in 16 (76.2%) patients; the most common abnormality in HRM was absence of peristalsis in 5 (23.8%) patients. Variables analyzed with HRM are shown in Table 2. We did not find association between any variable (Table 1 and 2) and the presence of abnormal HRM.

**Conclusion:** We found a lack of association between esophageal symptoms and abnormal findings in HRM. There was not association between CDQ and HRM. Although this study is limited by the number of patients analyzed, we think that due to the large impact of the esophageal involvement in SSc patients, we need to do a systematic esophageal study of this patients with the objective to decrease their morbidity.

**Table 1** Clinical and demographic variables

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<td>Age, mean (SD) years</td>
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<td>Male n (%)</td>
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<tr>
<td>BMI</td>
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<td>- Normal n (%)</td>
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<td>- Overweight n (%)</td>
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<td>- Obese n (%)</td>
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<td>SSc classification</td>
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<tr>
<td>- Limited n (%)</td>
<td>17 (80.9)</td>
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<tr>
<td>- Diffuse n (%)</td>
<td>2 (9.5)</td>
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<tr>
<td>- Scleroderma sine scleroderma n (%)</td>
<td>1 (4.8)</td>
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<tr>
<td>- Morphea n (%)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>mRSS, mean (SD)</td>
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<tr>
<td>- Antinuclear n (%)</td>
<td>15 (75)</td>
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<tr>
<td>- Anti-Scl70 n (%)</td>
<td>5 (23.8)</td>
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<td>- Anti-centromere n (%)</td>
<td>5 (23.8)</td>
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<td>Drugs</td>
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<td>- NSAID n (%)</td>
<td>2 (9.5)</td>
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<tr>
<td>- CCB n (%)</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td>- PPI n (%)</td>
<td>20 (95.2)</td>
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| SSc; Systemic Sclerosis, SD; standard deviation, BMI; body mass index, mRSS; modified Rodnan skin score, NSAID; Nonsteroidal anti-inflammatory drug, CCB; Calcium channel blockers, PPI; Proton-pump inhibitors.**

**Table 2** Esophageal characteristics and HRM findings

| n = 21 |
| Esophageal symptoms, n (%) | |
| - Dysphagia | 13 (61.9) |
| - Heartburn | 13 (61.9) |
| - Regurgitation | 9 (42.9) |
| - Cough | 10 (47.6) |
| - Chest Pain | 3 (14.3) |
| - Nausea | 4 (19) |
| - Vomiting | 1 (4.8) |
| CDQ questionnaire, mean (SD) | 6.04 (4.4) |
| Dysphagia classification* n (%) | |
| - No dysphagia | 9 (42.9) |
| - Dysphagia to normal solids | 6 (28.6) |
| - Dysphagia to soft solids | 6 (28.6) |
| - Abnormal n (%) | 16 (76.2) |
| SD; standard deviation, CDQ; Carlson-Dent questionnaire, HRM; esophageal high-resolution manometry.*according to Mellow and Pinkas**
Right Ventricular Diastolic Impairment Is Common in Systemic Sclerosis and Is a Marker of Several Organ-Target Damage of the Disease. Christophe Meune1, Dinesh Khanna2, Jamil Aboulhosn3, Jerome Avaouac4, Andre Kahn5, Daniel E. Furst6 and Yannick Allanore7. 1Paris 13 University, University Hospital of Paris-Seine-Saint-Denis, Cardiology Department, Bobigny, France, 2University of Michigan Health System, Ann Arbor, MI, 3Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 4Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, 5Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, 6University of California, Los Angeles, Department of Medicine, Los Angeles, CA.

Background/Purpose: Heart failure and cardiac dysfunctions both of intrinsic or secondary origin and targeting LV (left ventricle) and/or RV (right ventricle) are critical complications promoting mortality in systemic sclerosis (SSc). While several studies reported possible right ventricle (RV) alterations in SSc patients having pulmonary hypertension, only few and small series investigated RV function in unselected SSc patients. Therefore, the aim of the present study is to investigate LV and RV systolic and diastolic function in a large SSc cohort of unselected patients compared to a control group using comprehensive echocardiographic parameters.

Methods: We examined LV and RV systolic and diastolic functions, using echocardiography and Tissue Doppler echocardiography (TDE) indexes, in a cohort of 212 consecutive SSc patients seen during a 9 month-period at two institutions (Paris, France and Los Angeles, USA) and 50 healthy controls.

Results: Patients’ characteristics from the two institutions were very similar allowing combined analyses. When compared to controls, SSc patients had consistently impaired RV indices that include reduced RV contractility (p<0.001), larger right atrial area (p<0.001) (Table 1). Patients also exhibited alterations in LV contractility and diastolic function (p<0.001 each) (Table 1). Looking at associated parameters, in multivariate analysis, RV contractility as expressed by the TDE S1 parameter was associated with TDE LV contractility S1L (p=0.030), DLC0 (p=0.013) whereas RV diastolic impairment was associated with systolic pulmonary artery pressure (p=0.015). In a subset of 27 patients with proven pre-capillary PAH, comparison between SSc-PAH versus SSc free of PAH patients, revealed reduced LV diastolic function (measured by transmural E/A ratio (p=0.045) and Ee <10cm/s (p=0.029)), reduced overall RV contractility (21.5 versus 4.5%; P=0.03) and reduced RV diastolic function (transtricuspid E/A ratio; p=0.014 and 68% versus 29% with impaired function; p=0.001).

Conclusion: Whereas most previous studies focused on the LV, we report in the present controlled study that not only systolic but also diastolic RV dysfunction is common in SSc and that several cardiopulmonary factors seem to influence RV function in this multifaceted disease. Given that RV dysfunction and fibrosis are poor prognosticators, possibly associated with lethal ventricular arrhythmias, sudden death, exercise limitation, and impaired RV cardiac output, we assume that RV function should be closely investigated in SSc patients and that the impact on RV diastolic function of future therapies targeting PAH and/or primary myocardial involvement is to be assessed.

Table 1:

<table>
<thead>
<tr>
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<th>SSc patients (n=212)</th>
<th>Controls (n=50)</th>
<th>p</th>
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<tr>
<td>Age, years</td>
<td>55.3 ± 13.2</td>
<td>53.1 ± 11.0</td>
<td>0.201</td>
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<tr>
<td>Men/women</td>
<td>40/172</td>
<td>Aug-42</td>
<td>0.637</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76 ± 11</td>
<td>69 ± 15</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
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<tr>
<td>Systolic</td>
<td>122 ± 14</td>
<td>123 ± 14</td>
<td>0.536</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70 ± 9</td>
<td>69 ± 9</td>
<td>0.49</td>
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<td>LV indexes</td>
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<tr>
<td>Left ventricular end-diastolic diameter, mm</td>
<td>43 ± 6</td>
<td>47 ± 7</td>
<td>0.002</td>
</tr>
<tr>
<td>Interventricular septum thickness, mm</td>
<td>10 ± 3</td>
<td>10 ± 1</td>
<td>0.846</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>61 ± 7</td>
<td>67 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;55%, n (%)</td>
<td>8 (3.9)</td>
<td>0 (0.0)</td>
<td>0.361</td>
</tr>
</tbody>
</table>

Disclosure: A. Arana-Guajardo, None; M. Villarreal-Alarcon, None; G. Torres-Barrera, None; D. Vega-Morales, None; H. Maldonado-Garza, None; M. Garza-Elizondo, None.

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Abnormal Right Ventricular Longitudinal Strain Detected in Systemic Sclerosis Patients Prior to Abnormalities in Conventional Measures of Right Ventricular Size and Function Using Tissue Doppler Imaging. Ming-En Chung1, Laura K. Hummers2, Frederick M. Wigley3, Theodore P. Abraham4 and Ami A. Shah1. 1Johns Hopkins University School of Medicine, Baltimore, MD, 2Johns Hopkins University, Baltimore, MD.

Background/Purpose: Cardiac involvement in systemic sclerosis (SSc) adversely affects long-term prognosis, remaining undetectable despite frequent echocardiographic monitoring. Speckle tracking derived strain of the RV free wall was utilized to detect whether early changes in regional and global contractility are detectable in SSc patients in comparison to standard 2D measures of RV chamber size and function.

Methods: 138 SSc patients who had technically adequate, clinically indicated 2D echocardiograms were studied, and compared with a cohort of 40 age-matched non-scleroderma controls (C). Conventional 2D and off-line strain analyses were performed. Standard assessment of RV chamber size and function by 2D included linear dimensions of RV base and length, tricuspid annular plane systolic excursion (TAPSE), and RV fractional area change (FAC). RV longitudinal speckle-derived strain (RVLSS) was assessed in the basal, mid and apical free wall. Conventional echo parameters, global RVLSS, and RVLSS in each RV segment were compared between SSc and C by the Student’s t test. We also modeled RVLSS as a function of RV segment and disease group (SSc vs C) using Friedman’s Muhkenh1 test to account for the clustering of RV strain values across the 3 RV segments.

Results: Most conventional echo measures of RV size and function were not different between SSc patients and C, including TAPSE (SSc 22.5 ± 4.7 vs C 22.5 ± 4.7 cm; p=0.906), right atrial area (SSc 81 ± 2 vs C 81 ± 2 cm2, p=0.496), and right atrial area (SSc 2.2 ± 11.9 vs C 2.2 ± 11.9 cm2, p=0.832). While within the normal range, FAC in SSc patients was slightly decreased (48.9 ± 10.9% vs 52.7 ± 8.0%, p=0.045). In contrast to these conventional parameters, measures of RVLSS were significantly different between SSc and C. Global RVLSS was diminished in SSc compared to C (b 1.5, p=0.045). Regional differences in RVLSS were also noted: decreased in the apex (SSc −8.5 vs C −17.2%, p<0.001) and mid (SSc −12.4 vs C −17.8%, p<0.0001) segments and increased in the base (SSc −32.2 vs C −22.5%, p<0.0001) in SSc vs C. Among C, regional differences in RVLSS were detected in the basal segment relative to the apex (base-apex b −5.4%, p<0.0001) but not in the mid-apex comparison. In contrast, SSc had significant regional differences throughout (base-apex b −23.6, mid-apex b −3.9, both p<0.0001), especially when comparing the basal to apical segments. The base-apex difference was significantly greater in SSc compared to C (p<0.0001 for interaction). While SSc had a higher mean PASP than C (SSc 31.4 vs C 22.7 mmHg, p=0.0001), the differences observed in regional strain between SSc and C were unchanged when restricting our analyses to those with a PASP<35 mmHg.

Conclusion: Speckle-derived strain reveals a heterogeneous pattern of regional longitu

dinal systolic contraction in scleroderma, that is not detected by conventional echocardiographic measures. These data suggest that significant RV myocardial involvement is undetectable despite frequent echocardiographic monitoring. Speckle tracking derived strain of the RV free wall was utilized to detect whether early changes in regional and global contractility are detectable in SSc patients in comparison to standard 2D measures of RV chamber size and function.

Background/Purpose: Ultrasound has been used to measure scleroderma skin thickness, but it has not been established that routine clinical ultrasound equipment is adequate. We compared skin thickness measured with a common office instrument vs measurements using high frequency research ultrasound equipment, and determined the differences in measurement values and precision.

Methods: Repeated measurement of skin thickness of 1 normal volunteer at 5 reproducible sites on the dorsum of the proximal phalanx of a finger, the dorsum of a hand, the extensor surface and flexor surface of a forearm, and a lateral upper arm. A 15 MHz clinical ultrasound transducer and instrument (Sonosite, Bothell, WA), and 20 MHz and 50 MHz research transducers of a research ultrasound instrument (Sonosite, Bothell, WA) were used. After initial training, 3 examiners independently imaged all 5 sites with each transducer on 3 days over a period of one month. On each image, measurements of dermal thickness were made at 3 representative sites, and averaged to provide the thickness measure of that image.

Results: The overall average coefficient of variation (CV) was 8.6% for the 50 MHz transducer, 5.7% for the 20 MHz transducer, and 14.2% for the 15 MHz transducer. Measurements were more precise at the thicker skin of the arm (CV = 5.6%) than at thinner sites. Thickness measured with 15 MHz was smaller than those of the 20 and 50 MHz transducers at all sites, but was generally reproducible at each site. Skin thickness at the finger vs hand differed significantly using the 20 and 50 MHz transducers, but the 15 MHz transducer results at those 2 sites were not statistically distinguishable. Measurements by one examiner were consistently smaller than those of the other 2 observers, whose values matched closely. All showed the expected increase in thickness by site (figure).

Conclusion: The 15 MHz clinical ultrasound instrument is not as precise as higher frequency ultrasound equipment, especially in thin skin such as at the dorsum of the normal finger and hand. However, even at modestly thicker sites, such as the normal arm and forearm, the precision is acceptable. These data suggest that routinely-available mid-range clinical ultrasound equipment can be used to develop ultrasound-based skin thickness measurements, with the potential to improve the ability to monitor changes in skin thickness.

Disclosures: I. A. Sacksen, None; P. S. Pollock, None; M. H. Wener, None.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Pathogenesis, Animal Models and Genetics Sunday, November 16, 2011, 8:30 AM–4:00 PM

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Integrin Inhibitor Modulates Pulmonary Fibrosis in the Reactive Oxygen Species Murine Model of Systemic Sclerosis. Gianluca Bagnato1, Alessandra Bitto2, Natasha Irrera1, Gabriele Pizzino1, Neal Roberts2, Domenica Altavilla3, Francesco Squadrato3, Antonino Satta1 and Gianfilippo Bagnato3. 1University of Messina, Messina, Italy, 2University of Louisville, Louisville, KY, 3Universita Messina, Villafranca Tirrena, Italy.

Background/Purpose: Systemic sclerosis (SSc) is an acquired connective tissue disorder in which inflammation, immune dysregulation and vascular damage lead to fibroblast activation that results in fibrosis of the skin and internal organs. Development of therapies is hampered by lack of understanding of the underlying mechanism of disease. It has been recently shown that alterations in cell–matrix interactions are sufficient to initiate and sustain inflammatory and pro-fibrotic programmes [1]. Both SSc fibroblasts [2] and pulmonary T cells of patients affected by SSc with interstitial lung disease highly express αVβ3 and αVβ5 integrins and they are required for
lymphocytic infiltration and collagen accumulation [3]. The aim of the study is therefore to evaluate the effect of the αvβ3 and αvβ5 inhibitor (cilengiti
de) on the development of pulmonary fibrosis in the HOCl-induced murine model of systemic sclerosis.

Methods: Chronic oxidant stress SSC was induced in BALB/c mice by daily s.c. injections of HOCl for 6 weeks. 25 Mice were randomized in three arms: HOCl alone (n=10), HOCl + Cilengitide (n=10) or vehicle alone (n=5). Treatment with cilengitide 20 (mg/kg/p.d/day) was started four weeks after the administration of HOCl and main
tained throughout the remaining experimental period (2 weeks). Lung fibrosis was evaluated by histological studies. The severity of fibrosis was assessed using ordinal or nominal scales and the results compared nonparametrically. Lung concentrations of focal adhesion kinase (FAK) were evaluated by western blot analysis.

Results: The administration of HOCl induced lung fibrosis as demonstrated by routine histological analysis. Cilengitide significantly reduced the histopathological change of HOCl-induced pulmonary fibrosis (Figure 1A-D). Additionally, pulmonary FAK expression was increased in mice treated with HOCl and significantly modulated by cilengitide administration (Figure 1E).

Conclusion: The inhibition of integrin signaling could prove useful as future therapeutic targets for treatment of SSC. Further confirmatory results in a second animal model are needed to better assess the specific effect of cilengitide on the development of fibrosis and myofibroblast differentiation.

References:
3. Luzina IG, Todd NW, Nacu N et al. Regulation of pulmonary inflammation and fibrosis through the expression of integrins αvβ3 and αvβ5 on pulmonary T lymphocytes. Arthritis and Rheum. 2009 May;60(5):15309

Figure 1

Disclosure: G. Bagnato, None; A. Bitto, None; N. Irrera, None; G. Pizzino, None; N. Roberts, None; D. Altavilla, None; F. Squadrito, None; A. Saitta, None; G. Bagnato, None.

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Genetic Susceptibility Loci of Idiopathic Interstitial Pneumonitis Do Not Represent Risk for Systemic Sclerosis. Minghua Wu1, Shervin Assassi1, Gloria Salazar1, Olga Y Gorlova2, Wei V Chen2, Julio Charles2, Fredrick M. Wigley2, Laura K. Hummers3, Ami A. Shah4, Monique Hinchcliff4, Dinesh Khanna5, Elena Schioppu5, Kristine Phillips6, Daniel E. Furst7, Virginia D. Steen8, Murray Baron9, Marie Hudson9, Xiaodong Zhou10, Janet E. Pope11, Niall Jones12, Peter Docherty11, Nader A. Khalidi13, David B. Robinson11, Robert W. Simms14, Richard Silver12, Tracy Frech15, Barri J. Fessler11, Marvin J. Fritzel16, Jerry A. Miltior19, Barbara M. Segal17, Javier Martin20, John Varga21 and Maureen D Mayes22. 1University of Texas Health Science Center at Houston, Houston, TX, 2Geisel School of Medicine at Dartmouth, Hanover, NH, 3Johns Hopkins University School of Medicine, Baltimore, MD, 4Northwestern University Feinberg School of Medicine, Chicago, IL, 5University of Michigan, Ann Arbor, MI, 6University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 7Georgetown University Medical Center, Washington, DC, 8McGill University, Montreal, QC, 9St. Joseph’s Health Care, University of Western Ontario, London, ON, 10University of Alberta, Edmonton, AB, 11The Moncton Hospital, Moncton, NB, 12St. Joseph’s Hospital, McMaster University, Hamilton, ON, 13University of Manitoba, Winnipeg, MB, 14Boston University School of Medicine, Boston, MA, 15Medical University of South Carolina, Charleston, SC, 16University of Utah, Salt Lake City, UT, 17Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, 18Mitogen Advanced Diagnostics Laboratory, Faculty of Medicine, University of Calgary, Calgary, AB, 19University of Minnesota, Minneapolis, MN, 20Consejo Superior de Investigaciones Científicas, Granada, Spain.

Background/ Purpose: Systemic sclerosis (SSc) related interstitial lung disease (ILD) has phenotypic similarities to idiopathic interstitial pneumonia (IIP). The objective of this study was to assess whether genetic susceptibility loci which were recently identified in a large idiopathic interstitial pneumonia (IIP) genome-wide association study (GWAS) were also risk loci for SSc overall, for SSc-autoantibody subgroups or for severity of SSc-ILD.

Methods: A total of 2571 North-American Caucasian SSc patients and 4500 unaffected control subjects were investigated in two independent cohorts. The discovery cohort consisted of 1486 SSc cases and 3477 unaffected controls while the confirmation cohort consisted of 1085 additional SSc cases and 1023 unaffected controls. All patients were enrolled in the National Scleroderma Family Registry and DNA Repository and fulfilled the 1980 American College of Rheumatology classification criteria for SSc or had at least three of the five CREST features. Forced vital capacity % predicted (%FVC) as continuous outcome was used as a validated outcome measure for severity of ILD. Single nucleotide polymorphisms (SNPs) rs2736100 (TERT), rs2076295 (DPS), rs7427443 (AGZP1), rs7934606 (MUC2), rs2034650 (JVD), rs1983997 (MAPT), rs12610495 (DPPIV), rs6939295 (LRRC54), rs2609255 (FAM13A), rs11191865 (OBF1C), rs1278769 (ATP11A) and rs1379326 (CSMD1), which were identified/confirmed to be associated with IIP in a recently published GWAS (Fingerlin et al. Nat Genetics 2013) were genotyped and analyzed for their association with SSc and severity of SSc-ILD.

Results: In the discovery cohort, we observed nominally significant associations with SSc overall for LRRC54 rs69379295 (MAF = 0.29, OR = 1.14, CI 95% 1.03 to 1.25, p value = 0.009) and OBF1C rs11191865 (MAF = 0.52, OR = 1.09, CI 95% 1.00 to 1.19, p value = 0.0043). There were no significant associations in the anti-topoisomerase I (ATA) or anti-centromere (ACA) positive patient subgroups. However, DPS rs2076295 (β = −2.29, CI 95% −3.85 to −0.74, p value = 0.004) and MAPT rs1983997 (β = 2.26, CI 95% 0.35 to 4.17, p value = 0.02) were associated with forced vital capacity % predicted (% FVC) even after adjusting for ATA status. All SNPs observed to reach nominal significance levels in the discovery cohort were genotyped in the replication cohort. However, none of the above observed associations were confirmed in the replication cohort.

Conclusion: Herein, we add new evidence that SSc and SSc related ILD are genetically distinct from IIP. Our findings may have important implications for follow-up mechanistic studies and identification of therapeutic targets. Genetic background of SSc seems to be mummy while to innate and adaptive immune while IIP genetic susceptibility relates to epithelial cell injury and dysfunction, mucin production, and telomere length. Interstitial lung involvement in SSc-ILD and IIP might be the common end-product of two different pathological backgrounds.

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Elevated Penetratin 3 in Patients with Systemic Sclerosis: Associations with Vascular Manifestations and Defective Vasculogenesis. Yuichiro Shira1, Yuko Okazaki1, Yuuki Inoue1, Yuichi Tamura2, Hidekata Yaukoua2, Tsutomu Takeuchi3 and Masataka Kuwana3. 1Keio University School of Medicine, Tokyo, Japan, 2Keio Univ School of Medicine, Tokyo, Japan.

Background/Purpose: Penetratin 3 (PTX3) is a multi-functional pattern recognition protein involved in inflammation, extracellular matrix deposition, and suppression of neovascularization mediated by fibroblast growth factor-2 (FGF2). Several lines of recent evidence suggest that PTX3 is constitutively
overexpressed in fibroblasts and endothelial cells derived from systemic sclerosis (SSc) patients. The aim of this study is to examine roles of PTX3 in pathogenic processes of SSc.

**Methods:** We enrolled 171 patients with SSc and 19 age- and sex-matched healthy controls. Circulating levels of PTX3 and FGF2 were measured by enzyme immunoassay and their correlations with SSc-related organ involvement were evaluated. Univariate and multivariate analysis was conducted to investigate if PTX3 and FGF2 were correlated with the presence or future development of vascular manifestations, including digital ulcer (DU) and pulmonary arterial hypertension (PAH). Circulating CD34+ CD133+ endothelial progenitor cells (EPCs) were enumerated by flow cytometry. Effects of recombinant PTX3 on EPC differentiation were evaluated in pro-angiogenic cultures of mouse bone marrow mononuclear cells, followed by colony formation assay.

**Results:** PTX3 and FGF2 were significantly increased in SSc patients than in healthy controls ($P < 0.001$ and $P = 0.001$, respectively). When PTX3 and FGF2 levels were compared between two groups stratified by the presence or absence of individual organ involvement, PTX3 was increased in SSc patients with DU or PAH than in those without ($P < 0.001$ and $P = 0.006$, respectively), while FGF2 was reduced in patients with PAH ($P < 0.001$). Multivariate analysis revealed that elevated PTX3 was an independent parameter associated with the presence of DU (odds ratio (OR) = 1.50, $P < 0.001$) and PAH (OR = 1.23, $P = 0.002$), and was useful in predicting future occurrence of DU (hazard ratio = 1.12, $P = 0.04$). In contrast, reduced FGF2 was independently associated with the presence of PAH (OR = 0.91, $P = 0.02$). EPC counts were significantly reduced in patients with DU or PAH than in those without ($P = 0.003$ and 0.003, respectively), and were correlated negatively with circulating PTX3 concentration ($r = -0.53, P < 0.001$) and a PTX3/FGF2 ratio ($r = -0.35, P = 0.003$). Finally, exogenous PTX3 significantly inhibited differentiation of EPCs from mouse bone marrow stem cells in vitro.

**Conclusion:** PTX3 was elevated in circulation of SSc patients and was a useful biomarker that predicts the presence of DU and PAH as well as future development of DU. In addition, continuous exposure to a high PTX3 concentration may contribute to SSc vasculopathy through inhibition of vasculogenesis by exerting its suppressive effects on FGF2.

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**Systemic Sclerosis Patients with Anti-topoisomerase Antibodies Showed Significant Association with CCR6 Polymorphisms.**


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**Background/Purpose:** Systemic sclerosis (SSc), also known as sclerodermia, is an inflammatory autoimmune disease characterized by fibrosis of the skin and internal organs, vascular damage and altered immune responses with autoantibody production (especially anticientromere (ACA) and antitopoisoermerase I (ATA)). As a complex disease, SSc, is caused by a combination of genetic and environmental factors. In recent years, the number of new susceptibility loci associated with SSc has remarkably grown due to genome wide association studies (GWAS). Nevertheless, the current knowledge of the influence of SSc risk loci in the clinical sub-phenotypes is limited and one of the main reasons is the low sample size in sub-phenotypes that triggers a lower statistical power. In this regard, ATA SSc patients have been recently included with CCR6 gene variant and the main limitations of the study was the low sample size due to the low frequency of ATA among SSc patients (around 20%). Thus, in order to confirm the CCR6 association with ATA SSc, we performed an independent replication study in populations of European ancestry and a meta-analysis with the previous data published.

**Methods:** We selected for replication SNP rs3093024, in high linkage disequilibrium with the SNPs previously associated with ATA SSc, rs3093023 ($r^2 = 1$) and rs10846216 ($r^2 = 0.96$). We designed a replication study with two phases: In phase I, we analyzed 454 ATA SSc cases and 4,867 controls from available GWAS genotyped platform by Radstake et al. and in phase II, 446 ATA SSc cases and 2,998 controls from five additional European cohorts were genotyped using TaqMan SNP® genotyping assay. Approval of local ethical committees and informed written consent was obtained for all participants. The meta-analysis of our study with the previous one included 1,548 ATA SSc cases and 14,777 controls and reached statistical power of the analysis to 99% (OR 1.16, MAF 0.43, at the 5% significant level).

**Results:** Results obtained in meta-analysis showed significant association between SNP rs3093024 and ATA SSc patients ($P = 10.0 \times 10^{-4}$, OR = 1.16) (Table 1). Thus we confirm the association previously observed between CCR6 and ATA SSc patients harnessed the largest cohort of patients. The relevance of CCR6 gene lies in its function as specific marker for Th17 cells. These cells are characterized by the production of interleukin-17 (IL-17) which has been found to be increased in patients with SSc. Besides serum levels of IL-17 and ATA presence have been both correlated with disease severity. Interestingly, CCR6 expression levels and IL-17 levels showed correlation with a CCR6 functional variant which was in high linkage disequilibrium with SNP rs3093024 in rheumatoid arthritis patients.

**Conclusion:** Taken all together, our findings suggest that the presence of the risk variant of rs3093024 in CCR6 gene may acts as a marker of severity in SSc patients.

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**Increased Expression of Chemerin in Endothelial Cells Due to FIll Deficiency May Contribute to the Development of Digital Ulcers in Systemic Sclerosis.**

Kanae Nakamata, Yoshishide Asano, Takashi Taniguchi, Hayakazu Sumida, Naohiko Aozasa, Shinji Noda, Tetsuo Toyama, Takehiro Takahashi, Yohei Ichimura, Ayumi Yoshizaki and Shinichi Satoh. University of Tokyo Graduate School of Medicine, Tokyo, Japan.
Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disorder characterized by vascular injuries and fibrosis development. In SSc lesional skin, transcription factor Friend leukemia virus integration 1 (Fli1) is constitutively down-regulated in various cell types, especially by an epigenetic mechanism in dermal fibroblasts, and Fli1 deficiency is deeply related to the pathogenesis of SSc. In particular, endothelial Fli1 deficiency reproduces the histological and functional abnormalities characteristic of SSc vasculopathy in vivo. Recently, adipocytokines have drawn much attention in the research field of various autoimmune diseases. Chemerin is a member of adipocytokines with a chemotactic property, and has been shown to have pivotal roles in the pathogenesis of various autoimmune diseases. To elucidate the role of chemerin in the developmental process of SSc, we investigated the expression levels of chemerin in SSc lesional skin and the mechanism underlying its altered expression, and the clinical correlation of serum chemerin levels in SSc patients.

Methods: Expression of chemerin and its receptor, ChemR23, was evaluated by immunostaining and/or quantitative reverse transcription-real time PCR in human and/or murine skin. The mechanisms regulating chemerin expression in dermal fibroblasts and endothelial cells were examined by gene silencing technique and chromatin immunoprecipitation. Serum chemerin levels were determined by enzyme-linked immunosorbent assay in 64 SSc and 19 healthy subjects.

Results: In SSc lesional skin, chemerin was up-regulated in small blood vessels, down-regulated in activated fibroblasts surrounded with thickened collagen bundles, but not altered in inflammatory cells, while ChemR23 expression was comparable in various cell types. Chemerin expression was also markedly decreased in dermal fibroblasts of bleomycin-treated SSc model mice. Importantly, the decreased expression of chemerin was significantly reversed by blocking autocrine transforming growth factor (TGF-β) signaling with TGF-β1 antisense oligonucleotide in cultured SSc dermal fibroblast. As for endothelial cells, gene silencing of Fli1, which directly bound to the chemerin promoter, induced chemerin expression in human dermal microvascular endothelial cells and Fli1−/− mice exhibited elevated chemerin expression in dermal vessels. Regarding the correlation of serum chemerin levels with clinical features in SSc patients, serum chemerin levels inversely correlated with estimated glomerular filtration rate in SSc patients with renal dysfunction while, in SSc patients with normal renal function, patients with digital ulcers had higher serum chemerin levels than those without.

Conclusion: Chemerin is down-regulated in SSc dermal fibroblasts by autocrine TGF-β, while up-regulated in SSc dermal blood vessels through endothelial Fli1 deficiency. In SSc, dysregulated chemerin/ChemR23 axis by endothelial Fli1 deficiency may contribute to the development of SSc vasculopathy through altering angiogenic/angiostatic signaling pathways.

Disclosure: K. Akamata None; Y. Asano None; T. Taniguchi None; H. Sumida None; N. Aozasa None; N. Noda None; T. Toyama None; T. Takahashi None; Y. Ichimura None; A. Yoshizaki None; S. Sato None.

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Progranulin Overproduction Due to Fli1 Deficiency Contributes to the Resistance of Dermal Fibroblasts to Tumor Necrosis Factor α in Systemic Sclerosis

Yoko Ichimura1, Yohei Ichimura, Yoshihide Asano, Kaname Akamata, Shinji Noda, Takashi Taniguchi, Takehiro Takahashi, Tetsuo Toyama, Yayoi Tada, Makoto Sugaya, Shinichi Sato and Takafumi Kadono. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Progranulin (PGRN) is a wound healing-associated growth factor regulating fibroblast activation, angiogenesis, and inflammation, i.e. three major pathological components of SSc. Therefore, we hypothesized that PGRN is involved in the mechanism underlying dermal fibrosis of SSc.

Methods: PGRN expression levels were determined by immunohistochemistry and quantitative reverse transcription-PCR in the skin of human subjects and murine SSc models. The role of PGRN in dermal fibroblast activation was examined with gene silencing technique. Serum PGRN levels were determined by ELISA in 60 SSc and 16 healthy subjects.

Results: In immunostaining with human skin samples, the expression levels of PGRN were increased in SSc dermal fibroblasts compared with normal dermal fibroblasts, while comparable in inflammatory cells, endothelial cells, and epidermal keratinocytes between SSc and control subjects. This findings was also confirmed in vitro with cultured SSc dermal fibroblasts, showing a significant increase of PGRN mRNA expression compared with normal dermal fibroblasts. Furthermore, bleomycin-treated mice exhibited the up-regulated expression of PGRN in dermal fibroblasts, suggesting the potential contribution of this molecule to the pathological dermal fibrosis, including SSc. Importantly, transcription factor Fli1, whose deficiency due to epigenetic mechanism contributes to the constitutive activation of SSc dermal fibroblasts, bound to the promoter of the PGRN gene and gene silencing of Fli1 resulted in a robust increase in mRNA levels of PGRN gene in dermal fibroblasts. Consistently, the up-regulated expression of PGRN was observed in dermal fibroblasts of Fli1−/− mice in vivo. Given that PGRN serves as an antagonist of TNF-α, a pro-inflammatory cytokine with a potent anti-fibrotic effect on dermal fibroblasts, we hypothesized that PGRN renders SSc dermal fibroblasts resistant to the anti-fibrotic effect of TNF-α. Supporting our idea, TNF-α suppressed the expression of type I collagen in SSc dermal fibroblasts treated with PGRN siRNA, while in the cell lines treated with non-silencing scrambled RNA. To further assess the role of PGRN in SSc, we measured serum PGRN levels and examined their clinical correlation. Serum PGRN levels were elevated in early diffuse cutaneous SSc patients, especially in those with inflammatory skin symptoms, and positively correlated with C-reactive protein.

Conclusion: PGRN overproduction due to Fli1 deficiency may contribute to the constitutive activation of SSc dermal fibroblasts by antagonizing the anti-fibrotic effect of TNF-α. PGRN may also be involved in the inflammatory process associated with progressive skin sclerosis in early diffuse cutaneous SSc.

Disclosure: Y. Ichimura None; Y. Asano None; K. Akamata None; S. Noda None; T. Taniguchi None; T. Takahashi None; T. Toyama None; Y. Tada None; M. Sugaya None; S. Sato None; T. Kadono None.

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Molecular Characterization of Systemic Sclerosis Esophageal Pathology Identifies Inflammatory and Proliferative Signatures with Few Fibrotic Markers

Jaclyn Taroni1, Viktor Martyanov2, Chiang-Ching Huang3, J. Matthew Mahoney1, Ikou Hirano1, Tammara A. Wood3, Brandon Shetumi3, Guang-Yu Yang3, Darren Brenner3, Barbara Jung3, Swati Bhattacharyya3, Ort Almagor4, Jungwha Lee4, Arlela Sirajuddin5, Rowland W. Chang6, John Varga7, Michael Whitfield2 and Monique Hinchcliff5. 1Giesel School of Medicine, Dartmouth, Hanover, NH, 2University of Wisconsin, Milwaukee, Milwaukee, WI, 3University of Vermont, Burlington, VT, 4Northwestern University Feinberg School of Medicine, Chicago, IL, 5University of Illinois at Chicago, Chicago, IL, 6Northwestern University, Feinberg School of Medicine, Chicago, IL, 7Northwestern University, Chicago, IL.

Background/Purpose: Esophageal involvement in patients with systemic sclerosis (SSc) is common, but tissue-specific pathological mechanisms are poorly understood. Esophageal muscle atrophy without concomitant fibrosis is found in the majority of SSc patient autopsy specimens. We hypothesized that detailed characterization of SSc esophageal histopathology and molecular signatures at the level of gene expression would provide insights into SSc esophageal disease pathogenesis.

Methods: Esophageal biopsies were prospectively obtained during esophagogastroduodenoscopy (EGD) in 16 clinically well-characterized SSc patients and 7 subjects without SSc. Upper and lower esophageal biopsies were evaluated for histopathology and gene expression by DNA microarray. Biopsies were scored for basal cell hyperplasia, lymphocyte infiltration, and degree of collagen deposition. The presence of a hiatal hernia and/or esophagitis on gross examination of the esophageal lumen at the time of EGD was considered evidence for esophagitis. Transcripts with the most similar expression between an individual’s upper and lower biopsies, but most different expression between individuals, termed ‘intrinsic genes,’ were identified and hierarchically clustered to define molecular subsets (FDR <1.1%). Consensus clustering and SigClust formally confirmed the number of significant clusters within the cohort. Significance Analysis of Microarrays (SAM) identified differentially expressed transcripts between subsets, and g:Profiler identified functional terms enriched in subsets.

Results: Upper and lower esophageal biopsies showed nearly identical patterns of gene expression within an individual. Three groups of patients with SSc were identified molecularly: an inflammatory group (upregulated genes related to immune processes), a proliferative group (upregulated genes indicative of proliferating cells), and a non-inflammatory group (downregulated immune genes). The inflammatory signature was independent of esophagitis as assessed by basal cell hyperplasia grade, infiltrating lymphocyte counts, and presence of gross esophagitis/hiatal hernia indicating im-
Dissecting the Heterogeneity of Skin Gene Expression Patterns in Systemic Sclerosis. Shervin Assassi1, William Swindell2, Minghua Wu3, Filemon K. Tan1, Dinesh Khanna1, Daniel E. Furst1, Donald Tashkin3, Chang1. 1University of Texas Health Science Center at Houston, Houston, TX, 2University of Michigan, Ann Arbor, MI, 3University of California at Los Angeles, Los Angeles, CA.

Background/Purpose: To examine the heterogeneity of global transcriptome patterns in systemic sclerosis (SSc) skin from a large cohort of patients and controls. Methods: Skin biopsies from 61 patients (70.5% diffuse cutaneous involvement) enrolled in the GENISOS cohort or at the baseline visit of an imatinib study, as well as 36 unaffected controls of similar demographic background, were examined by Illumina HT-12 gene expression arrays. Follow-up quantitative real-time PCR experiments were also performed. Using a novel analytic approach based on expression profiles, we investigated how heterogeneity within SSc samples relates to specific disease-relevant cell types (e.g. fibroblasts or macrophages).

Results: We identified 2754 differentially expressed transcripts in SSc patients compared to controls. Clustering analysis revealed two prominent transcriptomes in SSc patients: Keratin and fibro-inflammatory signatures. Higher keratin transcript scores were associated with shorter disease duration and interstitial lung disease while higher fibro-inflammatory scores were associated with diffuse cutaneous involvement, higher skin score at biopsy site and higher modified Rodnan Skin Score. There were no significant associations with disease-related autoantibodies or concomitant treatment with immunosuppressive agents. A subgroup of patients with significantly longer disease duration had a normal-like transcript pattern.

Further analysis and immunohistochemistry staining indicated that the above-mentioned keratin signature was not a general marker of keratinocyte activation, but was in fact associated with an activation pattern in hair and adnexal structures.

As shown in Figure 1, analysis of cell type-specific signature scores revealed remarkable heterogeneity across patients (each row represents a patient sample). Significantly high scores were observed in the majority of patients for fibroblasts (72% of patients), microvascular (61%), and macrophages (54%). The majority of samples with significant fibroblast scores (35 of 44 = 80%) also had significantly increased macrophage and/or dendritic cell scores. Only a minority of samples showed significantly high CD4+ T-cell, CD8+ T-cell and plasma cell scores (18%, 21%, and 26%).

Conclusion: In this large gene expression data set, a prominent keratin signature was present in addition to a fibro-inflammatory signature, supporting the notion that molecular dysregulations in SSc skin are not confined to the dermal layer but are in fact present in several skin compartments. Furthermore, the novel cell-specific transcript analysis showed significant heterogeneity of inflammatory profiles from SSc skin, which might be useful for stratifying patients for targeted treatment and/or predicting their response to immunosuppression.
Conclusion: These results indicate the pivotal contribution of TLR4 to the pathogenesis in a BLM-induced SSc murine model and TSK/+. model, two major models which mimic early and late phase of SSc respectively. Our results indicate the critical role of TLR4 signaling in the pathogenesis of fibrosis, suggesting that the biomolecular TLR4 targeting might be a potential therapeutic approach to SSc.

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Identification of IL12RB1 As a Novel Systemic Sclerosis Susceptibility Locus


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Results: Forty-six single-nucleotide polymorphisms (SNPs) within the IL12RB1 region were screened in a discovery cohort comprising 1,871 SSc cases and 3,636 controls from the previously published Immunochip dense association signals (P-values between 5x10^-3 and 5x10^-5), which might result in real association signals that could be masked owing to a limited power. In this line, one of the SNPs showed suggestive association signals was IL12RB1, which encodes the beta 1 subunit of the interleukin-12 (IL-12) receptor. Interestingly, several IL-12 pathway-related genes are confirmed genetic risk factors in SSc pathogenesis in a BLM-induced SSc murine model and TSK/+(eQTL) that decreased IL12RB1 expression (P-value = 2.4 x 10^-81, Z-score = -19.10). Additionally, rs436857 showed evidence to affect the binding of several transcription factors. These results pinpoint rs436857 as the most likely causal variant for driving the reported association, narrowing down the signal to the promoter region of the gene.

Conclusion: The present study reports for the first time robust evidence for the implication of IL12RB1 in SSc genetic background and highlights the importance of the follow-up studies. The results reinforce the relevance of IL-12 pathway in SSc pathophysiology, shedding light on our understanding of the immune system processes implicated in SSc development, and suggest that blocking this pathway could be a possible new therapeutic target.

Disclosure: E. Lopez-Isac, None; L. Bossini-Castillo, None; S. Guerra, None; S. Assassi, None; Z. Zhou, None; C.P. Simeón, None; N. Ortego-Centeno, None; I. Castellvi, None; P. Carreira, None; O. Gorlova, None; L. Beretta, None; A. Santaniello, None; C. Lunardi, None; R. Hesselstrand, None; A. Nordin, None; G. Riemekestan, None; T. Witte, None; N. Hunzelmann, None; A. Kreuter, None; J.H. Distler, None; A. Voskuyl, None; E. Voskuyl, None; K. De Vries-Bouwstra, None; B. C. Koelman, None; A. Herrick, None; J. Worthington, None; C. Denton, None; C. Fonseca, None; T. R. D. Jakobstad, None; M. D. Hayes, None; J. Martin, None.

The Global miRNA Whole Blood Profile in Systemic Sclerosis and Its Correlation with Serum Cytokine Levels

Background/Purpose: Several studies have implicated miRNAs in the pathogenesis of systemic sclerosis (SSc). Recent advances in quantitative polymerase chain reaction (qPCR) allow simultaneous measurement of hundreds of miRNAs. The objective of this study was to use this technology to identify the unbiased, global miRNA profiling of SSc whole blood and evaluate its correlation with plasma cytokine levels.

Methods: We investigated the miRNA profile in SSc whole blood compared to unaffected controls using multiplex qPCR platform. We obtained 456 samples from 81 patients with SSc (≤5 yrs. on no immunosuppression) and 10 age-, gender- and ethnicity matched controls. Eight patients had diffuse disease and two had limited disease. The mean disease duration was 2.2 yrs. Levels of 752 miRNAs were determined. Unsupervised hierarchical clustering analysis was performed. Patient and control samples miRNA levels were compared and differences with a p<0.01, false discovery rate (FDR) <10% and fold change >2 were considered statistically significant.

A quantitative, multiplexed immunoassay designed to measure 45 cytokines, chemokines and acute-phase reactants was used to determine the serum cytokine levels (myriad human inflammationMAP) in order to correlate expression of miRNA with their predicted targets.

Results: The association of patient to control whole blood samples revealed 16 miRNAs that were differentially expressed (Table 1). All miRNAs, except for miR-10b-5p, were downregulated in SSc compared to controls. Notably four differentially expressed miRNA in whole blood originate from the same cluster located in 14q32.3. The unsupervised hierarchical clustering analysis of whole blood miRNA profile separated the two groups but three patients clustered along with controls.

In the cytokine analysis, MCP1 (CCL2), IL-10, MMP-9, TNFR2, VCAM1 and ICAM1 were differentially expressed in SSc patients. MiR-370 levels highly correlated with MCP-1 protein levels (r = -0.6, p=0.004) which is a predicted target of this miRNA.

Conclusion: To our knowledge, this is the first global, unbiased examination of miRNA in SSc whole blood and the first correlation of miRNA with SSc plasma cytokine levels. The miRNA profile showed 16 miRNAs that are dysregulated in SSc whole blood. MiR-370 levels were differentially expressed in SSc whole blood and highly correlated with MCP-1 protein levels. We have previously reported also an upregulation of this miRNA in SSc skin. Furthermore, miR-370 targeted TGFβR-II in two independent studies under-scoring its potential role in SSc pathogenesis.

<p>| Table 1. SSc whole blood dysregulated miRNA |</p>
<table>
<thead>
<tr>
<th>miRNA</th>
<th>Location</th>
<th>Fold Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-1228-3p</td>
<td>19p13.2</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>miR-506-3p</td>
<td>Xq27.3</td>
<td>0.33</td>
<td>&lt;0.001</td>
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SSc-PAH has a worse clinical outcome. We have previously shown that a model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal formed on whole lung isolates and explant cultured fibroblasts (n
hypertrophy and raised right ventricular pressures. Experiments were per-
fib mouse develops a structural pulmonary vasculopathy with smooth muscle
expression. Interestingly, both T
healthy controls (p
H11021/H11021/H11005/H11002

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4UCL, London, United Kingdom.

Background/Purpose: Scleroderma patients are susceptible to develop-
ment of pulmonary arterial hypertension (PAH) that has similarities to some
forms of heritable PAH. The basis for this susceptibility is unclear and SSc-PAH has a worse clinical outcome. We have previously shown that a TGFβ dependent mouse model of scleroderma (TβRII-lk-fib) develops PAH in response to pulmonary endothelial cell injury. Using this model as a platform and clinical material form SSc lungs we explored expression and proteasomal degradation of BMPRII that is implicated in development of heritable PAH.

Methods: We investigated BMP signalling in the lung in the TβRII-lk-fib model of PAH-SSc in which TGFβ signalling is upregulated. The TβRII-lk-fib mouse develops a structural pulmonary vasculopathy with smooth muscle hypertrophy and raised right ventricular pressures. Experiments were performed on whole lung isolates and explant cultured fibroblasts (n=6) from the TβRII-lk-fib mouse and compared with wildtype controls. TGFβ/BMP signalling pathways were investigated by Western blot and immunohistochemistry and qPCR. MG132, an inhibitor of proteasomal degradation, was used to explore the role of proteasomal degradation on BMPRII protein levels in vitro.

Results: The TβRII-lk-fib model has increased levels of pSmad2/3, indicative of enhanced TGFβ signalling. The TβRII-lk-fib model exhibits a significant reduction in BMPRII protein expression in whole lung isolates (1.43, 0.38) (p<0.05), and explant cultured fibroblasts (0.299, 0.09) (p<0.05). A reduction of BMPRII was also observed in whole lung (0.095, 0.03) and explant cultured lung fibroblasts from SSc patients compared to healthy controls (p<0.05) but there was an increase in BMPRII gene expression. Interestingly, both TβRII-lk-fib and SSc fibroblasts exhibited refractory responses to BMP4 (p<0.05). MG132 was able to restore BMPRII protein levels and restore BMP4 ligand response of SSc fibroblasts.

Conclusion: Here we demonstrate the TβRII-lk-fib transgenic murine model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal response to increased TGFβ signalling. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PAH in SSc. Furthermore, our results suggest that use of a proteasomal degradation inhibitor might reduce the risk of developing PAH by restoring BMPRII expression.

Disclosure: G. Salazar, None; M. Mayes, None; J. Hagan, None; M. Wu, None; J. D. Revelle, None; S. Assassi, None.

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Increased Degradation of BMPRII in a TGFβ Dependent Transgenic Mouse Model of Scleroderma with Susceptibility to Pulmonary Arterial Hypertension. Adrian J Gilbane1, Emma C. Derrett-Smith2, Andrew Pearce1, Christopher P Denton1 and Alan M. Holmes4. 1UCL Medical School, London, United Kingdom, 2UCL Medical School Royal Free

Campus, London, United Kingdom, 3Novartis, London, United Kingdom, 4UCL, London, United Kingdom.

Background/Purpose: Scleroderma patients are susceptible to development of pulmonary arterial hypertension (PAH) that has similarities to some forms of heritable PAH. The basis for this susceptibility is unclear and SSc-PAH has a worse clinical outcome. We have previously shown that a TGFβ dependent mouse model of scleroderma (TβRII-lk-fib) develops PAH in response to pulmonary endothelial cell injury. Using this model as a platform and clinical material from SSc lungs we explored expression and proteasomal degradation of BMPRII that is implicated in development of heritable PAH.

Methods: We investigated BMP signalling in the lung in the TβRII-lk-fib model of PAH-SSc in which TGFβ signalling is upregulated. The TβRII-lk-fib mouse develops a structural pulmonary vasculopathy with smooth muscle hypertrophy and raised right ventricular pressures. Experiments were performed on whole lung isolates and explant cultured fibroblasts (n=6) from the TβRII-lk-fib mouse and compared with wildtype controls. TGFβ/BMP signalling pathways were investigated by Western blot and immunohistochemistry and qPCR. MG132, an inhibitor of proteasomal degradation, was used to explore the role of proteasomal degradation on BMPRII protein levels in vitro.

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Conclusion: Here we demonstrate the TβRII-lk-fib transgenic murine model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal response to increased TGFβ signalling. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PAH in SSc. Furthermore, our results suggest that use of a proteasomal degradation inhibitor might reduce the risk of developing PAH by restoring BMPRII expression.

Disclosure: A. Yoshizaki, None; Y. Asano, None; T. Taniguchi, None; R. Saigusa, None; K. Nakamura, None; T. Yamashita, None; T. Takahashi, None; T. Toyama, None; Y. Ichimura, None; Z. Tamaki, None; M. Miyazaki, None; S. Suto, None.

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Distinctive Patterns of Telomere Shortening and Apoptosis in Limited Diffuse cutaneous Systemic Sclerosis. Jasper Broen1, Liane McGlynn2, Dagnara McGuinness3, Rita Wichers3, Jacqueline Thomson4, Rajan Madhok4, Robert Laffayi5, Carol A. Feghali-Bostwick6, Paul Shiel6 and T.R.D.J. Radstake1. 1University Medical Center Utrecht, Utrecht, Netherlands, 2University of Glasgow, Glasgow, United Kingdom, 3UMC Utrecht, Utrecht, Netherlands, 4Glasgow Royal Infirmary, Glasgow, United Kingdom, 5Boston University, Boston, MA, 6Medical University of South Carolina, Charleston, SC.

Background/Purpose: Aberrant telomere shortening and DNA damage responses have been previously described in SSc, here we aim to validate these observations and incorporate them in a functional and clinical relevant framework.

Methods: We measured telomere length in peripheral blood leukocytes, monocytes, B cells, myeloid dendritic cells, T cells and plasmacytoid dendritic cells from a total of 103 healthy controls, 121 lcSSc patients and 83 dcSSc patients. In addition, telomere measurements were performed in 21 monocygotic twin pairs with SSc. We finally analyzed apoptosis and telomere gene expression arrays to investigate underlying pathways and used them to stratify patients.

Results: We found that suffering from dcSSc is an independent risk factor for shorter telomeres in full blood cells, which is on the cellular level reflected by significantly shorter telomeres in T cells and pDCs compared to healthy controls and lcSSc (all p<0.001). Based on the analyses of 21 monocygotic twin pairs with SSc we conclude that this seems to be an inborn error in

Disclosure: A. Yoshizaki, None; Y. Asano, None; T. Taniguchi, None; R. Saigusa, None; K. Nakamura, None; T. Yamashita, None; T. Takahashi, None; T. Toyama, None; Y. Ichimura, None; Z. Tamaki, None; M. Miyazaki, None; S. Suto, None.
Several inflammatory, TGF local skin score of 1 or greater were different from healthy control. score (Pearson’s). results were assessed for difference (one-way ANOVA) in gene expression of genes we have previously identified as elevated in SSc skin. The expression data from primary human fibroblasts suggested that E4 treatment delineate the mechanism by which E4 abrogates fibrosis. Preliminary gene sequence 133–180, is a promising therapeutic agent for fibrotic disorders. E4 sclerosis (SSc) have no effective therapies and result in significant morbidity and local skin score may represent molecular events closest to clinical stratification.

**Conclusion:** Telomere shortening and apoptotic pathways are differentially regulated in lcSSc and dcSSc and provide novel avenues for patient stratification.

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Assessment of mRNA Gene Expression Based on Forearm Skin Score in Systemic Sclerosis Patients. Lisa Rice1, Giuseppina Stifano2, Jessica Ziemek3 and Robert Lafayatis4. Boston University Medical Center, Boston, MA, 1Boston University School of Medicine, Boston, MA.

**Background/Purpose:** The extent of skin disease in patients with systemic sclerosis is typically measured through physical examination of patients at 17 sites and involvement is quantified on a scale from uninvolved to severe involvement (0 to 3). The total of all 17 sites scores is defined as the Modified Rodnan Skin Score (MRSS). We have shown previously that gene expression of skin biopsies taken from the mid-forearm correlates well with overall skin disease as assessed by the MRSS. However, it remained unclear whether the success of such an approach represented a particularly accurate, molecular, quantification of local skin disease or a manifestation of altered gene expression known to occur in all the skin of systemic sclerosis patients, both lesional and non-lesional.

**Methods:** Skin biopsies (n=42) from the forearms of patients with diffuse cutaneous SSc (dcSSc) and healthy donors (n=5) were assessed for expression of genes we have previously identified as elevated in SSc skin. The results were assessed for difference (one-way ANOVA) in gene expression (p≤0.05) with forearm skin score (0 to 3) and correlation with forearm skin score (Pearson’s).

**Results:** Expression of all genes examined form patients showing a local skin score of 1 or greater were different from healthy control. Several inflammatory, TGFβ, and WNT regulated genes (CCL2, IL13RA1, COMP, THBS-1, ADAM12, and WIF1) showed a significant correlation with the local forearm score (1 or greater). Other inflammatory and macrophage related genes (IFI44, CD163, SL-SGEC1, CD14) showed no significant correlation between the level of gene expression and the local skin score.

**Conclusion:** The different relationships between local gene expression, and local versus systemic assessment of the skin score (MRSS) suggest a hierarchy of molecular events. Gene expression correlating most highly with the local skin score may represent molecular events closest to clinical manifestations. Altered gene expression that does not correlate with the skin score may represent molecular events further from clinical involvement. The total of all 17 sites scores is defined as the Modified Rodnan Skin Score (MRSS). The total of all 17 sites scores is defined as the Modified Rodnan Skin Score (MRSS).

**Disclosure:** L. Rice, None; G. Stifano, None; J. Ziemek, None; R. Lafayatis, None.

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The Anti-Fibrotic Effect of Endostatin-Derived Peptide Is Mediated By Urokinase. Tetsuya Nishimoto1, Takahisa Takihara1, Yunyun Su2, Roger Chambers1, Logan Makar1 and Carol Feghali-Bostwick1. 1Medical University of South Carolina, Charleston, SC, 2Tokai University School of Medicine, Kanagawa, Japan.

**Background/Purpose:** Fibroproliferative disorders such as systemic sclerosis (SSc) have no effective therapies and result in significant morbidity and mortality as a result of organ fibrosis. We recently demonstrated that the C-terminal domain of endostatin known as E4, corresponding to amino acid sequence 133–180, is a promising therapeutic agent for fibrotic disorders. E4 prevented and reversed both dermal and pulmonary fibrosis. Our goal was to delineate the mechanism by which E4 abrogates fibrosis. Preliminary gene expression data from primary human fibroblasts suggested that E4 treatment resulted in increased expression of urokinase (uPA).

**Methods:** Bleomycin (60 μg/mice) or Bleomycin in combination with E4 (10 μg/ml) was administered intratracheally to 6 to 8-week-old C57BL/6 male mice to induce lung fibrosis. Bronchoalveolar lavage (BAL) fluid was collected on days 3, 5, 7, and 14 post treatment, and the levels and activity of uPA and plasminogen activator inhibitor-1 (PAI-1), an inhibitor of uPA, were measured. Primary human fibroblasts were treated with TGF-β (10 ng/ml) to induce a fibrotic phenotype or TGF-β in combination with E4 (10 μg/ml). The mRNA and protein levels of uPA, PAI-1, matrix metalloproteinase-1 (MMP-1), and MMP-3 were determined using real-time PCR and immunoblotting, respectively. Secreted uPA activity was also measured in fibroblast supernatants. Since MMP-1 and MMP-3 are downstream effectors of uPA, we assessed MMP-1 and -3 activity using collagen and casein zymography, respectively. The mRNA levels of uPA and PAI-1 in human whole lung tissue and lung fibroblasts from 9 healthy control (HC) and 32 SSc patients were examined using real-time PCR.

**Results:** In vitro, bleomycin reduced uPA levels and activity and increased PAI-1 activity. E4 peptide partially blocked these effects. The reduction of PAI-1 caused by E4 administration preceded the increase in uPA activity, suggesting that a release from inhibition may explain in part the increase in uPA activity. In vitro, TGF-β reduced uPA levels and increased PAI-1 levels in primary fibroblasts. E4 peptide cancelled these effects and increased the uPA/PAI-1 ratio. Moreover, the expression and activity of MMP-1 and MMP-3 were increased by E4 treatment. The mRNA levels of uPA both in whole lung tissue and lung fibroblasts were comparable between HC and SSc patients, however, those of PAI-1 were increased in SSc patients, resulting in a decrease of the uPA/PAI-1 ratio.

**Conclusion:** Our results demonstrated that E4 increases uPA activity by both increasing uPA levels and activity and reducing PAI-1-mediated inhibition. The ability of E4 to reverse fibrosis can be explained by its ability to induce MMP-1 and MMP-3 levels and activity, thus promoting extracellular matrix degradation. In SSc patients, the uPA/PAI-1 balance shifted toward PAI-1. Taken together, our findings suggest that the anti-fibrotic effects of E4 peptide are mediated, at least in part, by the uPA fibrinolytic system, and that E4 peptide exerts its therapeutic effects in organ fibrosis via regulation of the urokinase pathway.

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Specific Autoantibody Profiles and Disease Subgroups Correlate with Circulating Micro-RNA in Systemic Sclerosis. Dirk Wutte1, Anting L. Carlsten2, Gabriel Teku1, Samantha Steen2, Marie Wildt1, Mauno Vihinen1, Roger Hesselstrand1 and Niels H. H. Heegaard1. 1Lund University, Lund, Sweden, 2Statens Serum Institut, Copenhagen, Denmark, 3Odense University Hospital, Odense C, Denmark.

Background/Purpose: Systemic sclerosis (SSc) is a serious autoimmune disease with clinical phenotypes of different prognosis, progression rate, and different extent of involvement of internal organs. Specific circulating autoantibody profiles contribute to forecasting the prognosis of SSc cases. Circulating micro-RNA (miRNA) profiles also are characteristic in SSc but clinical phenotypes, autoantibody profiles, and circulating miRNA profiles have not yet been correlated. The aim of the study, therefore, was to evaluate the expression profiles of cell-free plasma miRNAs in SSc and study their correlation with disease subgroups (limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)) and with clinical and paraclinical parameters including circulating autoantibody profiles.

Methods: Total RNA was purified from plasma and the abundance of 45 mature miRNAs were measured using quantitative polymerase chain reaction assays after reverse transcription. A total of 95 SSc patients (n=94 fulfilling the ACR criteria for SSc, n=1 with limited SSc) were included (lcSSc, n=63; dcSSc, n=32). The patients represented the following autoantibody subgroups: anti-centromere group (ACA, n=35); anti-DNA topoisomerase I group (ATA, n=20); anti-RNA polymerase III group (ARA, n=20); and anti-U1-RNP group (RNP, n=20). miRNA expression data, clinical data, autoantibody data, and other paraclinical data were analyzed for correlations. ANOVA showed significant difference between skin scores (p=0.003), with Scheffe post hoc analysis showing significant higher skin scores in Group 1 (p=0.005).

Conclusion: Our results confirm the value of dermal blister analysis in SSc, and identify key factors expressed locally. Whilst plasma analysis revealed some overlap with the blister fluid analysis, it did not reflect all of the changes present in the dermal microenvironment. This method profiles the local inflammatory process occurring within the skin and complements clinical and gene expression based classification, as well as suggesting markers of disease activity or treatment effect.

Disclosure: None.

761 IQGAP1 Enhances Contractility of Scleroderma Lung Fibroblasts and Promotes Bleomycin-Induced Pulmonary Fibrosis. Tanjana Akter1, Ilia Atanelishvili1, Yuichiro Shirai2, Sybil Prince Nelson2, Alvaro Garcia-Morales1, Thomas A. Morinelli1, Richard M. Silver1 and Galina S. Bogatkevich1. 1Medical University of South Carolina, Charleston, USA, Charleston, SC, 2Medical University of South Carolina, Charleston, USA, chareston, SC, 3Hospital la Zarzuela, Madrid, Spain, Madrid, Spain.

Background/Purpose: Scleroderma associated interstitial lung disease (SSc-ILD) is an irreversible and progressive complication and a leading cause of death among SSc patients. Constitutive overexpression of connective tissue growth factor (CTGF) has been observed in both in vivo and in vitro studies of SSc patients. Proteomic analysis of CTGF-activated lung fibroblasts demonstrated that CTGF induces IQ motif containing GTase activating protein (IQGAP1). IQGAP1 is a multifunctional scaffold protein that integrates diverse signal transduction pathways and regulates fibroblast migration. Our recent findings demonstrate the profibrotic role of IQGAP1 in the bleomycin-induced murine model of SSc-ILD. Here we report our latest data focusing on the molecular mechanism and pathophysiologic action of IQGAP1 in this mouse model of ILD.

Methods: Lung injury was induced in female C57BL/6 mice by a single intratracheal instillation of bleomycin (0.05 U/mouse). IQGAP1-siRNA and CTGF-siRNA were delivered by intranasal instillation every other day. Mice were sacrificed 3 weeks after bleomycin instillation and lungs were harvested. Lungs were perfused with neutral buffered formaldehyde, embedded in paraffin, stained with hematoxylin and eosin (H&E), and scored for fibrosis. Lung tissue was harvested, lyophilized and run on western blot. IQGAP1 knockout mice were challenged with bleomycin and histology was performed. Assessment of collagen deposition was assessed by Masson’s trichrome staining and by Sircol Collagen Assay. The role of IQGAP1 in F-actin filament formation was examined by immunofluorescence staining and by actin polymerization assay. The rate of actin polymerization was measured in terms of fluorescence intensity by Fluorometric Imaging Plate Reader.

Results: A profound antifibrotic effect was observed in the bleomycin lung fibrosis model when IQGAP1-siRNA treatment was combined with CTGF-siRNA treatment. Partial reduction of fibrosis was detected with treatment by either of these two siRNA’s alone. Western blot results showed that IQGAP1-siRNA decreased the expression of IQGAP1 by 70% and had no effect on CTGF expression. However, CTGF-siRNA reduced the expression of CTGF by 80% and IQGAP1 by 40%. A similar trend of reduction in fibrosis was observed in IQGAP1 knockout mice. Decreased collagen expression was detected by Masson’s trichrome stain and by Sircol Collagen Assay. Immunofluorescence staining of IQGAP1 and F-actin on human SSc lung fibroblasts demonstrated that IQGAP1 co-localizes with globular actin but not with filamentous stress fiber actin, indicating a crucial role of IQGAP1 in actin rearrangement. The actin polymerization assay demonstrated that the rate of actin polymerization is IQGAP1 dependent.

Conclusion: IQGAP1 forms a signal transduction complex with CTGF in lung fibroblasts, regulates the expression of α-SMA, and promotes pulmonary fibrosis. Inhibition of IQGAP1 has a marked antifibrotic effect in a bleomycin model of pulmonary fibrosis and should be considered as a potential new therapeutic target for the treatment of SSc-ILD.
763 Caveolin-1 and Peroxisome Proliferator-Activated Receptor Gamma Co-Regulate the Differentiation of Monocytes to Adipocytes and Myofibroblasts in Vivo and In Vitro. Rebecca Lee¹, Charles Reese¹, Michael Bonner¹, Beth Perry², Richard M. Silver², Richard P. Visconti¹, Stanley Hoffman¹ and Elena Tourkina¹. ¹Medical University of South Carolina, Charleston, SC, ²Medical University of South Carolina, Charleston, USA, 3Charleston, SC.

Background/Purpose: Skin fibrosis in scleroderma is associated with the loss of subcutaneous adipose tissue (lipodystrophy). The mechanisms underlying lipodystrophy and its relationship to fibrosis are not known. Monocytes are precursors of several cell types including myofibroblasts and adipocytes. We recently showed that this myofibroblast differentiation is inhibited by the master regulatory protein caveolin-1. Similarly, caveolin-1-deficient mice are lean with small adipocytes. The nuclear receptor PPARγ also regulates adipose differentiation and lipid homeostasis. Here we examine the coordinate roles of caveolin-1 and PPARγ in adipogenesis and fibrosis.

Methods: Mini-osmotic pumps are implanted into 10-week-old CD1 male mice. The pump delivers 100 U/kg bleomycin or saline and is removed on day 10. Mice are injected i.p. daily with 100 µl caveolin-1 scaffolding domain peptide (CSD, final concentration 0.1 mM) or phosphate-buffered saline (PBS) vehicle over the entire course of the experiment and sacrificed on day 28. Cutaneous fibrosis and lipodystrophy are analyzed histologically and immunohistochemically. Monocytes are obtained from scleroderma patients and healthy controls. Monocyte differentiation to adipocytes and myofibroblasts is evaluated using Oil red O stain and ASMA stain. PPARγ and caveolin-1 expression are determined by Western blot and immunohistochemistry.

Results: We previously observed a loss of subcutaneous adipose tissue coconutmit with dermal fibrosis in bleomycin treated mice, both of which were blocked by CSD. We now show that levels of caveolin-1 and PPARγ are reduced in adipocytes of SSc patients and bleomycin-treated mice. CSD significantly enhances the expression of PPARγ and FABP4 in adipocytes in bleomycin-treated mice. Low levels of PPARγ are observed in monocytes from SSc patients and are increased by CSD treatment. PPARγ ligand triligonide (TRL2) and CSD inhibit, and TGFβ promotes human monocyte differentiation to myofibroblasts. Conversely, these treatments have the opposite effects on monocyte differentiation into adipocytes. These treatments affected PPARγ signaling through their effects on PPARγ levels and localization.

Conclusion: The present studies demonstrate the importance of both caveolin-1 and PPARγ in the regulation of adipogenesis in fibrotic skin. These studies further validate CSD as a novel therapy for both fibrotic disease and healthy controls. Monocyte differentiation to adipocytes and myofibroblasts were blocked by CSD. We now show that levels of caveolin-1 and PPARγ in adipogenesis and fibrosis.

Disclosure: R. Lee, None; C. Reese, None; M. Bonner, None; B. Perry, None; R. M. Silver, None; R. P. Visconti, None; S. Hoffman, None; E. Tourkina, None.

764 ERG and FLI1 in Systemic Sclerosis-Associated Pulmonary Complications. Rong Han and Maria Trojanowska. Boston University, Boston, MA, 2NIH, Bethesda, MD, 3Baylor College of Medicine, Houston, TX, 4University of Texas Health Science Center at Houston, Houston, TX, 5Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease and several genetic loci increasing SSc susceptibility have been identified with small to modest effect sizes. We hypothesize that genetic epistasis along with rare variants and gene-environment interaction may explain the missing heritability. In this study, we test two seemingly distinct loci, rs2004640 on IRF5 and rs2736340 on BLK both of which have previously been associated with SSc, for genetic epistasis.

Methods: In this study, we combined genetic data from rs2004640 variant on IRF5 and rs2736340 variant on BLK from 1024 patients with SSc and 694 unrelated healthy controls from University of Texas and a Spanish case-control series of 395 SSc patients and 443 healthy controls. Odds ratios (OR) and biologic interactions as departures from additivity or multiplicity were analyzed by logistic regression. To quantify the amount of interaction in terms of departure from additivity of effects, the relative excess risk due to interaction (RERI), proportion attributable to interaction (AP), and the synergy index (S) were calculated. Interaction between the two SNPs was evaluated using the cross-product of the risk factors in a logistic-regression model as interaction criteria (multiplicative interaction). We adjusted for gender and cohort in the analyses. Recoding of IRF5, BLK genotypes from protective effects to risk effects were done to produce the meaningful measures for departures of additivity. Statistical analyses were performed using SAS 9.3. Gene expression array of PBMCs from PAXgene tubes were analyzed with BRB-ArrayTools.

Results: Both IRF5:rs2004640 and BLK: rs2736340 variants show independent association with SSc. The OR of single effects was 1.40 for IRF5:rs2004640 and 1.44 for BLK: rs2736340 (Table 1). We observed a significant multiplicative interaction between IRF5 GT/TT & BLK CT/TT genotypes as compared to IRF5 GG & BLK CC genotypes (p=0.02). The OR of joint effects for IRF5 GT/TT & BLK CT/TT genotypes was higher than the wildtype genotype (P=0.0003, OR = 2.26, 95%CI 1.7-3.1). RERI<0, AP<0, and S<1 mean negative interaction and less than additivity. P value of S is significant, but 95% CI includes 1.

PBMC RNA gene expression arrays predicted more T & B cell pathways in SSc as compared to controls for IRF5 GT/TT & BLK CT/TT genotypes and PPAR-γ and WNT signaling pathways in SSc as compared to controls for IRF5 GG & BLK CC genotypes.

Conclusion: In an effort to explore genetic epistasis we demonstrate genetic interaction using multiple methodologies between two well-replicated and distinct loci on IRF5 and BLK. We also observed differences in the gene expression pathways based on the IRF5 and BLK genotypes. Additional studies are needed to test them in other autoimmune diseases and discern their role at a molecular level.
chromatin immunoprecipitation in MDMECs
quantitative reverse transcription-PCR
determined by immunohistochemistry
Fli1 ECKO mice with a punch biopsy. Vascular structure was visualized by

OR of joint effect
IRF5 GGU/BLK CC
123/164
1
IRF5 GT, TT/BLK CC
599/506
1.74 (1.3–2.3)
IRF5 GGU/BLK CT, TT
134/90
2.16 (1.5–3.2)
IRF5 GT, TT/BLK CT, TT
563/377
2.26 (1.7–3.1)
Additivity
AP
P = 0.14
–0.28 (–0.7–0.09)
REI
P = 0.21
–0.64 (–1.7–0.4)
S
P = 0.005
0.66 (0.2–1.2)
Multiplicity
P = 0.02

IRF5 GGU/BLK CC Ssc v Controls
Top 10 Pathways (p<0.01)
Multi-step Regulation of Transcription by Pitx2
Proepithelin Conversion to Epithelin and Wound Repair Control
Control of Gene Expression by Vitamin D Receptor
T Cell Receptor Signaling Pathway
Role of MEF2D in T-cell Apoptosis
HIV induced T Cell Apoptosis
Role of PPAR-gamma Coactivators in Obesity and Thermogenesis
IFN gamma signaling pathway
Mechanism of Gene Regulation by Peroxisome Proliferators via PPARa (alpha)
Selective expression of chemokine receptors during T-cell polarization
Pertussis toxin-insensitive CCR5 Signaling in Macrophage
Antigen Dependent B Cell Activation
WNT Signaling Pathway
IL-10 Anti-inflammatory Signaling Pathway
METS affect on Macrophage Differentiation
TNFR2 Signaling Pathway
ADP-Ribosylation Factor
Lck and Fyn tyrosine kinases in initiation of TCR Activation

IRF5 GGU/TT & BLK C/T
Ssc v Controls
Top 10 Pathways (p<0.01)

OR of single effect
IRF5 GG
257/254
1
IRF5 GGU/TT
1162/883
1.40 (1.1–1.7)
BLK CC
722/670
1
BLK C/C/C
697/497
1.44 (1.2–1.7)

Table 1.

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Additivity

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Background/Purpose: Systemic sclerosis (SSc) remains unclear. Alterations in adaptive and innate immune responses, with increased T-cells that produce type 2 cytokines and impaired responsiveness to Toll-like receptors, have been reported in patients with SSc. Dendritic cells (DC) that participate in both innate and adaptive immunity are increasingly being investigated in the pathogenesis and immune intervention in various auto-immune diseases and other immune-mediated conditions. Little is known about the alterations and role of DC in SSc. Our goal in this study is to investigate alterations of DC subsets and their roles in the pathogenesis of SSc.

Methods: In order to investigate the time kinetics of DC alterations in the affected and lymphoid organs and to manipulate DCs in vivo, we used the bleomycin-induced mouse model where the exact timing of pathogenic insult is known. Although, the bleomycin or any of the currently available animal models do not reproduce all aspects of human SSc, bleomycin-induced dermal and pulmonary fibrosis mimics human SSc in many ways. C57BL/6 mice were injected with bleomycin or PBS for 2 weeks, and cells isolated from lung tissue or lavage, skin, lymph nodes, spleen and bone marrow were analyzed for various immune cell types including DC subsets namely myeloid DC (mDC) and plasmacytoid DC (pDC). To directly determine the role of pDC, these cells were depleted using an anti-PDCA1 antibody (Miltenyi Biotec) or an IgG isotype control antibody. Animals were euthanized 2 weeks after treatment. Disease was assessed by clinical and histological scoring.

Results: Both DC subsets were increased in the lungs of bleomycin-injected mice, with a more profound increase in pDCs that were significantly elevated in the lungs (p<0.008), skin (p<0.04), and their associated draining lymph nodes in bleomycin-injected mice compared to PBS controls. Neither DC subsets differed in the spleen of bleomycin-injected mice when compared to controls. Treatment with anti-PDCA1 antibody significantly reduced pDC numbers in the spleen and lung by two-fold as compared to animals injected with an isotype control antibody. pDC-depleted mice had a significant improvement in combined clinical disease severity score (p<0.001) and histopathology (p<0.009), along with a reduction in cellular infiltrates comprising of B-cells, T-cells, NK and NK-T cell as compared to control mice. qPCR array analysis of lung tissue for molecules potentially involved in DC function and recruitment of immune cells in the lungs revealed overexpression of multiple chemokine receptors including CCL2, CCL4, and CCL19, and differentially expressed genes that are involved in DC recruitment and activation.

Conclusion: A more profound accumulation of pDCs, as compared to the other major DC subset, in the affected organs and their draining lymph nodes, but less so in the lymphoid organs, of bleomycin-injected mice suggests a possible role of pDC in SSc process. Indeed, antibody depletion of pDC reduces skin and lung fibrosis in the bleomycin model. A significant reduction in several immune cell types in pDC-depleted mice suggests a major pathogenic role of pDC in inflammatory/fibrosis process.

Disclosure: S. Kajafa, None; I. Valera, None; A. Divekar, None; D. E. Fürst, Abbott, Actelion, Amgen, BMS, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/ Genentech, UCB. 5. R. Singh, None.
Transforming Growth Factor Beta Induces anti Angio and Vasculo-Genesis Phenotype in Dermal Fibroblasts through Secretion of Pigment Epithelium Derived Factor. Vasiliaki Liakou1, Margherita Scaria1, Giuseppina Abignano2, Emma C. Derrett-Smith3, Justin Gillespie4, Paola Ciprani5, Paul Emery6, Christopher P. Denton7, R Giovanetti8, Georgia Mauria9, Francesca Del Gallo9. 1Leeds Institute of Rheumatology and Musculoskeletal Medicine and Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L’Aquila, Leeds, United Kingdom, 2Signal Transduction and Angiogenesis group, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK, Leeds, United Kingdom, 3Leeds Institute of Rhetmatic and Musculoskeletal Medicine and Department of Biotechnological and LTHI Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, 4UCL Medical School Royal Free Campus, London, United Kingdom, 5Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom, 6Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L’Aquila, L’Aquila, Italy, 7NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, 8Università degli Studi dell’Aquila, L’Aquila, Italy, 9Leeds Institute of Rhetmatic and Musculoskeletal Medicine. University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune dis-order characterized by tissue fibrosis and vasculopathy. A proteomic analysis of the human skin fibroblasts from both SSc patients and controls revealed increased protein levels of Pigment Epithelium Derived Factor (PEDF), which is the maajor endogenous inhibitor of intraocular angiogenesis. Here we aimed to validate the findings in vitro and in vivo and determine whether PEDF could be involved in SSc vasculopathy.

Methods: PEDF expression was investigated in the skin and FBs of 4 early diffuse SSc patients and 4 healthy controls (HC) by immunohistochemistry (IHC), qRT-PCR and flowcytometry. Functional effects of PEDF on angiogenesis vasculogenesis were examined by Matrigel assays and CD31 IHC on organotypic (IHC), qRT-PCR and flowcytometry. Functional effects of PEDF on angio/diffuse (IHC), qRT-PCR and flowcytometry. Functional effects of PEDF on angio/diffuse SSc patients and 4 healthy controls (HC) by immunohistochemistry.

Results: Recombinant human PEDF inhibited tubulogenesis in vitro. SSc- FBs exhibited a reduction of scarring, and a significant reduction of collagen content in comparison to bleomycin treated SSc-FBs alone showed a significant reduction in ECM (collagen and fibronectin), secreted (CTGF and IGFBP-3), and intracellular (α-SMA) pro-fibrotic markers. MMS-350 decreased these markers when added at the same time and when added up to 6 hours after TGF-β. One analog that differed from MMS-350 in the replacement of an oxetanyl methylene side chain with a phenyl ring, KRL07-031, showed a decrease in ECM and pro-fibrotic factors at concentrations 10-fold lower than the parent compound. Both the survival and mouse weight improved in the MMS-350 treated mice. Collagen 1A2 mRNA levels were significantly reduced in MMS-350 treated mice. H&E staining of lung tissue from mice treated with bleomycin and MMS-350 exhibited a reduction of scarring, and a significant reduction of collagen content in comparison to bleomycin treated mice.

Conclusion: The results in this study show that MMS-350 is an anti-fibrotic agent and are consistent with recent data demonstrating the ability of MMS-350 to reduce fibrosis in thoracic irradiated C57BL/6N mice in vivo. MMS-350 significantly reduced pro-fibrotic factors and ECM proteins both in vitro and in vivo. A lipophilic analog of the MMS-350, KRL07-031, exhibited similar anti-fibrotic effect albeit at lower concentrations. Even though MMS-350 was effective at reducing pulmonary fibrosis induced by different triggers and that it is orally available make it an attractive lead candidate for the development of a therapy for organ fibrosis.

Disclosure: L. Mlakar, None; T. Takihara, None; M. Sprachman, None; P. Wipf, None; C. Feghali-Bostwick, None.

Detection of Proteins in Lung Tissues of Patients with Systemic Sclerosis: A Comparative Study Using Microarrays. Frank Schneider1 and Carol A. Feghali-Bostwick2. 1University of Pittsburgh, Pittsburgh, PA, 2Medical University of South Carolina, Charleston, SC.

Background/Purpose: Research on systemic sclerosis (SSc)-associated interstitial lung disease (ILD) has been hindered by the paucity of lung tissues, as SSc patients with lung involvement are not routinely biopsied. To gain further insights into the pathogenesis of lung fibrosis in SSc, we used lung tissue microarrays (TMAs) for the detection of 4 proteins of interest in SSc-associated ILD and idiopathic pulmonary fibrosis (IPF).

Methods: Lung tissues were obtained from the explanted lungs of patients undergoing lung transplantation. Normal lung tissues were obtained from controls. H&E sections were used for the selection of suitable regions. The remaining cores were used for the extraction of tissue microarrays (TMAs) for the detection of 4 proteins of interest in SSc-associated ILD and idiopathic pulmonary fibrosis.

Results: TTF-1, thrombomodulin, laminin, and Smaa4 were detected in all cores on the TMA slide. The distribution of the proteins differed in normal lungs compared to fibrotic lungs since the two subepithelial layers in normal lungs are closely apposed in the absence of fibrosis. We observed subtle differences in distribution and levels of protein expression between SSc and IPF: TTF-1 expression appeared reduced in areas of fibrosis and inflammation.
in both diseases. Thrombomodulin staining of airway basal cells was weaker and patchier in SSC than IPF. Laminin expression was reduced in areas of fibrosis in both SSC and IPF, but IPF lungs showed stronger laminin staining around vessels compared to SSC lungs. Nuclear Smad4 expression was more prominent and more widespread in perivascular smooth muscle cells of SSC than IPF lungs.

**Conclusion:** Lung TAMs are useful to simultaneously compare localization and expression levels of proteins in lung tissues from multiple patients and controls. Our initial IHC findings suggest that differences exist in the distribution and levels of TGF-β1, thrombomodulin, laminin, and Smad4, and such differences can be identified using TAMs.

**Disclosure:** F. Schneider, None; C. A. Feghali-Bostwick, None.

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**Development of a Bifluorescent Lineage Tracker Reporter Mouse Strain to Analyze the Phenotypic Conversion of Endothelial Cells into Myofibroblasts in Vivo. Application to Study the Synergistic Effects of Endothelin-1 on TGF-β1-Induced Endothelial-to-Mesenchymal Transition.** Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Sceloderma Center, Thomas Jefferson University, Philadelphia, PA.

**Background/Purpose:** Endothelial-to-mesenchymal transition (EndoMT) may be a crucial pathway in generating activated myofibroblasts, cells that play a pivotal role in the development of tissue and organ fibrosis in diseases such as Systemic Sclerosis (SSCs). It has been previously demonstrated that endothelin 1 (ET-1) synergistically enhances TGF-β-induced EndoMT in vitro in murine lung endothelial cells (ECs). The purpose of this study was to develop a mouse model expressing a green distinct fluorescent label in ECs (green fluorescent protein; GFP) and a red fluorescent label in fibroblasts (mCherry protein) to allow monitoring of EndoMT in vivo.

**Methods:** Homozygous Tie2GFP transgenic mice expressing GFP under control of the EC specific Tie2 promoter (Tie2GFP mice) were crossed with homozygous mice expressing a doxycycline inducible red fluorescent mCherry protein in mesenchymal cells and fibroblasts under control of the Collal promoter (Col1mCherry mice) to generate heterozygous bifluorescent Tie2GFP-Col1mCherry mice. At 4 weeks of age, osmotic pumps containing either saline, 2.5 μg TGF-β, or 2.5 μg TGF-β+5.0 μg ET-1 were implanted subcutaneously in the right intrascapular region of the mice (2 mice per treatment group). The pumps deliver their contents at a rate of 0.5 μl/h over a 2 week period. Mice received IP injections of 1 mg/kg doxycycline every other day starting at 2 weeks post-implantation of the pump and were sacrificed one week later. Both lungs and two skin samples, one at the pump dispersal site and one opposite to the pump site, were isolated. A portion of each tissue was fixed in formalin and processed for histopathologic analysis (hematoxylin/eosin and Masson’s trichrome stains) whereas another portion of each tissue was fixed in formalin and processed for histopathologic analysis. The eight SSC patients included five individuals that mapped to the inflammatory subset and three from the fibroproliferative subset.

**Results:** Histopathology studies in samples from TGF-β-treated mice showed mononuclear cell infiltration and peribronchial fibrosis and diffuse interstitial fibrosis in lungs. Dermal fibrosis was present in both samples of skin. ET-1 synergistically enhanced the severity of fibrosis in all three tissues. Hydroxyproline levels in skin taken from the site of the osmotic pump demonstrated a 61% increase in response to TGF-β alone and a 113% increase (~2.2 fold) in response to TGF-β+ET-1 whereas skin from the opposite side of the back displayed a 29% increase in response to TGF-β alone and a 102% increase (~2 fold) in response to TGF-β+ET-1. In the lung, TGF-β increased hydroxyproline levels by 38% and TGF-β+ET-1 increased hydroxyproline levels by 75%.

**Conclusion:** Tie2GFP-Col1mCherry mice represent a valuable resource for monitoring EndoMT in vivo. ET-1 plays an important in vivo role in regulating EndoMT by causing a synergistic potentiation of TGF-β-induced EndoMT. Since ET-1 plays a crucial role in the pathogenesis of SSC-associated pulmonary arterial hypertension and may play a profibrotic role in skin and lung fibrosis, the results described here identify a novel mechanism supporting the concept that ET-1 plays a key pathogenic role in vivo in SSC-associated tissue fibrosis.

**Disclosure:** P. J. Wermuth, None; S. A. Jimenez, None.

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**RNA-Seq and Mir-Seq Analysis of SSC Skin Across Intrinsic Gene Expression Subsets Shows Differential Expression of Non-Coding RNAs Regulating SSC Gene Expression.** Zhenghui Li1, Eleen Marmarelis1, Kun Q2, Lionel Brooks3, Patricia Pioli4, Howard Chang5, Robert Lafyatis3 and Gabriela Riemekasten5. 1Geisel School of Medicine at Dartmouth, Hanover, NH, 2Stanford University School of Medicine, Stanford, CA, 3Boston University, Boston, MA.

**Background/Purpose:** Systemic sclerosis (SSc) is an autoimmune disease with a heterogenous and complex phenotype. Previously, our lab has identified four gene expression subsets (fibroproliferative, inflammatory, limited and normal-like) among SSC patients by their gene expression in skin using DNA microarrays. We have extended these findings by using RNA-Seq in a subset of SSC skin biopsies to detect mRNA levels, splice variants, novel non-coding RNAs, and coding region SNPs in a lower background signal over microarray.

**Methods:** We performed RNA-Seq on eight SSC patients and four healthy controls and skin biopsies. The eight SSC patients included five individuals that mapped to the inflammatory subset and three from the fibroproliferative subset. We sequenced the small and large RNA fraction extracted from each biopsy by Illumina Solexa sequencing. We obtained 90–100 million 50 bp paired-end reads for the mRNA fraction and 25 – 50 million 36 bp reads for the miRNA fraction.

**Results:** Our analyses reveal significant (p<0.05) gene expression differences between healthy controls and SSC patients, as well as between intrinsic subsets. Specifically, we found >1000 genes are significantly expressed in the inflammatory and the fibroproliferative subsets of patients. Many of the significant genes are involved in cellular proliferation or immune responses, consistent with results found by DNA microarray hybridization. We did not observe any significant differential splicing between the healthy controls and the SSC patients. We identified 228 novel long non-coding RNAs (lncRNAs) that are significantly differentially expressed in the inflammatory subset and fibroproliferative subsets. The lncRNAs differentially expressed in the inflammatory subset map to Gene Ontology terms including inflammatory response, immune response, response to wounding, and defense response and those in the fibroproliferative group map to cell cycle, M phase, and RNA metabolism.

**Conclusion:** To summarize, we conducted the first comprehensive RNA-Seq study in SSC skin and identified differentially expressed non-coding RNAs genome-wide. Our findings show that a complex network of regulatory factors controls the disease specific gene expression subsets in SSC skin.

**Disclosure:** Z. Li, None; E. Marmarelis, None; K. Qu, None; L. Brooks, None; P. Pioli, None; H. Chang, None; R. Lafyatis, None; M. Whitfield, Celdara, LLC, 9.

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**Functional Autoantibodies from Patients with Systemic Sclerosis Reactive to Angiotensin II Type 1 and Endothelin-1 Type A Receptor Induce Inflammatory Lymphocyte Infiltration into Lungs of Mice.** Angela Kili1, Clement Braesch2, Anja Kühl1, Jeannine Guenther3, Mike O. Becker1, Gerd Burmester1, Thomas Walther4 and Gabriela Riemekasten2. 1Charité University Hospital, German Rheumatism Research Center, a Leibniz Institute, Berlin, Germany, 2Charité University Hospital, Berlin, Germany, 3Charité University Medicine, Berlin, Germany, 4University College Cork, Cork, Ireland, 5Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany.

**Background/Purpose:** Functional autoantibodies reactive to the angiotensin II type 1 receptor (AT1R) and endothelin 1 type A receptor (ETAR) were found in increased levels in systemic sclerosis (SSc) patients, with clinical connections to lung involvement. Functional effects on T-lymphocyte migration were studied previously in vitro and first in vivo experiments on C57BL/6 mice demonstrated agonistic effects on lung architecture. Here, functional effects of anti-AT1R and
anti-ETAR autoantibodies on inflammatory cell infiltration into lungs of mice deficient for the AT receptor and on their respective WT mice (129 × C57BL/6), were studied for the first time.

Methods: Female mice deficient for AT1a, AT1b, and AT2 receptor (ATR −/−, 129 × C57BL/6, n=5 per group) and WT controls (129 × C57BL/6, n=4 per group) were treated with SSc-IgG with elevated levels of anti-AT, R and anti-ET, R autoantibodies. In control experiments same groups were treated with healthy donor IgG (NC-IgG). IgG samples were transferred into ATR −/− and into WT groups five times over three months. Lungs were examined using histological staining and an index-system was developed to assess CD3+ T-lymphocyte infiltration around vessels. Samples were analysed in a blinded fashion using imageJ software.

Results: Mice of the ATR −/− and WT group treated with SSc-IgG showed a dramatically decreased survival in both groups, with worst survival rate in the ATR −/− group. Groups with the control treatment NC-IgG showed a better survival compared to SSc-IgG, with a slightly lower survival rate in ATR −/− group, than in the WT group. Histological analyses of lungs revealed a statistically higher T-lymphocyte infiltration in both groups with SSc-IgG than with NC-IgG. Furthermore, ATR −/− group with SSc-IgG showed a statistically higher infiltration rate than WT group with SSc-IgG.

Conclusion: These preliminary experiments demonstrate a dramatic survival reduction by treatment with SSc-IgG containing anti-AT,R and anti-ET,R autoantibodies (SSc-IgG) in both groups, ATR −/− and WT. Moreover, a major inflammation in ATR −/− and in WT mice was induced by SSc-IgG, reflected by T-lymphocyte infiltration into lung tissue. Increased inflammation in ATR −/− vs. WT group by SSc-IgG, suggests a possible ETAR-mediated inflammation in ATR −/− mice. Anti-AT,R and anti-ET,R autoantibodies react presumably in a cross-reactive way and mice deficient for angiotensin-receptors could therefore enable detailed studies of ETAR-mediated effects, providing thereby a deeper understanding of involved mechanisms. Moreover, the data demonstrate the recruitment and activation of immune cells by autoantibodies and could as a result offer deeper insight into autoantibody-mediated T-lymphocyte recruitment and reveal potential therapeutic targets for treatment of SSc.

Disclosure: A. Kill, Actelion Pharmaceuticals US, 2; C. Brasseh, None; A. Kühl, None; J. Guenther, None; M. O. Becker, None; G. Burmester, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5, AbbVie, BMS, Pfizer, Merck, UCB, Roche, 8; T. Walther, None; G. Riemekasten, Actelion Pharmaceuticals US, 2; CellTrend, 5.

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Endothelin-1 Synergistically Increases TGF-β-Induced Hif1α Expression Under Normoxic Conditions during Endothelial-to-Mesenchymal Transition in Murine Endothelial Cells. A Novel Mechanism for the Fibrogenic Effects of Endothelin.

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Background/Purpose: Tissue hypoxia is a consequence of vascular damage and Hif-1α accumulation is a major mechanism of hypoxia response pathways. HIF-1α induces the transcriptional upregulation of expression of numerous genes encoding proteins involved in vascular repair including soluble growth factors (TGF-β and VEGF), and extracellular matrix components (type I collagen and fibronectin), rendering HIF-1α as a positive regulator of wound healing and a potential mediator of organ repair and tissue fibrosis, suggesting that HIF1-α may play an important role in the pathogenesis of fibrotic diseases such as Systemic Sclerosis (SSc). Recent studies have shown that TGF-β causes a potent increase in HIF-1α protein levels. Since endothelin 1 (ET-1) synergistically enhances TGF-β mediated endothelial-to-mesenchymal transition (EndoMT), we examined the transcriptional regulation of Hif-1α and of several of its downstream targets in response to TGF-β alone or TGF-β in combination with ET-1 in cultured murine lung microvascular endothelial cells (MVEC).

Methods: Murine pulmonary MVEC were isolated from C57Bl/6 mice employing trypsin/collagenase tissue digestion followed by sequential immunomagnetic selection with anti-CD31 and anti-CD102 antibodies. The purified EC were treated in monolayer cultures with ET-1 (100 ng/mL) in the presence and absence of TGF-β1 (10 ng/mL) and the induction of Hif-1α as well as several Hif-1α targets including lysi1 oxidase (Lox), Lox-like 1 protein (Loxl1), Loxl2, Loxl3, and Loxl4 was assessed employing semi-quantitative RT-PCR.

Results: Exposure of murine pulmonary MVEC to ET-1 induced a three-fold increase in Hif-1α levels compared to non-treated controls. TGF-β1, however, induced a nearly 500-fold increase in expression whereas samples treated with TGF-β1 plus ET-1 increased Hif-1α transcript levels nearly 2500-fold compared to the saline control. This profound synergistic increase was abrogated by the dual ET-1 receptor antagonist, Bosentan, demonstrating that the observed effect was indeed mediated by ET-1. Similarly, TGF-β alone induced significant increases in the expression of Hif-1α target genes Lox, Loxl1, Loxl2, Loxl3 and Loxl4. ET-1 alone did not alter the expression of these genes whereas ET-1 in combination with TGF-β synergistically increased their levels. Bosentan abrogated the increased expression levels of these genes observed for TGF-β plus ET-1, indicating that the synergistic increases were mediated by ET-1.

Conclusion: TGF-β potently increased Hif-1α and Hif-1α target gene expression in murine pulmonary MVEC under normoxic conditions. ET-1 synergistically enhanced these effects. Since vascular damage plays a crucial role in SSc-associated pulmonary arterial hypertension pathogenesis and participates in the development of skin and lung fibrosis, the results described here identify ET-1 as a potentially key regulator of TGF-β-mediated activation of Hif-1α in response to vascular damage causing a synergistic enhancement of Hif-1α-mediated profibrotic effects suggesting that this process may play a key pathogenic role in SSc-associated tissue fibrosis and fibroproliferative vasculopathy.

Disclosure: P. J. Wermuth, None; S. A. Jimenez, None.
Conclusion: This meta-analysis confirms HLA-DRBI*04 as a GCA susceptibility allele but fails to show a susceptibility effect of HLA-DRBI*01, despite sharing amino acids in common in the third hypervariable region. Variations in population frequency of HLA-DRBI*04 might help explain worldwide variations in GCA incidence; latitude appears to make an independent contribution to GCA risk.

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A Candidate Gene Approach Identifies IL33 as a Novel Genetic Risk Factor for GCA. Ana Márquez1, Roser Solans2, José Hernández-Rodríguez3, Maria C. Cid4, Santos Castañeda5, Marc Ramentol6, Luis Rodríguez-Rodríguez7, Javier Navráez8, Ricardo Blanco9, Norberto Ortego-Centeno10, Øyvind Palm11, Andreas P. Diamantopoulos12, Niko Braun13, Frank Moosig14, Torsten Witte15, Lorenzo Beretta16, Claudio Lunardi16, Marco A. Cimmino17, Augusto Vaglio15, Carlo Salvareani15, Miguel A. Gonzalez-Gay18 and Javier Martin19.1 Instituto de Parasitología y Biomedicina López-Neyra (IPBLN-CSIC) and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, 2Hospital Vall d’Hebron, Autonomous University of Barcelona, Barcelona, Spain, 3Hospital Clinic University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, 4Department of Rheumatology, Hospital de la Princesa, IIS-Princesa, Madrid, Spain, 5Department of Internal Medicine, Hospital Vall d’Hebron, Barcelona, Spain, 6Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, 7Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain, 8Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain, 9Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, 10Oslo University Hospital and University of Oslo, Oslo, Norway, 11Hospital of Southern Norway Trust, Kristiansand, Norway, 12Department of Internal Medicine, Division of Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany, 13Department of Clinical Immunology and Rheumatology, University of Luebeck, Bad Bramstedt, Germany, 14Hannover Medical School, Hannover, Germany, 15Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, 16University degli Studi di Verona, Verona, Italy, 17Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, 18University Hospital of Parma, Parma, Italy, 19Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy, 20Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain, 21Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: IL-33, through binding to its receptor ST2 (suppression of tumorigenicity 2), encoded by the interleukin 1 receptor-like 1 (IL1RL1) gene, activates mast cells and Th2 lymphocytes. Additionally, IL-33 acts as an activator of endothelial cells promoting angiogenesis and vascular permeability. Different studies have supported a pathogenic role of IL-33 axis in autoimmunity. Interestingly, an increased expression of this cytokine and its receptor has been detected in the inflamed arteries of GCA patients, mainly in endothelial cells of newly formed vessels, thus suggesting a possible role of IL-33 in the angiogenesis-dependent inflammation in GCA. The aim of the present study was to investigate for the first time the potential influence of the IL33 and IL1RL1 loci on GCA predisposition.

Methods: A total of 1,363 biopsy-proven GCA patients and 3,908 healthy controls from four European case/control sets (Spanish cohort: 894 cases and 2,047 controls, German cohort: 103 cases and 444 controls, Italian cohort: 255 cases and 1,141 controls, and Norwegian cohort: 111 cases and 276 controls) were combined in a meta-analysis. Six genetic variants: rs3939286, rs7025417 and rs7044343, within the IL33 gene, and rs2058660, rs2310173 and rs13015714, within the IL1RL1 gene, previously associated with autoimmunity, were genotyped using predesigned TaqMan® assays.

Results: A consistent association between the rs7025417 polymorphism and GCA was evident in the overall meta-analysis, under both allele (P=0.041, OR=0.88, CI 95% 0.78–0.99) and recessive (P=0.34, OR=0.80) models. No statistically significant differences between allele or genotype frequencies for the other IL33 and IL1RL1 genetic variants were detected in this pooled analysis.

Conclusion: Our results clearly evidenced the implication of the IL33 locus in the genetic network underlying GCA. This study, together with previous findings, supports an important role of this cytokine in the inflammatory process occurring in GCA.

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Influence of the IL17A Locus in Giant Cell Arteritis Susceptibility. Javier Martin1, Ana Márquez2, José Hernández-Rodríguez3, Maria C. Cid4, Roser Solans5, Santos Castañeda6, Inmaculada C. Morado7, Javier Navráez8, Victor M. Martinez-Taboada9, Norberto Ortego-Centeno10, Bernardo Sopeta11, Jordi Monfort12, Maria Jesús García-Villanueva13, Luis Caminal-Montero14, Eugenio De Miguel15, Ricardo Blanco16, Øyvind Palm11, Øyvind Mølberg16, Joerg Latus17, Niko Braun18, Frank Moosig19, Torsten Witte15, Lorenzo Beretta21, Alessandro Santaniello22, Giulia Pazzola23, Luigi Boiardì24, Claudio Lunardi16 and Miguel A. Gonzalez-Gay25.1 Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, 2Instituto de Parasitología y Biomedicina López-Neyra (IPBLN-CSIC) and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, 3Hospital Vall d’Hebron, Autonomous University of Barcelona, Barcelona, Spain, 4Hospital Clinic University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, 5Department of Rheumatology, Hospital de la Princesa, IIS-Princesa, Madrid, Spain, 6Department of Clinical Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, 7Hospital Clinic University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, 8Hospital Vall d’Hebron, Autonomous University of Barcelona, Barcelona, Spain, 9Department of Rheumatology, Hospital de la Princesa, IIS-Princesa, Madrid, Spain, 10Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain, 11Hospital Clínico San Cecilio, Granada, Spain, 12Hospital Clinic University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, 13Department of Internal Medicine, Hospital Vall d’Hebron, Autonomous University of Barcelona, Barcelona, Spain, 14Hospital Clínico San Carlos, Madrid, Spain, 15Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain, 16Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, 17Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain.
Background/Purpose: A recent study has showed that the number of Th17 lymphocytes is significantly increased in patients with GCA, resulting in an imbalance between Th17 and regulatory T cells. In addition, an increased expression of IL-17A, a Th17 cytokine leading to pro-inflammatory responses, has been detected in temporal artery samples from GCA patients. Considering the proposed crucial role of Th17 cells in this vasculitis, we aimed to assess whether polymorphisms at the IL17A gene are involved in the genetic predisposition to GCA and its main clinical subgroups.

Methods: We carried out a large meta-analysis including a total of 1,266 biopsy-proven GCA patients and 3,779 healthy controls from four European populations (Spanish cohort: 931 cases and 1,845 controls). Five SNPs, which tag over 86% of the variability of this locus, were genotyped using TaqMan® assays. Allelic combination and dependency tests were also performed.

Results: In the pooled analysis, two of the five analyzed polymorphisms showed evidence of association with GCA (rs2275913: OR=1.85 [1.06–1.29]; rs7747909: OR=1.17 [1.06–1.29]; rs7747909: P MH=8.49\times10^{-3}). An independent effect of rs2275913 and rs7747909 was evident by conditional regression analysis. In addition, the haplotype harboring the risk alleles better explained the observed association than the polymorphisms independently (likelihood P-value,<10^{-10}).

Conclusion: Our study provides clear evidence of the role of IL17A as a novel genetic risk locus for GCA, thus contributing to the advance in the knowledge of the genetic network underlying this vasculitis susceptibility.

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PTPN22 rs2476601 and Susceptibility to Biopsy Proven Giant Cell Arteritis (GCA) in an Australian Sample. Susan Lester¹, Alex Hewitt², Linda Bradbury³, Elisabeth De Smidt⁴, Andrew Harrison⁴, Graeme Jones⁴, Geoffrey O. Littlejohn⁵, Tony R. Merriman⁶, Bain Shenstone⁶, Malcolm D. Smith⁶,³⁷, Maureen Rischmueller¹, Matthew A. Brown¹² and Catherine L. Hill¹¹. ¹Queen Elizabeth Hospital, Woodville South, Australia, ²University of Western Australia, Perth, Australia, ³The University of Queensland, Brisbane, Australia, ⁴University of Melbourne, Melbourne, Australia, ⁵University of Otago, Wellington, New Zealand, ⁶University of Tasmania, HOBART, Australia, ⁷Monash Medical Center, Melbourne, Australia, ⁸University of Otago, Dunedin, New Zealand, ⁹Concord Hospital, Sydney, Australia, ¹⁰Repatriation General Hospital, Adelaide SA, Australia, ¹¹The Queen Elizabeth Hospital, SA, Australia, ¹²University of Queensland Diamantina Institute, Brisbane, Australia, ¹³University of Adelaide, Adelaide, Australia.

Background/Purpose: The aetiology and genetic background of GCA remains unclear, although genetic susceptibility is known to play a role. Recently, an association with the minor, loss of function, allele of PTPN22 rs2476601 (R620W), was reported in a Spanish cohort of biopsy-proven GCA (odds ratio = 1.62, 95% CI 1.29–2.04, p = 0.0001). Therefore, dysregulation of TCR signaling may be implicated in the pathogenesis of GCA. The aim of this study was to determine the association between the PTPN22 rs2476601 minor (A) allele and biopsy-proven GCA in an Australian cohort.

Methods: rs2476601 genotyping was performed by a Taqman assay (C_16201387_A, Applied Biosystems) in 209 GCA cases. Genotype data from 1407 healthy ethnically-matched unrelated postmenopausal women included in the Anglo-Australian Osteoporosis Genetics Consortium study of bone density variation were used as healthy controls. All GCA cases were temporal artery biopsy proven, and were recruited in Australia by the Arthritis Genomics Recruitment Initiative in Australasia (AGRIA). The mean age of GCA patients at diagnosis was 73 yrs (SE 8 yrs), with 68% female.

Results: The frequency of the A allele was 0.093 in GCA cases and 0.103 in the controls. Overall, there was no evidence of an association between GCA and controls (OR = 0.89, 95% CI 0.63, 1.27, p = 0.52). A random effects meta-analysis of replication datasets from Germany¹, Norway¹, UK¹, and Australia, included 769 GCA patients and 14,214 controls, did not reach statistical significance (OR 1.21, 95% CI 0.73, 2.00, p = 0.32). Similarly, a random effects meta-analysis which included the original Spanish dataset (1,392 GCA cases and 15,943 controls), also did not reach statistical significance (OR 1.31, 95% CI 0.90, 1.90, p = 0.11).

Conclusion: There was no statistically significant association between PTPN22 rs2476601 in this Australian GCA cohort. Nor does a meta-analysis of combined, available data reach statistical significance. However, an association with small effect size cannot yet be definitively excluded, and further studies may be required.

Background/Purpose: Activation of dendritic cells (DCs) is one of the earliest inciting events in Giant Cell Arteritis (GCA). TLR 2 is expressed on DCs in normal temporal arteries and is also found ubiquitously throughout the macrovasculature. 1 Stimulating temporal arteries implanted into SCID mice with TLR2-activated dendritic cells. 2 Therefore TLR 2 is likely to play a major role in the pathogenesis of GCA while the exact mechanisms involved are yet to be fully elucidated.

This study examines the functional effects of TLR 2 on induction of pro-inflammatory cytokines, angiogenesis and cell migration in GCA.

Methods: 15 patients with biopsy proven GCA and meeting 1990 ACR classification criteria for GCA were prospectively recruited. To directly examine the effects of TLR 2 on pro-inflammatory cytokines, growth factors and gelatinase expression in GCA, ex-vivo temporal artery (TA) whole tissue explant models were established. PBMCs and TA explants were cultured in the presence of Pam3CSK4 (a TLR 2 agonist) (1μg/ml) for 24 hours. Supernatants were harvested and assayed for IL-6, IL-8 Ang2, and VEGF by ELISA and MMP-2 and MMP-9 by gelatin zymography. Endothelial cell tube formation was assessed following culture with TLR 2-induced TA explant conditioned media. To examine the effect of TLR 2 on migration/ invasion in GCA, TA explants were embedded in Matrigel, stimulated with Pam3CSK4 and myofibroblast outgrowths observed. Myofibroblasts were also isolated from TA explants, cultured and wound repair assays performed. To examine the effects of TLR 2 on cytoskeletal architecture, cultured myofibroblasts were treated with Pam3CSK4 and stained for F-actin.

Results: In PBMC cultures, Pam3CSK4 induced a 7.7 and 3.6 fold increase in expression of IL6 and IL8 respectively, from a basal IL-6 level of 34.58 ± 6.77 pg/ml to 266.1 ± 117.6 pg/ml and basal IL-8 level of 1769 ± 731.7 pg/ml to 6388 ± 1632 pg/ml. In temporal artery explant cultures stimulation with Pam3CSK4 increased expression of IL-6 from 26,800 ± 9209 pg/ml to 47,494 ± 10,946pg/ml (p = 0.01). Expression of IL-8 was also increased from basal levels of 20,593 ± 8224 pg/ml to 40,793 ± 16,670 pg/ml (p = 0.058).

Supernatants from culture supernatants were analyzed by Western Blotting for IL-6 and IL-1β. Pam3CSK4 signifi cantly increased Ang 2 expression from basal levels of 727.9 ± 1632 pg/ml to 47494 ± 4596.6 pg/ml (p = 0.011). There was a trend towards increased expression of VEGF, from basal levels of 107.5 ± 33.38 pg/ml to 200 ± 69.95pg/ml but this was not statistically significant. (p = 0.19) Differential effects for MMP2/9 expression were observed on zymography. Pam3CSK4 induced endothelial cell tube formation. Pam3CSK4 also promoted myofibroblast outgrowths from the TA explants and cytoskeletal disassembly in the cultured myofibroblasts.

Conclusion: In an ex vivo temporal artery culture model, Pam3CSK4, a TLR 2 agonist, enhances production of pro inflammatory mediators, promotes angiogenesis, myofibroblast migration and cytoskeletal rearrangement. TLR2 signalling may therefore play a role in driving vascular inflammation and remodelling in GCA, and may represent a potential therapeutic target in GCA.

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Methods: We identified target antigens for AECA in patients with GCA using agarose 2-dimensional electrophoresis (agarose 2DE) and WB followed by mass spectrometry and accessed to pathophysiological roles in GCA. To detect antigens recognized by GCA sera predominantly in extracted proteins from endothelial cells (EC-specific proteins), the results of agarose 2DE-WB using human aortic endothelial cells (HAEC) were compared with that using human aortic adventitial fibroblasts. Furthermore, to detect antigens on HAEC recognized predominantly in sera with GCA (GCA-specific proteins), the results of 2DE-WB using sera from GCA were compared with that using sera from healthy donors.

Results: A total of 31 proteins identified from 23 protein spots recovered from 2DE gel were determined successfully. Three proteins, Ezrin, Zyxin and Fk506-binding protein 4, were EC-specific proteins as well as GCA-specific proteins. Gene Ontology analysis showed the EC-specific protein group was mainly classified into the metabolism and the defense and immunity group. In the GCA-specific protein group, the proteins were classified into broad functional categories except for metabolism group. By IPA analysis, more than half of the identified proteins were closely related ubiquitin. Regarding relationships between the identified proteins and cytokines, chemokines, and adhesion molecules, TNF-α was also involved in this signaling network. Using both proteomics and immunocytochemical analyses, we report here for the first time the identification of a specific target antigen for AECA in GCA, zyxin, a focal adhesion protein. Anti-zyxin antibodies were detected in 37% of patients with GCA and in 15% of patients with Takayasu’s arteritis but not in healthy controls. Interestingly, the titer of anti-zyxin antibodies tended to be higher in all untreated patients with GCA than in treated patients. Half of GCA patients with polymyalgia rheumatica had antibodies to zyxin. Using immunocytochemistry analysis, we observed that zyxin translocated from cytoplasm or membrane to the nucleus in ECs stimulated with TNF-α and IL-1β, respectively. Using zyxin siRNA knockdown, zyxin mainly regulates IL-8 production from ECs stimulated with TNF-α and IL-1β, respectively. Furthermore, the increased IL-8 production via zyxin from ECs was inhibited by treatment with glucocorticoids and treatment with anti-zyxin antibodies. Because zyxin is a target antigen for AECA in GCA and because zyxin is involved in regulating inflammatory responses in ECs via its translocation to the nucleus, the presence of anti-zyxin antibodies in GCA strongly implicates these antibodies in the pathogenesis of GCA or in disease progression.

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Rho Kinase (ROCK) Activity in Aortitis: Comparison of Giant Cell Arteritis (GCA), Takayasu Arteritis (TA) and Isolated Aortitis (IA).

Background/Purpose: Aberrant ROCK activity is implicated in the pathogenesis of many autoimmune and vascular disease states as ROCKs promote Th17 differentiation and vascular remodeling. Increased ROCK activity has been demonstrated in temporal artery biopsies from GCA patients and ROCK is proposed to play a role in aortic aneurysm formation; however the role of ROCK in aortitis is unknown. The aim of this study was to assess ROCK activity in aortic specimens from patients with GCA, TA and IA.

Methods: All aortic aneurysm specimens with histopathologic evidence of aortitis diagnosed during a 1 year period at a single institution identified and corresponding medical record reviewed. Patient history and ACR criteria were used to confirm diagnosis of GCA, TA, or IA. Those with IgG4 disease were excluded. Paraffin-embedded specimens were stained for Phospho-Ezrin/Radixin/Moesin (pERM), a surrogate of ROCK activity, using immunohistochemical stain. Sections also stained for the un-phosphorylated ERM Ezrin/Radixin/Moesin (pERM), a surrogate of ROCK activity, using immuno

Results: Of 12 eligible aortitis cases, 4 were in those with prior history of GCA of which 3 had TA and 5 had IA. Expected demographic differences noted between groups. In all compartments, pERM staining was notably more intense than ERM staining positive for pERM, though TA patients had poorly incompletely identified, which hampers our understanding of the roles of AECA in disease pathogenesis.

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Novel Roles for Zyxin in the Pathogenesis of Giant Cell Arteritis. Rie Karasawa1, Paul A. Monach2, Mayumi Tamaki1, Takahiro Okazaki1, Masamichi Oh-Ishi3, Yoshio Kodera4, Toshiko Sato2, Shoichiro Ozaki2, Kaiyu Jiang5, Kazuo Yudoh6, James N. Jarvis7 and Peter A. Merkel1. 1Institute of Medical Science, St. Marriana University School of Medicine, Kawasaki, Japan, 2Vascularitis Center, Boston University School of Medicine, Boston, MA, 3St. Marriana University School of Medicine, Kawasaki, Japan, 4School of Science, Kitasato University, Sagamihara, Japan, 5The University at Buffalo, Buffalo, NY, 6Vascularitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: The mechanisms of the blood vessel injury in giant cell arteritis (GCA), a systemic vasculitis characterized by inflammation of large- and medium-sized vessels, remain to be fully solved. Anti- endothelial cell antibodies (AECA) are antibodies that are detected frequently in vasculitis, including GCA. However, AECA target molecules have been

Methods: To examine the effects of TLR 2 on induction of pro-inflammatory cytokines, angiogenesis and cell migration in GCA, we examined the first time the identification of a specific target antigen for AECA in GCA, zyxin, a focal adhesion protein. Anti-zyxin antibodies were detected in 37% of patients with GCA and in 15% of patients with Takayasu’s arteritis but not in healthy controls. Interestingly, the titer of anti-zyxin antibodies tended to be higher in all untreated patients with GCA than in treated patients. Half of GCA patients with polymyalgia rheumatica had antibodies to zyxin. Using immunocytochemistry analysis, we observed that zyxin translocated from cytoplasm or membrane to the nucleus in ECs stimulated with TNF-α and IL-1β, respectively. Using zyxin siRNA knockdown, zyxin mainly regulates IL-8 production from ECs stimulated with TNF-α and IL-1β, respectively. Furthermore, the increased IL-8 production via zyxin from ECs was inhibited by treatment with glucocorticoids and treatment with anti-zyxin antibodies.

Conclusions: Zyxin is a target antigen for AECA in GCA. Because zyxin is involved in regulating inflammatory responses in ECs via its translocation to the nucleus, the presence of anti-zyxin antibodies in GCA strongly implicates these antibodies in the pathogenesis of GCA or in disease progression.

Disclosure: R. Karasawa, None; P. A. Monach, None; M. Tamaki, None; T. Okazaki, None; M. Oh-Ishi, None; Y. Kodera, None; T. Sato, None; S. Ozaki, None; K. Jiang, None; K. Yudoh, None; J. N. Jarvis, None; P. A. Merkel, None.
greater proportion of pERM negative inflammatory cells (CD 163+ histiocytes) than those with GCA or IA. All patients, including 10 with non-inflammatory aortic aneurysms, had intense pERM staining of stromal cells in the adventitia and vasa vasaorum, which was not affected by use of medications or co-morbidities known to influence ROCK (Table 1).

**Conclusion:** The markedly more intense pERM staining compared to ERM in the vasculature and lymphoctic infiltrate from those with GCA, TAB, and IA suggest the ROCK pathway is active in these disease states, though no major differences in intensity between groups was noted. The pERM intensity in vessels of non-aortitis aneurysm controls supports the idea that ROCK may promote aneurysm development. ROCK activation likely reflects a response to vascular damage and repair regardless of etiologic mechanism, though staining in the infiltrating lymphocytes suggests ROCK is also involved in the inflammatory response in aortitis. These findings may ultimately have therapeutic implications, if confirmed in larger cohorts, especially in GCA as inhibition of ROCK may mitigate the initial inflammatory milieu as well as aneurysm formation, the most significant late disease manifestation.

Table 1: Patient Demographics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Diagnosis/Disease</th>
<th>Disease Duration (year)</th>
<th>Immunosuppression</th>
<th>Symptom*</th>
<th>ACRE Use</th>
<th>Statin Use</th>
<th>Tobacco Use</th>
<th>Hypertension</th>
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<td>n</td>
<td>y</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
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<td>71M</td>
<td>GCA</td>
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<td>n y former</td>
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</tbody>
</table>

GCA= Giant Cell Arteritis, TAB=Takayasu Arteritis, IA=Isolated Aortitis PMR=Polymerized Rheumatism

*Strains used for congenital adrenal hyperplasia.

**Disclosure:** L. Lally, None; N. Narula, None; R. F. Spiera, None.

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Temporal Artery Microbiome in Giant Cell Arteritis. Alison Clifford1, Pauline Funchain2, Lisa Lystad3, Charissa Peterson4, Jessica Altemus4, Gary Lofek3, Guilhem Clary4, Cédric Broussard3, Christian Federici2, Claire Le Jeune1, Elisabeth Vidal1, Antoine Brezin2, Veronica witko-Sarsat5, Loïc Guéguin6 and Luc Mouton. 1National Reference Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, 2Laboratoire d’immunologie, EA3842, Faculté de médecine, Limoges, Limoges, France, 3Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, 4Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, 5Service d’ophtalmologie, hôpital Cochin, AP-HP, Paris, France.

**Background/Purpose:** Whether infectious agents play a part in giant cell arteritis (GCA) remains controversial. We have performed the first microbiome study of snap-frozen temporal arteries, collected and processed under sterile conditions, from GCA patients and controls using metagenomic sequencing.

**Methods:** Patients undergoing temporal artery biopsy for possible GCA were prospectively enrolled. Biopsies were collected under strictly sterile conditions and split, with one part sent for routine histopathological review and one part snap-frozen for microbiome studies. Patients were classified according to clinical presentation as either biopsy-positive GCA (TA+), biopsy-negative clinically classical GCA (TA-) or controls. Long-read 16S ribosomal RNA (rRNA) sequencing was used to describe the entire microbiome of temporal arteries. Total DNA was isolated, and V1-V4 regions of the gene encoding bacteria-specific 16S rRNA were amplified and Sanger sequenced. Taxonomic classification of bacterial sequences was performed using an in-house analysis pipeline and relative abundances of species were calculated. Microbiomes were plotted by principal-coordinate analysis (PCoA) using a de novo operational taxonomic unit (OTU) picking protocol (using the MacQIME 1.7 toolkit). Functional composition of microbiomes was analyzed using the PICRUSt bioinformatics package.

**Results:** Eleven patients were enrolled, including 3 TA+ GCA patients, 2 TA- GCA patients and 6 controls. All patients were receiving empiric prednisone therapy at time of biopsy and 1 control patient was also receiving doxycycline. Using PCoA, the microbiomes of control temporal arteries clustered tightly together in the center of the plot, showing high degrees of taxonomic relatedness, while GCA microbiomes (both TA+ and TA- patients) plotted in the periphery, clearly separated from controls. One control outlier was noted. Stratification of the samples by prednisone dosage did not account for the separation of GCA and controls on PCoA. Taxonomic classification revealed a wide variety of bacteria in each temporal artery (mean 10.8 species/control vs 10.6 species/GCA), with no overarching species common to all. Significant upregulation of 4 functional pathways (nucleotide metabolism, steroid hormone biosynthesis, biosynthesis of siderophore group nonribosomal peptides, and electron transport) was identified in the GCA microbiomes (both TA+ and TA-) as compared to controls.

**Conclusion:** Temporal arteries are not sterile. They are inhabited in the both the control and diseased state by a community of bacteria. GCA temporal artery microbiomes (from both TA+ and TA- patients) differ from controls with respect to both the taxonomy and function of bacterial species present. Whether these shifts in the GCA microbiome represent the cause or effect of vascular inflammation remains to be elucidated. * contributed equally to this work

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Increased Migration and Proliferation Potential Characterize Vascular Smooth Muscle Cells from Patients with Giant Cell Arteritis. Alexis Regent1, Kim-Heang Ly2, Mathieu Groh3, Chabha Khifer3, Sébastien Lofek1, Guilhem Clary4, Philippe Chafey4, Cédric Broussard3, Christian Federici2, Claire Le Jeune1, Elisabeth Vidal1, Antoine Brezin2, Veronica witko-Sarsat5, Loïc Guéguin6 and Luc Mouton. 1National Reference Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, 2Laboratoire d’immunologie, EA3842, Faculté de médecine, Limoges, Limoges, France, 3Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, 4Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, 5Service d’ophtalmologie, hôpital Cochin, AP-HP, Paris, France.

**Background/Purpose:** The pathophysiology of GCA is poorly understood. Questions remain regarding the mechanisms underlying vascular remodeling.

**Methods:** Vascular smooth muscle cells (VSMC) were cultured from temporal artery biopsies (TAB) of consecutive patients suspected of GCA. We selected four patients with biopsy proven GCA (TAB+-GCA), four patients with biopsy-negative GCA (TAB–GCA), and four patients with another diagnosis than GCA (GCA-control). Normal human aorta VSMC were used as control. Proteomes of VSMC from patients in TAB–GCA, TAB+GCA or GCA-control groups were compared using two-dimension DIGE (2D-DIGE) at pH range of 3–11. Transcriptomic analysis of VSMC from patients within the three GCA groups was performed using affimmetrix chips. Proliferation of VSMC was performed with BrDU proliferation assay ELISA kit in unstimulated condition and with paixillin siRNA.

**Results:** We could identify 16, 28 and 2 protein spots that were differentially expressed between VSMC from TAB–GCA and GCA-control patients, between TAB–GCA and TAB+GCA patients and between TAB–GCA and GCA-control patients respectively (fold change≥1.5 and p≤0.05). Principal component analysis differentiated VSMC proteomes from TAB–GCA, TAB+GCA and GCA-control. Ingenuity analysis comparing TAB–GCA and aorta revealed that identified proteins interact with paixillin. Genes differentially expressed between VSMC from patients with TAB–GCA, TAB–GCA and GCA-control were involved in cellular movement, organinal injury, tissue development, and cancer.

Unstimulated proliferation and in the presence of paixillin siRNA are currently being investigated in order to evaluate its potential involvement in the dysregulated proliferative phenotype observed in VSMC from GCA patients.

**Conclusion:** VSMC from patients with GCA expressed proteins that confer increased proliferation and migration potential. Inhibition of the increased proliferation of VSMC during GCA through paixillin targeting might represent a promising therapeutic approach in patients with GCA.

Disclosure: A. Regent, None; K. H. Ly, None; M. Groh, None; C. Khifer, None; S. Lofek, None; G. Chafey, None; P. Chafey, None; C. Broussard, None; C. Federici, None; C. Le Jeune, None; E. Vidal, None; A. Brezin, None; V. witko-Sarsat, None; L. Guéguin, None; L. Mouton, None.
Novel Inhibitory Effects of Mast Cells in Aortitis Involves Aortic Expression of Suppressor of Cytokine Signaling-1. Jason Springer, Vineesh Raveendran, Donald Smith, Mehrdad Maz and Kottarapatt Dileepan. University of Kansas Medical Center, Kansas City, KS.

Background/Purpose: Early in the pathogenesis of Giant Cell Arteritis (GCA) dendritic cells interact with T cells of both Th1 and Th17 origin. IL-6: released by Th17 T-cells, macrophages and endothelial cells; plays an important role in the pathogenesis of GCA. Mast cells (MCs) are important constituents of the immune system. They possess both pro-inflammatory and anti-inflammatory functions. There is an increased presence of mast cells in the temporal arteries of GCA patients. Furthermore, MCs have been shown to have an immunomodulatory effect in an MPO-associated vasculitis mouse model. The mechanism by which MCs modulate vascular inflammation in large vessel vasculitis, such as GCA, is not known. Suppressor of Cytokine Signaling-1 (SOCS-1), a JAK-STAT inhibitor, plays a role in inhibiting cytokine signaling. The objective of this study was to test the hypothesis that MCs regulate LPS induced aortic IL-6 production through SOCS-1 proteins.

Methods: Two month old C57Bl/6 mice were randomized into 4 treatment groups. The treatment groups were administered intraperitoneal injections with: saline (control), Compound 48/80 (C48/80, MC degranulating agent, 1mg/kg), LPS (1mg/kg) or C48/80+LPS. Mice were sacrificed at either 24 hours (single injection) or 10 days (serial injections), and blood and aortas were collected for various analyses as presented in ‘Results’. Data were analyzed for statistical significance and p < 0.05 was considered significant.

Results: In the single injection groups, LPS significantly enhanced serum IL-6 (350±146 pg/ml vs 21.3±5.5 pg/ml) and aortic IL-6 gene expression (18.0±5.4 fold vs 1±0.025 fold) compared to normal saline-injected mice. When MCs were degranulated by C48/80, LPS-induced aortic expression of IL-6 and serum IL-6 were significantly reduced when compared to LPS alone (IL-6: 101 ± 13 pg/ml vs 350±146 pg/ml; IL-6 mRNA: 4.3±0.5 vs 18.0±5.4 fold change). Aortic expression of SOCS-1 mRNA was found to be 2- and 3-fold higher, respectively, in the LPS and C48/80 + LPS groups compared to controls. In mice receiving serial injections, there were significantly higher levels of IL-18 and tissue inhibitor of metalloproteinase-1 (p<0.0001) in the LPS and LPS+C48/80 groups compared to controls. Thrombopoietin was significantly higher in the LPS group compared to the C48/80 and control groups but no difference was seen between C48/80 + LPS compared to C48/80 group alone. No significant differences between groups were seen for IL-1 alpha, IL-1 beta, monocyte chemotactic protein (MCP)1, MCP-3 or VEGF-A.

Conclusion: These results demonstrate that MC degranulation inhibits LPS- induced aortic expression of IL-6 and systemic production of IL-6. The inhibitory effect of MCs was associated with an increased expression of SOCS-1 in the aorta. This suggests that SOCS-1 plays a role in mast cell-mediated regulation of IL-6 as well as other cytokines associated with the pathogenesis of GCA homeostasis. Identifying the MC factor or factors involved in the inhibition of LPS-induced inflammation in the aorta may provide novel therapeutic strategies for GCA.

Disclosure: J. Springer, None; V. Raveendran, None; D. Smith, None; M. Maz, None; K. Dileepan, None.

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Incidence, Prevalence and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy. Mariagrazia Catanozzi1, Pierluigi Macchioni1, Luigi Boiard1, Francesco Muratore1, Giovanna Restuccia1, Alberto Cavazza1, Ferdinando Luberto2 and Carlo Salvareni1. Azienda USL Reggio Emilia, Reggio Emilia, Italy,1Arcispedale S Maria Nuova, Reggio Emilia, Italy,2Azienda Usl Reggio Emilia, Reggio Emilia, Italy.

Background/Purpose: To investigate the incidence, prevalence and mortality of biopsy proven giant cell arteritis (GCA) over a 27-year period in a defined area of northern Italy.

Methods: All patients with incident GCA diagnosed from January 1, 1986 to December 31, 2012 living in the Reggio Emilia area were identified through computerized hospital discharge diagnosis and a structured review of all histopathology reports. Patients were followed up from the time of diagnosis until either their death or December 31, 2012.

Results: Two hundred and eighty-five patients (75 men and 210 women), had biopsy proven GCA according to the histopathological examination. Mean ±SD age at diagnosis was 74.4±7.3 years. The mean annual incidence rate (IR) of GCA was 58.16/106 (95% CI: 51.4–64.9). The mean IR was 31.1/106 (95% CI: 26.9–35.4) among women and 11.6/106 (95% CI: 8.9–14.2) for men (p < 0.05). The estimated incidence for people over 50 y was 78.11 (95% CI: 67.4–88.7) for women and 33.4 (95% CI: 25.7–41) for men. The lowest IR occurred in male patients in the 30–59 years age group (5.13/106; 95% CI: 1.4–13.1), the highest IR was observed in female patients 80–84 years age group (215.4/106; 95% CI: 184.7–297.2). IR difference between sex was significant only in the 60–69 age group (IR male/female 14.6/6.1, 95% CI 7.0–26.9 vs 49.8–88.4). The average annual IR increased from 5.63/106 during 1986–1988 to 45.23/106 during 1998–2000 period and was stable thereafter with IR of 30–23/106. Point prevalence on December 31st 2012 was 304.5/106 (95% CI: 258.0–355.7) (women 453.1, 95% CI: 376–514.1, men 148.8, 95% CI: 105–204.2).

At histological examination 13.6% (39 pts) had only small vessels perivascular involvement (adventitial vasa vasorum and peri-adventitial vasculitis). Prevalence of small vessels involvement was significant higher among male patients (male 30% vs 7%female, p < 0.001). One hundred and twenty-nine patients (45.2%) died during the follow-up period (median survival after diagnosis 152 months [range 4–320 months]). Survival did not differ nor between gender or between different histopathological pattern.

Conclusion: This population-based study is the first to report the incidence of biopsy proven GCA in Italy. Our average annual IR is similar to that reported in the period 1984–1988 in Finland (1).

Reference

Disclosure: M. Catanoso, None; P. Macchioni, None; L. Boiardi, None; F. Muratore, None; G. Restuccia, None; A. Cavazza, None; F. Luberto, None; C. Salvareni, None.

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Background/Purpose: Giant cell arteritis (GCA) is the most common form of vasculitis. The highest incidence rates of GCA have been reported from Southern Norway (29–32/100000 >50 years) and mortality rates have been reported not to be different from the background population. However, data are from the end of 80’s to the early 90’s and no recent reports exist. The aim of this study was to examine the incidence and standardized mortality ratios (SMR) of GCA in Southern Norway in the period of the last 13 years.

Methods: GCA patients were identified by using the hospital records during the years 2000–2013. The ICD-10 coding system (M31.5–6) was used to identify the patients and the diagnoses were carefully verified. In addition, a retrospective study of the archives of the Department of Pathology was conducted, in order to identify patients with biopsy that were not registered by the ICD-10 system. SMR was calculated by using the death rates of the Norwegian population per 100 000.

Results: Mean age (95% CI) among the 212 identified GCA patients was 73.2 (72.0–74.4) years. Among them, 60 were males [mean age 73.4 years (71.0–75.7)] and 152 females [mean age 73.2 years (71.8–74.5)]. One-hundred fifty-five patients (73.1%) had a positive biopsy of the temporal artery, 42 patients (19.9%) a negative and in 15 patients (7.0%) biopsy was not performed. All the patients with a negative or not performed biopsy satisfied the ACR classification criteria for GCA.

The incidence rate for GCA was 17.2 per 100 000 >50 years (males 10.4 and females 23.4). The incidence rate of the biopsy-proven GCA was 12.6 per 100 000 >50 years. The yearly distribution of the incidence rates of GCA in Southern Norway is displayed in figure 1.

Among the 212 GCA patients, there were 52 deaths during the period 2000–2014. The overall SMR was 0.5 (95%CI 0.3–0.6) [0.5 for males (95%CI 0.3–0.7), and 0.4 for females (95%CI 0.3–0.6)]. For biopsy-proven GCA the SMR rates were 0.7 (95%CI 0.4–1.0) for males and 0.4 (95%CI 0.2–0.5) for females.

Conclusion: The incidence rate of GCA in Southern Norway during the years 2000–2013 is 45 % lower than this reported in previous studies. However, a rising tendency of the incidence rates has been noticed at the last 5 years (fig 1). Interestingly, the mortality of GCA patients appears to be lower compared to the background population. Better quality of health care in this group of patients could be a reason.
Cardiovascular Risk Factors and Incident Giant Cell Arteritis. Gunnar Tomasson & Jóhannes Björnsson, Vilhruður Gudnason, Yaqing Zhang & Peter A. Merkel.

Background/Purpose: To assess the effect of cardiovascular risk factors on incidence GCA within a longitudinal cohort study in which detailed information on cardiovascular risk factors has been collected.

Methods: The data source is the Reykjavik Study (RS), a population-based, prospective cohort study with a primary focus on cardiovascular disease. All persons born in 1907–1935 that were living in Reykjavik, Iceland or adjacent communities on December 1, 1967 were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors, including smoking habits, blood pressure, diabetes, body mass index, and serum cholesterol was obtained. All temporal artery biopsies (TABs) obtained from 1961–2009 on members of the cohort were identified. Their characteristics are presented in Table 1.

Results: Data were obtained from 19,241 subjects that were followed for a median 23.1 (IQR: 17.6–29.4) years after the age of 50. During the follow-up of 444,396 person-years, 194 subjects had GCA, corresponding to an incidence rate of 45.0 (95% CI: 38.8–51.2) per 100,000 person-years after the age of 50. Woman had increased incidence of GCA compared to men. IRR = 2.03 (95% CI: 1.49–2.76). BMI was inversely associated with GCA; subjects with a BMI >25 had an IRR = 0.68 (95% CI: 0.50–0.90). Smoking was inversely associated with GCA among men IRR = 0.51 (95% CI: 0.30–0.86), but not women IRR = 1.12 (95% CI: 0.79–1.57). Hypertension was associated with incident GCA among men IRR = 1.91 (95% CI: 1.12–3.25), but not among women IRR = 0.86 (95% CI: 0.60–1.24). Serum cholesterol was not associated with incident GCA.

Conclusion: This study confirms a high incidence of GCA in Iceland. Lower BMI is associated with the occurrence of GCA. Among men, hypertension is positively associated with GCA and smoking is inversely associated with incident GCA.

Disclosure: G. Tomasson, None; J. Björnsson, None; V. Gudnason, None; Y. Zhang, None; P. A. Merkel, None.

Fast-Track Diagnostic Procedure for Giant Cell Arteritis. Alojzija Hočevar1, Ziga Rotar2 and Matija Tomšič3.

Background/Purpose: Giant cell arteritis (GCA) represents the most common primary vasculitis among adults aged 50 years or above. Recently, the national annual incidence rate in this population was determined at 10.5 per 105. GCA may lead to ischemic complications, which among others include permanent visual loss in up to 20% of patients and ischemic stroke in 2–4%. Early diagnosis and initiation of treatment is thus of paramount importance. At our secondary/tertiary level department of rheumatology we examine majority of patients with referral diagnosis of GCA within 24 hours from referral, and those referred during the week-end in up to 72 hours. Also, rheumatologists have been performing temporal artery biopsies (TAB) ourselves for decades with an excellent safety record. Snap frozen TAB specimens are processed and analyzed at the attached university institute of pathology. Results: are obtained within three hours from TAB. Since September 2011 Color Doppler ultrasonography of temporal arteries (CDS-TA) is routinely performed in every potential case of GCA to aid diagnosis and guide TAB. Our aim was to analyze the performance of this approach to GCA patient work-up.

Methods: We retrieved and analyzed electronic and paper patient charts of patients diagnosed with GCA form September 1, 2011 to May 31, 2014. Appropriate descriptive statistical methods were used describe our cohort.

Results: During the 32 month observation period, 66 new GCA cases were identified. Their characteristics are presented in Table 1. Median (interquartile range (IQR), range) symptom duration prior to presentation was 30 (14–77), range 2–365) days. Patients were referred to our outpatient clinic by their general practitioners (33/66), infectious disease specialists (13/66), specialists of internal medicine (12/66) ophthalmologists (6/66), and neurologists (2/66). Except for two polymyalgia rheumatica patients, all other patients were glucocorticoid naïve at the time of diagnostic procedures. CDS-TA was performed in 65/66, and TAB in 54/66 cases. Median time to CDS-TA (IQR, range) was 0 (0–1); 0–6 days, and 1 (0–1.75); 0–15 day for TAB. CDS-TA, and TAB were performed on the day of referral to our department in 48/66 (73%), and 20/66 (30%) of patients, respectively. Notably, 24/66 (36.4%) patients reported visual manifestations. Unilateral permanent visual loss developed in 4/66 patients (6.1%)—in one patient despite prompt initiation of glucocorticoid treatment, and in the remaining three cases 13 days, 14 days, and 2 months before diagnosis. One patient had an ischemic stroke 8 days prior to diagnosis.

Conclusion: This fast-track pathway enables us to obtain a definitive diagnosis even before the initiation of treatment, and might contribute to a relatively low incidence of irreversible sight loss in our cohort compared to reported data, as well as avoidance of overtreatment with glucocorticoids.

Characteristics

| % female   | 69.7 |
| age (mean ± SD) | 73.2 ± 8.0 |
| smoking (%) | 27 (40.9) |
| new onset/type headache (%) | 48 (72.7) |
| scalp tenderness (%) | 16 (24.2) |
| jaw claudication (%) | 21 (31.8) |
| visual symptoms (%) | 24 (36.4) |
| blurred vision (%) | 15 (22.7) |
| diplopia (%) | 8 (12.1) |
| transient visual loss (%) | 3 (4.5) |
| permanent visual loss (%) | 4 (6.1) |
| ptosis (%) | 1 (1.5) |
| dry cough (%) | 12 (18.2) |
| clinically changed TA (%) | 40 (60.6) |
| symptoms of large vessel disease (%) | 7 (10.6) |
| general symptoms (%) | 45 (68.2) |
| fever (≥38°C) (%) | 14 (21.2) |
| weight loss (%) | 36 (54.5) |
| polymyalgia rheumatica (%) | 9 (13.6) |
| ESR (mm/h; ref. ≤15–32) (median) (IQR) | 80 (57–95) |
| CRP (mg/l; ref. ≤5.0) (median) (IQR) | 63 (32–122) |
| SAA (mg/l; N <6.4) (median) (IQR) | 192 (66–488) |
| positive TAB #/ all biopsies (%) | 43/54 (79.6) |
| positive CDS-TA #/ all CDS-TA (%) | 50/65 (76.9) |
| US signs large vessel disease #/ all CDS (%) | 19/58 (32.7) |

Disclosure: A. Hočevar, None; Z. Rotar, None; M. Tomšič, None.

Association Between Histological Features and Clinical Features of Patients with Biopsy Positive Giant Cell Arteritis. Kimberley Ting1, Susan Lester2 and Catherine L. Hill3.

1The Queen Elizabeth Hospital,
Background/Purpose: Temporal artery biopsy is the gold standard for diagnosing giant cell arteritis (GCA). The pathology of GCA characteristically involves transmural infiltrates, giant cell formation and intimal hyperplasia. However the significance of histopathology characteristics, in terms of clinical features and complications of GCA, remains unknown. The aim of this study was to investigate the association between histological biopsy features and clinical features, such as blindness, in patients with biopsy positive GCA.

Methods: Positive temporal artery biopsies registered on the South Australian Giant Cell Arteritis Registry were identified between 1991 and 2013 (n=186). Clinical and serological data was recorded using both patient questionnaire and case note review. Patients without clinical data were excluded from the analysis (n=42). Statistical analysis was performed using chi-squared and Wilcoxon’s tests.

Results: 144 biopsy positive GCA cases were analysed. The mean age at biopsy was 77 years. 71% were female, and in total 30% experienced blindness. Although not individually significant, transmural inflammation (p = 0.11), luminal thrombus (p = 0.17) and giant cells (p = 0.20) were more frequent in GCA patients with blindness, whereas fragmentation of the internal elastic lamina (p = 0.04), and intimal thickening (p = 0.02) were more frequent in GCA patients without blindness (Table 1). The presence of giant cells was associated with transmural inflammation (p = 0.06), jaw claudication (p = 0.02), and higher inflammatory markers. In contrast, characteristics of patients with intimal thickening included a lower frequency of giant cells (0.01) and jaw claudication (p = 0.01), and lower inflammatory markers.

Table 1: Association Between Histopathology and Blindness

<table>
<thead>
<tr>
<th>Histological Feature</th>
<th>GCA with Blindness n (%)</th>
<th>GCA with Blindness n (%)</th>
<th>p value</th>
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<tr>
<td>Giant cells</td>
<td>29/35 (85%)</td>
<td>61/82 (74%)</td>
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<tr>
<td>Macrophages</td>
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</tr>
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<td>Transmural Inflammation</td>
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<td>32/67 (47.8%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fragmentation of internal elastic lamina</td>
<td>15/36 (41.7%)</td>
<td>53/85 (62.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Intimal thickening</td>
<td>13/36 (36.1%)</td>
<td>51/85 (60%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Luminal Thrombus</td>
<td>6/26 (16.7%)</td>
<td>7/85 (8.2%)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Conclusion: Giant cells are strongly associated with jaw claudication and systemic markers of inflammation. We did not find any histological features that were individually significantly associated with an increased risk of blindness in GCA patients. However patients with intimal thickening by histology are less likely to have giant cells, have less acute systemic inflammation, and have a lower risk of blindness. This group may reflect a different disease subgroup or late stages of inflammation, highlighting the challenges in the pathological diagnosis and biopsy reporting of active GCA.

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Correlations Between Histopathological Findings and Clinical Manifestations in a Large Monocentric Cohort of Patients with Biopsy-Proven Giant Cell Arteritis. Luigi Boiardi1, Francesco Muratore1, Alberto Cavazza2, Giovanna Restuccia2, Pierluigi Macchioni3, Giuseppe Germano1, Nicolo Pipitone1, Gianluigi Bajocchi1 and Carlo Salvareni2. Arcispedale S Maria Nuova, Reggio Emilia, Italy, 1Arcispedale S Maria Nuova, Reggio Emilia, Japan.

Background/Purpose: Temporal artery biopsy (TAB) showing transmural inflammation is considered the gold standard for the diagnosis of giant cell arteritis (GCA). In some cases of GCA, inflammation is confined to the periadventitial small vessels, the vasa vasorum and/or the adventitia. These pathological patterns are closely resembling classic GCA, but the final significance of this more limited inflammation need more confirmation. The aim of our study was to describe and correlate the different histological subsets of GCA with demographic and clinical manifestations in a large monocentric cohort of biopsy positive GCA patients.

Methods: All TABs performed for suspected GCA between 1986 and 2012 were reviewed by a single pathologist. Based on the localization of the inflammation, positive TABs were classified into 4 categories: small vessel vasculitis (SVV), with inflammation limited to small periadventitial vessels devoid of muscular coat; vasa vasorum vasculitis (VVV), with inflammation surrounding the adventitial vasa vasorum; inflammation limited to adventitia (ILA), with inflammation spreading from vasa vasorum to the adventitia without extension to the media; transmural inflammation (TMI), with external elastic lamina disruption and extension of the inflammation to the media.

Results: 317 TABs were positive for inflammation and were classified as:
- 253 (79.8%) TMI
- 18 (5.7%) ILA
- 19 (6.0%) VVV
- 27 (8.5%) SVV

Compared to patients with TMI, those with SVV and VVV had a significantly lower frequency of headache (55.6% vs 77.9%, p = 0.010 for SVV and 57.9% vs 77.9%, p = 0.048 for VVV), jaw claudication (7.4% vs 44.7%, p < 0.0001 for SVV and 15.8% vs 44.7%, p = 0.015 for VVV), abnormalities of TA at physical examination (33.3% vs 71.3%, p = 0.0001 for SVV and 47.1% vs 71.3%, p = 0.036 for VVV), halo at TA color duplex sonography (CDS) (27.3% vs 72.4%, p = 0.0001 for SVV and 16.7% vs 72.4%, p = 0.0001 for VVV), systemic symptoms (only for VVV, 42.1% vs 66.8%, p = 0.029), and our hospital between January 1986 and December 2012. Positive TABs showing only small vessel vasculitis and/or vasa vasorum vasculitis without transmural inflammation were excluded from the comparison analysis. Histopathologic features evaluated were: the severity of inflammation and intimal hyperplasia, both graded on a semiquantitative scale (mild=1, moderate=2 severe=3), the presence of intraluminal acute thrombosis, calcifications, giant cells, fibrinoid necrosis and laminar necrosis, consisting in a band of coagulative necrosis sometimes bordered by palisading histiocytes and following the internal elastic lamina.
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Is Temporal Artery Biopsy the Gold Standard for the Diagnosis of Giant Cell Arteritis? Marina Scolnik1, Aldo Fabian Ojeda2, Valeria Scaglioni3 and Enrique R. Soriano4. 1Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina. 2Departamento de Reumatologia, Hospital de Clinicas, FCM-UNA, Asuncion, Paraguay. 3Rheumatology Unit, Internal Medical Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: The only test that confirms diagnosis of Giant Cell Arteritis (GCA) is a temporal artery biopsy showing vasculitis with mononuclear cell inflammatory infiltrates, often with giant cells. Due to the focal and segmental nature of the infiltrates, areas of inflammation may be missed by the biopsy. Some imaging modalities may aid in the diagnosis such as color duplex ultrasonography of the temporal arteries. When the clinical suspicion is strong and temporal biopsy is negative or can’t be performed, patients are treated as GCA. Our objective was to analyze all patients with GCA seen at our hospital in order to address value of temporal biopsy result in relation to the clinical course.

Methods: We retrospectively reviewed electronic medical records of patients registered in our hospital between 2000-2013 with the problem: vasculitis, Giant Cell Arteritis or Temporal Arteritis. Patients fulfilling ACR 1990 criteria for GCA were included. Clinical and laboratory data were collected. Temporal biopsies were reviewed. Ultrasound of temporal arteries was performed by an experienced vascular sonographer if requested by the treating rheumatologist and the finding of the halo sign was considered compatible with GCA diagnosis.

Results: 101 patients were included with GCA diagnosis, 79 females (78.2%), with a mean age at diagnosis of 74.9 years (SD 8.1). Temporal biopsy was positive in 52 patients, negative in 21 and was not performed in 28. Clinical characteristics are shown in table 1 grouped by biopsy result. Multivariate analysis showed that abnormal temporal pulse on examination had an OR of 19.7 (CI 2.9–131.9) for predicting a positive biopsy. Having symptoms of polymyalgia rheumatica (PMR) and age were also associated with a positive biopsy (OR 4.5, CI 1.03–19.4, and OR 1.11, CI 1.01–2.8 respectively). No differences were found in clinical presentation, treatment relapses or recurrences between groups. Ultrasound was performed in 42 patients (41.6%). Results according to temporal biopsy are shown in table 2. Ultrasound had an overall sensitivity of 29%, and a specificity of 25% and a specificity of 84% versus temporal biopsy; it helped in diagnosing 2 patients with negative biopsy and 6 patients without biopsy.

Conclusion: Abnormal temporal pulse, PMR symptoms and age were associated with a positive biopsy. Clinical presentation, course, treatment and relapses/recurrences didn’t differ between patients with positive or negative or unperformed biopsy. In our experience, clinical judgement continues to be relevant in the diagnosis of GCA, aided partially by biopsy, less so by ultrasound.
Background/Purpose: Colour Doppler ultrasoundography (CDU) of the temporal (TA), axillary (AA) and common carotid arteries (CA) has excellent sensitivity and specificity for the diagnosis of GCA, typically showing halos (dark areas around the arterial walls) and stenoses or occlusions. The CDU pattern of patients with extra cranial and cranial GCA has been reported to substantially differ; visual impairment and age are inversely correlated to eye symptoms. The presence of a dilated and tortuous pulse, hard tendon (tendon xanthomata) and an erythematous, hyperemic area was described. The presence of a dilated and tortuous pulse, hard tendon (tendon xanthomata) and an erythematous, hyperemic area was described.

Disclosure: S. Singh, None; A. Hutchings, None; W. Forrester-Barker, None; B. Dasgupta, None; A. P. Diamantopoulos, None; P. Lanyon, None; M. Magliano, None; B. McDonald, None; K. Wolfe, None; R. Luqmami, None.

794 Colour Doppler Ultrasonography Findings in Giant Cell Arteritis (GCA) and Their Relationship with Clinical Manifestations. Cristina Ponte1, Ruth Geraldes2, Anthea Crane3, Andrew Judge3, Peter C. Grayson4, Ravi Suppiah5, Joanna Robson6, Richard A. Watts1, Peter A. Merkel7 and Raoul Luqmani1. 1University of Oxford, Oxford, United Kingdom, 2Lisbon Academic Medical Centre, Lisbon, Portugal, 3National Institutes of Health, Bethesda, MD, 4Auckland District Health Board, Auckland, New Zealand, 5Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, 6Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Colour Doppler ultrasoundography (CDU) of the temporal (TA), axillary (AA) and common carotid arteries (CA) has excellent sensitivity and specificity for the diagnosis of GCA, typically showing halos (dark areas around the arterial walls) and stenoses or occlusions. The CDU pattern of patients with extra cranial and cranial GCA has been reported to substantially differ; visual impairment and age are inversely correlated to eye symptoms. The presence of a dilated and tortuous pulse, hard tendon (tendon xanthomata) and an erythematous, hyperemic area was described. The presence of a dilated and tortuous pulse, hard tendon (tendon xanthomata) and an erythematous, hyperemic area was described.

Disclosure: C. Ponte, None; R. Geraldes, None; A. Crane, None; A. Judge, None; P. C. Grayson, None; R. Suppiah, None; J. Robson, None; R. A. Watts, None; P. A. Merkel, Genentech and Biogen IDEC Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals UK, 5, Sanofi-Aventis Pharmaceutical, 5, ChemoCentryx, 5, R. Luqmami, None.

795 High Interobserver Agreement on Ultrasonographic Findings in Patients with Large Vessel Vasculitis. Andreas P. Diamantopoulos1, Julia Geiger2, Frode Lohne3, Geirmund Myklebust1 and Wolfgang A. Schmidt4. 1Hospital of Southern Norway Trust, Kristiansand, Norway, 2University Children’s Hospital, Zurich, Switzerland, 3Unilabs Rüttigen Kristiansand, Kristiansand, Norway, 4Immanuel Krankenhaus, Berlin, Germany.

Background/Purpose: Ultrasound has a high sensitivity and specificity regarding the diagnosis of giant cell arteritis (GCA). Ultrasound can also depict extracranial large vessel vasculitis (LVV) in both GCA and Takayasu arteritis (TA) patients. Until now, no studies have examined the inter-observer agreement of the ultrasonographic findings in LVV patients. Hence, the aim of this study was to examine the inter-observer agreement of ultrasonographic examination of temporal arteries and large vessels in LVV patients.

Methods: This study is a part of the MUSES project (Magnetic resonance angiography vs Ultrasonography in Systemic large Vessel vasculitis), a prospective cross-sectional study. Patients who were diagnosed with LVV by ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in vascular ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in vascular ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in vascular ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in vascular ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in vascular ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014.
Early Halo Sign Features on Ultrasound Examination of Treated Patients with Giant Cell Arteritis. Ana Sofia Serafim1, Starjeet Singh1, Jennifer Piper1*, Andreas Hutchings2, Mike Bradburn4, Bhaskar Dasgupta5, Wolfgang A. Schmidt6, Andreas P. Diamantopoulos7, Bhaskar Dasgupta5, Wolfgang A. Schmidt6, Andreas P. Diamantopoulos7, Eugene McNally6 and Raashid Luqmani1. 1Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, 2University of Oxford, Oxford, United Kingdom, 3London School of Hygiene and Tropical Medicine, London, United Kingdom, 4Sheffield University, Sheffield, United Kingdom, 5Lisbon Academic Medical Centre, Lisbon, Portugal, 6Southend University Hospital, Essex, United Kingdom, 7Immanuel Krankenhaus, Berlin, Germany, 8Hospital of Southern Norway Trust, Kristiansand, Norway, 9Oxford University, Oxford, United Kingdom.

Background/Purpose: The TABUL study (Temporal Artery Biopsy Vs Ultrasound in diagnosis of Giant Cell Arteritis) is assessing the relative performance of ultrasound and temporal artery biopsy for diagnosing GCA. All patients with newly suspected GCA underwent a single ultrasound scan of both temporal and axillary arteries within 7 days of commencing glucocorticoid therapy. We aimed to examine the ultrasound response to treatment as a potential biomarker in GCA, by measuring differences in the size of the halo around the arteries with different steroid duration within a 7 day period; furthermore we correlated the halo size with ischaemic symptoms of GCA.

Methods: At 796 patients with suspected GCA at baseline were included in this analysis. Using the IBM SPSS Statistics package v20, we performed a cross-sectional analysis with linear and logistic regression models to determine the relationship of the halo size with days of steroid treatment and with ischaemic symptoms of GCA (jaw and tongue claudication, amaurosis fugax and reduced, lost or double vision).

Results: We included 214 women and 87 men (mean age 72.6 and 71.2 years old respectively) from 20 different recruitment centres. Fifty percent were scanned on the second day of steroid treatment or before. Forty three percent (131 patients) had one or more temporal segments with a halo, 48.5% (146 patients) had bilateral temporal artery halos and 12.6% (38 patients) had axillary involvement. The linear regression model showed a consistently smaller halo size over the 7 days of steroid treatment (p<0.005) for the temporal arteries. The likelihood of finding a halo diminished with time, which was confirmed in a logistic regression until day 4 of steroid treatment (p<0.005), whereas this trend was not possible to predict after that time. At least one ischaemic symptom was present in 42% of the patients: jaw claudication in 48.2% (146 patients), reduced or lost vision in 36.6% (111 patients), double vision in 8.6% (26 patients), tongue claudication in 6.6% (20 patients) and amaurosis fugax in 4% (12 patients). The prevalence of jaw claudication was more frequent in patients with a halo (p<0.05). The symptomatic side of temporal arteries correlated significantly with the ipsilateral ultrasound findings (p<0.05 for right and left side findings on physical examination).

Conclusion: In newly diagnosed GCA, ultrasound halo size decreases with steroid treatment and correlates with the presence of ischaemic symptoms, supporting its early use as a diagnostic and potentially prognostic marker. We are exploring the potential value of change in halo size in individual patients over time to determine its value in monitoring response to treatment.

Disclosure: A. P. Diamantopoulos, None; J. Geiger, None; F. Lohné, None; G. Myklebust, None; W. A. Schmidt, Novartis Pharma AG, 2, Mundipharma, 2.
Peripheral Arterial Disease in Patients with Giant Cell Arteritis: A Systematic Review and Meta-analysis

Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase cardiovascular disease risk secondary to accelerated atherosclerosis. Similarly, there are data to suggest that patients with giant cell arteritis (GCA), another common chronic inflammatory condition, have an increased risk of coronary artery disease. However, the data on peripheral arterial disease (PAD) remain unclear due to conflicting epidemiological studies. Thus, to further investigate this association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of PAD in patients with GCA versus participants without it.

Methods: Two investigators (P.U. and P.C.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2014 using the terms “giant cell arteritis” and “temporal arteritis” combined with the terms “peripheral artery disease”, “peripheral vascular disease” and “arterial occlusive disease”. A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between GCA and clinically relevant PAD and (2) odds ratios (OR’s), relative risk (RR’s) or hazard ratio (HR’s) or standardized incidence ratio (SIR’s) with 95% confidence intervals (CI’s) were provided. Study eligibility was independently determined by the two investigators noted above. The quality of each study was, again, independently assessed by the two investigators using Newcastle-Ottawa scale. RevMan 5.2 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model. Statistical heterogeneity was assessed using the Cochran’s Q test.

Results: Out of 460 potentially relevant articles, four studies (three retrospective cohort studies and one case-control study) were identified and included in our data analysis. The pooled risk ratio of PAD in patients with GCA was 1.77 (95% CI, 1.01 to 3.12). The statistical heterogeneity of this meta-analysis was high with an I² of 89%.

Conclusion: Our study demonstrated a statistically significant increased PAD risk among patients with GCA.
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The aim of this study was to determine the prevalence and incidence of VTEs in patients with giant cell arteritis (GCA) using a standard case definition. The data source was the Vasculitis Clinical Research Consortium Longitudinal Studies of TAK and GCA, which enrolled patients with new onset or established disease. At baseline visits any history of VTE was recorded to determine the baseline prevalence of VTE. Also collected are data on traditional VTE risk factors such as history of malignancy, hematological disease, and other autoimmune diseases, and use of oral contraceptives or hormone replacement therapy. In follow-up visits, the occurrence of any new/interval VTEs is recorded. The timing of new VTEs in relation to the diagnosis of LVV or to flares of LVV was also evaluated.

Results: 159 patients with TAK and 256 patients with GCA were included for analysis. In patients with TAK, 5 patients (3.1%) had a history of VTE recorded at the baseline visit. No patients had identifiable traditional risk factors for VTE. 4 of the 5 events occurred within 4 years of diagnosis. New VTEs occurred in 4 patients with TAK over a mean observation period of 2.6 years after the baseline visit (incidence 1.0 per 100 person-years vs. a rate of 0.06 per 100 person-years in age matched controls). No patients experienced a flare of vasculitis when a new VTE was recorded. One patient with TAK with a new VTE had a history of inflammatory bowel disease. The overall prevalence of VTE in patients with TAK was 5.7%. In the GCA group, a history of VTE was recorded at the baseline visit in 12 patients (4.7%). One patient had a history of estrogen use; no other patients with VTE had a history of identifiable traditional risk factors for VTE. Over a mean observation period of 3.2 years after the baseline visit, no patients with GCA experienced a new VTE (incidence 0.0/100 person-years). All 21 VTEs in the patients with LVV occurred in females (p < 0.05). 19% of VTEs occurred within one year of diagnosis of LVV.

Conclusion: This is the first large study to describe VTEs in patients with TAK and GCA using a standardized case definition. Patients with TAK but not GCA appear to have an increased risk of developing VTEs after diagnosis, especially among female patients. VTEs in LVV appear likely to occur more frequently around the time of the diagnosis of LVV. In LVV the pathogenesis of VTE, the role of prophylactic antplatelet/anticoagulation therapy, and determining if VTEs should be considered a criterion for disease relapse are all areas for future study suggested by these results.

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Inpatient Complications in Patients with Giant Cell Arteritis: Increased Risk of Thromboembolism, Delirium and Adrenal Insufﬁciency. Sebas-tian Unizony, Mariano Menendez, Naina Rastalsky and John H. Stone. Massachusetts General Hospital, Boston, MA.

Background/ Purpose: The morbidity and mortality of hospitalized giant cell arteritis (GCA) patients has been largely unexplored. The aim of this study was to analyze inpatient complications experienced by patients with GCA.

Methods: We used the Nationwide Inpatient Sample (NIS) database to study a large group of patients admitted with medical and surgical problems that commonly affect the elderly (pneumonia, myocardial infarction, ischemic stroke and femoral neck fracture). Patients were divided in 2 cohorts based on whether or not they carried the diagnosis of GCA. Outcomes evaluated included inpatient mortality, the occurrence of adrenal insufficiency (AI), deep vein thrombosis (DVT), pulmonary embolism (PE), and delirium. GCA and non-GCA groups were compared using chi-square tests. Multivariable logistic regression analysis was performed to control for potential confounders such as age, sex, characteristics of the admitting hospital (teaching versus non-teaching; urban versus rural), and the presence of co-morbid conditions such as diabetes, hypertension, chronic kidney disease, coronary artery disease, and congestive heart failure. In order to maintain the family-wise error rate below a significance level of 0.05, adjustment for multiple comparisons was applied using Bonferroni’s method.

Results: From 2008 to 2011, 8,203,447 patients older than 50 years of age were discharged from acute care facilities across the US after admission with pneumonia (3,232,939), myocardial infarction (2,180,990), ischemic stroke (1,623,564), or hip fracture (1,165,954). Among these individuals, a group of 9,311 (0.11%) carried the diagnosis of GCA. Compared to the non-GCA cohort, GCA patients were significantly older (mean age 80 versus 74 years, p < 0.001) and predominantly female (76% versus 53%, p < 0.001). Most hospitalizations in both GCA and non-GCA subjects occurred in urban locations (90%). During hospitalization, 4.1% of the patients with GCA died in comparison to 4.8% of the individuals without GCA (p = 0.006). After accounting for potential confounding factors, multivariable logistic regression analysis showed that the OR for in-hospital mortality among GCA subjects was 0.73 (95% CI 0.66 – 0.81; p < 0.001). In contrast, when compared with the non-GCA population, those with GCA suffered from DVT (1.5% versus 0.7%), PE (0.9% versus 0.6%), delirium (3.1% versus 1.5%), and AI (1.3% versus 0.3%) significantly more often (p < 0.001). Multivariate analyses revealed that GCA persisted as an independent risk factor for each of these complications. The OR for DVT was 2.08 (95% CI 1.76 – 2.45, p < 0.001); for PE, 1.58 (95% CI 1.27 – 1.96, p < 0.001); for delirium, 1.60 (95% CI 1.42 – 1.80, p < 0.001); and for AI, 4.95 (95% CI 4.13 – 5.93, p < 0.001).

Conclusion: GCA patients admitted for pneumonia, myocardial infarction, ischemic stroke and femoral neck fracture had a slight but significant reduction in inpatient mortality compared to the general population. However, GCA was an independent risk factor for AI, DVT, PE and delirium in the hospitalized population. Increased awareness among providers caring for inpatients with GCA may help prevent, diagnose and treat these important complications.

Disclosure: S. Unizony, None; M. Menendez, None; N. Rastalsky, None; J. H. Stone, None.

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Corticosteroid-Related Adverse Events in Patients with Giant Cell Arteritis: A Claims-Based Analysis. Gordon H. Sun1, Khaled Sarsour2, Eunice Chang1, Michael S. Broder3, Neil Collinson4, Kate Tuckwell5, Pavel Napalkov6 and Micki Klearman7. 1Partnership for Health Analytic Research, LLC, 2Beverly Hills, CA, 3Genentech, Inc., a Member of the Roche Group, 4South San Francisco, CA, 5Roche Products Ltd., Welwyn Garden City, United Kingdom.

Background/ Purpose: Giant cell arteritis (GCA) is an inflammatory vasculitis preferentially affecting large and medium-sized arteries with an incidence of 1 to 30/100,000. High-dose oral corticosteroids (CS) are the mainstay of GCA therapy. We examined the risk of oral CS-related adverse events in a US commercially insured population.

Methods: This was a retrospective cohort study using MarketScan® during 2003–2012. We identified GCA patients who had at least 2 medical claims with a GCA diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification code 446.5), had at least 1 oral CS prescription fill within 6 months before or after the first GCA diagnosis, and were at least 50 years old. Patients were followed for at least 1 year until disenrollment or study end. We measured oral CS use in 3 ways: cumulative number of days, cumulative prednisone-equivalent exposure, and contemporaneous use (time from the date of interest to last oral CS use). We prospectively reviewed published literature to identify adverse events of interest known to
be associated with oral CS use. Adverse events included cataracts, glaucoma, pneumonia, opportunistic infections, peptic ulcer disease, and bone-related conditions. We conducted Cox regression analyses to model oral CS use across time and the resultant risk of developing adverse events.

**Results:** The cohort contained 2,497 GCA patients with mean age 71 years, 71% women, and mean Charlson comorbidity index 1.5. Median initial oral CS dose in the cohort was 40 mg/day. Patients required a median 190 days to reduce this dose to ≤7.5 mg/day and received a median cumulative oral CS dose of 3,380 mg until this level was reached. They required a median 210 days to reach ≤5.0 mg/day and received a median 3,600 mg until this level was reached.

Patients with any adverse event were prescribed more days of oral CS (median 195 vs. 102.5 days) and received a higher cumulative prednisone-equivalent dose (median 3,400 vs. 2,145 mg) than those without an adverse event.

After adjusting for patient characteristics, each additional 1 gram increase in cumulative prednisone-equivalent exposure increased the hazard ratio of developing a first adverse event by 3% (p < .001). Similar patterns of increase were observed for individual adverse events, as well as for adverse event risk regardless of the method used to measure oral CS use (Table). Each additional cumulative month of oral CS increased the hazard ratio for first adverse event by 1% (p = .003). For current oral CS users, the hazard ratio for first adverse event was 1.47 (p = .001) compared to non-users.

**Conclusion:** In a large cohort of GCA patients, high-dose oral CS use was near-universal. Patients were maintained on oral CS for a median 7 months before tapering to a daily dose of ≤5.0 mg. By multiple measures, high-dose oral CS use was associated with a significantly increased risk of adverse events.

**Methods:** Clinical data was available from patients with both IBD and vasculitis with follow-up >6 months enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies, followed in Canadian Vasculitis research network (CanVasc) centers, and/or in the University of Toronto's IBD clinic. Individuals in which ANCA-associated vasculitis (AAV) and IBD were diagnosed within the same 12-month period were excluded because diagnostic misclassification as IBD is common at initial presentation of ileocolitis due to vasculitis. A systematic review of the literature (through 02/2014) for patients with IBD and vasculitis was conducted through a PubMed search. The main characteristics of patients with Takayasu arteritis (TAK) were compared to those patients in the VCRC with TAK but no IBD.

**Results:** 32 patients (17 VCRC, 15 CanVasc) with vasculitis and IBD satisfying our study criteria were identified. The main group included 13 patients with large vessel vasculitis (LVV): 12 TAK and 1 giant cell arteritis; 8 patients had CD and 5 had UC. Eight patients had AAV (6 granulomatosis with polyangiitis, GPA), 2 eosinophilic granulomatosis with polyangiitis, EGPA, 5 isolated cutaneous vasculitis, and 6 other vasculitides (Kawasaki, IgA nephropathy, polyarteritis nodosa, or central nervous system vasculitides). Patients with LVV and AAV were mostly female (1821) with a median age of 20 (8 to 52) and 27 (17 to 58) years at diagnosis of IBD and vasculitis, respectively. The diagnosis of IBD preceded that of vasculitis in 12/13 LVV and 8/8 AAV patients, 3/5 with cutaneous vasculitis and 3/6 with other vasculitides.

305 other patients with IBD and vasculitis were identified in the literature, distributed among 4 similar subsets: LVV (n = 143, 116 female, 69 CD, 74 UC, 132 TAK, 87 with IBD preceding vasculitis), cutaneous vasculitis (n = 66, 33 with IBD preceding vasculitis), AAV (n = 19, 13 GPA, 3 MPA, 3 EGPA), and other vasculitides (n = 77, including IgA vasculitis, renal vasculitis, CNS vasculitis, polyarteritis nodosa, Kawasaki disease, vasculitic neuropathy).

As shown in the Table, no differences other than in ethnicity (likely due to center or publication biases) and age at IBD diagnosis were observed between patients with TAK with or without IBD. Mortality was low.

**804 Vasculitis and Inflammatory Bowel Diseases: A Study of 32 Patients with Both Conditions and Systematic Review of the Literature.** Alice S1, Natasha Dehghan2, Nader A. Khalidi3, Lilian Barra4, Simon Carretta5, David Cuthbertson6, Gary S. Hoffman7, Curry L. Koenig8, Carol A. Langford9, Carol McAlear10, Paul Monach11, Larry W. Moreland12, Philip Seo13, Ulrich Specks14, Steven R. Ytterberg15, Gert Van Assche16, Peter A. Merkel16 and Christian Pagnoux16.

**Vasculitis and Inflammatory Bowel Diseases: A Study of 32 Patients with Both Conditions and Systematic Review of the Literature.** Alice S1, Natasha Dehghan2, Nader A. Khalidi3, Lilian Barra4, Simon Carretta5, David Cuthbertson6, Gary S. Hoffman7, Curry L. Koenig8, Carol A. Langford9, Carol McAlear10, Paul Monach11, Larry W. Moreland12, Philip Seo13, Ulrich Specks14, Steven R. Ytterberg15, Gert Van Assche16, Peter A. Merkel16 and Christian Pagnoux16.

**Conclusion:** These findings highlight the risk in patients with IBD (both CD and UC) to develop vasculitis, especially TAK. Further investigation of patients with both vasculitis and IBD may provide intriguing insights into common underlying mechanisms.

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**805 Takayasu Arteritis and Ulcerative Colitis –High Concordance Ratio and Genetic Overlap.** Chikashi Terao1, Takayoshi Matsumura2, Hajime Yoshii3, Yohei Kin you4, Yasuhiro Maegima5, Yoshikazu Nakao5, Meiko Takahashi6, Etsuko Amiya7, Natsuko Tamura8, Toshiki Nakajima9, Tomoki Oruguch10, Tetsuya Horita11, Mitsuru Matsukura12, Yuta Kochi13, Akiyoshi Ogimoto14, Motohisa Yamamoto15, Hiroki Takahashi16, Shingo Nakayama16;
Kazuyoshi Saito1, Yoko Wada1, Ichiei Narita1, Yasushi K waguchi2, Hisashi Yamakana1, Koichiro Ohmura1, Tatsuya Atsumi1, Kazuo Tanemoto14, Tetsuro Miyata2, Masatasa Kuwashita1, Issei Komuro3, Yashaharu Tabara1, Atsuhisa Ueda3, Mitsuki Isobe3, Tsuneyo Mimori1 and Fumihiko Matsuoka1.

1 Kyoto University Graduate School of Medicine, Kyoto, Japan, 2Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, 3Yokohama City University Graduate School of Medicine, Yokohama, Japan, 4Tokyo Medical and Dental University, Tokyo, Japan, 5Osaka University Graduate School of Medicine, Osaka, Japan, 6Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, 7Hokkaido University Graduate School of Medicine, Sapporo, Japan, 8Ehime University Graduate School of Medicine, Ehime, Japan, 9Sapporo Medical University School of Medicine, Sapporo, Japan, 10University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, 11Niigata University Graduate School of Medicine and Dental Sci ences, Niigata, Japan, 12Tokyo Women’s Medical University, Tokyo, Japan, 13Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 14Kawasaki Medical School, Kurashiki, Japan, 15Keio University School of Medicine, Tokyo, Japan.

### Background/Purpose: Takayasu arteritis (TAK) is a systemic vasculitis affecting large arteries and large branches of the aorta. Ulcerative colitis (UC) is a prevalent autoimmune colitis. Since TAK and UC share HLA-B*52:01, we hypothesized that UC is a common complication of TAK.

### Methods: A total of 470 consecutive patients with TAK from 14 Japanese institutions were registered. We found that 29 patients out of 470 patients with TAK suffered from UC (6.2% (95%CI:4.2%-8.7%)). The patients with the two diseases did not display higher frequency of aortic regurgitation (AR) or severer AR than patients without UC. While the TAK patients with UC had higher percentage of Th1 and Th17 cells than HC, and R-group had higher percentage of Th17 cells than HC, and R-group had higher percentage of TH1 cells in patients with TAK compared to healthy controls, suggesting their role that regulates differentiation and activation of Th1 and Th17. In the present study, we investigated the association of this SNP with clinical characteristics and pathophysiology of TAK.

### Results: 1) In 84 patients with TAK, 68 were the risk group (R-Group: AA+AC) and 16 were the non-risk group (NR-Group: CC). The complication rate of aortic regurgitation (AR) was 51% in R-Group, significantly higher than 13% in NR-Group (p<0.01). The ultrasound-evaluated severity of AR was higher in R-Group (p<0.01). GFR tended to be lower in R-Group than in NR-Group (70.5 vs. 80.3 mL/min/1.73m², p=0.2). The complication rate of abdominal arterial lesions was 58% in R-Group, significantly higher than 27% in NR-Group (p<0.05). 2) In 21 patients with TAK analyzing T cells, 14 and 7 were R-Group and NR-group, respectively. In CD4+ T cells, CXCR3+ (Th1) cells were 6.9% in patients (7.5% in R-Group and 5.7% in NR-Group), tended to be higher than 5.7% in HC (p=0.16), while CCR6+ (Th17) cells were 16.0% in patients (16.5% in R-Group and 15.4% in NR-Group), significantly higher than 8.3% in HC (p<0.01). In CD4+ T cells, IFN-γ+ cells in R-group was significantly higher than in NR-group (23% vs. 18%, p=0.02), while IL-17+ cells were not significantly different between R-Group and NR Group (0.7% vs. 1.4%, p=0.37).

### Conclusion: In TAK patients with the risk allele of IL-12B, the complications of aortic valve and abdominal arteries were more frequent than in patients without the risk group. TAK patients show that this SNP may be involved in the pathophysiology of TAK through increased expression of cytokines.

### Disclosure: T. Nakajima, None; H. Yashitufu, None; C. Terao, None; K. Kitagori, None; R. Nakashima, None; Y. Imura, None; N. Yukawa, None; K. Ohmura, None; T. Fuji, None; T. Mimori, None.

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### Serum Cytokine Profiles in Takayasu’s Arteritis: A Search for a Biomarker, Fatma Alibaz-Oner1, P. Sibel Yentur2, Guher Saruhan-Direskeneli3 and Haner Direskeneli1.

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### Background/Purpose: Assessment of disease activity is one of the main difficulties in patients with Takayasu Arteritis (TAK) during follow-up. In this study, we aimed to investigate serum interleukin (IL)-6, IL-8, IL-10, IL-18, IL-23 and granulocyte-macrophage colony-stimulating factor (GM-CSF), as possible biomarkers of disease activity in patients with TAK.

### Methods: The study included 51 patients (age: 30.6±12.2 years, F/M: 45/6) with TAK and 42 age and sex matched healthy controls (age: 38.1±7.4 years, F/M: 38/4). All patients with TAK fulfilled the criteria of American College of Rheumatology (ACR) and were evaluated by physician’s global assessment (PGA: active/inactive) and ITAS2010 (Indian Takayasu Clinical Activity Score) in terms of clinical activity at baseline and follow-up visits. Commercial enzyme linked immunoassay test (ELISA) kits were used for the measurements of serum IL-6, IL-8, IL-10, IL-18, IL-23 and GM-CSF.

### Results: At baseline, 21 (41.2%) patients were active assessed with PGA and 8 (15.7%) by ITAS2010. Serum IL-10 and IL-18 were significantly higher in patients with TAK (IL-6, IL-8 and HC levels were significantly higher in patients with TAK (IL-6, IL-8 and HC, respectively; 194.7±485 (0–2555) vs 64.3±156.8 (0–748), 49.4±189 (0–1349) vs 8.4±23.8 (0–97), 535.1±252 vs 268.8±216.2), whereas GM-CSF, IL-10 and IL-23 levels were similar to healthy controls. Comparing baseline and follow-up visits, IL-8 levels significantly decreased in follow-up together with a decrease of clinical activity by PGA, whereas IL-23 levels significantly increased. IL-18 levels were associated with disease activity assessed with ITAS2010, but not with PGA. IL-18 was also the only cytokine correlated with GFR. No association of IL-6 levels were observed with disease activity.

### Conclusion: We found significantly increased IL-6, IL-8 and IL-18 levels in patients with TAK compared to healthy controls, suggesting their role in disease pathogenesis. However, no consistent association of any

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cytokine is observed with disease activity to use as a biomarker. In addition to anti-IL-6 treatment currently investigated, blockage of other pro-inflammatory cytokines IL-8 and IL-18 might be new therapeutic approaches in refractory TAK.

Disclosure: F. Alibaz-Onen, None; P. S. Yentur, None; G. Saruhan-Direskeneli, None; H. Direskeneli, None.

808 Biomarkers of Disease Activity in Vasculitis. Alicia Rodriguez-Pla1, Roscoe L. Warner2, David Cuthbertson3, Simon Carette4, Gary S. Hoffman5, Nader A. Khalidi2, Curry L. Koening6, Carol A. Langford7, Kathleen Maksimovicz-Mckimmon7, Larry W. Moreland8, Christian Pagnoux9, Philip Sse10, Ulrich Specks12, Kenneth J. Warrington12, Steven R. Ytterberg13, Peter A. Merkel13, Kent J. Johnson12, Paul A. Monach14 and For the Vasculitis Research Consortium15. 1Boston University, Boston, MA, 2University of Michigan, Ann Arbor, MI, 3University of South Florida, Tampa, FL, 4University of Toronto, Toronto, ON, 5Cleveland Clinic Foundation, Cleveland, OH, 6McMaster University, Hamilton, ON, 7Cleveland Clinic, Cleveland, OH, 8University of Pittsburgh, Pittsburgh, PA, 9Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, 10Mayo Clinic, Rochester, MN, 11Vasculitis Center, University of Pennsylvania, Philadelphia, PA, 12Vasculitis Center, Boston University School of Medicine, Boston, MA, 13U Pennsylvania, Philadelphia, PA.

Background/Purpose: To identify circulating proteins that distinguish between active vasculitis and remission in giant cell arteritis (GCA), Takayasu’s arteritis (TAK), polyarteritis nodosa (PAN) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss), using a panel of markers known to be elevated in ANCA-associated vasculitis.

Methods: 22 serum proteins (MMP-3, NGAL, ACE, sIL-6R, osteopontin, PAI-1, PDGF-AB, RANTES, sICAM-1, TIMP-1, BCA-1, G-CSF, GM-CSF, IFNγ, IL-15, IL-18, IL-18BPa, sIL-2Ra, IL-6, IL-8, IP-10, and sTNFRII) linked to possible pathways relevant to vasculitis were measured using a microarray platform. Disease activity during the past 28 days was classified by physician global assessment (PGA), where remission is indicated by PGA = 0 and active disease by PGA 1–10. Spearman’s correlation was used to study the association between serum proteins and ESR. To compare marker values between active disease and remission, mixed models were used to account for repeated measures with unequal spacing between visits. Prednisone and immunosuppressive treatments were included as independent variables. Fold-change (FC) in marker values between active and mean remission values was used as the measure of effect.

Results: 479 samples from 174 patients (66 GCA, 35 TAK, 31 PAN, 42 EGPA, with 1 active visit and 3 remission visit samples per patient) were tested. 440 samples (92%) were obtained while the patient was on treatment. Disease activity ranged from PGA 1 to 9. In GCA, sIL-6R (FC 1.1, p = 0.024), BCA-1 (FC 2.08, p = 0.008), GM-CSF (FC 32.5, p = 0.04; 7 patients with FC >2), IL-18BPa (FC 1.16, p = 0.026), sIL-2Ra (FC 2.03, p = 0.018), IL-6 (FC 2.54, p = 0.032), and TIMP-1 (FC 1.18, p = 0.034) were significantly higher in active than remission samples; in TAK, only IL-18BPa was higher in active than in remission samples (FC 1.16, p = 0.029); and in PAN, only MMP-3 was significantly different, being higher in remission samples (FC 0.71, p = 0.045), ESR was significantly elevated in active GCA (FC 1.43, p < 0.001) and PAN (FC 1.45, p = 0.013). Significant differences were observed in TAK or EGPA. The correlation of ESR with the majority of the protein markers was weak; the highest correlation was observed in GCA with IL-6 (r = 0.34, p < 0.0001). FC and p-values were similar when use of prednisone and other immunosuppressive drugs were included in the models. The majority of the samples were obtained while the patients were on prednisone (81.2% of the active and 79.1% of the remission samples). Trajectories of selected markers are shown in Figure 1.

Conclusion: This study identifies several potential biomarkers of disease activity in GCA, although effect sizes were modest in this partially-treated cohort. Promising markers included several cytokines (IL-6, GM-CSF, BCA-1), soluble cytokine receptors (sIL-6R, IL-18BPa), and the metalloproteinase inhibitor TIMP-1. Larger studies are needed to test the utility of these biomarkers for disease monitoring.

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Background/Purpose: Takayasu arteritis (TA) is a chronic inflammatory disease that primarily affects large vessels, such as the aorta and its main branches. To report clinical features, morphologic findings, treatment and long-term outcome of a large cohort of patients with TA, and to determine risk factors for the occurrence of severe ischemic complications (SIC) during follow-up.

Methods: We performed a retrospective multicenter study of characteristics and outcomes of 182 patients with TA fulfilling the American College of Rheumatology criteria. Characteristics at presentation, SIC, relapses and deaths were recorded.

Results: The median age [interquartile range] at onset of symptoms was 31 [24; 45] years and with a predominance of females (85%). The median delay of diagnosis was 10 [0; 47] months. The most common clinical findings were vascular bruits (52%), unequal or absent pulses (47%), and upper extremity blood pressure discrepancy >10 mm Hg (44%). Major complications at diagnosis were hypertension (36%), aneurysms (24%), and aortic regurgitation (18%). Forty percent of patients had extensive disease at diagnosis according to Numano type V. Twenty percent of patients had another inflammatory or auto-immune disease associated to TA, mostly ankylosing spondylitis, crohn disease and sarcoidosis. Stenotic lesions were 3.1-fold more common than were aneurysms (78% versus 25%, respectively). Revascularization procedure was required for 49% of patients. The median delay between diagnosis and first surgery or endovascular intervention was 5 [0; 17.5] months. Glucocorticoids were prescribed in 151 (83%) patients. The median delay in initiation of corticosteroids was 1 [0; 5] months. Fifty eight percent of patients required additional immunosuppressive agent. The median delay in initiation of the first immunosuppressor was 11 [2; 29.5] months. Twenty six percent of patients required three or more antihypertensive drugs. SIC occurred in 38 (21%) patients after TA diagnosis. SIC-free
survival at 10 years was 82% in patients without refractory hypertension versus 34% in patients with refractory hypertension (i.e., requiring ≥ 3 antihypertensive drugs) (P = 0.003). SIC-free survival at 5 years was 89% in patients with immunosuppressive agent versus 78% without immunosuppressive agent (P = 0.175). In multivariable analysis, predictive variables for the occurrence of SIC after TA diagnosis were refractory hypertension (OR 12.03 [95%CI 2.78–52.07], P = 0.001), relapse (OR 7.11 [95%CI 1.82–27.78], P = 0.005) and SIC at time of TA diagnosis (OR 4.65 [95%CI 1.10–19.67], P = 0.036). Forty percent relapsed after a median follow-up of 69 [31; 145] months. The median relapse-free survival was 16 [7; 62] months. The mortality rate was 12%. Five of 7 (71%) deaths were related to cardiovascular complication.

**Conclusion:** In this cohort of TA patients, risk factors for late-developing SIC were refractory hypertension, relapse and SIC at time of TA diagnosis. Immunosuppressive agents may reduce late-developing SIC. Despite prolonged and intensive therapy, TA remains a major cause of cardiovascular morbidity.


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**Damage Assessment in Takayasu Arteritis Using Takayasu Arteritis Damage Score (TADS),** Debashish Danda¹, Ruchika Goel², Raheesh Ravindran and George Joseph². ¹Christian Medical College, Vellore Tamilnadu, India, ²Christian Medical College & Hospital, Vellore, India.

**Background/Purpose:** Takayasu arteritis (TA) is a prototype large vessel vasculitis. Assessment of disease activity and damage has been challenging in TA due to lack of composite indices and biomarkers. TADS is damage index devised by the Indian Rheumatology Association Vasculitis Group. It consists of 42 items with 8 from cardiovascular system, classified under 7 headings. Only features persistently present at least at 50%.

**Methods:** TADS and DELTAK were calculated prospectively at baseline visit for incident patients with TA (ACR 1990 classification criteria) from our rheumatology and cardiology clinics between May 2012 and May 2014. TADS of this prospective cohort was compared with that calculated retrospectively for TA patients presenting to us prior to May 2012. SPSS version 16 was used; data was depicted as median (Inter Quartile Range) and Pearson’s correlation coefficient between TADS and selected parameters was done.

**Results:** A total of 102 consecutive TA patients (80 females, 22 males) with age of 27.5 (20.7–36) years, disease duration of 27 (9.8–65.8) months and diagnostic delay of 12 (6–36) months were recruited. Type 5 was the commonest angiographic type (n=60; 59%) with DELTAK of 9 (7–13) at presentation. Coronaries and pulmonary artery were involved in 18 and 9 patients respectively. Median TADS score at presentation was 6.0 (4–10) with a third of our patients (n=34) having very high damage score (TADS >8). Absent arterial pulse (59%), persistent claudication (59%), hypertension (56%), persistent dyspnea (41%) and cardiac damage (23.5%) contributed to most of the damage as reflected in TADS. Period of delay in diagnosis and age at presentation did not correlate with the damage score (r= - 0.073 and -0.87 respectively).

A marginally lower TADS (6.0 (4–10)) at presentation in the prospective cohort of 102 patients was noted as compared to that [8(4–11)] of the earlier retrospective cohort of 48 patients whose TADS was calculated from hospital records. No other parameter was different between these two cohorts. A follow up of these 48 patients for 36 (24–57) months showed an insignificant rise in TADS to 9(6–12) at the last recorded visit from 8(4–11) at baseline, in spite of treatment with steroids and 2nd line cytotoxic agents in all.

**Conclusion:** This is the first study using TADS for damage assessment in a large cohort of TA. Over these years, TA continues to be associated with high damage score right from its initial presentation.

Ongoing damage can probably be prevented by aggressive immunosuppression from early disease.


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**Biologies in Takayasu Arteritis: Preliminary Data from the French Registry,** Arsene Mekinian¹, Chloe Comarmond², Mathieu Resche Regon³, Tristan Mirault¹, Jean-Emmanuel Kahn⁴, Marc Lambert⁴, Jean Sibilia⁵, Antoine Neel⁶, Miguel Hiez⁶, Emmanuel Messas⁷, Pascal Cohen¹, Geraldine Muller², Sabine Berthier³, Zahir Amoura⁴, Isabelle Marie⁵, Christian Lavigne⁶, Marie Anne Vandenhende⁷, Hervé Devilliers⁷, Sébastien Abad⁸, Loïc Guillemin⁹, Mohamed Hamidou¹⁰, Bertrand Godet¹¹, Patrice Cacoub¹², Olivier Fain¹³, and David Saadoun¹⁴. ¹DHU 2iB, Internal medicine, Saint Louis Hospital, Paris, France, ²DHU 2iB, Internal medicine, Pitie-Salpetriere, AP-HP, ³HEGP hospital Vascular and cardiology Department, Paris, France, ⁴Hôpital Pitie-Salpetriere, AP-HP, ⁵UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, ⁶HEGP vascular and cardiology department, Paris, France, ⁷Hospital Saint Antoine, Pitie-Salpetriere, AP-HP, ⁸Internal Medicine, Foch Hospital, Suresnes, France, ⁹Internal Medicine University Lille Hospital, Lille, Lille, France, ¹⁰University Hospital of Strasbourg, Strasbourg, France, ¹¹Internal Medicine, Nantes, France, ¹²Hôpital Pitie-Salpetriere, AP-HP, ¹³UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, ¹⁴HEGP Hospital Vascular and cardiology Department, Paris, France, ¹⁵National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, ¹⁶Internal Medicine, Dijon, France, ¹⁷Dijon Hospital, Dijon, France, ¹⁸Pitié-Salpêtrière Hospital (AP-HP), Paris, France, ¹⁹CHU de Rouen, Rouen, France, ²⁰CHU d’Angers, Angers, France, ²¹Internal Medicine, Bordeaux, France, ²²Departement de Medicine Interne, hospital Saint-Antoine, Paris, France, ²³Groupe Hospitalier Pitié-Salpêtrière, Service de Médecine Interne, Hôpital Cochin, 75005 Paris, France, ²⁴CHU Hôtel Dieu, Nantes, Nantes, France, ²⁵Service de médicine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, ²⁶Hôpital Saint-Antoine, DHU 2B, Service de Médecine Interne, paris, France.

**Background/Purpose:** The aim of this registry is to determine: (1) the real-life use of various biological targeted treatments in Takayasu arteritis (TA) in France; (2) to compare the efficacy of different biologics among them; (3) to evaluate the tolerance.

**Methods:** French practitioners from the departments of internal medicine, of vascular medicine and rheumatology were contacted to declare the patients with TA under biologics. Complete response was defined as the NIH<2 with prednisone<10 mg/day, the partial response as NIH and prednisone decrease at least at 50%.

**Results:** Forty eight patients with TA (age 42 years [20–55], 38 women) were included with 74 treatment lines including various biologics. The biologics were mostly used in second-line (n=21; 29%) and third-line regimen (n=27; 37%) for steroid dependence, non-response or relapses. At the initiation of the biologics, the vascular symptoms were present in 39 (67%) cases, constitutional signs in 25 (46%), with radiological activity in 37 (64%) of cases. NIH was ≥2 in 62 (93%) cases.

Among the biologics, most of the patients were treated by infliximab (59%), etanercept (8%), adalimumab (8%), tocilizumab (19%), anakinra (3%) and rituximab (3%). The biologics duration was 1.8±1.1 year, with the mean follow-up of 3±1.5 years. A complete/ partial response to biologics was shown in 15 (39%) and 17 (44%) of patients at 3 months, and 23 (62%) and 4 (11%) at 6 months, whereas a non-response was noted in 7 (18%) and 10 (27%), respectively. During the follow-up, NIH, C-reactive protein levels and prednisone amount significantly decreased (p<0.001). Only 58% of patients were still under steroids at 3 years versus 82% before biologics.

The comparison of patients treated with TNFa antagonists (n=55) to patients with tocilizumab (n=14) showed that the number of partial/complete responses was similar at 3 and 6 months, as were the NIH scale and the C-reactive protein activity, with radiological activity decreasing significantly (p<0.001). Only 58% of patients were still under steroids at 3 years versus 82% before biologics.

The comparison of patients treated with TNFa antagonists (n=55) to patients with tocilizumab (n=14) showed that the number of partial/complete responses was similar at 3 and 6 months, as were the NIH scale and the associated immunosuppressive agents.

Six infliximab related reactions were noted (influniximab in 5 cases and tocilizumab in one), one EBV reactivation (influniximab) and 5 severe infections (3 with infliximab, one with etanercept and tocilizumab, respectively). One patient under tocilizumab experienced severe neutropenia (<500/mm³), but without any infection or antibiotics need in relation with tocilizumab.
Two neoplasms occurred during the biologics treatment, one lung cancer (infliximab) and one breast cancer (tocilizumab).

**Conclusion:** This is the first nationwide registry of TA treated by biologics which show an overall response rate to biologics, with similar response rates between TNFα antagonists and tocilizumab.

### Table 1 Presenting Demographics & Disease Parameters

<table>
<thead>
<tr>
<th>Demographic/Disease Parameter</th>
<th>Mean Age</th>
<th>Female (%)</th>
<th>White (%)</th>
<th>Comorbidities</th>
</tr>
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<tbody>
<tr>
<td><strong>Structural Renal Disease (%)</strong></td>
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<td>2 (13)</td>
<td>8 (50)</td>
<td>3 (19)</td>
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<tr>
<td><strong>Inflammatory Bowel Disease (%)</strong></td>
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<td>1 (6)</td>
<td>5 (31)</td>
<td>3 (19)</td>
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<tr>
<td><strong>Hypertension (%)</strong></td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>8 (50)</td>
<td>3 (19)</td>
</tr>
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<td><strong>Other (%)</strong></td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>8 (50)</td>
<td>3 (19)</td>
</tr>
<tr>
<td><strong>Mental Illness (%)</strong></td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>8 (50)</td>
<td>3 (19)</td>
</tr>
<tr>
<td><strong>≥ 3 ACR Criteria Met (%)</strong></td>
<td>18 (40)</td>
<td>18 (40)</td>
<td>45 (56)</td>
<td>9 (56)</td>
</tr>
</tbody>
</table>

**Figure 1.** Cumulative probability of activation in patients with clinically inactive TA

**Disclosure:** S. H. Bae, None; S. Hong, None; S. M. Ahn, None; D. H. Lim, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

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**Prognosis of Clinically Inactive Takayasu’s Arteritis.** Seung-Hyeon Bae, Seokchon Hong, Soo Min Ahn, Doo-Ho Lim, Yong-Gil Kim, Chang-Keun Lee and Bin Yong, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

**Background/Purpose:** Takayasu’s arteritis (TA) is a chronic inflammatory vasculitis, and immunosuppressants including glucocorticoids are generally required for treatment. Although, some portions of patients with TA have no evidence of active disease at the time of diagnosis, but the prognosis has not been reported. Therefore, aim of our study is to investigate the outcome and to identify the predictors of activation of clinically inactive TA.

**Methods:** We reviewed data of patients who was diagnosed with TA according to the 1990 ACR classification criteria between January 1990 and December 2012 at the Asan Medical Center. Patients were classified as an inactive disease at the time of diagnosis, based on the NIH definition of active disease in TA. During follow-up, activation of TA was defined based on acquisition of criteria for active disease. The pattern of vascular involvement was classified according to the International Conference on TA in Tokyo, 1994.

**Results:** Total 199 TA patients were identified, and 59 (29.6%) patients were classified as inactive disease at the time of diagnosis. The mean age of 59 patients was 42.9 ± 12.9 years and 50 (84.7%) patients were female. The median follow-up duration was 58 months (IQR, 37.0–107.0). During follow-up, 13 (22.0%) patients experienced disease-activation of TA with median 37.0 months (IQR, 23.5–46.5) after the diagnosis of TA (activation group). On the other hand, remaining 46 (78.0%) patients did not experience the activation (stable group). There were no significant differences in baseline clinical characteristics and laboratory findings between activation group and stable group. The presence of renovascular hypertension, however, was more commonly observed in activation group than in stable group (4/13, 38.5% vs. 4/46, 8.7%, p = 0.019). Further, type V, which is the most extensive type in involved pattern, was found more frequently in activation group (12/13, 92.3%) than in stable group (18/46, 39.1%, p = 0.008). In a multivariate analysis, involvement of type V (OR = 10.969, 1.144–105.182, p = 0.038) was significantly associated with increased risk for disease activation in clinically inactive TA. In addition, the cumulative probability of activation was significantly higher in TA patients with type V than those without type V by Kaplan–Meier analysis (p = 0.002) (Figure 1).

**Conclusion:** In the present study, substantial portions of patients with clinically inactive TA at diagnosis experienced an activation of disease during long-term follow-up. We suggested that the type V angiographic pattern can be used as an important predictor for disease activation.

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**Long-Term Outcomes of Takayasu’s Arteritis Patients with Renal Involvement.** Cortisande Baldwin1, Aladdin Mohammad2 and David Jayne3. 1University of British Columbia, Vancouver, BC, 2Lund University, Lund, Lund, Sweden, 3Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom.

**Background/Purpose:** Takayasu’s Arteritis (TAK) is a chronic inflammatory large vessel vasculitis characterized by granulomatous inflammation of the aorta and its branches. TAK incidence is 2.6/million annually in Minnesota. Prevalence is higher in Asian and Indian populations. TAK predominantly affects younger woman under 40 years of age. Renal artery involvement (RAI) in TAK is a poor prognostic factor. However, long-term outcomes of TAK patients with RAI have not been reported.

**Methods:** We performed a retrospective chart review of 37 patients from Addenbrookes’ Hospital, UK, and 13 patients from Skane University Hospital, Sweden. Diagnosis of TAK was based on the presence of constitutional symptoms, elevated inflammatory markers, and vascular abnormalities on angiography. RAI was identified based on conventional, CT or MR angiography. Data was collected on patient demographics and presenting symptoms, signs, co-morbidities, blood pressure and medications. Laboratory values including creatinine, erythrocyte sedimentation rate, and e-reactive protein were collected. Disease activity was assessed using the Indian Takayasu Activity Index 2010 (ITAS2010). Irreversible organ damage was assessed using the vasculitis damage index (VDI). Worsening or improved renal function was defined as a drop or increase in eGFR > 20%.

**Results:** Sixteen of 50 (32%) TAK patients were identified to have RAI. Presenting demographics and disease parameters are summarized in Table 1. Two patients had structural renal disease (PUI obstruction and prior renal surgery undefined) and are among the 7 patients with renal asymmetry; one was among the nine patients with pre-existing hypertension. The three with eGFR < 60 ml/min had moderate renal dysfunction (eGFRs of 45, 57, and 59 ml/min).
Follow-up data is presented in Table 2. Median follow-up duration was 8.8 years (10 months - 30 years). Among the 13 with hypertension including two who developed hypertension over the follow-up period; 11 were on anti-hypertensive drugs. Among the six patients with renal asymmetry; five were known and one developed this over the follow-up period. Among those with eGFR < 60 ml/min at presentation, one improved, one declined (patient with PUJ obstruction), and one remained stable.

Table 2: Follow-up Disease Parameters

<table>
<thead>
<tr>
<th></th>
<th>Pre and Post Demographics</th>
<th>Presentation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td>13 (9–18)</td>
</tr>
<tr>
<td>Systemic Therapy (%)</td>
<td>–</td>
<td>15 (94)</td>
<td>7 (1–13)</td>
</tr>
<tr>
<td>Angiography**</td>
<td>–</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>Unchanged (%)</td>
<td>–</td>
<td>12 (86)</td>
<td></td>
</tr>
<tr>
<td>Improved (%)</td>
<td>–</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Complete Resolution (%)</td>
<td>–</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Median VDI (range)**</td>
<td>–</td>
<td>5 (0–9)</td>
<td></td>
</tr>
<tr>
<td><strong>Change in eGFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable (%)</td>
<td>–</td>
<td>7 (44)</td>
<td></td>
</tr>
<tr>
<td>Improved (%)</td>
<td>–</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>Reduced (%)</td>
<td>–</td>
<td>3 (19)</td>
<td></td>
</tr>
</tbody>
</table>

* Follow-up ITAS2010 score only available for 10 patients ** Follow-up renal angiography available for 14 patients *** Not calculated at presentation

Conclusion: The prevalence of RAI in this population (32%) is comparable to that in the literature. Hypertension was common. Most patients had normal eGFRs, despite severe disease. Disease progression was minimal. Our results suggest renal prognosis is better than previously thought.

Disclosure: C. Baldwin, None; A. Mohammad, None; D. Jayne, None.

Tocilizumab in Giant Cell Arteritis: Multicenter Open-Label Study of 22 Patients.

Montserrat Santos-Gómez1, Javier Loricera1, Ricardo Blanco1, Jose L. Hernández1, Antonio Mera2, Eva Pérez-Pampín3, M. Enriqueta Pérez-Pampín4, Santos Castañeda-Sanz2, Alicia Humbria5, Jaime Calvo-Alen6, Elena Aurreroccecha7, Javier Narváez2, Amalia Sánchez-Andrade8, Paloma Vela9, Elvira Díez Álvarez10, Cristina Mata10, Pablo Lluch Mesquida10, Concepción Moll Tuduri10,11, Vanesa Calvo-Río10,11, Francisco Ortiz-Sanjuán10,11, Trinitario Pina Murcia10,12, Carmen Gonzalez-Vela13, Leyre Riancho-Zarrabeitia14 and Miguel A. González-Gay15.

1Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, 2Hospital Clínico Universitario de Santiago de Compostela. Spain, Santiago de Compostela, Spain, 3Hospital Universitario de La Princesa. Madrid. Spain, Madrid, Spain, 4Hospital Universitario La Princesa. IIS-Princesa, Madrid, Madrid, Spain, 5Hospital Universitario de La Princesa. IIS-Princesa, Madrid, Madrid, Spain, 6Hospital Universitario de La Princesa. IIS-Princesa, Madrid, Madrid, Spain, 7Hospital Universitat Raval. Barcelona. Spain, Barcelona, Spain, 8Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 9Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 10Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 11Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 12Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 13Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 14Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, 15Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Giant cell arteritis (GCA) is a primary vasculitis that involves the aorta and its major branches. It usually affects people aged more than 50 years. GCA may be refractory to standard therapy with corticosteroids that, in turn, may be associated with substantial adverse events. Tocilizumab (TCZ) has demonstrated efficacy in single cases or in small series of patients with GCA. Our aim was to assess the efficacy and side-effects of TCZ in a multicenter study of patients with refractory GCA.

Methods: Multicenter open-label study of patients with refractory GCA. TCZ was used because of inadequate response to corticosteroids and in most cases to other therapies. All the patients meet the 1990 ACR criteria for GCA. TCZ therapy was used at standard dose of 8 mg/kg/monthly.

Results: 22 patients (17 women/ 5 men; mean age±SD was 69±8 years) were assessed. Sixteen (73%) of them had a positive temporal artery biopsy. The main clinical features at the time of TCZ onset were: polymyalgia rheumatica (n=15), asthenia (n=7), headache (n=5), constitutional syndrome (n=4), jaw claudication (n=2), visual manifestations (n=2), claudication of the lower limbs (n=1), chest pain (n=1), arthritis (n=1), dyspnea (n=1) and scapular pain (n=1). Fifteen patients also had aortitis. Besides corticosteroids and before TCZ therapy, 19 patients had received several traditional immunosuppressive agents: methotrexate (n=19), azathioprine (n=1) and leflunomide (n=1). In addition, 2 patients had been treated with other biologic agents before starting on TCZ. One patient received etanercept that was switched to TCZ due to inefficacy. Another patient received infliximab that was switched to rituximab, then to abatacept and finally to TCZ because of inefficacy. Most patients experienced clinical and laboratory improvement within the first 3 months after the onset of TCZ (Table). After a median [IQR 25th–75th] follow-up of 6 [3–16] months, the erythrocyte sedimentation rate decreased from a median value of 44 [20–81] to 12 [3–20] mm/1st hour. Similarly, C-reactive protein levels also decreased from a median initial value of 1.9 [1.2–5.4] to 0.2 [0.1–0.9] mg/dL. A corticosteroid sparing effect was also achieved (from a median [IQR] prednisone dose of 18.75 [10–45] mg/day at TCZ onset to 5 [0–7.5] mg/day at last visit). In 3 patients TCZ was discontinued due to severe neutropenia (351 neutrophils/mm3); recurrent pneumonia; and cytomegalovirus infection, respectively. One of the patients had died after the second infusion of TCZ as the result of a stroke in the setting of an infectious endocarditis.

Conclusion: In our series, TCZ seems to be effective in the treatment of GCA refractory to corticosteroids and other immunosuppressive agents.

Table

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>Basal*</th>
<th>Month 3*</th>
<th>Month 6*</th>
<th>Month 12*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyalgia rheumatica, %</td>
<td>68</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>Constitutional syndrome, %</td>
<td>18</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
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<tr>
<td>Headache, %</td>
<td>23</td>
<td>10*</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>Laboratory parameters, median [IQR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>1.9 [1.2–5.4]*</td>
<td>0.1 [0.01–0.3]*</td>
<td>0.1 [0.01–0.2]*</td>
<td>0.3 [0.1–1.8]*</td>
</tr>
<tr>
<td>Prednisone dose (mg/day), median [IQR]</td>
<td>18.75 [10–45]*</td>
<td>9.37 [5–10]*</td>
<td>5 [5.6–25]*</td>
<td>2.5 [0–5]*</td>
</tr>
</tbody>
</table>

*p<0.05 compared to baseline

Disclosure: M. Santos-Gómez, None; J. Loricera, None; R. Blanco, None; J. L. Hernández, None; A. Mera, None; E. Pérez-Pampín, None; M. E. Peiró, None; S. Castañeda-Sanz, None; A. Humbria, None; J. Calvo-Alen, None; E. Aurreroccecha, None; J. Naveiro, None; A. Sánchez-Andrade, None; P. Vela, None; E. Diez Álvarez, None; C. Mata, None; P. Lluch Mesquida, None; C. Moll Tuduri, None; V. Calvo-Río, None; F. Ortiz-Sanjuán, None; T. Pina Murcia, None; C. Gonzalez-Vela, None; L. Riancho-Zarrabeitia, None; M. A. González-Gay, None.

ACR Plenary Session I: Discovery 2014

Sunday, November 16, 2014, 11:00 AM–12:30 PM

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Netosis Induced Histone Citrullination Facilitates Onset and Propagation of Rheumatoid Arthritis. Dong Hyun Sohn1, Kazuhiro Onuma1, Chris Rhodes1, Xiaoyan Zhao1, Tal Gazit2, Rami Shiao1, Justyna Fert Bober3, Danye Cheng1, Lauren J. Lahey4, Heidi Wong5, Jennifer van Eyk1, William H. Robinson1 and Jeremy Sokolove1.

1VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, 2University of Washington, Seattle, WA, Johns Hopkins University and Cedars Sinai Medical Center, Los Angeles, CA, 3Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Anti-citrullinated protein antibodies (ACPs) are characteristic of rheumatoid arthritis however, their presence years before onset of clinical RA is perplexing. Although multiple putative citrullinated
antigens have been identified, including citrullinated products of NETosis, no studies have demonstrated the capacity of these antigens to initiate inflammatory arthritis. We sought to identify citrullinated products of NETosis targeted by the RA immune response and with the capacity to drive inflammatory arthritis.

Methods: We performed proteomic analysis of human NETs to identify all citrullinated proteins including those targeted as part of the RA immune response. Using a combination of ELISA and IHC we compared RA and OA serum, synovial fluid and synovial tissue for levels of histone 2B (H2B), anti-H2B antibodies, as well as H2B-containing immune complexes. Using macrophage activation assays we assessed the effect of histone citrullination on immunostimulatory capacity and evaluated the stimulatory capacity of native and citrullinated H2B-containing immune complexes. Finally, we immunized mice with citrullinated H2B (cH2B) with and without the induction of low grade collagen induced arthritis to assess the potential for anti-cH2B antibodies to mediate arthritis in vivo.

Results: Proteomic interrogation of NET-derived proteins, RA serum, synovium, and synovial fluid identified robust targeting of NET-derived citrullinated histones by the ACPA immune response. Over 90% of RA patients have anti-cH2B antibodies and over half have measurable levels of synovial fluid H2B immune complexes. We observe that histone citrullination increases innate immunostimulatory capacity and that immune complexes containing citrullinated histones both activate macrophage cytokine production and propagate NETosis. Finally, we demonstrate that autoimmunity to cH2B is arthritogenic, both by primary immunization as well as immune serum transfer, but only in the setting of underlying low grade articular inflammation.

Conclusion: We identify cH2B as an antigenic target of the ACPA immune response and our findings suggest that intra-articular histone citrullination can link innate immunity via NETosis and adaptive immunity via generation of citrullinated histone immune complexes. The generation of citrullinated histone antigens during low grade articular inflammation provides a potential mechanism for the conversion from asymptomatic ACPA seropositivity to clinical RA.

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TRNT1 Missense Mutations Define a New Periodic Fever Syndrome. Angeliki Giannelou1, Qing Zhou2, Monique Stoffels3, Amanda Ombrello4, Deborah Stone5, Jehad H. Edwan6, Martin Pelletier6, Wanxia Tsai7, Katherine Calvo8, Sergio Rosenzweig9, Karyl Barron10, Massimo Gadina11, Ivona Aksentijevich12 and Daniel L. Kastner2. 1National Institute for Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, 2National Human Genome Research Institute, Bethesda, MD, 3National Human Genome Research Institute, Bethesda, MD, 4National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, 5NIAMS NIH, Bethesda, MD, 6Immune Regulation Section, Autoimmunity Branch, Bethesda, MD, 7NIAMS/NIH, Bethesda, MD, 8National Institutes of Health Clinical Center, Bethesda, MD, 9National Institute of Allergy and Infectious Diseases, Bethesda, MD, 10NIH, Bethesda, MD, 11NIAMS/NIH, Bethesda, MD.

Background/Purpose: Two thirds of the 1700 patients seen at our NIH clinic for autoinflammatory diseases do not have a genetic diagnosis. Whole exome sequencing permits analysis of most of the protein coding regions of the human genome.

Methods: With the use of whole exome sequencing and candidate gene screening, we identified five children from four unrelated families, who had unexplained autoinflammatory disease and shared mutations in one common gene. One family from Saudi Arabia was consanguineous with two affected daughters. The second family of mixed Czech and British background had one affected boy. The third and fourth families were of mixed European ancestry from the United States and each family had one affected daughter. We performed additional experiments in patients samples including flow cytometry, immunophenotyping, cytokine profiling, mitochondria related function and ribosomal assembly assays. Protein function was studied with morpholino knockdowns in zebrafish embryos.

Results: All patients carried missense recessive mutations in one common gene, the TRNT1 (tRNA Nucleotidyl Transferase, CCA-Adding, 1), on chromosome 3. The two affected Saudi Arabian sisters were homozygous for a p.H215R missense mutation, while the other three children were compound heterozygous for a missense mutation, p.I223T or p.R99W, and one shared mutation p.D163V. The p.H215R mutation was not found in any public database neither in 1061 Arab control DNA samples. From the three Caucasian mutations, the p.R99W was novel whereas the p. I223T and p.D163V were found at a very low allele frequency (<0.001) at the NHLBI exomedatabase. All mutations affect highly conserved amino acid residues and are predicted to be damaging to the protein function. All children had recurrent episodes of high fevers with negative sepsis work up that occurred in association with microcytic anemia, and a spectrum of multisystem features. Neurologic involvement ranged from mild developmental delay to nystagmus, hypotonia, optic nerve atrophy, and sensorineural hearing loss. Other variables manifestations include dysmorphic fea-
tures, musculoskeletal and gastrointestinal symptoms, B cell immunodeficiency and hypogammaglobulinemia. Studies performed so far, point towards a maturation defect of the B cell lineage in the bone marrow, as a possible cause of the observed immunodeficiency. Preliminary data from cytokine analysis in two patients have shown elevated levels of the proinflammatory cytokines interleukin 6 and type I interferon, suggesting possible therapeutic targets. Knockdown of the zebrafish TRNT1 homologue caused hydrocephaly, defects in tail development, anemia and a reduction in the number of hair cells present in the lateral line, that has function resembling human inner ear.

Conclusion: The CCA-adding TRNT1 enzyme catalyzes the addition of the CCA terminus to the 3 prime end of all tRNAs precursors, a step that is essential for tRNA aminocacylation and protein synthesis. The discovery that missense mutations in this essential and ubiquitously expressed gene cause a newly defined periodic fever syndrome, will allow further understanding of mechanisms underlying inflammation.

Disclosure: A. Giannelos, None; Q. Zhou, None; M. Stoffels, None; A. Ombrello, None; D. Stone, None; J. H. Edwan, None; M. Pelletier, None; W. Tsai, None; K. Calvo, None; S. Rosenzweig, None; K. Barron, None; M. Gadina, None; I. Aksentijevich, None; D. L. Kastner, None.

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Mortality in a Large Cohort of Patients with Early Rheumatoid Arthritis That Were Treated-to-Target for 10 Years. I.M. Markusse, 1 L. Driven, 1 J.H. van Groenendaal, 1 K.H. Han, 1 H.K. Rondag, 1 P.J.S.M. Kerstens, 1 W.F. Lem, 2 T.W.J. Huizinga 2 and C.F. Allaart. 1Leiden University Medical Center, Leiden, Netherlands, 2Fransescus Hospital, Roosendaal, Netherlands, 3MCRZ hospital, Rotterdam, Netherlands, 4Haga Hospital, The Hague, Netherlands, 5Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands.

Background/Purpose: Recent studies showed diverging results about mortality trends in patients with rheumatoid arthritis (RA). Our aim was to determine survival after 10 years of treat-to-target therapy in patients with early RA, to compare these survival rates with the general population and to define risk factors for mortality during the 10 years duration of the BeSt study.

Methods: The BeSt study enrolled 508 Dutch patients with recent-onset active RA (1997 criteria) who were randomized to: sequential monotherapy, step-up therapy, initial combination including either prednisone or infliximab. During 10 years, all patients were treated-to-target, aiming at a disease activity score (DAS) ≤2.4. Kaplan-Meier curves and the log-rank test were used to compare survival rates in the four treatment strategies. Standardized mortality ratios (SMR) were calculated to compare the BeSt population to the general Dutch population, matched by age, gender and calendar year. Cox regression was used to calculate hazard ratios (HR) to determine baseline risk factors for increased mortality in the BeSt population.

Results: During 10 years, 72 of 508 patients died at a mean age of 75 years. No difference in survival was observed between the treatment strategies (p=0.805) (figure), with 16/126, 15/121, 21/133 and 20/128 deaths in arm 1 to 4, respectively. Based on the general Dutch population, 62 deaths were expected and 72 deaths occurred, resulting in an overall SMR of 1.16 (95% confidence interval, CI 0.92 – 1.46). Comparing the general population to each of the treatment strategies resulted in a SMR (95% CI) of 1.00 (0.61 – 1.64), 1.02 (0.61 – 1.69), 1.30 (0.85 – 1.99) and 1.32 (0.85 – 2.04) in arm 1 to 4, respectively. In the BeSt population, baseline age (HR 1.13, 95% CI 1.10–1.16), male gender (HR 1.78, 95% CI 1.06–2.99), smoking at baseline (HR 5.19, 95% CI 3.08–8.75) and health assessment questionnaire at baseline (HR 1.89, 95% CI 1.29–2.76) were associated with an increased risk of mortality. Randomization arm was not associated with an increased risk of mortality (arm 1 as reference category; arm 2 HR 0.99, 95% CI 0.49 – 2.00; arm 3 HR 1.27, 95% CI 0.66 – 2.44; arm 4 HR 1.25, 95% CI 0.65 – 2.41).

Conclusion: After 10 years of continued tight controlled treatment in patients with rheumatoid arthritis in the BeSt study, the survival rate was comparable to the general Dutch population, without differences between the treatment strategies. Higher age, male gender, smoking and worse functional ability were associated with an increased risk of mortality within our study population. These results suggest that treatment targeted at DAS ≤2.4 prevents increased mortality previously associated with RA, and that the medication used in these strategies does not increase mortality.

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Background/Purpose: RA has been associated with increased mortality compared to general population estimates. Previous studies were limited due to the inability to directly compare RA patients to controls, short follow-up, and lack of detailed data on clinical, lifestyle, and serologic factors. We evaluated mortality among women followed prospectively prior to RA diagnosis, directly comparing to women without RA.

Methods: We conducted a study of RA and mortality among 121,700 women followed from 1976 to 2010 in the Nurses’ Health Study (NHS). Incident RA was validated by medical record review according to the 1987 ACR RA criteria and classified by serostatus. Women who reported RA or other connective tissue diseases before the start of NHS were excluded. Women were followed from cohort entry to death or end of follow-up and were censored for loss to follow-up. Deaths were validated by the National Death Index; death certificate and medical record review determined cause of death. Cox regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD), cancer, and respiratory mortality for women with RA compared to women without RA. We obtained HRs for mortality by RA duration and serologic RA phenotype. Models were adjusted for age, demographics and other mortality factors, including physical activity, smoking, obesity, comorbidities, and family history of cancer, CVD, and diabetes.

Results: We validated 960 incident RA cases and identified 25,699 deaths in 34 years of NHS follow-up. Of the 261 deaths among women with RA, 75 (29%) were from cancer, 58 (22%) were from CVD, and 43 (16%) were from respiratory causes. Compared to women without RA, women with RA had increased all-cause mortality that remained significant after adjusting for age and other mortality factors (HR 2.07, 95% CI 1.83–2.35). Mortality was significantly increased for seropositive (HR 2.33, 95% CI 2.00–2.71) and seronegative RA (HR 1.60, 95% CI 1.30–1.98) compared to non-RA women. Each five years of RA duration conferred a 32% (95% CI 27–36%) increased mortality compared to non-RA. Women with RA had significantly increased risk for mortality from CVD (HR 1.87, 95% CI 1.44–2.43), cancer (HR 1.35, 95% CI 1.07–1.69) and respiratory (HR 4.50, 95% CI 3.28–6.17) causes compared to women without RA. Respiratory mortality for women with seropositive RA was six-fold higher than non-RA women (HR 6.23, 95% CI 4.38–8.85).

Conclusion: In 34 years of prospective follow-up, women diagnosed with RA had a two-fold increased risk of death from any cause compared to women without RA. Respiratory mortality was six-fold higher in seropositive RA and women with RA were significantly more likely to die from CVD and cancer than women without RA. Respiratory mortality appears to be an important but understudied cause of death in RA. These findings provide evidence of high RA mortality burden that is unexplained by traditional mortality predictors.

Table. Hazard ratios for all-cause and cause-specific mortality in RA serologic phenotypes among women in the Nurses’ Health Study, 1976–2010

<table>
<thead>
<tr>
<th>Mortality Category</th>
<th>All-cause Mortality HR (95% CI)</th>
<th>CVD-Specific Mortality HR (95% CI)</th>
<th>Cancer-Specific Mortality HR (95% CI)</th>
<th>Respiratory-Specific Mortality HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<td>1.13 (1.06–1.20)</td>
<td>1.17 (1.09–1.26)</td>
<td>1.24 (1.16–1.32)</td>
<td>1.22 (1.14–1.32)</td>
</tr>
</tbody>
</table>

Disclosure: I. M. Markusse, None; L. Dirven, None; J. H. van Groenendaal, None; K. H. Han, None; H. K. Rondag, None; P. J. S. M. Kerstens, None; W. F. Lem, None; T. W. J. Huizinga, None; C. F. Allaart, None.
Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves the Response of Active Ankylosing Spondylitis: Results of a 52-Week Phase 3 Randomized Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Dominique L. Baeten1, Juergen Braun2, Xenofon Baraliakos2, Joachim Sieper3, Maxime Dougados4, Paul Emery5, Atul A. Deodhar6, Brian Porter7, Ruvie K. Liao8, Shephard Mpofu8 and Hanno Richards8. 1Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Nether- lands; 2Charite Universitatsmedizin Berlin, Berlin, Germany; 3Charite Universitatsmedizin Berlin, Berlin, Germany; 4University René Descartes and Hôpital Cochin, Paris, France; 5University of Leeds, Leeds, United Kingdom; 6Oregon Health and Sciences University, Portland, OR; 7Novartis Pharma AG, East Hanover, NJ; 8Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: A phase 2, proof-of-concept study indicated that secukinumab, an anti-IL-17A monoclonal antibody, suppressed signs and symptoms of active ankylosing spondylitis (AS) by Week (Wk) 6. We present Wk 16 and Wk 52 efficacy and safety data from MEASURE 1 (NCT01358175), a phase 3 study assessing secukinumab vs. placebo (PBO) in patients (pts) with AS.

Methods: Pts with active AS fulfilling modified New York Criteria and BASDAI ≥ 4, despite current or previous therapy with NSAIDs, DMARDs and/or anti-TNF agents, were randomized to receive: i.v. secukinumab 10 mg/kg (Wk 0, 2, 4) followed by s.c. secukinumab 75 mg every 4 wks (10 IV → 75 SC), s.c. secukinumab 150 mg every 4 wks (10 IV → 150 SC), or PBO on same i.v. and s.c. schedules. Endpoints included ASAS20 at Wk 16 (primary), ASAS40, hsCRP, SF-36 PCS, ASQoL and ASAS partial remission. Statistical analyses followed a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity. PBO pts were randomized to receive: i.v. secukinumab 10 mg/kg at Wk 1 and s.c. secukinumab 75 mg or 150 mg at Wk 5, respectively, and/or anti-TNF agents, were randomized to receive: i.v. secukinumab 10 mg/kg at Wk 1 and sustained through 52 wks. Secukinumab was well tolerated through 52 wks with no unexpected safety findings.

Table. Summary of 16-week efficacy results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 16 Data</th>
<th>Placebo (N = 122)</th>
</tr>
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<tbody>
<tr>
<td>Secukinumab 10 mg/kg</td>
<td>59.75%*</td>
<td>60.95%*</td>
</tr>
<tr>
<td>(N = 124)</td>
<td>28.7%</td>
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<tr>
<td>Secukinumab 10 mg/kg</td>
<td>31.1%*</td>
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</tr>
<tr>
<td>(N = 124)</td>
<td>41.6%*</td>
<td>13.1%</td>
</tr>
<tr>
<td>No RA*</td>
<td>0.45 ± 1.09*</td>
<td>0.40 ± 1.09*</td>
</tr>
<tr>
<td>RA*</td>
<td>6.5–8.3 years, mean BASDAI 6.05–6.51,</td>
<td>5.55 – 8.3 (N = 125)</td>
</tr>
<tr>
<td>(LSM ± SE)*</td>
<td>0.595*</td>
<td>0.96</td>
</tr>
<tr>
<td>ASAS50</td>
<td>2.34 ± 0.175*</td>
<td>2.32 ± 0.172*</td>
</tr>
<tr>
<td>(N = 124)</td>
<td>–0.59 ± 0.180*</td>
<td></td>
</tr>
<tr>
<td>ASAS partial remission</td>
<td>16.15%*</td>
<td>15.25%*</td>
</tr>
<tr>
<td>(N = 124)</td>
<td>3.3%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: The selective IL-17A inhibitor secukinumab provided rapid and significant improvement of signs and symptoms in pts with active AS, regardless of prior anti-TNF exposure. Improvements were observed from Wk 1 and sustained through 52 wks. Secukinumab was well tolerated through 52 wks with no unexpected safety findings.

Disclosure: D. L. Baeten, Research grants from Boehringer Ingelheim, Janssen, MSD, Novartis, Pfizer, 2, 9, Consulting fees from AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, UCB, 5; J. Braun, Honoraria for talks: AbbVie (Abbott), Amgen, BMS, Boehringer, Celgene, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 9, Novartis Pharma AG, East Hanover, NJ, 3, Novartis Pharma AG, Basel, Switzerland.

ACR Concurrent Abstract Session

Epidemiology and Public Health I: Drug and Vaccine Safety

Sunday, November 16, 2014, 2:30 PM–4:00 PM
Table: Incidence rate of herpes zoster per 1000 person years by 10 year age group and auto-immune disease or comparator cohort

<table>
<thead>
<tr>
<th>Age group</th>
<th>Healthy</th>
<th>SLE</th>
<th>IBD</th>
<th>RA</th>
<th>AIs</th>
<th>PSA</th>
<th>PSO</th>
<th>AS</th>
<th>Gout</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>21–30</td>
<td>2.7</td>
<td>24.6</td>
<td>11.5</td>
<td>6.6</td>
<td>N/A</td>
<td>5.9</td>
<td>N/A</td>
<td>5.9</td>
<td>2.9</td>
<td>7.8</td>
</tr>
<tr>
<td>31–40</td>
<td>3.3</td>
<td>15.2</td>
<td>5.0</td>
<td>8.3</td>
<td>9.8</td>
<td>3.7</td>
<td>8.1</td>
<td>5.2</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>3.9</td>
<td>17.5</td>
<td>10.4</td>
<td>10.0</td>
<td>8.5</td>
<td>6.4</td>
<td>6.4</td>
<td>5.2</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>51–60</td>
<td>5.6</td>
<td>20.7</td>
<td>14.6</td>
<td>14.2</td>
<td>9.7</td>
<td>8.3</td>
<td>6.4</td>
<td>5.2</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>6.4</td>
<td>22.7</td>
<td>17.1</td>
<td>15.0</td>
<td>13.2</td>
<td>12.3</td>
<td>6.4</td>
<td>5.2</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>(ref)</td>
<td>7.8</td>
<td>23.6</td>
<td>16.3</td>
<td>15.9</td>
<td>12.6</td>
<td>10.3</td>
<td>6.4</td>
<td>5.2</td>
<td>14.6</td>
<td></td>
</tr>
</tbody>
</table>

Disclosed: H. Yun, Amgen; S. Yang; None: L. Chen; None: F. Xie; None: K. L. Winthrop; Pfizer Inc; 2, Pfizer, UCB, AbbVie, Genentech; 5, J. Baddley, BMS, 2, Merck, Astellas, Pfizer; 5, K. G. Saag, None; J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5, J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie.

821

Pregnancy Outcome in Women Treated with Adalimumab for the Treatment of Rheumatoid Arthritis. Christina D Chambers¹, Diana L Johnson², Limin Xu³ and Kenneth L Jones²

¹University of California San Diego Department of Family and Preventive Medicine, La Jolla, CA
²University of California San Diego Department of Pediatrics, La Jolla, CA

Background/Purpose: Adalimumab is a fully human monoclonal antibody to tumor necrosis factor alpha and is approved for several indications including rheumatoid arthritis (RA).

Methods: The OTIS Collaborative Research Group conducted a prospective cohort study in the U.S. and Canada between 2004 and 2013 comparing pregnancy outcomes in women with RA treated with adalimumab for some period of the first trimester to women with RA not treated with any adalimumab in pregnancy. No women in either group were also treated with methotrexate, but women may have been treated with another DMARD or steroid. An additional comparison group included women without any autoimmune disease. All three groups were recruited prior to 19 completed weeks gestation and followed by extensive telephonic interviews throughout pregnancy and after birth. Medical records were reviewed, and a subset of live born infants received dysmorphological examination by a study physician (blinded to the mother’s status). Outcomes were compared using logistic regression techniques and survival methods as appropriate with adjustment for confounders using propensity scoring if two or more confounders were identified.

Results: Seventy-four women exposed to adalimumab, 80 disease-matched comparison women, and 218 non-diseased women enrolled in the study. All women in the adalimumab-exposed group had at least one dose of the drug and were treated in the first trimester; approximately 43% of those women used the medication in all three trimesters. The overall lost-to-follow up rate was 5.9%. Disease severity, as measured by the HAQ at the time of enrollment and at 32 weeks gestation, was similar between the two disease-matched groups. The rate of major defects in the exposed, disease-matched, and non-disease comparison groups was 5.6%, 7.8% and 5.5% respectively. In adjusted analysis, there was no significant difference in the overall rate of major malformations among live births in the adalimumab exposed vs. disease-matched group (adjusted Relative Risk (RR) 1.14, 95% Confidence Interval (CI) 0.26, 4.93). A total of 234 infants (70% of live born infants) received the study-related physical examination. The proportion of children with 3 or more minor malformations in the three groups did not differ, and there was no specific pattern of minor malformations identified. Using Cox Proportional Hazards modeling, the adjusted hazard ratio (HR) for spontaneous abortion was 1.96 (95% CI 0.47, 8.26) comparing the adalimumab vs. disease-matched groups; the rate was elevated in comparison to the non-disease group (adjusted HR 3.79, 95% CI 1.01, 14.23), although the number of events was small. The rate of preterm delivery did not differ significantly among groups, nor did the proportion of infants who were small for gestational age.

Conclusion: Pregnant women with RA who are treated with adalimumab during the first trimester compared to women with the same underlying condition do not appear to be at increased risk of any of the adverse pregnancy outcomes evaluated. Although the sample size is small, these results provide reassuring data to women with RA who require treatment with adalimumab.


822

Meloxicam and Risk of Myocardial Infarction: A Population-Based Cohort Study. Deepan Dalal¹, Maureen Dubreuil², Yuqing Zhang³, Christine Peloquin⁴, Tuhina Neogi⁵, Hyon Choi⁶ and David T. Felson⁷, ¹Boston Medical Center, Boston, MA, ²Boston University School of Medicine, Boston, MA.

Background/Purpose: Certain non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of myocardial infarction (MI). MI risk for different NSAIDs varies largely because of different levels of cyclooxygenase (COX) 2 inhibition. Given this differential MI risk, it is clinically important to understand which NSAID options are safer vs. which ones confer an increased risk. For example, naproxen has shown no increased risk of MI whereas diclofenac has shown an increased risk. However, Meloxicam, which is considered to inhibit COX-2 selectively over COX-1, is used widely across the world, but the risk of MI with Meloxicam has not been quantified.

Methods: The Health Improvement Network (THIN) is a national population-based cohort of over 10 million patients from 580 general practices in the UK. We conducted a nested case-control study of patients between 35 and 89 years of age who had at least 1 year of enrollment between 2000 and 2013 in the cohort and at least 1 prescription for an NSAID. Individuals with a history of MI were excluded. Cases of MI were identified by Read codes and the date of MI was considered the index date. Each case...
was matched with up to 4 unique controls on age, sex and practice ID. NSAID exposure was categorized as remote (greater than 60 days prior), recent (between 1 and 60 days) or current to the index date. Current NSAID users were further classified as Naproxen, Diclofenac, Meloxicam or other NSAID users. Multivariate logistic regression analysis with 6 categorical variables for NSAID exposure categories was conducted to determine the risk of MI among various current NSAID users compared with that of remote users, adjusting for potential confounders including traditional cardiac risk factors, comorbidities and cardiovascular drug use.

**Results:** We identified 9817 MI cases and 12860 matched controls from the cohort. The cases had a higher prevalence of traditional cardiac risk factors, more frequent use of cardiovascular medications, and a higher prevalence of chronic kidney disease and inflammatory arthritis (Table 1). The adjusted odds ratio (aOR) for MI with current Meloxicam use was 1.40 (95% CI, 1.15–1.71) as compared with remote NSAID use. While, the aOR with current Naproxen use was 1.01 (95% CI, 0.84–1.22) and with current Diclofenac use was 1.35 (95% CI, 1.21–1.5).

**Conclusion:** In this large population-based cohort, Meloxicam significantly increased the risk of MI at a level similar to that of Diclofenac. Drugs like Diclofenac and Meloxicam are widely used across the world should be used cautiously because of the increased risk of MI they pose.

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>MI Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>9817</td>
<td>12860</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.8 ± 12.4</td>
<td>63.1 ± 12.2</td>
</tr>
<tr>
<td>Female</td>
<td>4039 (41.1%)</td>
<td>5571 (43.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker 2965 (30.2%)</td>
<td>4914 (38.2%)</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker 2724 (27.7%)</td>
<td>2413 (19.5%)</td>
</tr>
<tr>
<td></td>
<td>Current smoker 2493 (25.4%)</td>
<td>1876 (14.6%)</td>
</tr>
<tr>
<td>BMI</td>
<td>Underweight 1635 (16.7%)</td>
<td>2657 (20.7%)</td>
</tr>
<tr>
<td></td>
<td>Normal 1572 (16.0%)</td>
<td>2102 (16.3%)</td>
</tr>
<tr>
<td></td>
<td>Overweight 2426 (24.7%)</td>
<td>2816 (21.9%)</td>
</tr>
<tr>
<td></td>
<td>Obese 2708 (28.3%)</td>
<td>4098 (31.9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1699 (17.3%)</td>
<td>1502 (11.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1547 (15.8%)</td>
<td>1582 (12.3%)</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>4989 (49.8%)</td>
<td>5433 (42.6%)</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>926 (9.4%)</td>
<td>735 (5.7%)</td>
</tr>
<tr>
<td>Inflammatory rheumatic disease</td>
<td>1984 (20.2%)</td>
<td>2187 (17.0%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>3822 (38.9%)</td>
<td>5003 (38.9%)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>2575 (26.2%)</td>
<td>2342 (18.2%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3433 (35.2%)</td>
<td>2995 (23.3%)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>2503 (25.5%)</td>
<td>2336 (18.2%)</td>
</tr>
<tr>
<td>Statins</td>
<td>3402 (34.7%)</td>
<td>3188 (24.8%)</td>
</tr>
</tbody>
</table>

### Odd Ratios of MI by NSAID Use of Interest

<table>
<thead>
<tr>
<th>NSAID Use</th>
<th># Cases</th>
<th># Controls</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent (Remote use)</td>
<td>4422</td>
<td>6258</td>
<td>1.0</td>
</tr>
<tr>
<td>Current Naproxen use</td>
<td>291</td>
<td>383</td>
<td>1.01 (0.84, 1.22)</td>
</tr>
<tr>
<td>Current Diclofenac use</td>
<td>1089</td>
<td>1234</td>
<td>1.35 (1.21, 1.50)</td>
</tr>
<tr>
<td>Current Meloxicam use</td>
<td>262</td>
<td>291</td>
<td>1.40 (1.15, 1.71)</td>
</tr>
</tbody>
</table>

**Disclosure:** D. Dalal, None; M. Dubreuil, None; Y. Zhang, None; C. Peloquin, None; M. Sasu, None; C. Mihai, None; A. M. Gherghe, None; R. Dobrota, None; R. Oanea, None; S. Pintilie, None; M. Milescu, None; I. Ancuta, None; A. Martin, None; M. Sasu, None; C. Ciofu, None; L. Macovei, None; V. Stoica, None; M. Bojinca, None.

**S362**

### 823

**Impact of Oral Glucocorticoid Therapy on Mortality in Patients with Rheumatoid Arthritis and Diabetic Mellitus.** Mohammad Movahedi and William G Dixon. Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

**Background/Purpose:** Glucocorticoid (GC) therapy is known to increase the risk of new-onset type 2 diabetes mellitus (DM). Furthermore, GC therapy increases blood glucose in diabetic patients, thereby potentially leading to worse outcomes. This study aimed to examine the impact of GC use on all-cause and cardiovascular (CV) mortality in patients with RA and DM, and to compare to the impact of GC use on mortality in patients with RA but no DM.

**Methods:** Adult patients with RA were identified from the Clinical Practice Research Datalink, a UK primary care research database. Type 2 DM was defined using READ codes, anti-diabetic treatment or abnormal blood results. GC exposure was identified from oral GC prescriptions. Mortality data, including cause of death, were obtained through linkage to the Office for National Statistics. All-cause and CV mortality rates with 95% confidence interval (CI) were calculated for ever/never GC use and categories of cumulative dose. Data were analysed using multivariable time-dependent Cox models to assess the association between GC and death, adjusting for potential confounders.

**Conclusion:** In a country with high TB burden, where all patients initiated on TNFi are screened for latent TB at baseline, new TB infection exceeds latent TB reactivation. TB incidence in these patients is much higher than in the general population and baseline screening does not solve the problem of latent TB reactivation. New TB infection exceeds 9.33/100,000 PY from 2001 to 2013, and 2/9 per 100,000 PY from 2001 to 2013, while the remaining TB cases were more likely new TB infection.

**Disclosure:** A. Soare, None; C. Mihai, None; A. M. Gherghe, None; R. Dobrota, None; R. Oanea, None; S. Pintilie, None; M. Milescu, None; I. Ancuta, None; A. Martin, None; M. Sasu, None; C. Ciofu, None; L. Macovei, None; V. Stoica, None; M. Bojinca, None.

**S362**

### 824

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**Methods:** Adult patients with RA were identified from the Clinical Practice Research Datalink, a UK primary care research database. Type 2 DM was defined using READ codes, anti-diabetic treatment or abnormal blood results. GC exposure was identified from oral GC prescriptions. Mortality data, including cause of death, were obtained through linkage to the Office for National Statistics. All-cause and CV mortality rates with 95% confidence interval (CI) were calculated for ever/never GC use and categories of cumulative dose. Data were analysed using multivariable time-dependent Cox models to assess the association between GC and death, adjusting for potential confounders.
Results: We studied 3,397 patients with RA and DM and 17,883 patients with RA but no DM with a median follow-up of 3.6 and 5.3 years, respectively, during which 699 (266 from CVD cause) and 2,887 (1,016 from CVD cause) patients died. All-cause mortality rate was 4.6 (95% CI 4.3–5.0) and 2.7 (95% CI 2.6–2.8) per 100 person-years (pyrs) in DM and non-DM cohorts, respectively.

In patients with RA and DM, the adjusted relative risk (aRR) and absolute risk difference (ARD) of all-cause mortality were 2.0 (95% CI: 1.6–2.4) and 0.2 per 100 pyrs (95% CI: 0.1–0.3) in ever GC use compared to never GC use, respectively. Risk of all-cause mortality was increased with increasing cumulative dose category. Similar results were observed for risk of CV mortality in association with cumulative GC dose.

Whilst the aRR for all-cause mortality was lower in patients with RA and DM compared to patients without DM (2.0 vs 2.3), the ARD was higher (4.2 vs 2.9 per 100 pyrs). The table below shows the association between GC use patterns and all-cause and CV mortality.

<table>
<thead>
<tr>
<th>Oral GC pattern</th>
<th>RA and DM</th>
<th>All cause mortality</th>
<th>RA but no DM</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use</td>
<td>aRR</td>
<td>ARD Per 100 pyrs</td>
<td>aRR</td>
<td>ARD Per 100 pyrs</td>
</tr>
<tr>
<td>Ever use</td>
<td>2.0 (1.6–2.4)</td>
<td>4.2 (3.5–5.0)</td>
<td>2.3 (2.0–2.5)</td>
<td>2.9 (2.7–3.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral GC pattern</th>
<th>RA and DM</th>
<th>CV mortality</th>
<th>RA but no DM</th>
<th>CV mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use</td>
<td>aRR</td>
<td>ARD Per 100 pyrs</td>
<td>aRR</td>
<td>ARD Per 100 pyrs</td>
</tr>
<tr>
<td>Ever use</td>
<td>2.0 (1.4–2.7)</td>
<td>1.4 (0.9–1.9)</td>
<td>1.8 (1.5–2.2)</td>
<td>0.9 (0.8–1.1)</td>
</tr>
</tbody>
</table>

Conclusion: Oral GC therapy is associated with higher all-cause and CV mortality in RA patients with DM, although residual confounding may explain some of the association. Whilst the aRR is slightly lower that seen in patients with RA but no DM, the higher background mortality rate in patients with DM means this lower aRR is associated with more excess deaths.

Disclosure: M. Movahedi, None; W. G. Dixon, None.

825

Serious Infections on TNF Inhibitors: Have the Risks Changed over Calendar Time, and How High Are They? Elizabeth V. Arkema1, Johan Asklings1 and the ARTIS Study group2. 1Karolinska Institutet, Stockholm, Sweden, 2Karolinska Institutet och Svensk Reumatologisk förening, Solna, Sweden.

Background/Purpose: The rheumatoid arthritis (RA) population starting tumor necrosis factor inhibitors (TNFi) today is much different in terms of accumulated and concurrent disease activity and comorbidity, than patients starting treatment 10 years ago. Still, few studies have investigated time-trends in infection risks and their determinants, on a clinically relevant scale. Our aim was to calculate the absolute risk of serious infection (SI) within 1 year of TNFi-initiation in patients with RA in Sweden and to examine whether the risk changes over calendar time and patient characteristics.

Methods: Patients with RA who initiated a TNFi from 2004 to 2011 were included from the Anti-Rheumatic Therapies in Sweden (ARTIS) register. Patient demographics, concomitant medications and clinical measures were collected from the patient’s first visit (baseline). ICD-10 codes for SI hospitalizations were identified in the inpatient registry (2004–2012) and linked to the study population using each patient’s unique personal identification number. We calculated the absolute risk of SI hospitalization within 1 year of treatment start using modified Poisson regression models stratified by risk factors previously identified by the German biologics registry, RABBIT: concomitant corticosteroid use, total number of risk factors (age ≥60, previous serious infection 1 year before TNFi-initiation, COPD or chronic kidney disease). We additionally stratified risks by calendar year of initiation (2004–2007 vs. 2008–2011) and investigated other comorbidities (cardiovascular disease, diabetes, number of hospitalizations, days hospitalized, outpatient visits) and disease activity measurements (DAS-28 and its components, HAQ, disease duration).

Results: We included 3562 biological-initiators with RA. A total of 344 (4.0%) individuals had at least one SI hospitalization within a year of biological initiation (2004–2007 4.4%; 2008–2011 3.7%). Serious infection risk decreased over time in age and sex-adjusted models (p value for calendar year 0.02) but when adjusted for comorbidities, year of TNFi-initiation was no longer significantly associated with a decreased risk of SI (p = 0.15). Individuals who were older, male, with longer disease duration, a history of infection and higher disease severity were at an increased risk of SI. Our results from 2004–2007 were very similar to those reported by RABBIT. When examining risks from 2008–2011, the majority of the increased risk was observed in individuals with 3 or 4 risk factors (Figure).

Conclusion: Risks of SI within 1 year of TNFi initiation were similar to those reported by the German Biologics Register 2004–2007. Although the population starting TNFi has changed over time, the one-year risks of SI has only dropped modestly, but the relative importance of SI risk factors has changed, such that infection risk calculators need be updated using contemporary data.

Disclosure: E. V. Arkema, None; J. Asklings, AstraZeneca; Pfizer, 2; T. A. Study group, Abbvie, Merck, BMS, Pfizer, SOBI, AstraZeneca, Roche, UCB, 9.

ACR Concurrent Abstract Session

Metabolic and Crystal Arthropathies I: Clinical Aspects

Sunday, November 16, 2014, 2:30 PM–4:00 PM

826

Comparison of Classification Criteria for Gout Using Monosodium Urate Crystal Identification By a Certified Examiner As the Gold-Standard in a Large Multi-National Study. William Taylor1, Nicola Dalbeth2, Jaap Fransen3, Tuhina Neogi4, H. Ralph Schumacher Jr.5 and Tim Jansen6,1. University of Otago Wellington, Wellington, New Zealand, 2University of Auckland, Auckland, New Zealand, 3Radboud University, Nijmegen, Netherlands, 4Boston University School of Medicine, Boston, MA, 5University of Pennsylvania V A Medical Center, Philadelphia, PA, 6Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Most gout is managed in primary care where the diagnosis seldom relies upon identification of MSU crystals. Several classification criteria for gout have been developed but there is little information on the relative performance of these criteria, especially in comparison to competent identification of MSU crystals in synovial fluid. This study,
undertaken as part of an ACR-EULAR project to update gout classification criteria compares the performance of existing criteria.

**Methods:** Investigators from 25 sites in 16 countries contributed data on consecutive patients with at least 1 recent swollen joint or subcutaneous nodule that conceivably might be gout. All patients underwent arthrocentesis or tissue aspiration and examination of synovial fluid or tissue with polarizing microscopy by an examiner who had undergone a 2-step certification procedure. Case-control status was defined by the presence or absence of MSU crystals. Data were collected that enabled classification into each of 5 published classification criteria for gout. Both full and survey versions of 1977 American Rheumatism Association (ARA) criteria were used for this analysis. The original NEW YORK and ROME criteria and a modification to contain only clinical items were included. Specificity, sensitivity and AUC were calculated and the differences in test performance were assessed with logistic regression. The reference category was MEX for each regression model.

**Results:** Data from 983 patients (509 cases, 474 controls) were collected, of whom 702 were male. The mean (SD) age was 58.1 (17.2) and duration of disease since first ever symptoms was 7.8 (24.6) years. Controls had a clinical diagnosis of gout (MSU crystals not observed by microscopy, n=50), CPPD (109), osteoarthritis (67), rheumatoid arthritis (69), septic arthritis (10), SLE (5), spondyloarthropathy (71), undifferentiated arthritis (60), rheumatoid arthritis (51). Not all patients could be classified by every criterion because of missing data, particularly radiographs.

The performance of the criteria is shown in the Table. Analysis of subjects without tophi generally led to minor differences in criteria performance. Excluding controls with a clinical diagnosis of gout led to slightly better specificity (85% vs MEX of 84% NEW YORK). Overall, sensitivity was very high. The high sensitivity of the ARA (full) and NEW YORK criteria is due to the fact that presence of MSU crystals is sufficient for classification; therefore all cases meet these criteria by study design. The sensitivity of ARA, ROME and NEW YORK criteria are greatly reduced by excluding MSU crystal data. MEX has worse specificity than all other criteria sets and NETH has worse specificity than NEW YORK or ROME.

**Conclusion:** Although sensitivity of existing criteria is satisfactory, the specificity of every set is less than 80%, which is not ideal. There is a need for better performing criteria.

---

**Table 1. Incidence Rates and Relative Risks (RR) for Alzheimer’s disease by Gout Status (Total and Subgroups)**

<table>
<thead>
<tr>
<th>Status</th>
<th>N Cases</th>
<th>Follow-up (person-years)</th>
<th>Incidence Rate (per 1000 person-years)</th>
<th>Adjusted RR (95% CI)</th>
<th>p Value for Interaction</th>
</tr>
</thead>
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<td>Total</td>
<td>51807</td>
<td>17257.17</td>
<td>0.5 (0.4 to 0.6)</td>
<td>0.06 (0.04 to 0.09)</td>
<td>0.05 (0.03 to 0.07)</td>
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<td>0.4 (0.3 to 0.5)</td>
<td>0.05 (0.03 to 0.07)</td>
<td>0.05 (0.03 to 0.07)</td>
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<td></td>
<td>0.6 (0.5 to 0.7)</td>
<td>0.07 (0.05 to 0.09)</td>
<td>0.07 (0.05 to 0.09)</td>
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<td>0.51 (0.40 to 0.63)</td>
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<td>4.6</td>
<td>0.8 (0.7 to 0.9)</td>
<td>0.58 (0.49 to 0.68)</td>
<td>0.62 (0.52 to 0.73)</td>
<td>0.0003</td>
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**Disclosure:** W. Taylor, Pfizer Inc, 5, Metabolix, 5, Abbvie, 9; N. Dalbeth, Ardea, 5; AstraZeneca, 5; Takeda, 5, Metabolix, 5, Menarini, 5, Savient, 5, Novartis Pharmaceutical Corporation, 8; Fonterra, 9; Novartis Pharmaceutical Corporation, 2, Fonterra, 2, Takeda, 2; N. Dalbeth, Ardea, 5, L. Frasnelli, None; T. Neogi, None; H. R. Schumacher Jr., Takeda, 2; Abbvie, 2; Regeneron, 5, AstraZeneca, 5; Novartis Pharmaceutical Corporation, 5, Metabolix, 5, Ardea, 5; T. Jansen, Abbvie, 2, UCB, 5, Abbvie, 5; AstraZeneca, 5; UMS, 5; Jansen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceutical Corporation, 5; Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8; S873
Extent of Urate Deposition in Asymptomatic Hyperuricemia and Symptomatic Gout: A Dual Energy Computed Tomography Study. Nicola Dalbeth1, Meaghan House2, Opetaa Aati3, Paul Tan4, Christopher Franklin5, Anne Horne6, Gregory Gamble7, Lisa K. Stamp8, Anthony Doyle9 and Fiona M. McQueen1. 1University of Auckland, Auckland, New Zealand, 2University of Otago, Christchurch, New Zealand.

Background/Purpose: Recent studies have reported that ultrasound features of urate crystal deposition are present in some asymptomatic individuals with hyperuricemia, suggesting that subclinical urate deposition occurs prior to presentation with symptomatic disease. Dual energy computed tomography (DECT) allows both specific detection and volume measurement of urate crystals. The aim of this study was to compare the frequency and volume of DECT urate deposits in people with asymptomatic hyperuricemia and symptomatic gout.

Methods: DECT scans of both feet were prospectively obtained from asymptomatic individuals with serum uric acid ≥5mg/dL, recruited from community laboratories (n=25), and those with crystal proven gout without clinically apparent tophi (n=33). The gout group was separated into two groups: early gout (pre-defined as onset of symptoms in the preceding 3 years, n=14), and late gout (disease duration >3 years, n=19). Asymptomatic individuals with serum uric acid <6mg/dL (negative controls, n=10) and individuals with crystal proven tophaceous gout (positive controls, n=20) were studied to optimize the DECT settings. Two readers, blinded to all clinical features including gout status and serum uric acid, independently scored the scans for the presence and sites of urate deposition, and measured the urate volume in both feet using automated volume measurement software. For the purposes of analysis, DECT urate deposits were considered to be present if scored by both readers.

Results: DECT urate deposits were observed in 6/25 (24%) participants with asymptomatic hyperuricemia, 11/14 (79%) participants with early gout and 16/19 (84%) participants with late gout (p<0.001, Figure 1A). In those with urate deposits, the volume of urate deposition was significantly lower in those with asymptomatic hyperuricemia, compared with the early and the late gout groups (Figure 1B). Similar urate volumes were observed in the early and late gout groups (Figure 1B). DECT urate deposition was observed in both joints and tendons in the asymptomatic hyperuricemia group, but significantly less frequently than in both the early and late gout groups (p≤0.001 for both joint and tendon sites).

Conclusion: Although DECT can detect urate deposition in the feet of some asymptomatic individuals with hyperuricemia, these deposits are far more frequently observed in those with symptomatic gout. Urate deposit volumes are also greater in those with symptomatic disease. These data suggest that a threshold of urate crystal volume may be required before symptomatic gout occurs.

Disclosure: N. Dalbeth, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9, M. House, None; O. Aati, None; P. Tan, None; C. Franklin, None; A. Horne, None; G. Gamble, None; L. K. Stamp, None; A. Doyle, None; F. M. McQueen, None.

Asymptomatic Deposit of Monosodium Urate Crystals Associates to a More Severe Coronary Calcification in Hyperuricemic Patients with Acute Coronary Syndrome. Mariano Andrés1, María Amparo Quintanilla2, Francisca Sivera3, Paloma Vela4 and Juan Miguel Ruiz-Nodar5. 1Hospital General Universitario de Elda, Alicante, Spain, 2Universidad Miguel Hernández, Alicante, Spain, 3Hospital Universitario de Elda, Alicante, Spain, 5Hospital General Universitario de Alicante, Alicante, Spain.

Background/Purpose: Increased cardiovascular (CV) risk in gout relates to crystal-driven inflammation. Monosodium urate (MSU) crystals are found in ~25% of patients with asymptomatic hyperuricemia (AH) by ultrasound (US) [1,2]. Whether AH patients with crystal deposits depict an increased CV risk has not been assessed so far. We aimed to assess the association between the deposit of MSU crystals in AH and the severity and extension of the coronary atherosclerotic disease (CAD).

Methods: Cross-sectional study, approved by the local ethics committee. Consecutive patients with AH (serum uric acid [SUA] >7.0 mg/dL) admitted due to an acute coronary event were selected. Those with current urate lowering treatment (ULT) were excluded. US of both knees and 1st MTP joint was performed to detect signs of MSU crystals deposition: double contour sign, snow storm sign, tophus or joint effusion. When present, US-guided arthrocentesis was performed to confirm MSU crystals by polarized light microscopy. US and microscopy findings were later reviewed by a blinded rheumatologist. CAD was assessed through the severity of coronary artery calcification (absent, mild, moderate or severe) and the total of significant coronary lesions (>50% of the diameter) at coronaryography by a blinded cardiologist. Traditional CV risk factors were also collected. Association between coronaryographic features and crystal identification was analysed by logistic regression for binary variables and lineal regression for continuous variables.

Results: Fifty-one patients were enrolled, median (p25–75) age 73 years (59–81), 76.5% males. Median SUA at admission was 7.6 mg/dL (7.08–8.6). Moderate-to-severe calcification was present in 21 (41.2%) patients, and the median number of significant coronary lesions was 3.0 (2–5). US found lesions in 49 (96.0%) patients: joint effusion in 94.1%, tophi in 9.8%, double contour sign in 9.8% and snow storm sign in 3.9%. Arthrocentesis was performed in 48 patients. MSU crystals were identified in 11 patients (21.6% of total). No significant differences between groups were found in traditional CV risk factors or SUA levels. The presence of moderate to severe coronary calcification significantly differed between groups and strongly associate to the detection of MSU/crystals [Table]. The number of significant lesions did not associate to MSU crystals identification, though a trend towards more lesions in MSU+ patients was noted.

Conclusion: Our study found a more severe coronary calcification in those AH patients with deposits of MSU crystals. These patients might benefit from ULT aiming to reduce their CV risk, but this should be addressed in future studies.

Disclosure: M. Andrs, None; M. A. Quintanilla, None; F. Sivera, None; P. Vela, None; J. M. Ruiz-Nodar, None.

References:

Table.

<table>
<thead>
<tr>
<th>Model</th>
<th>MSU+ patients (n=11)</th>
<th>MSU- patients (n=40)</th>
<th>p-value</th>
<th>Association analysis</th>
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<td>Moderate-severe coronary calcification (n,%), p-value</td>
<td>8 (72.7%)</td>
<td>13 (32.5%)</td>
<td>0.016</td>
<td>OR 9.406* (95%CI 1.459, 60.637)</td>
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<tr>
<td>Significant coronary lesions (median, p25–75)</td>
<td>4.0 (3.0–5.0)</td>
<td>3.0 (1.3–4.0)</td>
<td>0.137</td>
<td>β 0.693 (95%CI-0.596, 1.982)</td>
</tr>
</tbody>
</table>

MSU: monosodium urate; OR: odds ratio; CI: confidence interval. * Model adjusted for age, gender, hypertension, diabetes, dyslipidemia, smoking, glomerular filtration rate and serum uric acid at admission.

Disclosure: M. Andrs, None; M. A. Quintanilla, None; F. Sivera, None; P. Vela, None; J. M. Ruiz-Nodar, None.
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Background/Purpose: A prototype anticancer drug (RLBN1001) induced marked hypouricemia in human subjects (≤ 1.0 mg/dl) were not dose-related, indicating the minimal effective dose was below the lowest administered dose in this study (100 mg/m²/d). At both low and high doses, hypouricemia was associated with increased urinary excretion of both UA and total oxypurines, suggesting bifunctional equilibrium effects on both production and excretion. We found that the RLBN1001 prototype was a potent inhibitor of URAT1 but not GLUT9a, a modest inhibitor of XO, and a potent clastogen in the MMN assay. We iteratively synthesized a series of novel analogs and identified new compounds that are potent inhibitors of both XO (i.e., 4-fold more potent than allopurinol) and URAT1 (equivalent to lesinurad), but devoid of genotoxicity. One compound showed moderate inhibition of GLUT9b (data not shown), but other compounds showed minimal effects on this target. Data for reference and selected new compounds are shown in the table.

Conclusion: Having established compelling clinical POC with the RLBN1001 prototype, we have synthesized a library of unique compounds with strongly enhanced activities that both reduce UA production and enhance UA excretion. A lead compound is expected to enter initial clinical trials as a novel, potential first-line treatment for hyperuricemic patients with gout.

<table>
<thead>
<tr>
<th>Compound</th>
<th>URAT1 Inhibition IC50 mM Mean ± SEM</th>
<th>XO Inhibition IC50 mM Mean ± SEM</th>
<th>MMN</th>
</tr>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>&gt;300</td>
<td>2.8 ± 0.33</td>
<td>ND</td>
</tr>
<tr>
<td>Benzbromarone</td>
<td>0.2</td>
<td>0.2</td>
<td>ND</td>
</tr>
<tr>
<td>Lesinurad</td>
<td>3.54</td>
<td>&gt;300</td>
<td>ND</td>
</tr>
<tr>
<td>RLBN1001</td>
<td>5.4 ± 1.0</td>
<td>274</td>
<td>+</td>
</tr>
<tr>
<td>RLBN2022</td>
<td>1.2</td>
<td>&gt;300</td>
<td>+</td>
</tr>
<tr>
<td>RLBN2027</td>
<td>6.3</td>
<td>243</td>
<td>+</td>
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<tr>
<td>RLBN2023</td>
<td>2.6 ± 0.6</td>
<td>1.1</td>
<td>Negative</td>
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<td>9.4 ± 0.6</td>
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<td>RLBN1002</td>
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<tr>
<td>RLBN3050</td>
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Disclosure: R. P. Warrell Jr., Relburn-Metabolomics, Inc., 3; A. Khukovits, None; K. Barnes, None; C. Satyanarayana, None; C. Cheseman, None; J. Piwinski, Relburn-Metabolomics, Inc., 3.

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Background/Purpose: Acute pseudogout is the most dramatic clinical manifestation of calcium pyrophosphate crystal deposition (CPPD). CPPD is most commonly sporadic and age-related but can rarely occur secondary to metabolic diseases or a familial trait. Published case reports also suggest that acute pseudogout can occur as a consequence of bisphosphonate therapy. This matched case-control study aimed to examine whether acute pseudogout is associated with bisphosphonate prescription with the preceding 60 days.

Methods: The study was nested within the UK Clinical Practice Research Datalink (CPRD) which houses clinical data from over 600 general practices. Cases aged ≥18 years with a first-ever diagnosis of pseudogout between 01/03/1987 and 31/12/2012 were individually matched for age, gender and practice to four controls without pseudogout. The exposure of interest was prescription of an oral bisphosphonate in the 60 days prior to the diagnosis of pseudogout. It was estimated that 2147 eligible cases of pseudogout would be identified conferring 98% power to detect an odds ratio (OR) of 2.0. Bivariate and conditional logistic regression was used to assess the association between oral bisphosphonate prescriptions and pseudogout and then adjusted for hyperparathyroidism, osteoarthritis, rheumatoid arthritis, and prescription of diuretics and corticosteroids. Analyses were then repeated for individual bisphosphonates. In order to address the possibility of misdiagnosis of crystal arthritis, a sensitivity analysis was undertaken excluding cases or controls who had a prior diagnosis of gout. ORs were presented as incident rate ratios (IRR) with 95% confidence intervals (CI).

Results: 2011 cases of incident pseudogout were identified and successfully matched to 8013 controls (mean age 72 years; male 52%). Those with incident pseudogout were more likely than controls to have received a bisphosphonate prescription in the preceding 60 days (6.1% vs 3.8%; IRR 1.69; 95%CI 1.35, 2.11). On multivariate analysis, this association attenuated slightly (IRR 1.33; 95%CI 1.05, 1.69). A significant similar association was seen for prescription of alendronic acid (multivariate IRR 1.35; 95%CI 1.02, 1.79) but not etidronate disodium, risedronate sodium, ibandronic acid or sodium clodronate although the absolute number of prescriptions for these drugs was small. After excluding known cases of gout, multivariate associations with both any bisphosphonate (IRR 1.43; 95%CI 1.11, 1.84) and alendronic acid (IRR 1.53; 95%CI 1.14, 2.06) remained.

Conclusion: Bisphosphonate prescription appears to be a risk factor for pseudogout, independent of co-morbid conditions and medications. Prescribers should be aware of this uncommon cause of acute pseudogout.

Disclosure: E. Roddy, None; S. Muller, None; Z. Paskins, None; S. Hider, None; M. Blagojevic-Bucknall, None; C. Mallen, None.

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NOD2-Associated Autoinflammatory Disease: The Largest Cohort Study. Qingping Yao, Min Shen, Christine McDonald, Felicitas Lachwuan and Bo Shen. Cleveland Clinic, Cleveland, OH.

Background/Purpose: NOD2-associated autoinflammatory disease (NAID) is an emerging systemic inflammatory disease. The aim is to report our extended study of the phenotypic and genotypic features of the disease.

Methods: A total of 143 adult patients with autoinflammatory phenotypes at presentation were suspected of having NAID over the past 4 years. All patients were genotyped for the NOD2 mutations. They were then clinically followed and prospectively studied. All patients were divided into two groups predicated on the presence or absence of the NOD2mutations. NAID was diagnosed according to our previously reported criteria. The data of the 2 groups were compared and analyzed.

Results: Of 143 patients, we identified 46.9% of patients carrying NOD2 mutations. The genotype frequencies were significantly higher than historical healthy controls, with IVS8+158 being 35.7%, R702W 11.2% and rare mutations 14.0% (Table 1). The frequency of IVS8+158 was significantly higher than non-Jewish white Crohn’s patients. Fifty seven of the 67 NOD2 positive patients were diagnosed with NAID. The remaining included 5 cases of Crohn’s disease, 2 ulcerative colitis, 2 Blau syndrome, and 1 autoimmune disease. The frequency of NAID was estimated to be 3%-7% of our outpatients.

All 57 NAID patients were white with 68.4% of women. The mean age at onset was (33.2 ± 14.0) years, and the mean disease duration at diagnosis was (10.6 ± 8.3) years. NAID was sporadic in 93% of cases. The phenotypic features of this disease included periodic fever (63.2%), dermatitis (91.2%) and inflammatory arthritis/arthritis (87.7%) (Table 2). Compared with NOD2 negative patients, the skin disease was overrepresented by dermatitis manifested as erythematous patches or plaques on trunk (Figure 1). Oligo-symptomatic arthritis were common mainly involving the lower extremities. Distal lower extremity swelling was more common (Figure 1). There were gastrointestinal symptoms in 73.7% but without inflammatory bowel disease and sicca-like symptoms in 56.1%. Pericarditis and pleuritis were occasionally
seen. Acute phase reactants were elevated in 40.4%, and autoantibodies are largely absent, with only 8.8% of patients having low titers of ANA. Associated NOD2 gene mutations were IVS8+158 (80.7%) and/or R702W (26.3%), and rare mutations (24.1%) (Table 2).

Of the 76 NOD2 mutation negative subjects, 28 patients turned out to have autoimmune diseases and 4 cases of autoinflammatory disease. The remaining were still non-diagnostic. The medications used to treat the disease entailed nonsteroidal anti-inflammatory agents (34.5%), glucocorticoids (36.4%), sulfasalazine (32.1%) and biologics (7.1%). Prednisone and sulfasalazine were found effective and 2 cases were treated with infliximab and tocilizumab.

**Conclusion:** The largest cohort study has demonstrated that the NOD2 genotype frequencies are significantly higher in our study patients and associated with NAID. NAID represents a genetically complex autoinflammatory disorder, and is distinct from Crohn’s disease. This disease is more prevalent than initially thought, with an estimated frequency of about 5% in our rheumatology outpatients. This report will further increase awareness of this entity in the medical community.

**Disclosure:** Q. Yao, None; M. Shen, None; C. McDonald, None; F. Lachouane, None; B. Shen, None.

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**Canakinumab Use in Patients with Cryopyrin-Associated Periodic Syndrome: Interim Safety and Efficacy Results from Beta-Confident Registry**

**Background/Purpose:** The three phenotypes in the order of severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome/neonatal onset cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), of canakinumab (CAN) use in CAPS patients (pts) in clinical practice from the using physician global assessments (PGA).

**Methods:** 47 pts resulting in an incidence rate of 13.2 SAEs/100 pyr. The most common procedures, but records all observed and reported adverse events (AEs) and SAES or AEs potentially related to treatment with CAN.

**Results:** 47 pts resulting in an incidence rate of 13.2 SAEs/100 pyr. The most common procedures, but records all observed and reported adverse events (AEs) and SAES or AEs potentially related to treatment with CAN.

**Conclusion:** nearly half the pts had no disease activity while most others had mild/moderate disease activity, at the current data cut-off. There was no evidence of loss of effect with time.

**Disclosure:** H. M. Hoffman, Novartis Pharmaceutical Corporation, 5; J. B. Kuenemere-Deschner, Novartis, 2, Novartis, 5; P. N. Hawkins, None; T. van der Poll, None; U. A. Walker, Novartis, 5; K. Abrams, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1; H. H. Tilson, Novartis, 5.

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**Interleukin-18 (IL-18) As a Biomarker for Diagnosis and Evaluation of Disease Activity in Patients with Adult Onset Still’s Disease and Systemic Onset Juvenile Idiopathic Arthritis**

**Background/Purpose:** Establishing the diagnosis of adult onset Still’s disease (AOSD) as well as of systemic onset juvenile idiopathic arthritis (sJIA) is very challenging. Mostly it is still a diagnosis of exclusion. Along with IL-1β, IL-6 and TNFa, IL-18 is one of the cytokines which seem to play a pivotal role in the pathogenesis of both diseases. It has been described as a potential biomarker to support the diagnosis of AOSD and sJIA. Regarding the importance of IL-18 as a marker for disease activity published data are so far conflicting. The aim of the study was to clarify the role of IL-18 as a diagnostic marker and its importance as a measure for disease activity in AOSD and sJIA.

**Methods:** Thirty adult patients diagnosed with AOSD and twenty children diagnosed with sJIA were included in the study. Twenty adults and three children were analyzed repeatedly. At each visit patients underwent clinical evaluation and laboratory analysis. IL-18 serum levels were determined using an IL-18 ELISA (MBL, Japan) according to the manufacturer’s instructions. As comparison groups served 65 adults and 23 children with other rheumatic diseases. To evaluate the disease activity Rau’s criteria and CRP values were used. Active disease was defined as a Rau’s score >2 and/or CRP> 2 ULN.

**Results:** In 83 samples from 30 AOSD patients IL-18 levels were determined. At the time of blood sample collection clinical parameters were obtained as well. In active disease (n=27) patients showed a mean activity score of 3.9±2.14 and a mean CRP value of 106.5±86.1 mg/l. Patients in remission (n=43) showed a mean activity score of 0.14±0.35, and mean CRP value of 5.6±1.5 mg/l. IL-18 levels were significantly increased in patients with active AOSD compared to patients in remission and to the comparison group with a median of 16327 pg/ml, 470 pg/ml, and 368 pg/ml, respectively (p<0.001). In active disease (n=16) the sJIA cohort showed a mean activity score of 3.4±1.0 and mean CRP value of 133.9±81.8 mg/l. Analogous to AOSD in active sJIA the median IL-18 serum level with 21512 pg/ml was significantly higher than in the comparison group (n=25) with a median IL-18 serum level of 2580 pg/ml (p<0.001) and a mean CRP value of 67.6±7.7 mg/l.

For evaluation of IL-18 serum levels as marker for AOSD or sJIA a receiver operating characteristic curve analysis was used. At a cut-off point of 5000 pg/ml IL-18 specificity for AOSD was 96.9 %, and sensitivity 63.3 % (AUC=0.870, p<0.001). For diagnosis of sJIA in children a cutoff value of 10000 pg/ml was chosen with a specificity of 100 % and a sensitivity of 60 % (AUC=0.774, p = 0.003).

In 11 AOSD patients with active disease at the first visit (Rau’s score 4.2±1.5) the reduction of disease activity (Rau’s score 0.4±0.7) went along with a significant reduction in IL-18 serum levels from medians of 12500 pg/ml to 402 pg/ml (Wilcoxon sign rank test p<0.001).

**Conclusion:** We could confirm earlier publications that highly elevated IL-18 serum levels are common in active AOSD and sJIA, with up to 1000fold higher concentrations compared to other rheumatic diseases. A clear association of IL-18 serum levels with disease activity in AOSD was found. The results give further evidence for the use of IL-18 as diagnostic biomarker in AOSD and sJIA.

**Disclosure:** H. Kudela, None; S. Drynda, None; A. Lux, None; G. Hornett, None; J. Kekow, None.

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**Relapsing Polychondritis Can be Characterized By 3 Different Clinical Phenotypes: Analysis of a Series of 142 Patients**

Jeremie Dion1, Nathalie Costedoat-Chalumeau1, Damien Sène2, Judith Cohen-Bittan3, Gaëlle Leroux2, Charlotte Dion2, Camille Frances3 and Jean-Cherette P4. 1National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin,

**Disclosure:** H. M. Hoffman, Novartis Pharmaceutical Corporation, 5; J. B. Kuenemere-Deschner, Novartis, 2, Novartis, 5; P. N. Hawkins, None; T. van der Poll, None; U. A. Walker, Novartis, 5; K. Abrams, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1; H. H. Tilson, Novartis, 5.
Background/Purpose: We previously described clinical characteristics and evolution of 142 patients with relapsing polychondritis (RP) followed in a single center and seen at least once since 2000 (1). A cluster analysis was performed with the aim to identify different subtypes of RP.

Methods: A cluster analysis using a k-means clustering method preceded by a multiple correspondence analysis was performed on 142 patients with RP according to Michet’s criteria.

Results: We identified 3 clusters corresponding to 3 distinct clinical phenotypes (Table 1). Cluster 1 (n=12, 8%) corresponded to the more severe phenotype, with a mortality rate of 58% and intensive care unit (ICU) admission rate of 50%. This cluster mainly included men (83%), older at diagnosis, with myelodysplasia (83%), cutaneous (92%) and cardiac (58%) involvement, but with rare tracheobronchial involvement. They were more frequently treated with biologics (58%) than with immunosuppressive agents (33%).

Cluster 2 (n=37, 26%) was characterised by patients with predominant tracheobronchial (76%) involvement and abnormal functional respiratory test results (57%). None had myelodysplasia, and cardiac involvement was less frequent (24%). The prognosis was intermediate: mortality was 14%, but these patients with high infection rate (35%) were frequently admitted to ICU (27%). They frequently received immunosuppressive agents (84%).

Cluster 3 (n=93, 65%), the largest and least severe, was mainly composed of women (68%) with infrequent tracheobronchial (3%) and hematological involvement (2% had myelodysplasia and 5% another hematological disease). Few patients died (4%) or were admitted to ICU (2%). All patients with long-lasting remission (n=15) were in this group.

Conclusion: Using cluster analysis, we were able to distinguish three distinct subgroups of RP. Cluster 1 and 2 had the worst prognosis: older men with myelodysplasia were more likely to have a fatal issue and patients with a respiratory tract involvement were more likely to be admitted to intensive care and had an intermediate survival. By contrast, the last group, mainly composed of patients without hematological or respiratory involvement, had a good prognosis. These results need to be confirmed in further studies.


Table 1: Cluster analysis of 142 patients with relapsing polychondritis

<table>
<thead>
<tr>
<th>Demographical data</th>
<th>Overall series N=142</th>
<th>Cluster 1 n=12 (8%)</th>
<th>Cluster 2 n=37 (26%)</th>
<th>Cluster 3 n=93 (65%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>86 (61)</td>
<td>2 (17)</td>
<td>21 (57)</td>
<td>63 (68)</td>
<td>0.003</td>
</tr>
<tr>
<td>Men</td>
<td>56 (39)</td>
<td>10 (83)</td>
<td>16 (43)</td>
<td>30 (32)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤55 years</td>
<td>109 (77)</td>
<td>5 (42)</td>
<td>33 (89)</td>
<td>75 (81)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>33 (23)</td>
<td>7 (58)</td>
<td>4 (11)</td>
<td>18 (19)</td>
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<td>Clinical phenotype</td>
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</tr>
<tr>
<td>Laryngeal</td>
<td>61 (43)</td>
<td>2 (17)</td>
<td>25 (68)</td>
<td>34 (37)</td>
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<td>32 (22)</td>
<td>1 (8)</td>
<td>28 (76)</td>
<td>3 (3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Audiologic/ventilatory</td>
<td>48 (34)</td>
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<td>15 (41)</td>
<td>27 (29)</td>
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<td>Ophthalmological</td>
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<td>11 (92)</td>
<td>18 (49)</td>
<td>51 (55)</td>
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<td>Cutaneous</td>
<td>40 (29)</td>
<td>11 (92)</td>
<td>6 (16)</td>
<td>23 (25)</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>15 (11)</td>
<td>3 (25)</td>
<td>6 (16)</td>
<td>6 (6)</td>
<td>0.06</td>
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<td>Myelodysplasia</td>
<td>12 (8)</td>
<td>10 (83)</td>
<td>0 (0)</td>
<td>2 (2)</td>
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<td>Other hematological disease</td>
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<td>1 (3)</td>
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<td>Cardiac</td>
<td>38 (27)</td>
<td>7 (58)</td>
<td>9 (24)</td>
<td>22 (24)</td>
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<td>Abnormal functional respiratory test result</td>
<td>29 (20)</td>
<td>2 (17)</td>
<td>21 (57)</td>
<td>6 (6)</td>
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<td>Steroids</td>
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<td>37 (100)</td>
<td>84 (90)</td>
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<td>Biological agents</td>
<td>22 (15)</td>
<td>7 (58)</td>
<td>12 (32)</td>
<td>3 (3)</td>
<td>&lt;0.0001</td>
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<td>Immunosuppressive agents</td>
<td>56 (39)</td>
<td>4 (33)</td>
<td>31 (84)</td>
<td>21 (23)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Disease evolution</td>
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<td>Death</td>
<td>16 (11)</td>
<td>7 (58)</td>
<td>5 (14)</td>
<td>4 (4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Serious infection</td>
<td>26 (18)</td>
<td>7 (58)</td>
<td>13 (35)</td>
<td>6 (6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>18 (13)</td>
<td>6 (50)</td>
<td>10 (27)</td>
<td>2 (2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Long lasting remission</td>
<td>15 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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Categorical Change in 6MWD in Patients with Connective Tissue Disease Associated Pulmonary Arterial Hypertension Receiving Ambirotan over 3 Years.

Artey Fischer1, Virginia D. Steen2, Steven Nathan3, Hunter Gillies4, James Tlslov5 and Chris Blair1.


Background/Purpose: The 6MWD is a valuable tool for evaluating response to therapy in patients with pulmonary arterial hypertension and may be considered a surrogate measure for survival in PAH. However, due to musculoskeletal and other non-PAH related factors, there has been a less robust effect on 6MWD in patients with CTD-PAH. We analyzed the ARIES database to determine the percentage of CTD-PAH patients who have achieved categorical changes in 6MWD while receiving ambisentan.

Methods: Data from the combined ARIES 1 & 2 placebo controlled studies (ARIES-C) as well as the extension study (ARIES-E) were used. Based upon the previously determined MID of 26m in the overall PAH population participating in the ARIES clinical trials (Minnai, ATS 2014), we chose to evaluate the number of patients achieving changes from their baseline 6MWD in 30m intervals. Analysis was broken down by 6MWD at the end of each year through year 3 and observed cases are reported. Patients who discontinued participation prior to completing year three continued to have survival status evaluated and overall survival status is reported. Adverse events over three years are also reported.

Results: There were 124 CTD-PAH patients who participated in the ARIES clinical trials. At the end of year 3, 6MWD data was available for 55 patients and was unavailable for 69 patients (died = 29, missing 6MWD, alive = 30, and missing 6MWD with survival status unknown = 1). Of these patients with an evaluable 6MWD at each yearly interval, the majority [57/91 (63%) at year 1, 43/75 (57%) at year 2, and 32/55 (58%) at year 3] demonstrated improvement from baseline and this was maintained throughout the three years. Additionally, of the patients demonstrating improvement in 6MWD, most were categorized as demonstrating an improvement of at least +60m over baseline which is well above the MID. At the completion of 3 years, survival status is unknown for 11 of the 124 CTD-PAH patients participating. Of the 113 patients where survival status is known, 84 (74.3%) were alive at three years. Adverse events occurring over 3 years were consistent with observed AEs in both PAH and CTD, and were consistent with the known profile of ambisentan.

Conclusion: Although CTD-PAH patients often do not have a robust improvement in 6MWD, among patients with CTD-PAH who received ambisentan and had evaluable 6MWD, the majority demonstrated increases in 6MWD over 3 years with 58.2% maintaining improvement by the end of year 3.

Disclosure: A. Fischer, Gilead Sciences, Inc., InterMune, 2, Gilead Sciences, Inc., Actelion Pharmaceuticals US, 8, Actelion Pharmaceuticals US, Gilead Sciences, Inc., InterMune, 5, V. D. Steen, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Sciences, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berhing, 2, InterMune, 2, Bayer, 5, S. Nathan, Actelion Pharmaceuticals US, Bayer, Boehringer-Ingelheim, Gilead Sciences, InterMune, Novartis, Roche, United Therapeutics, 5, Actelion Pharmaceuticals US, Bayer, Gilead Sciences, United Therapeutics, 8, Actelion Pharmaceuticals US, Bayer, Boehringer-Ingelheim, Gilead Sciences, InterMune, United Therapeutics, 2, H. Gillies, Gilead Sciences, Inc., 1, Gilead Sciences, Inc.,
Progressive Multifocal Leukoencephalopathy Associated with Biologic Therapy in Rheumatic Diseases: Strengthening Association with Rituximab.

A background of the interaction between rituximab and PML, requiring continued treatment with anti-TNF therapy, despite their widespread use, suggests that a causal biologic immunosuppressive therapies. The small numbers of cases involved and cofactors of PML.

Methods: A Freedom of Information Act request was submitted for all cases of PML and/or JC virus infection within the FDA AERS database, updated through August 27, 2012. MedWatch forms with identified ARD were selected for further analysis. Exclusions included: [1] cases where the ARD was not the primary indication for biologic therapy [2] where another condition was the key underlying factor for PML (e.g. HIV positivity) [3] where PML was classified as unconfirmed. A case was considered as confirmed PML once there was a clear description of compatible clinical and neuroimaging findings and positive identification of the JC virus by PCR in cerebrospinal fluid AND/OR compatible findings on brain biopsy or autopsy.

Results: 30 confirmed cases of PML associated with biologic therapy in the setting of ARD were identified (11 SLE, 11 RA, 5 dermatomyositis, 3 other). Median age was 53 yrs (range 28–76yrs), 25 were female. Rituximab (RTX) and anti-TNF therapies were the most recently administered biologic therapy in 26 and 4 cases respectively. There were no cases in which abatacept, tocilizumab, belimumab or anakinra was the most recently administered biologic therapy.

PML developed after a median of 2 courses of RTX (range 1–5). The median interval between the first and last infusion of RTX and the development of PML was 15 months (range 1–66) and 5 months (range 0–66) respectively. 4 patients were receiving concomitant cyclophosphamide (Cyc), 5 additional patients had previously received Cyt. 18/26 were receiving one or more additional immunosuppressive therapies at the time of diagnosis. PML 7/26 had received an anti-TNF therapy prior to treatment with rituximab. Two RTX-treated patients had received chemotherapy for malignancy prophylaxis (cancer, MALT lymphoma), had a prior history of breast cancer, 5 additional patients had documented significant lymphopenia.

4 patients developed PML during treatment with anti-TNF therapy, 1 receiving concomitant Cyc and 1 treated with Cyc prior.

Conclusion: PML is a rare event overall in ARD patients treated with biologic immunosuppressive therapies. The small numbers of cases involved and existence of confounders in many cases precludes definitive attribution of causality. However, the relative paucity of confirmed cases in patients recently treated with anti-TNF therapy, despite their widespread use, suggests that a causal relationship is less likely. In contrast, albeit rare, there is a discordant signal regarding the association between rituximab and PML, requiring continued pharmacovigilance.

Disclosure: E. Molloy, GlaxoSmithKline. 5, L. H. Calabrese, Genentech and Biogen IDEC Inc. 5, Pfizer Inc. 5, GlaxoSmithKline. 5.
Table 1

<table>
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<tr>
<th>Characteristic</th>
<th>All patients n=1089</th>
<th>No NSAIDs n=886</th>
<th>NSAIDs n=223</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>55 (16)</td>
<td>55 (16)</td>
<td>53 (15)</td>
<td>0.044</td>
</tr>
<tr>
<td>Gender, n (%) female</td>
<td>847 (78)</td>
<td>676 (78)</td>
<td>171 (77)</td>
<td>0.659</td>
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<tr>
<td>Average DAS, mean (SD)</td>
<td>4.0 (1.3)</td>
<td>3.9 (1.3)</td>
<td>4.4 (1.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>Average HAQ, mean (SD)</td>
<td>1.625 (0.875, 2.125)</td>
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<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Disease duration in years, median (IQR)*</td>
<td>7 (4, 11)</td>
<td>6.9 (4, 11)</td>
<td>7.3 (4, 11)</td>
<td>0.874</td>
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<tr>
<td>Methotrexate use, n (%)</td>
<td>614 (56)</td>
<td>491 (57)</td>
<td>123 (55)</td>
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</tr>
<tr>
<td>Biologic use, n (%)</td>
<td>152 (12)</td>
<td>107 (12)</td>
<td>25 (11)</td>
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<td>Treated hypertension, n (%)</td>
<td>301 (28)</td>
<td>249 (29)</td>
<td>52 (23)</td>
<td>0.106</td>
</tr>
<tr>
<td>Exposure time (person years)</td>
<td>4633</td>
<td>3751</td>
<td>882</td>
<td></td>
</tr>
<tr>
<td>Number of CV events</td>
<td>63</td>
<td>53</td>
<td>10</td>
<td></td>
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<tr>
<td>Incidence CV events/1000 person years (95% CI)</td>
<td>12.1 (9.5, 15.5)</td>
<td>12.6 (9.5, 16.5)</td>
<td>10.0 (4.8, 18.5)</td>
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<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>n/a</td>
<td>ref</td>
<td>0.77 (0.39, 1.51)</td>
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<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>n/a</td>
<td>ref</td>
<td>0.78 (0.36, 1.68)</td>
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</tbody>
</table>

*Missing data for HAQ present preclude meaningful analysis across cohort

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Vascular Calcifications on Hand and Wrist Radiographs Are Associated with Cardiovascular Risk Factors, Antigen-Specific Anti-Citrullinated Protein Antibodies, and Mortality in Rheumatoid Arthritis. E. Blair Solow, Fang Yu, Geoffrey M. Thiele, Jeremy Sokolove, William H. Robinson, Zachary M. Pruhs, Kaleb Michaud, Kaleb Michaud, Alan R. Erickson, Harlan Sayles, Gail S. Kerr,Angelo L. Gatto, Liron Chapman, Lisa A. Davis, Grant W. Cannon, Andreas M. Reimold, Joshua Baker, Pascale Schwab, Daniel Anderson, and Ted R. Mikuls. UT Southwestern Medical Center, Dallas, TX, University of Nebraska Medical Center, Omaha, NE, OMaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, VA Palo Alto Health Care system and Stanford University, Palo Alto, CA, VA Palo Alto VA Medical Center and Stanford University, Palo Alto, CA, Washington DC VAMC, Georgetown and Howard University, Washington, DC, Birmingham VA Medical Center and University of Alabama at Birmingham, Birmingham, AL, Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, Salt Lake City VA and University of Utah, Salt Lake City, UT, Dallas VA and University of Texas Southwestern, Dallas, TX, University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA, Oregon Health & Science University, Portland, OR.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased mortality due to cardiovascular disease (CVD). Select antigen-specific anti-citrullinated protein antibodies (ACPA) are associated with atherosclerotic burden in RA. Furthermore, citrullinated proteins have been localized in atherosclerotic plaque. Vascular calcifications (VC) may be found incidentally on hand and wrist radiographs in RA. This study examined the relationship of VC with CVD risk factors, ACPA subtypes, and all-cause mortality in RA.

Methods: Hand and wrist radiographs from 906 RA patients were scored for the presence of VC as either "positive" or "negative". Patient characteristic variables were compared using univariate and multivariable logistic regression. ACPA were measured using an enzyme-linked immunosorbent assay for second generation anti-cyclic citrullinated peptide (CCP2) antibodies, then 19 distinct ACPA subtypes were measured by a bead-based immunoassay and sorted based on q-values calculated by Significance Analysis of Microarrays (SAM). ACPA associations with VC were further examined using multivariable quantile regression. VC and all-cause mortality were examined using Cox proportional hazards regression.

Results: Ninety-nine (11%) patients demonstrated VC on hand and wrist radiographs (Table 1). In multivariable analyses, factors associated with VC included diabetes (OR 2.85; 95% CI 1.43, 5.66, p=0.003), history of CVD (OR 2.48; 95% CI 1.01, 6.09, p=0.047), prednisone use (OR 1.90; 95% CI 1.25, 2.91, p<0.003), current vs. never smoking (OR 0.06; 95% CI 0.01, 0.23, p=0.001) and former vs. never smoking (OR 0.36; 95% CI 0.27, 0.48, p=0.001). In the ACPA subtype analyses using SAM, antibodies to citrullinated forms of Apolipoprotein E (anti-Cit-ApoE), fibrinogen, and vimentin, but not anti-CCP antibody, were differentially expressed in patients with VC (Table 2). The association of anti-Cit-ApoE with VC remained significant following all multivariate adjustments, as well as adjustment for known CVD. After adjusting for significant covariates and stratifying by age and gender, VC were associated with increased all-cause mortality (HR = 1.41; 95% CI 1.12, 1.78, p=0.004).

Conclusion: In this cohort, ~1 in 10 RA patients had VC on hand and wrist radiographs. VC were associated with traditional CVD risk factors and prednisone use and yielded an independent association with all-cause mortality. ACPA targeting Cit-ApoE were increased among patients with VC. Mechanisms underpinning the association of select ACPA with CVD in RA warrant further investigation.
Lipid Control and Cardiovascular Risk for Patients with Rheumatoid Arthritis Compared with Matched Non-Rheumatoid Arthritis Patients. J. An1, E. Alemoa2, K. Reynolds3, H. Kawabata4, D. H. Solomon4, K. P. Liao4, T. C. Cheetham4. 1Western University of Health Sciences, Pomona, CA, 2Bristol-Myers Squibb, Princeton, NJ, 3Kaiser Permanente Southern California, Pasadena, CA, 4Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: Lipid levels are known to be lower in patients with RA compared with the general population; however, differences in cardiovascular (CV) risk associated with lipid control between patients with RA and non-RA patients remain uncertain. The purpose of this study is to evaluate the association between low-density lipoprotein cholesterol (LDL) control and CV outcomes among RA and matched non-RA populations.

Methods: Between 01/01/2007 and 12/31/2011, adult patients with RA were identified within Kaiser Permanente Southern California. Two age- and sex-matched cohorts were identified as non-RA: 1) 1:4 matched general population, and 2) 1:1 matched osteoarthritis (OA) population. Individuals were followed from their index date until the first CV outcome (myocardial infarction, angina, stroke, transient ischemic attack, intermittent claudication, heart failure or CV disease death), end of enrollment or death from other causes. Univariate and multivariate Cox proportional hazard analyses were conducted for patients treated for dyslipidemia who had ≥1 LDL measurement during the follow-up period. LDL measures closest to the end of follow-up were used to define LDL control (mg/dL) stratified by CV risk.

Results: Cohort 1 consisted of 1,522 patients with RA and 6,511 matched patients from the general population; Cohort 2 had 1,746 patients with RA and 2,554 matched patients with OA. Median follow-up was 3.1 years for Cohort 1, and 4.0 years for Cohort 2. Mean (SD) age was 63.5 (10.2) years for both cohorts; there were 71.4% females in Cohort 1 and 75.8% in Cohort 2. In addition to dyslipidemia, 74.2% of patients with RA had hypertension, 40.9% had diabetes, 46.7% were obese, 10.5% were smokers, 41.3% had high CV risk, and 51.3% had medium CV risk. Traditional CV risk factors were higher in RA compared with general (Cohort 1) or OA populations (Cohort 2). Mean (SD) LDL levels (mg/dL) were 96.8 (32.7) for RA, 100.1 (35.1) for the general population, and 99.1 (34.3) for the OA population. The rate of LDL control was 78.7% for both the RA and general populations, and 80.0% for the OA population. Adjusting for age, sex, hypertension, antihypertensive medication use, smoking status, and diabetes, controlled LDL was associated with a 33% reduced CV risk compared with uncontrolled LDL in patients with RA hazard ratio [HR] [95% CI] = 0.67 [0.46, 0.96] (vs no control)*. Controlled LDL was also associated with a reduced CV risk compared with uncontrolled LDL in the general population (HR = 0.72 [0.55, 0.95]). Similar HR results were found in the OA population; however, the association was not statistically significant (HR = 0.76 [0.53, 1.07]) (Table).

Conclusions: LDL control was associated with a reduced CV risk in the RA and matched general populations. These results suggest an important role for LDL control in preventing CV events among patients with RA as well as non-RA patients.

Disclosures: J. An, BMS, Genentech, Merck, 2; E. Alemoa, Bristol-Myers Squibb, 1; K. Reynolds, None; H. Kawabata, Bristol-Myers Squibb, 1; K. P. Liao, None; T. C. Cheetham, BMS, Gilead, 2.

Is Rheumatoid Arthritis a Coronary Heart Disease Risk Equivalent, Similar to Diabetes? Jie Zhang, Shao Yang, Fenglong Xie, Huifeng Yan, Paul M. Muntner, Emily Levitan, Monica Safford, Kenneth G. Saag, Javinder Singh, Jeffrey R. Curtis. 1Univ. of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL, 3University of Alabama at Birmingham School of Public Health, Birmingham, AL, 4The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Recently cholesterol treatment guidelines recommend that diabetes (DM) should be considered a CVD risk equivalent to a history of coronary heart disease (CHD). Despite the well-recognized increased CVD risk in rheumatoid arthritis (RA) patients, the guidelines do not recommend that RA should be considered a CHD risk equivalent. We compared the incidence of hospitalized acute myocardial infarction (MI) among patients with DM alone, RA alone, both conditions and neither of them.

Methods: Using a mix of private and public health plans claims data from 2006 to 2010 with medical and pharmacy coverage; we identified 4 mutually exclusive cohorts: patients with 1) RA and DM; 2) RA only; 3) DM only; 4) Neither RA nor DM. Patients with prevalent CHD during a baseline period of ≥1 year were excluded. Acute MI was defined as ≥1 inpatient hospital claim with a discharge ICD-9 code in any position for 410.x (excluding 410.x2) and at least one overnight stay, unless the patient died. We compared the age- and gender-specific incidence rates (IRs) of acute MI across the four cohorts and calculated differences in IRs between select cohorts.

Results: We identified 1,070,212 eligible participants in our study. MI IRs were highest among adults with both RA and DM, followed by those with DM alone, with RA alone, and lowest in those without either condition. Findings were consistent for both sexes and across all age strata (Table). Among women 41 years of age or older, the absolute difference in IRs between the two cohorts peaked at 4.3 cases per 1,000 Person-Years (PYs) among those 71 or older. Among men, the peak difference (4.61 cases per 1,000 PYs) was observed among those 51–60 years of age. We found large increases in MI IR among RA patients if they were also diagnosed with DM, especially among women with the greatest difference (9.3 cases per 1,000 PYs) observed among women 51–60 years of age.

Conclusion: In this analysis, the incidence of MI was consistently lower in patients with RA alone than in those with DM alone, which does not support RA as a CHD risk equivalent. Our findings have important clinical implications in the treatment of hyperlipidemia for RA patients.
### Exercise Is Associated with Protective Cardiovascular Risk Profile Including Increased HDL Particle Number in Patients with Rheumatoid Arthritis

**Background/Purpose:** Patients with rheumatoid arthritis (RA) have increased cardiovascular risk. In the general population, exercise improves several cardiovascular risk factors, including HDL cholesterol concentrations. Although exercise is known to improve quality of life measures in patients with RA, less is known about its effects on cardiovascular risk factors, particularly lipoprotein particle concentrations, which provide information not always concordant to that of lipoprotein cholesterol concentrations. Therefore, we examined the hypothesis that increased exercise is associated with beneficial effects on cardiovascular risk factors, including HDL particle concentration.

**Methods:** Patient-reported exercise outside of daily activities was quantified as metabolic equivalents measured in minutes per week (METmin/week), according to the 2011 Compendium of Physical Activities, in 165 patients with RA. Hypertension was defined as current use of antihypertensive agents or systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg. Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA). Standard lipid profiles were measured by our diagnostic clinical laboratory, whereas HDL and LDL particle concentrations were determined by nuclear magnetic resonance spectroscopy (LipoScience). The relationship between METmin/week and cardiovascular risk factors was assessed with Spearman correlation and with linear and logistic regression with adjustment for age, race, and sex.

**Results:** The mean ± standard deviation [range] of exercise was 311 ± 786 METmin/week [0 – 7200 METmin/week]. Exercise was inversely associated with heart rate (P = 0.02), waist-hip ratio (P = 0.02), and systolic blood pressure (0.03), but not with the degree of insulin resistance (HOMA) or BMI. We found no significant association between exercise and LDL or HDL cholesterol concentrations. Exercise was positively associated with the concentration of both total and small HDL particles (P = 0.003 and P = 0.001, respectively), but not with LDL particle concentrations (Table). Those who exercised had 2.6 μmol/L greater HDL particle concentration (P = 0.002) and 2.8 μmol/L greater small HDL particle concentration (P = 0.001), after adjustment for age, race, and sex.

**Conclusion:** The amount of self-reported exercise in patients with RA was independently associated with beneficial changes in several cardiovascular risk factors including heart rate, waist-hip ratio, systolic blood pressure and HDL particle concentration.

### ACR Concurrent Abstract Session Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy I: Safety of Biologics and Small Molecules in Rheumatoid Arthritis - Malignancy and Infection

**Disclosure:** K. Byram, None; A. Oesper, None; M. F. Linton, None; S. Fazio, None; C. M. Stein, None; M. Ormseth, None.

**Frequency of Significant Infection in Patients with RA Following Initiation of Rituximab with up to 5 Years of Follow-up in a US Observational Study**


1The University of Alabama at Birmingham, Birmingham, AL, 2Oregon Health & Science University, Portland, OR, 3University of California at Los Angeles, Los Angeles, CA, 4Genentech, Inc., South San Francisco, CA, 5Genentech, Inc, South San Francisco, CA, 6Rheumatic Disease Center, Glendale, WI.

**Background/Purpose:** Rituximab (RTX) is an approved treatment for rheumatoid arthritis (RA) in patients (pts) with an inadequate response to anti-TNF therapy (aTNF-IR). Long-term infection risk data of RTX use in real-world settings are limited. The objective of this study was to describe the frequency of significant infections in pts with RA initiating RTX in the US.

**Methods:** SUNSTONE was a prospective observational cohort study designed to evaluate the safety of RTX in TNF-IR RA pts in a real-world setting. Pts were evaluated and treated according to their physicians’ standard practices and followed at visits every 6 months. Pts were followed for 5 years (regardless of RTX discontinuation or start of another biologic DMARD), until death, withdrawal of consent or loss to follow-up. Significant infections were defined as infections that meet FDA serious AE criteria or require IV antibiotics. For calculation of incidence rates (IRs), pts were censored at the time of first event, switch to another biologic DMARD, death, withdrawal of consent or loss to follow-up. IRs by year after RTX initiation and by RTX course are described. Course was defined as 2 × 1000-mg infusions separated by ≥21 days. Pts not treated according to this regimen were excluded from the course analysis. Among pts who switched to another biologic DMARD during follow-up, the IRs of significant infection before and after switch were also calculated. IR calculations after switch were censored at the time of first event, death, withdrawal of consent or loss to follow-up. IRs per 100 pt-yrs (PY) are reported.

**Results:** Overall, 938 pts (3778 PY) received RTX (82% F; median age, 58 yrs; median disease duration, 9 yrs; 72% RF+). Mean duration of follow-up was 4 yrs and mean number of RTX courses was 4; however, not all pts were treated following the labeled dose regimen. Four pts with insufficient information to calculate IRs were excluded. Significant infections were reported in 160 pts (17%), with an IR of 6.4 (95% CI, 5.5 to 7.4). IRs in 1-y increments following RTX initiation were 7.1 (95% CI: 5.5–9.2), 6.5 (95% CI: 4.8–8.3), 8.0 (95% CI: 5.9–10.9), 9.2 (95% CI: 6.6–12.7) and 7.0 (95% CI: 4.7–10.3) in years 0–1, 1–2, 2–3, 3–4, and 4–5, respectively. See table for IR and 95% CI by course; exposure is less than 100PY from Course 7 onward resulting in wide 95% CIs around IR estimates. Among 338 pts who switched to another biologic DMARD, IRs before and after switch were 4.6 (95% CI, 3.1 to 6.7) and 4.5 (95% CI, 3.3 to 6.2), respectively.
Conclusion: Data from SUNSTONE with up to 5 years of follow-up showed that risk of significant infection among pts with refractory RA that were treated with RTX after an inadequate response to a TNF inhibitor did not increase over time and with multiple courses. In addition, switch from RTX to another biologic DMARD was not associated with an increased risk of significant infection.

Discussion: The risk of cancer with TNF-a inhibitor (TNFi) in patients concomitantly exposed to Non-Biological Immunosuppressants Differs According to the Indication. Layla Saliba, Guillaume Moulière, Malak Aboutaam, Yves Grappin, Leila Chenal, Bernadette Baldin, Jean-Louis Montastruc, and Héléne Bagheri; Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, Toulouse, France; Toulouse University Hospital, Department of Internal Medicine, University of Toulouse, INSERM UMR 1027, Toulouse, France; Reims University Hospital, Pharmacovigilance Regional Center, Reims, France; Nancy University Hospital, Pharmacovigilance Regional Center, Nancy, France; Nice University Hospital, Pharmacovigilance Regional Center, Nice, France.

Background/Purpose: The risk of cancer with TNF-a inhibitor (TNFi) in patients concomitantly exposed to Non-Biological Immunosuppressants (NBIS) is high, especially in RA. A study in RA, AS and PsA showed that patients treated with NBIS alone (biological naive), suggested that the excess risk of some lymphomas in IBD was due to NBIS treatment. In contrast, it suggests that there is no increased risk of cancer with exposure to both TNFi and NBIS compared with NBIS alone in RA (ROR: 5.43, 95% CI[3.52–8.38]). The signal was significant for every type of cancer, but was the most important for NMSCs (ROR: 20.17, 95% CI[2.49–163.36]). In contrast, no signal was found in AS, psoriasis/PsA and IBD, whatever the type of cancer. As regards the secondary objective, there was no difference between TNFis. Sensitivity analyses carried out to detect event- or drug-related competition biases.

Results: Out of the 1,918 reports meeting the study population definition, 217 were cases (135 solid and 82 basal cancers). RA was the leading indication among the study population (n=1200), followed by IBD (n=422), psoriasis or PsA (n=126), and AS (n=92). Exposure to TNFi was found in 156 (72.7%) cases (infliximab, 48.9%, adalimumab, 28.8% and etanercept, 37.2%) and in 69% (43.0%) non-cases (infliximab, 6.3%, adalimumab, 18.8% and etanercept, 18.8%). A safety signal was found as regards the risk of cancer with exposure to both TNFi and NBIS compared with NBIS alone in RA (ROR: 5.43, 95% CI[3.52–8.38]). The signal was significant for every type of cancer, but was the most important for NMSCs (ROR: 20.17, 95% CI[2.49–163.36]). In contrast, no signal was found in AS, psoriasis/PsA and IBD, whatever the type of cancer. As regards the secondary objective, there was no difference between TNFis. Sensitivity analyses confirmed these results.

Conclusion: This study adds strong argument for an increased risk of cancer, and particularly NMSCs, in RA patients exposed to TNFi in addition to NBIS compared with NBIS alone. The signal seems similar with infliximab, adalimumab and etanercept. In contrast, it suggests that there is no signal in AS, psoriasis/PsA and IBD.

846 Rheumatoid Arthritis, Anti-Tumor Necrosis Factor Therapy, and Risk of Squamous Cell and Basal Cell Skin Cancer- a Nationwide Population Based Prospective Cohort Study from Sweden. Pauline Raauchou1, Julia F Simard2, Charlotte Askder-Hagellberg3, Johan Asklings4 and the ARTIS Study group1, 1Karolinska Institutet, Stockholm, Sweden, 2Stanford School of Medicine, Stanford, CA, 3Swedish Medical Products Agency, SE-751 03 Uppsala, Sweden, 4Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 5Karolinska Institutet och Svensk Reumatologisk förening, Solna, Sweden.

Background/Purpose: There is a concern that tumor necrosis factor inhibitors (TNFi) may interplay with tumor biology and increase the risk of cancer, in particular cancer types already associated with states of immune perturbation, such as skin cancers. We therefore investigated the risk of first squamous cell (SCC) and basal cell (BCC) cancers in TNFi-treated rheumatoid arthritis (RA) compared to biologics-naïve RA, and also in biologics-naïve RA compared to the general population, taking several potential confounders into account.

Methods: Through register-linkages, we assembled a cohort of biologics-naïve patients with RA (n=54,450), one cohort of patients with RA starting TNFi-treatment as first biologic 1998–2011 (n=10,974), and a general population comparator cohort (matched 5:1 to the biologics-naïve RA patients). Individuals with a history of organ transplantation and/or invasive malignancy were excluded. The primary outcome was defined as first in situ or invasive SCC (1998–2011), and first BCC (2004–2011) during follow-up. Hazard ratios (HR) were estimated adjusting for several potential confounders including invasive malignancy during follow-up, use of immuno-suppressive medications and history of non-melanoma skin cancer. We performed a series of sensitivity analyses using different definitions of the study population, risk window, and outcome.

Results: Comparing biologics-naïve RA to the general population, the HR of first in situ or invasive SCC in RA was 2.01 (95% CI 1.80–2.33). Based on 168 vs. 803 first invasive or in situ SCC, the adjusted HR was 1.20 (95% CI 0.96–1.51) comparing TNFi-treated to biologics-naïve RA. The HR of SCC was driven mainly by in situ lesions. Similarly, comparing biologics-naïve RA to the general population, the HR of first BCC was 1.22 (95% CI 1.23–1.34). Based on 169 vs. 1,439 first BCC, the adjusted HR was 1.01 (95% CI 0.85–1.21) comparing TNFi-treated to biologics-naïve RA.

Conclusion: RA (in the absence of TNFi-treatment) was associated with a doubled risk of SCC. TNFi-treatment was associated with a further 20% increase in the risk of in situ, but not invasive SCC. For BCC, RA (in the absence of TNFi treatment) was a much weaker risk factor, and TNFi treatment did not increase the risk of BCC. Whilst we cannot exclude surveillance bias as an explanation for our findings regarding SCC, the risks observed call for vigilance of skin lesions in RA, irrespective of treatment.

Table 1. Occurrence and hazard ratios (HR) with 95% confidence intervals (CI), of squamous cell cancer (SCC) in 10,974 TNFi-treated, compared to 41,031 biologics-naïve Swedish rheumatoid arthritis (RA)-patients. Occurrence and hazard ratios (HR) with 95% confidence intervals (CI), of basal cell cancer (BCC) in 7,397 TNFi-treated, compared to 38,679 biologics-naïve Swedish RA-patients.

<table>
<thead>
<tr>
<th>Squamous cell cancer</th>
<th>Biologics-naïve RA</th>
<th>HR^2</th>
<th>HR^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFi (n events/ person-years)</td>
<td>1606/66,010</td>
<td>803/221,081</td>
<td>1.24 (1.04–1.47)</td>
</tr>
<tr>
<td>Invasive</td>
<td>61/66,673</td>
<td>334/223,571</td>
<td>1.12 (0.84–1.50)</td>
</tr>
<tr>
<td>Basal cell cancer</td>
<td>1606/24,932</td>
<td>14/184,441</td>
<td>1.14 (0.97–1.36)</td>
</tr>
</tbody>
</table>

Conclusion: RA exposed for skin, county and civil status. Adjusted for age

HR^2 Stratified for sex, county, civil status, and education level. Adjusted for age, country of birth, co-morbidities during follow-up (chronic obstructive pulmonary disease, psoriatic arthritic, any chronic skin disease, non-melanoma skin cancer, malignant melanoma, all-site cancer, and joint surgery/total organ transplantation, ever use of cyclosporine, cyclophosphamide or azathioprine.

Disclosure: P. Rauchou; None, J. F. Simard; None, C. Askder-Hagellberg; None, J. Asklings; None, T. A. Study group, Abbvie, Merck, BMS, Pfizer, SOBI, AstraZeneca, Roche, UCB, 9.
Safety of TNF Inhibitor Therapy in Patients Who Have Had a Prior Malignancy. Seung-Hyeon Bae, Doo-Ho Lim, Soo Min Ahn, Seokhan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: A few is known about the effects of biologic therapy in patients with a history of a solid cancer. According to the 2012 updated American College of Rheumatology Recommendations, it is possible to start or resume any biologic agent in patients who have been treated for solid tumor (level of evidence C). But, there is no evidence in patients with history of a solid cancer within the past 5 years because of the lack of studies examining the risk of recurrent cancer in this subgroup. The purpose of this study was to explore the influence of TNF inhibitor (TNFi) therapy in patients with prior cancer treatment within the past 5 years.

Methods: The medical records of all patients (n=859) that received TNFi therapy at a single rheumatology clinic between June 2005 and May 2014 were retrospectively reviewed. Among them, data from patients who had a history of solid cancer treatment before TNFi therapy were collected and patient outcomes were evaluated especially for those who have been treated cancer within the last 5 years.

Results: Of 859 patients who underwent TNFi therapy, 22 patients (1 on infliximab, 11 on etanercept, 7 on adalimumab and 3 on golimumab) had a history of malignancy before initiating TNFi therapy for ankylosing spondylitis (AS) and rheumatoid arthritis (RA) (Table 1). The median AS, RA disease duration was 8 (3.75–12.25) years and median time to TNFi therapy after prior cancer treatment was 62.5 (21.25–140.25) months. Most common site of prior cancer is stomach (36.4%) and followed by thyroid, colorectum, liver, kidney, and breast. There was no recurrence of previous cancer during 40 (7.0–50.75) months of TNFi therapy. Especially, 10 patients started TNFi therapy before 5 years prior cancer treatment (Table 2). All of our 10 cases were limited in an early stage without distant metastasis. When they have been followed for 36 months, recurrence of cancer was not found.

Conclusion: Our results suggest that starting TNFi therapy in patients with history of solid cancer in locally limited stage is safe even less than 5 years after prior cancer treatment.

Table 1 Clinical characteristics of patients with prior cancer history when starting TNFi

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(range), years</td>
<td>63 (41-81)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>AS</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>RA</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Disease duration of AS and RA, median(IQR), years</td>
<td>3 (1.25–5)</td>
</tr>
<tr>
<td>Time to TNFi therapy after prior cancer treatment, median(IQR), month</td>
<td>62.5 (21.25–140.25)</td>
</tr>
<tr>
<td>TNFi, n (%)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>infliximab</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>etanercept</td>
<td>11 (50)</td>
</tr>
<tr>
<td>adalimumab</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>golimumab</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Site of prior cancer, n (%)</td>
<td>11 (49.5)</td>
</tr>
<tr>
<td>stomach</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>colorectum</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>gallbladder</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>liver</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>kidney</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>breast</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>skin (non melanoma)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>cervix</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>thyroid</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Duration of TNFi use, median(IQR), month</td>
<td>10.5 (7.0–50.75)</td>
</tr>
<tr>
<td>Incidence of cancer recur, n (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis, RA: rheumatoid arthritis, IQR: interquartile range; TNFi: TNF inhibitor

Table 2. Clinical characteristics of 10 patients who starting TNFi less than 5 years after prior cancer treatment

<table>
<thead>
<tr>
<th>Age, years/ sex</th>
<th>Diagnosis</th>
<th>Site of prior cancer</th>
<th>Type/t staging</th>
<th>Treatment</th>
<th>TNFi inhibitor</th>
<th>Duration of TNFi therapy in month</th>
<th>Cancer recur</th>
</tr>
</thead>
<tbody>
<tr>
<td>60F RA</td>
<td>liver</td>
<td>HCC T1N0M0</td>
<td>surgical resection</td>
<td>1</td>
<td>A</td>
<td>75</td>
<td>No</td>
</tr>
<tr>
<td>41F RA</td>
<td>stomach</td>
<td>MALFoma low grade</td>
<td>Hypothesis: eradication</td>
<td>42</td>
<td>A</td>
<td>64</td>
<td>No</td>
</tr>
<tr>
<td>73F RA</td>
<td>thyroid</td>
<td>PTC TNM0</td>
<td>surgical resection</td>
<td>8</td>
<td>G</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>78F RA</td>
<td>skin</td>
<td>BCC</td>
<td>surgical resection</td>
<td>2</td>
<td>E</td>
<td>45</td>
<td>No</td>
</tr>
<tr>
<td>64M AS</td>
<td>stomach</td>
<td>AGC T2N1M0</td>
<td>surgical resection, adjuvant chemotherapy</td>
<td>22</td>
<td>E</td>
<td>235</td>
<td>No</td>
</tr>
<tr>
<td>62F AS</td>
<td>kidney</td>
<td>BCC T1N0M0</td>
<td>surgical resection</td>
<td>47</td>
<td>E</td>
<td>56</td>
<td>No</td>
</tr>
</tbody>
</table>

Rheumatologic diagnosis and No. of patients. All 356 99 211 46 673 170 422 81
RA 245 77 129 39 499 143 288 68
AS 22 17 0 0 22 3 19 0
PsA 49 11 34 4 92 18 65 9
Other 40 6 31 3 60 6 50 4
Age at start of follow-up, years | 52 (18-85) |
Age at diagnosis, years | 45 (3-74)  |
Follow-up time, years | 3.5 (0.0-11.3) |
Person-years of observation | 1409 1531 |

Disclosure: S. H. Bae, None; D. H. Lim, None; S. M. Ahn, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

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Malignant Progression of Precancerous Lesions of the Uterine Cervix Following DMARD Therapy in Female Arthritis Patients. René Cordtz1, Lene Møller kjær2, Bente Glinborg1, Merete Lund Hetland1 and Lene Dreyer1. 1Copenhagen University Hospital Gentofte, Hellerup, Denmark. 2The Danish Cancer Society, Copenhagen, Denmark. 3Copenhagen University Hospital Glostrup. On behalf of all departments of Rheumatology in Denmark., Glostrup, Denmark.

Background/Purpose: Recent studies have found that a high proportion of female rheumatoid arthritis (RA) patients are chronic carriers of high-risk HPV-strains and that these patients are at increased risk of high-grade cervical dysplasia (CD) and cervical cancer. There are uncertainties regarding the safe use of biological DMARDs (bDMARDs) in arthritis patients with premalignant conditions. The aim of the present study was to investigate the occurrence of premalignant lesions of the uterine cervix progressing to a more malignant stage or developing another HPV-associated cancer in female RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients treated with bDMARDs or conventional synthetic DMARDs (csDMARDs).

Methods: In this observational study, we used the nationwide Danish DABNO Registry covering > 90% of rheumatologic patients treated with bDMARDs in routine care and also patients treated with csDMARDs have been registered since 2006. Patient data from RA, AS and PsA patients registered from 2000–2011 was linked with data from The Danish Cancer Registry. We specifically included patients with a history of mild, moderate and severe cervical dysplasias (CD) or carcinoma in situ (CIS) of the cervix, including both CD/CIS diagnosed before or after DABNO entry. Patients were followed up for a cancer diagnosis or progression of the premalignant grading of the lesion from the date of diagnosis of CD/CIS of the cervix or first registration in DABNO, whichever came latest. End of follow-up was date of diagnosis with cervical cancer or other HPV-associated cancer (vulvar, vaginal, anal or oropharyngeal cancer), other cancer diagnosis, death or end of 2011, whichever came first.

Results: We identified 905 arthritis patients with a history of CD or CIS. Of these, 806 were diagnosed with CD/CIS prior to DABNO entry, while the remaining 99 were diagnosed during their time registered in DABNO. Overall, 356 had ever been exposed to bDMARDs and 673 to csDMARDs of which 124 patients switched from csDMARD to bDMARD therapy and therefore contributed with person-years of observation in both csDMARD and bDMARD groups. The table shows the number of arthritis patients registered in DABNO with a history of CD/CIS and characteristics of the RA patients. Only 1 of the 356 bDMARD exposed patients experienced malignant progression from CD to CIS of the cervix. None were diagnosed with cervical cancer or any other HPV-associated cancer after DMARD treatment initiation during 2740 person years of observation.

Conclusion: Our findings suggest that DMARD – and bDMARD treatment in particular – has limited harmful effects on precancerous lesions of the uterine cervix in female arthritis patients, but more patients and longer follow-up are required to confirm these findings.

Table: Number of arthritis patients in DABNO with a diagnosis of cervical dysplasia (CD) or carcinoma in situ of the cervix (CIS) and occurrence of malignant progression. Characteristics of RA patients at first registration according to ever biological DMARD (bDMARD) or conventional synthetic DMARD (csDMARD) exposure, respectively.*

Background/Purpose: Treatment of rheumatoid arthritis (RA) is challenging due to the potential extent for RA patients: adrenal insufficiency 15 patients, anaphylaxis 15 patients, and suicide attempts 15. 22 patients. 3. ACR20, ACR50, and ACR70 response rates for pts enrolling within 14 days of participation; for all other pts, BL was the start of the LTE study. Primary endpoints were adverse events (AEs) and laboratory parameters improved upon nilotinib treatment in axial SpA. During the trial one serious adverse event occurred, which was considered unrelated to the study drug. There were no unexpected safety signals in comparison with published large scale data on nilotinib in chronic myeloid leukemia (CML).

Conclusion: This proof-of-concept study supports the concept that mast cells can contribute to synovial inflammation in SpA and that tyrosine kinase inhibition targeting these cells has a biological and clinical immunomodulatory effect in peripheral but not axial SpA. These results support further clinical evaluation of nilotinib in larger clinical trials in pure peripheral SpA, as well as evaluation of other drugs targeting mast cells in SpA.


Disclosure: R. Cordtz, None; L. Mellemkjær, None; B. Glinborg, None; M. L. Høfteland, None; L. Dreyer, None.

849 Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis (RA). Here we report tofacitinib safety, tolerability, and durability of response through 72 months (m) in long-term extension (LTE) studies.

Methods: Data were pooled from two open-label studies (NCT00413699 [ongoing; database unlocked as of April 2014 data cut-off] and NCT00661661) of patients (pts) with RA who participated in randomized Phase (P1), P2, or P3 tofacitinib studies. Treatment was initiated with tofacitinib 5 or 10 mg BID as monotherapy or with background DMARDs; data from both dose levels were included. Baseline (BL) was that of P1, P2, or P3 studies for pts enrolled within 14 days of participation; for all other pts, BL was the start of the LTE study. Primary endpoints were adverse events (AEs) and laboratory safety data. Confirmed (2 sequential abnormalities) data are reported for decreased hemoglobin (Hgb), absolute neutrophil counts, absolute lymphocyte counts, and increases >50% from BL in creatinine. Secondary endpoints included ACR responses, DAS28-4(ESR), and HAQ-DI. Safety data were included over 84 m and efficacy data up to Mo 72 (limited pt numbers [n=29] post-Mo 72 for efficacy).

Results: Overall, 4,888 pts were treated for a mean (maximum) duration of 918 (2,535) days. Total tofacitinib exposure was 12,359 pt-years (pt-y).

In peripheral SpA (n=13) synovial inflammation was markedly reduced after 12 weeks of nilotinib treatment as evidenced by histopathology (decrease in number of infiltrating CD68+ and CD163+ macrophages and mast cells). Compared to placebo the mRNA expression of c-Kit as mast cell marker (p=0.037) and of pro-inflammatory cytokines such as IL-6 (p=0.024) were reduced. The improvement of synovial inflammation was paralleled by a decrease in serum biomarkers of inflammation such as C-reactive protein (CRP) from 9.2 (IQR 1.7–33.1) to 5.2 (IQR 1.7–25.1) mg/L (p=0.024) and calprotectin from 359.9 (IQR 183.3–484.9) to 287.9 (IQR 116.7–457.1) ng/mL (p=0.055). Also clinical parameters such as patient’s global assessment of disease activity (week 0: 52 [IQR 43–65] vs week 12: 21 [IQR 0–51] mm; p=0.031) and Ankylosing Spondylitis Disease Activity Score (ASDAS) (week 0: 2.2 [IQR 1.2–3.0] vs week 12: 1.1 [IQR 0.7–2.4]; p=0.031) showed improvement upon 12 weeks of nilotinib but not placebo treatment, and this improvement was further augmented at week 24. In sharp contrast to peripheral SpA, neither serum biomarkers of inflammation nor clinical parameters improved upon nilotinib treatment in axial SpA. During the trial one serious adverse event occurred, which was considered unrelated to the study drug. There were no unexpected safety signals in comparison with published large scale data on nilotinib in chronic myeloid leukemia (CML).

Conclusion: This proof-of-concept study supports the concept that mast cells can contribute to synovial inflammation in SpA and that tyrosine kinase inhibition targeting these cells has a biological and clinical immunomodulatory effect in peripheral but not axial SpA. These results support further clinical evaluation of nilotinib in larger clinical trials in pure peripheral SpA, as well as evaluation of other drugs targeting mast cells in SpA.
A Tailored Approach to Reduce Dose of Anti-TNF Drugs Is Equally Effective, but Substantially Less Costly Than Standard Dosing in Patients with Ankylosing Spondylitis over One Year: A Propensity Score-Matched Cohort Study.  
Jakub Zavada1, Michal Uher2, Katarina Sislo3, Sarka Forejtova4, Katerina Jarosova5, Herman F. Mann6, Jiri Vencovsky7 and Karel Pavelka8.
1Charles University, Prague, Czech Republic, 2Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, 3Institute of Rheumatology, Prague, Czech Republic, 4Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, 5Institute of Rheumatology and Clinic of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Czech Republic, 6Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: To compare effectiveness, safety and costs of standard versus individually tailored reduced doses of anti-TNF drugs in patients with Ankylosing Spondylitis (AS) after achieving low disease activity.

Methods: This was a single center prospective observational study performed within the national biologics registry. The anti-TNF dose tapering strategy was chosen by treating physicians, without pre-specified protocol. We used propensity score (PS) methodology to identify 2 cohorts of patients matched for relevant baseline characteristics (table 1) who were treated with either reduced (n=53) or standard (n=83) doses of TNF inhibitors. One year outcomes and costs of anti-TNF drugs were compared between both PS-matched cohorts.

Results: In the reduced dosing group the median dose of TNF inhibitor corresponded to 0.67, and 0.5 of the standard dose initially, and at 12 months, resp., and 21% of patients required return to standard dosing regimen. The mean change per year in BASDAI, CRP, HAQ and BASFI, as well as QALY area under the curve were no different between both groups (table 2). The hazard ratio (95% confidence interval) of reduced versus standard dosing group for relapse and any adverse event was 1.46 (0.66; 3.9), and 0.36 (0.22; 1.44) resp. (Figure 1) Mean difference (95% confidence interval) in cost of anti-TNF drugs was –421 (–4707; –3701) € per year of treatment in favor of reduced dosing strategy.

Conclusion: In AS patients after reaching low disease activity, a tailored approach to reduce doses of anti-TNF drugs produced similar clinical outcomes at 1 year, but was substantially less costly.

Acknowledgements: This work was supported by project of MHCR for conceptual development of research organization 023728

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard dosing group (n=83)</th>
<th>Reduced dosing group (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>43 (52.4%)</td>
<td>22 (41.5%)</td>
<td>0.612</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>50.3 (8.3)</td>
<td>52.4 (7.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD)</td>
<td>75.3 (13.3)</td>
<td>77.3 (14.9)</td>
</tr>
<tr>
<td>HLA B27 positive</td>
<td>n(%)</td>
<td>70 (86.6%)</td>
<td>48 (90.6%)</td>
</tr>
<tr>
<td>Disease duration prior to the start of anti-TNF therapy (years)</td>
<td>Mean (SD)</td>
<td>2.6 (2.0)</td>
<td>1.9 (1.7)</td>
</tr>
<tr>
<td>Disease duration prior to the start of anti-TNF therapy (months)</td>
<td>Mean (SD)</td>
<td>34.8 (16.4)</td>
<td>34.4 (13.6)</td>
</tr>
<tr>
<td>Periarticular joint involvement</td>
<td>n(%)</td>
<td>20 (24.1%)</td>
<td>18 (34.0%)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>Mean (SD)</td>
<td>4.0 (3.7)</td>
<td>4.3 (7.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>n(%)</td>
<td>19 (22.9%)</td>
<td>11 (20.8%)</td>
</tr>
<tr>
<td>RA</td>
<td>n(%)</td>
<td>33 (39.8%)</td>
<td>17 (32.1%)</td>
</tr>
<tr>
<td>AS</td>
<td>n(%)</td>
<td>19 (22.9%)</td>
<td>11 (20.8%)</td>
</tr>
<tr>
<td>Concomitant glucocorticoids</td>
<td>n(%)</td>
<td>12 (14.7%)</td>
<td>13 (24.5%)</td>
</tr>
<tr>
<td>Concomitant DISABD</td>
<td>n(%)</td>
<td>6 (7.2%)</td>
<td>9 (17.0%)</td>
</tr>
<tr>
<td>Anti-TNF agents</td>
<td>n(%)</td>
<td>15 (18.1%)</td>
<td>22 (41.5%)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>n(%)</td>
<td>9 (10.8%)</td>
<td>6 (11.3%)</td>
</tr>
</tbody>
</table>

Table 2 Measures of activity/function, quality of life, and costs of anti-TNF therapy over one year of observation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard dosing group (n=83)</th>
<th>Reduced dosing group (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI at baseline</td>
<td>Mean (SD)</td>
<td>4.1 (2.3)</td>
<td>4.4 (2.3)</td>
</tr>
<tr>
<td>BASDAI at 12 M</td>
<td>Mean (SD)</td>
<td>2.3 (1.4)</td>
<td>2.2 (1.2)</td>
</tr>
<tr>
<td>Change in BASDAI (per year)</td>
<td>Mean (95% CI) reference</td>
<td>–0.87 [–1.20; –0.55]</td>
<td>–0.83 [–1.12; –0.55]</td>
</tr>
</tbody>
</table>

Figure 1

Disclosure: J. Zavada, None; M. Uher, None; K. Sislo, None; S. Forejtova, None; K. Jarosova, None; H. F. Mann, None; J. Vencovsky, None; K. Pavelka, None.

Safety and Efficacy of Certolizumab Pegol over 96 Weeks in Patients with Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Joachim Sieper1, Martin Rudwaleit2, Desiree M. van der Heijde3, Walter P. Maksymowycz4, Maxime Dougados5, Philip Mease6, Jurgen Braun7, Atul A. Deodhar8, Bengt Hoepken9, Tommi Nurminen10 and Robert B. M. Landewe11. 1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Endokrinologikum, Berlin, Germany, 3Leiden University Medical Center, Leiden, Netherlands, 4University of Alberta, Edmonton, AB, 5Université Paris René Descartes and Hôpital Cochin, Paris, France, 6Swedish Medical Center and University of Washington, Seattle, WA, 7Ruhr-University Bochum, Herne, Germany, 8Oregon Health and Sciences University, Portland, OR, 9UCB Pharma, Monheim, Germany, 10Amsterdam Rheumatology Center, Amsterdam, Netherlands.

Background/Purpose: Previous reports of RAPID-axSpA (NCT01087762) demonstrated efficacy and safety of certolizumab pegol (CZP) in patients (pts) with axial spondyloarthritis (axSpA) including pts with ankylosing spondylitis (AS) and pts with non-radiographic (nr-)axSpA to Week (Wk) 48. Here, we report the clinical efficacy and safety of CZP in axSpA from a 96-wk interim data cut of RAPID-axSpA.

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Methods: The RAPID-axSpA trial is double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts fulfilled ASAS criteria and had active axSpA. Pts originally randomized to CZP (200 mg Q2W or 400 mg Q4W, following 400 mg loading dose [LD]) at Wks 0, 2, 4 continued on their assigned dose in the OL phase; PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200 mg Q2W or CZP 400 mg Q4W after Wk24 or, for non-responders, after Wk16. We present efficacy data for all pts originally randomized to CZP (combined dose regimens). Outcome variables assessed included ASAS20/40 and BASDAI50 responses and ASAS PR, ASDAS, ASDAS ID, ASDAS MI, BASDASL, BASFI and BASMI-linear. Data are shown as observed case and with imputation (NRI for categorical measures; LOCF for continuous measures). Safety set consists of all pts treated with ≥1 dose of CZP to Wk96.

Results: 325 pts were randomized, of whom 218 received CZP from Wk0. Of CZP-randomized pts, 203 (93%) completed to Wk24, 191 (88%) to Wk48 and 174 (80%) to Wk96. The proportion of pts achieving ASAS20/40 and PR responses was maintained from Wk24 through to Wk96 (Figure). Similar improvements were seen with both dosing regimens (data not shown) and in both AS and nr-axSpA pts. Rapid clinical improvements were also observed in pts originally randomized to PBO who switched to CZP at Wk16 or Wk24 (data not shown). In the safety set (N in pts originally randomized to PBO who switched to CZP at Wk16 or Wk24 = 112, person-yrs), serious infections was 2.7, including 1 confirmed case of active tuberculosis.

Conclusion: In RAPID-axSpA, improvements in both CZP dosing regimens observed over 24 wks in clinical efficacy and patient-reported outcomes were maintained to Wk96. Outcome variables assessed included ASAS20/40 and BASDAI50 responses and ASAS PR, ASDAS, ASDAS ID, ASDAS MI, BASDASL, BASFI and BASMI-linear. Data are shown as observed case and with imputation (NRI for categorical measures; LOCF for continuous measures). Safety set consists of all pts treated with ≥1 dose of CZP to Wk96. No deaths or malignancies were reported in the overall 96-wk period.

Background/Purpose: Most studies of the safety profile of TNF inhibitors (TNFi) – in particular to cancer risks – have been performed in patients with rheumatoid arthritis. To date, however, TNFi, mainly used in patients with axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA), i.e., in populations with different age/sex distributions and with potentially different underlying risks for cancer. The aim of this study was to assess risks of overall and site-specific cancers in patients with AxSpA and PsA treated (vs. not) with TNFi and to compare these risks to the risk in the general population. To do this we used pooled data from two Scandinavian biologics registers and other population-based data-sources.

Methods: By linking data from the Swedish (ARTIS) and Danish (DANBIO) biologics registers, we assembled a cohort of 8,156 (ARTIS = 4,901 and DANBIO = 3,255; total person-years = 29,011) patients with AxSpA (57%) and PsA (43%) that started a TNFi 2001–2010. From the Swedish National Patient Register we identified a national TNFi-naive AxSpA/PsA comparator cohort (n = 24,058, person-years = 112,714), and a Swedish age- and sex-matched general population comparator cohort (n = 103,380, person-years = 535,345). The first invasive cancer for each subject was identified through linkage with the nationwide Swedish and Danish Cancer Registers (2001–2010). Subjects with previous cancers were excluded in all three cohorts. Age- and sex-standardized incidence rates and relative risks (RR) were calculated for cancer overall, and for six specific cancer sites (lung-, colorectal-, female breast-, prostate cancer, malignant melanoma, and lymphoma).

Results: In total we identified 129 cancers among the TNFi treated patients, 744 in the TNFi-naïve cohort, and 3,259 in the general population comparator cohort. TNFi-naïve patients were not at increased cancer risk vs. the general population (RR = 1.00), but displayed a lower risk for colorectal cancer (RR = 0.70). Based on 129 incident cancers, TNFi-treated patients did not have a higher risk of cancer (vs. TNFi-naive patients), RR = 0.80 (95% CI 0.68–0.93). Based on the national clinical data from Sweden and Denmark, TNFi treatment in patients with AxSpA and PsA was not associated with any significantly increased risks of cancer overall, nor for the six most common cancer types. The tendency towards decreased risks for lung, and prostate cancer following TNFi treatment may reflect selection related to pre-treatment screening. Furthermore, we observed a decreased risk of colorectal cancer in AxSpA/PsA.

Table: Age- and sex-standardized relative risks (RR) of overall and site-specific cancers in patients with axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA) from ARTIS and DANBIO treated with TNFi (n = 8,156, person-years = 29,011) versus a Swedish AxSpA/PsA comparator cohort (n = 24,058, person-years = 112,714) and a Swedish general population comparator cohort (n = 103,380, person-years = 535,345) from 2001 to 2010.
Golimumab Versus Paminodronate for the Treatment of Axial Spondylo-
arthropathy (SpA): A 48-Week Randomized Controlled Trial. Chi Chiu Mok, Angela Li, Kai Li Chan and Ling Yin Ho. Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: To compare the efficacy of golimumab/GLM and pamidronate(PAM) in the treatment of SpA.

Methods: Inclusion criteria: (1) patients ≥18 years of age; (2) fulfills the 2009 ASAS classification criteria for axial SpA; (3) Active spondylitis defined by a BASDAI score of ≥4 (with spinal pain score ≥4), despite treatment with NSAIDs for ≥3 months. Exclusion criteria: (1) Hepatitis B/C carriers; (2) Biological treatment in the past year; (3) Major surgery within 8 weeks; (4) Active infection; (5) Pregnancy/lactation; (6) Contraindications to anti-TNF or bisphosphonates. Patients were randomized to receive GLM (50mg subcutaneously monthly) or PAM (60mg intravenously monthly) in a 2:1 ratio on top of existing therapies. Latent tuberculosis was screened and treated in the GLM arm. Assessment for clinical efficacy (BASDAI, BASFI, CRP, ESR, CRP, ASDAS, VAS pain, global assessment, SF36) was performed at week 0,2,4,8,16,20,24,32,40 and 48. MRI of the spine and SIJ was performed at week 0, 24 and 48 and graded by the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system (SIJ score 0–72; spinal score 0–108). The primary efficacy endpoint was the proportion of patients who achieved the ASAS20 response at week 48. Intra-group paired data over time were compared by the paired Students’ t-test whereas inter-group differences were compared by ANCOVA with adjustment for baseline values.

Results: 30 patients were recruited (83% men; age 33.4±10.9 years; disease duration 4.4±3.4 years) – 20 assigned to GLM and 10 assigned to PAM. Baseline demographic and clinical characteristics were not significant different between the two arms, except for a non-significantly higher mean ASDAS (CRP) (4.07±0.77 vs 3.70±0.65) and SIJ SPARCC (15.8±17.7 vs 7.8±5.93) score in GLM-treated patients. At week 48, a higher proportion of patients achieved ASAS20 (50% vs 20%; p=0.03) and ASAS40 (35% vs 0%; p=0.04) responses in the GLM compared to the PAM group. The ASDAS, BASDAI, BASFI, CRP and ESR levels significantly improved with GLM treatment but not with PAM. Interestingly, patient reported outcomes such as pain score and SF36 improved significantly in both treatment groups. In patients treated with GLM, the SPARCC SIJ score (15.8±17.7 vs 3.80±5.19; p<0.01) and spine (11.4±10.8 to 3.56±5.65; p<0.01) scores at week 48 decreased significantly compared to baseline. However, there was only a modest but non-significant reduction in the corresponding MRI scores observed in PAM-treated patients. There was no serious adverse events (SAEs) reported and the frequency of any adverse events (AEs) was not significantly different between the two arms. Minor upper respiratory infection (URI) was the commonest AE (30%), followed by dyspepsia (10%) and deranged liver function (10%) in GLM-treated patients. In patients treated with PAM, the common AE was post-infection fever / myalgia / headache (30%), followed by dyspepsia (10%), phlebitis (10%) and minor URI symptoms (10%).

Conclusion: In patients with axial SpA, GLM was more effective than PAM in reducing clinical disease activity and MRI spinal / SIJ inflammation. PAM led to improvement in subjective pain and quality of life but did not have significant effects on MRI inflammation, CRP or ESR.

Disclosure: C. C. Mok, None; A. Li, None; K. L. Chan, None; L. Y. Ho, None.


Background/Purpose: Previous studies evaluating predictors of major clinical response in patients with non-radiographic axial SpA (nr-axSpA) receiving treatment with anti-TNF agents have been limited by the heterogeneity of patients recruited according to classification criteria and/or duration of disease. We aimed to assess the predictive capacity of active and structural lesions on MRI of the sacroiliac joints (SIJ) in a cohort of patients selected according to objective measures of inflammation and limited duration of disease.

Methods: Patients had axial SpA per the Assessment of SpondyloArthritis (ASAS) classification criteria, but did not meet modified NY radiographic criteria. Patients had symptoms for ≥3 months and ≤5 years, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and failed ≥2 NSAIDs. Patients were randomly assigned to etanercept 50 mg/week or placebo, then after 12 weeks, all patients received open-label etanercept 50 mg/week. Clinical and health outcomes were assessed throughout the study, and MRI of the SIJ and spine was performed by two central readers at baseline, week 12 and 48 to assess bone marrow edema (BME) using the Spondyloarthritis Research Consortium of Canada (SPARCC) score. Additionally, a post-hoc analysis was conducted to score structural lesions using the SPARCC SIJ structural method (SSS), which assesses fat metaplasia, erosion, backfill, and ankylosis on T1-weighted spin echo (TIWSE) MRI. Two independent readers scored baseline and 48 week TIWSE MRI scans from 187 cases blinded to patients and short tau inversion recovery (STIR) MRI scans. Mean scores of the readers were used. Baseline high sensitivity CRP (hsCRP) levels, SPARCC MRI inflammation and SSS erosion scores were analyzed using logistic models of week 48 ASAS40 and ASDAS major improvement (ASDAS MI change ≥2.0), adjusted for treatment.

Results: Mean (SD) age was 32.7 (8.6) years, 60.5% were male, and mean (SD) duration of disease symptoms was 2.5 (1.8) years. A total of 73% of patients were human leukocyte antigen B27 (HLA-B27) positive and 81% met the ASAS MRI imaging criteria at baseline. Baseline CRP, SPARCC SIJ inflammation, and SSS erosion scores, but not fat metaplasia, backfill, or ankylosis were significant predictors of both ASAS40 and ASDAS MI responses at week 48 in both last observation carried forward and observational data analyses (see table). The higher the baseline value the greater the likelihood of response.

Table: Logistic Models of week 48 ASAS40 or ASDAS MI for each of the baseline SSS components, adjusted for treatment

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Baseline Predictor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS40, LOCF</td>
<td>CRP</td>
<td>1.09 (1.00, 1.19)</td>
<td>0.0432</td>
</tr>
<tr>
<td>ASAS40, LOCF</td>
<td>SSS Erosion Score</td>
<td>1.09 (1.00, 1.19)</td>
<td>0.0432</td>
</tr>
<tr>
<td>ASAS40, LOCF</td>
<td>SPARCC SIJ</td>
<td>1.06 (1.02, 1.10)</td>
<td>0.0006</td>
</tr>
<tr>
<td>ASAS40, OC</td>
<td>CRP</td>
<td>1.05 (1.01, 1.09)</td>
<td>0.0110</td>
</tr>
<tr>
<td>ASAS40, OC</td>
<td>SSS Erosion Score</td>
<td>1.09 (1.00, 1.19)</td>
<td>0.0412</td>
</tr>
<tr>
<td>ASAS40, OC</td>
<td>SPARCC SIJ</td>
<td>1.05 (1.01, 1.08)</td>
<td>0.0057</td>
</tr>
<tr>
<td>ASDAS M1, LOCF</td>
<td>CRP</td>
<td>1.17 (1.11, 1.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASDAS M1, LOCF</td>
<td>SSS Erosion Score</td>
<td>1.11 (1.03, 1.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASDAS M1, LOCF</td>
<td>SPARCC SIJ</td>
<td>1.07 (1.04, 1.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASDAS M1, OC</td>
<td>CRP</td>
<td>1.15 (1.09, 1.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASDAS M1, OC</td>
<td>SSS Erosion Score</td>
<td>1.12 (1.03, 1.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASDAS M1, OC</td>
<td>SPARCC SIJ</td>
<td>1.07 (1.04, 1.11)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LOCF=last observation carried forward, OC=observed case, CI=confidence interval

Conclusion: The presence of objective manifestations of active disease as indicated by CRP and inflammatory or erosive lesions on MRI prior to the start of anti-TNF therapy has predictive capacity for major treatment responses.

Disclosure: W. Maksymowych, Pfizer Inc, 2, Pfizer Inc, 5, S. Wichuk, None; H. Jones, Pfizer Inc, 3, Pfizer Inc, 1; A. Szumski, Pfizer Inc, 5, L. Marshall, Pfizer Inc, 1, Pfizer Inc, 3; J. Bukowski, Pfizer Inc, 1, Pfizer Inc, 3; R. Lambert, None.

A Pathogenic Role for the Gut Microbiota in Murine Antiphospholipid Syndrome and Lupus. Silvio M. Vieira, Andrew Yu, Michael Hilitesperger, Odelya E. Pagovich, Elein Timiakou, William Ruff, John Sterka and Martin Kriegel. Yale School of Medicine, New Haven, CT.
Background/Purpose: The etiology of lupus-associated antiphospholipid syndrome (APS) is unknown but microbial triggers have been implicated in transient antiphospholipid antibody production in both mice and humans. We hypothesize that a constant trigger of autoantibody lies within the gut microbiome and tested if persistent reactivity to β2-glycoprotein 1 (β2-GPI) and mortality in the spontaneous (NZW x BXSB x F1) F2 model of lupus-associated APS are sustained by specific members of the gut microbiota.

Methods: (NZW x BXSB x F1) hybrid male mice were treated orally with combined or single antibiotics (vancomycin, metronidazole, neomycin and ampicillin) targeting different microbial community structures starting at 6 weeks of age. Female TLR7 transgenic C57BL/6 mice were similarly treated with broad-spectrum antibiotics. Sera, urine and fecal pellets were collected longitudinally and analysed for anti-β2-GPI titers, proteinuria from lupus nephritis and eubacterial 16S rDNA load by real-time PCR. H&E slides were prepared from tissues for histologic analysis. Splenocyte proliferation was assessed by [3H]-thymidine incorporation.

Results: Not only broad-spectrum antibiotics but also vancomycin or ampicillin alone lowered anti-β2-GPI antibodies at 4 months of age (n=5 each; p=0.014) and protected mice from deaths due to coronary microthrombosis, pulmonary emboli or strokes (n=5 each; p=0.005). Proliferation of splenocytes to the autoantigen (using recombinant β2-GPI) was diminished compared to anti-CD3-induced proliferation (n=8 each; p=0.0012). Proteinuria due to lupus nephritis was also suppressed in microbiota-depleted mice (n=8 each; p=0.026). Furthermore, mortality from systemic lupus-like disease was significantly reduced in lupus-prone TLR7 transgenic C57BL/6 mice treated with antibiotics (n=9–10 each; p=0.0154).

Conclusion: Vancomycin-sensitive gut commensals are necessary for anti-β2-GPI antibody-induced thrombembolic deaths. Broad-spectrum antibiotics selectively reduced T cell proliferation to β2-GPI but not anti-CD3, suggesting antigen-specific effects of the gut microbiota. These results support that Gram-positive members of the gut microbiota are fundamentally involved in the pathogenesis of APS. The gut microbiota modulates also lupus pathogenesis in two spontaneous models, suggesting that not only APS but also SLE is dependent on the gut microbial community composition we are currently defining to identify novel biomarkers and treatment targets.

Disclosure: S. M. Vieira, None; A. Yu, None; M. Hitsperger, None; O. E. Pagovich, None; E. Tiniauk, None; W. Ruff, None; J. Sterpka, None; M. Kriegel, None.

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Amelioration of Systemic Lupus Erythematosus (SLE) in NZM 2328 Mice By Selectively Blocking Engagement of Two BAFF Receptors. Chaim O. Jacob, Ning Yu and William Stohl. University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: BAFF, a potent B cell survival factor, is an established therapeutic target in SLE, with the anti-BAFF antibody, belimumab, being FDA-approved for the treatment of SLE. Nevertheless, large percentages of SLE patients failed to respond to belimumab in the seminal phase-III trials, pointing to an ongoing need for upstream therapeutic targets. Inhibition of one or more of the individual BAFF receptors (BCMA, TACI, BR3) may, in principle, be more efficacious than global inhibition of BAFF. Indeed, whereas the contribution of BAFF to SLE has been the subject of substantial investigation, the contributions of the individual BAFF receptors to SLE have undergone only limited investigation to date. In the SLE-prone NZM 2328 (NZM) mouse model, NZM mice singly-deficient in any BAFF receptor develop clinical SLE with a time course indistinguishable from that of NZM wild-type (WT) mice, demonstrating sufficient functional redundancy among the BAFF receptors to render any single BAFF receptor dispensable to the development of SLE in these mice. To determine whether elimination of combinations of BAFF receptors could be clinically beneficial, we examined the effect of eliminating discrete pairs of BAFF receptors on the development of disease in NZM mice.

Methods: NZM mice singly-deficient in BCMA, TACI, and BR3 were intercrossed to yield NZM mice deficient two BAFF receptors (NZM.Br3−/−.Bcma−/−, NZM.Br3−/−.Taci−/−, and NZM.Bcma−/−.Taci−/−). These mice were evaluated for BAFF receptor expression and lymphocyte phenotype by flow cytometry, for renal immunopathology by immunofluorescence and histopathology, and for clinical disease by assessment of proteinuria (≥5+ by dipstick) and death.

Results: The only BAFF receptor expressed by NZM.Br3−/−.Bcma−/− mice is TACI; the only BAFF receptor expressed by NZM.Br3−/−.Taci−/− mice is BCMA; and the only BAFF receptor expressed by NZM.Bcma−/−.Taci−/− mice is BR3. All B cell subsets are reduced in NZM.Br3−/−.Bcma−/− and NZM.Br3−/−.Taci−/− mice but are increased in NZM.Bcma−/−.Taci−/− mice. All T cell subsets, other than naïve CD4+ cells, are reduced in NZM.Br3−/−.Taci−/− mice but are increased in NZM.Bcma−/−.Taci−/− mice. CD4+ memory cells are reduced in NZM.Br3−/−.Bcma−/− mice. Renal immunopathology and clinical disease are significantly delayed and attenuated in NZM.Br3−/−.Bcma−/− and NZM.Br3−/−.Taci−/− mice but are significantly accelerated in NZM.Bcma−/−.Taci−/− mice (Figure 1).

Conclusion: Elimination of both BR3 and TACI (while retaining BCMA) or both BR3 and BCMA (while retaining TACI) markedly inhibits development of SLE in NZM mice. By extension, selective pharmacologic targeting of BR3 + TACI (while preserving BCMA engagement) or BR3 + BCMA (while preserving TACI engagement) may represent a successful therapeutic approach in human SLE.

Disclosure: C. O. Jacob, None; N. Yu, None; W. Stohl, None.

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ABT-199, a Potent and Selective BCL-2 Inhibitor, Prevents Lupus Nephritis in the Spontaneous NZB/W F1 Mouse Model By Depleting Selective Lymphocyte Populations While Sparing Platelets. Li Chun Wang1, Stuart Perper1, Annette Schwartz1, Christian Goess1, Liz O’connor2, Dovona Hartmann1, Cundace Graff2, Andrew Souers2, Joel Levenson2, Steven Eلمore2 and Lisa Olson1. 1AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, 2AbbVie Inc, North Chicago, IL.

Background/Purpose: Proteins in the BCL-2 family are key regulators of apoptosis, or programmed cell death. Navitoclax, a selective inhibitor of both BCL-2 and BCL-X(L) demonstrated efficacy in the IFNα-induced lupus nephritis model in NZB/W F1 mice and data are presented as Kaplan-Meyer survival curves. Changes in lymphocytes and platelets in peripheral blood were assessed by Cytdell 3700 blood analyzer. Renal pathology was evaluated by a board certified pathologist. IgG deposition and changes in leukocyte subsets in the kidney were evaluated by immunohistochemistry. Circulating anti-dsDNA antibody levels were determined using a semi-quantitative ELISA assay. In a separate study NZB/W F1 mice were treated daily with vehicle or ABT-199 at 30mg/kg for 16 weeks, leukocyte subsets in spleen, kidney and bone marrow were analyzed by flow cytometry.

Results: ABT-199 treatment dose-dependently reduced the incidence of severe proteinuria compared to vehicle control and conferred 100% survival at the higher doses in the spontaneous NZB/W F1 lupus model. Treatment with ABT-199 also resulted in attenuated glomerulonephritis, tubular dilatation and IgG deposition in the kidney. ABT-199 treatment resulted in reductions in numbers of B220+, CD3+, F4/80+ and CD138+ cells in the kidneys compared with vehicle-treated mice. Consistent with its BCL-2 selectivity profile, ABT-199 mediated efficacy in NZB/WF1 mice correlated with a dose-dependent reduction of lymphocytes in peripheral blood (45% reduction for ABT-199 11mg/kg vs. vehicle; 70% reduction for ABT-199 100 mg/kg vs. vehicle) with no effect on platelet numbers. ABT-199 also demonstrated a significant reduction in the numbers of splenic T cells (CD4+ , CD8+) and B cells (transitional, marginal zone, and memory). Interestingly, other B cell subsets (transitional 1, marginal zone, and B1) were largely unaltered. ABT-199 did not impair early B cell development or the number of CD138+ long-lived plasma cells in the bone marrow. These data were consistent with the unlabeled anti-dsDNA titers in these animals.
Conclusion: Treatment of spontaneous lupus in NZB/W F1 mice with the BCL-2 selective inhibitor ABT-199 resulted in preservation of renal function and complete protection against severe proteinuria and mortality. ABT-199 treatment resulted in lymphopenia and a reduction of cell infiltration into the kidney while sparing circulating platelets. Splenic marginal zone B cells, the first line of defense against blood-borne pathogens, were resistant to ABT-199. Taken together, these data underscore the essential role of BCL-2 in the pathogenesis of lupus and support a role for BCL-2 selective inhibition in the treatment of autoimmune disease.


OT-II mice were injected i.v. into Rag1KO mice in combination with or humans. In line with the observation, T-cell-specific Egr-2-deficient mice (study suggests that polymorphisms in the early growth response gene-2 of Tokyo, Tokyo, Japan. Egr2 CKO or B6/H11001 Cell Responses. Tomohisa Okamura1, Kaoru Morita1, Matiro Inoue1, Toshihiko Koma1, Yukiko Iwashita1, Shuji Sumitomo1, Shinichiro Nakachi1, Hirofumi Shoda1, Keishi Fujio2 and Katsuhiko Yamamoto1. 1Graduate School of Medicine, the University of Tokyo, Tokyo, Japan; 2The University of Tokyo, Tokyo, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production and associated with a wide range of clinical manifestations. Recent case-control association study suggests that polymorphisms in the early growth response gene-2 (EGR2), a zinc-finger transcription factor, influence SLE susceptibility in humans. In line with the observation, T-cell-specific Egr-2-deficient mice show lupus-like autoimmune disease. We previously described CD4+ CD25+ Foxp3+ regulatory T cells (Treg) that characteristically express both lymphocyte activation gene 3 (LAG3, CD223) and Egr2 (hereinafter referred to as 'LAG3'). Therefore, we have examined whether LAG3 Treg suppress the development of follicular helper T cell (TFH) and germinal center B cell (GC), antibody production, and disease progression in lupus-prone MRL-Fas+/+ (MRL/pr) mice.

Methods: B cells from C57BL/6 (B6) mice and helper T (Th) cells from OT-II mice were injected i.v. into Rag1KO mice in combination with or without LAG3 Treg from B6, Egr2 conditional knockout (CKO) (Egr2/-/- CD44+Cd4-/-), or Foxp3-mutated B6/pr mice. Mice were subsequently immunized with NP-OVA/alum 24 hr after the cell transfer. Mice were re-immunized with NP-OVA/alum 14 days after the first immunization. Serum anti-NP antibody levels were analyzed by ELISA, and splenocytes were analyzed by FACs 7 days after the re-immunization. To examine the therapeutic effects of LAG3 Treg in lupus-prone mice, 8-week-old MRL/pr mice were randomly assigned to specific treatment groups. Ten-week-old MRL/pr mice in the treatment group were injected i.v. with LAG3 Treg, CD4+ CD25+ Treg, or naive T cells obtained from MRL/+ mice. Mice were sacrificed at 18 weeks of age to examine pathological alterations. Anti-dsDNA antibodies were measured by ELISA.

Results: Transfer of LAG3 Treg from wild type (WT) mice, but not Egr2 CKO or B6/pr mice, significantly suppressed NP-specific antibody responses and the development of GCB and Tfh1 in Rag1KO mice transferred with B cells and OT-II Th cells. Interestingly, LAG3 Treg produce high amounts of transforming growth factor-beta (TGF-beta) (in Egr2- and Foxp3-dependent manner. Treatment with a TGF-beta or Fasl blocking antibody cancelled the suppressive activity of WT LAG3 Treg. Adoptive transfer of LAG3 Treg from control MRL/+ mice significantly suppressed the progression of nephritis and autoantibody production in MRL/pr mice. In contrast, CD4+ CD25+ Treg and naive T cells from MRL/+ mice exhibited no significant therapeutic effect upon transfer to MRL/pr mice. TGF-beta-blockade also abrogated the therapeutic effects of MRL/+ LAG3 Treg in MRL/pr mice.

Conclusion: These results clarified the molecular basis underlying TGF-beta-producing LAG3 Treg-mediated B cell regulation, which indicated that LAG3 Treg may be a suitable target for immune manipulation in autoantibody-mediated autoimmune diseases, including SLE.

Disclosure: T. Okamura, None; K. Morita, None; M. Inoue, None; T. Komai, None; Y. Iwasaki, None; S. Sumitomo, None; S. Nakachi, None; H. Shoda, None; K. Fujio, None; K. Yamamoto, UCB Pharma, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai, 5, UCB Pharma, Pfizer, Abbott, Santen, Mitsubishi-Tanabe and Eisai, 2.


Background/Purpose: G protein-coupled receptors (GPCRs), including chemokine receptors on leukocytes, signal through G protein Gβγ subunits. An important target of Gβγ is phosphoinositide 3 kinase (PI3Kγ), a major isoform of PI3K whose receptor-dependent activation relies primarily on the Gβγ subunit. We hypothesized that Gβγ inhibition may be an effective treatment for lupus as it will prevent PI3Kγ activation which is upstream of T and B cell survival and the migration and activation of innate immune cells. Here, we evaluated the effects of gallein, a small molecule novel Gβγ inhibitory compound (Lehmann 2008; Mol Pharmcol 73: 410), in lupus prone mice.

Methods: 18 week old NZB/NZW mice were treated daily with 20 mg/kg or 35 mg/kg gallein (intraperitoneal injection) or vehicle (n=8 per group) for 15 weeks. For therapeutic intervention, mice with established disease (26 weeks old) were treated for 4 weeks with gallein at 35 mg/kg. Lymphocytes were enumerated by flow cytometry, auto-reactive antibody secreting cells (ASC) were quantitated by ELISPOT, kidney inflammation was evaluated by histology (H&E, immunofluorescence), and renal function was assessed by monitoring changes in proteinuria. To determine the effect of gallein on cell migration, BM neutrophils or Jurkat T cells were stimulated in the presence of IMPL (250nM) or CXCL2 (30 or 100 ng/ml).

Results: In a prevention model, gallein therapy significantly abrogated the progression of proteinuria (35 mg/kg: p=0.0001, 20mg/kg: p=0.0116). There was no significant dose dependent effect on the decline in the number of T cells (20 mg/kg: p=0.0495, 35 mg/kg: p=0.0001) and central memory T cells (35 mg/kg: p=0.0029) in spleens of lupus prone mice. Mice treated with a high dose of gallein (35 mg/kg) had a significant reduction in the number of T follicular helper cells (p=0.0092) and germinal center B cells (p=0.0411). Although auto-reactive IgG ASC and dsDNA specific ASC were not reduced in the spleen, mice treated with gallein (35 mg/kg) had a reduction in IgG3- and dsDNA- ASC in the BM (p=0.0029 and 0.0571). Strikingly, both doses of gallein caused a marked reduction in the number of dsDNA- ASC in the kidneys (20 mg/kg: p=0.0103, 35 mg/kg: p=0.0308). Treated mice also had a significant reduction in glomerular, interstitial inflammation (p=0.01 and 0.03 respectively), perivascular inflammation (35 mg/kg: p<0.0001), and IgG deposition. Treatment of mice with established disease also resulted in a significant reduction in the numbers of IgG3 (p=0.0173) and dsDNA-ASCs (p=0.0031) in the kidneys and reduced proteinuria (p=0.0236). Gallein inhibited the migration of WT murine neutrophils and cultured Jurkat T cells in response to IMPL and CXCL12, respectively. Similarly, in vivo administration of gallein in NZB/NZW mice resulted in a less efficient migratory response of BM isolated neutrophils in response to CXCL2.

Conclusion: These results suggest that Gβγ inhibition with gallein may modulate the generation of PCs in GC reactions as well as alter the kidney inflammatory milieu and PC survival niche in lupus, possibly by influencing the influx and function of inflammatory cells.

Disclosure: T. Owen, None; J. Rangel-Moreno, None; J. To, None; B. Goldman, None; A. Smrcka, None; J. H. Anolik, None.

861

Ultraviolet B Generates Type 1 Interferon and Induces Autoantibody-Mediated Disease in a Mouse Model of Cutaneous Lupus. Clayton Sontheimer and Keith B. Elkon. University of Washington, Seattle, WA.

Background/ Purpose: Photosensitivity is a common symptom in patients with systemic lupus erythematosus (SLE) and lupus skin lesions often contain plasmacytoid dendritic cells (pDC). The mechanisms linking ultraviolet (UV) light to immunization and cutaneous inflammation is not well understood. While in vitro experiments have suggested that UV-induced apoptosis exposes lupus-specific nuclear antigens and immune complex mediated inflammation, this has not been shown in vivo. Here, we asked whether, and under what conditions, UVB-induced inflammation could induce Type I interferon (IFN-I) and the roles of pDCs and also autoantibodies in cutaneous lupus.

Methods: Shaved C57BL/6 (B6), IFNAR KO, BDC2.1, DTR, and huIFNAR2 transgenic mice were irradiated with narrowband UVB at 100 mJ/cm2/day for 5 consecutive days. To induce interface dermatitis, shaved and depilated mice were subject to 15 strokes of tape stripping using medical tape (3M). Serial punch biopsies (6 mm) were obtained at 3, 24, and 72 hrs following UVB exposure or tape stripping. PDCs were detected in enzyme

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digested skin samples by flow cytometry (CD45+, Ly6C+, PDC-1+, CD11c+, Siglec H+). Skin samples were examined for mRNA expression by QPCR of pro-inflammatory cytokines and Interferon Stimulated Genes (ISG). mRNA fold change was calculated by comparison with non-irradiated control mice. In experiments with huFcgR2A Tg mice, mice were irradiated as above but injected i.p. at the time of the final UVB exposure with purified immunoglobulin pooled from human lupus patients and the skin was examined by immunofluorescence for the presence of human IgG.

Results: Whole skin scraping induced a robust ISG response associated with the presence of pDC in the skin, repeated UVB exposure induced a more modest IFN-I skin response with bimodal peaks at 3 and 72 hrs when compared to control mice (p<0.05, n=20). UVB-irradiated IFNAR KO mice had increased levels of pro-inflammatory cytokines TNFα and IL-6 at (p<0.01) at 3 and 24 hr time points, n=12-13 and had increased levels of inflammation by visual scoring suggesting a protective role for IFN-I. Interestingly, pDCs did not appear to be the source of IFN following UVB as pDC-depleted BDC2 DTR mice maintained moderate expression of ISGs. Immunoglobulin from human lupus patients, but not IVIG, localized to the skin at the dermal/epidermal junction following UVB of FcgR2A transgenic and wild-type mice, but FcgR2α signaling was required for cellular uptake and enhanced Type I IFN signaling (p<0.05, n=5-9).

Conclusions: In the normal host, repeated doses of UVB induce a protective, pDC-independent Type1 IFN response in the skin that attenuates pro-inflammatory signals and limits tissue damage. In contrast, in situations protective, pDC-independent Type1 IFN response in the skin that attenuates and limits tissue damage. In contrast, in situations

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## Table 1

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<thead>
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<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
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## Table 2

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### Disclosures

C. Sontheimer, None; K. B. Elkon, None.

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### ACR Concurrent Abstract Session

**Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Cardiovascular Disease and Pregnancy**

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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### 862

**Risk Factors for Changes in Subclinical Atherosclerosis As Measured By Carotid Intima Media Thickness (IMT) and Plaque over 5 Years in Women with Systemic Lupus Erythematosus (SLE), Apinya Lertranakul1, Peggy W. Wu2, Alan Dyer1, William Pearce1, Emma Barinas-Mitchell1, Tanakul Lertratanakul1, Peggy W. Wu1, Alan Dyer1, William Pearce1, Emma Barinas-Mitchell1, None; 1Northwestern University, Chicago, IL, 2University of Pittsburgh, Pittsburgh, PA, 3Northwestern University and Feinberg School of Medicine, Chicago, IL.

**Background/Purpose:** Women with SLE have increased rates of subclinical atherosclerosis. We have investigated which risk factors may be related to the increase in subclinical atherosclerosis, as measured by carotid plaque and IMT in women with SLE (cases) and without SLE (controls), over 5 years.

**Methods:** Baseline data including demographics and cardiovascular risk factors (CVRF) were collected from 151 cases and 126 controls in the Study of Women with Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Cardiovascular Disease and Pregnancy, Sunday, November 16, 2014, 2:30 PM–4:00 PM (C4) (mg/dl)

### Table 1

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### Disclosures

A. Lertratanakul, None; P. W. Wu, None; A. Dyer, None; W. Pearse, None; E. Barinas-Mitchell, None; T. Thompson, None; R. Ramsey-Goldman, None.

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### 863

**Metabolic Syndrome in Young Premenopausal Female Lupus Patients Is Mainly Influenced By Therapies.** Luciana Muniz1, Rosa M.R. Pereira1, Thiago Silva1, Eloisa Bonfa2 and Eduardo Ferreira Borba1. 1University of São Paulo, São Paulo, Brazil, 2Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

**Background/Purpose:** A high prevalence of metabolic syndrome (MetS) has been observed in Systemic Lupus Erythematosus (SLE) patients, but there are scarce data about the main factors for MetS in young patients. The aim of the present study was to evaluate MetS frequency in premenopausal SLE patients and to identify factors that could contribute to this condition.

**Methods:** One hundred and three female SLE patients (fulfilled the revised American College of Rheumatology criteria) with age less than 40 years old were selected. Demographical, clinical, laboratory and therapeutic data about SLE and MetS were assessed. Thirty-five healthy female age-matched were selected as controls. MetS was defined according to the 2009 Joint Interim Statement. Data analysis (SAS 9.3): t Student’s test or Mann-Whitney’s test (continuous data) and chi-square test or Fisher’s exact test

### Disclosures

A. Lertranakul, None; P. W. Wu, None; A. Dyer, None; W. Pearse, None; E. Barinas-Mitchell, None; T. Thompson, None; R. Ramsey-Goldman, None.
(categorical variable) was performed as appropriate. Multivariate analysis used the Poisson regression.

Results: A higher frequency of MetS (22.3 vs. 5.7%, p = 0.03) was observed in SLE group even as higher mean homeostasis model assessment index (HOMA-IR) (1.8 ± 0.9 vs. 1.3 ± 1.0, p = 0.0008) and mean systematic coronary risk evaluation (SCORE) risk (1.4 ± 0.8 vs. 1.1 ± 0.4, p = 0.01). Regarding MetS criteria, hypertension (42.7 vs. 2.9%, p < 0.0001) and waist circumference (83.5 vs. 37.1%, p < 0.0001) were most frequently observed in SLE group. The comparison of SLE patients with and without MetS showed no differences in mean disease duration and damage index score but higher SLE Disease Activity Index (SLEDAI) scores (median [range] 2 [0–31] vs. 2 [0–14], p = 0.006) and more frequently previous (73.9 vs. 51.2%, p = 0.05) and current renal (34.8 vs. 10.0%, p = 0.008) disease in MetS-SLE group. MetS-SLE patients had higher current prednisone dose (20 [0–60] vs. 5 [0–60] mg/dl, p = 0.018), cumulative dose (41.48 ± 27.81 vs. 24.7 ± 18.66 g, p = 0.023) but no differences in the duration of its use or methylprednisolone pulse use. A higher frequency of chloroquine use was identified in SLE patients without MetS (90.0 vs. 65.2%, p = 0.008). In multivariate analysis, only current chloroquine use (prevalence ratio [PR] = 0.29; 95% confidence interval [CI] 0.13–0.64) and cumulative prednisone dose (PR = 1.01; 95% CI 1.01–1.04) were associated with MetS in SLE. Patients that were not using chloroquine had a 3.48-fold higher risk of MetS and the prevalence of MetS increased by 2% for each increase of one gram of cumulative prednisone dose. The chloroquine use reduced the estimated prevalence of MetS even in patients on steroids and this benefit appears to be greater the higher the cumulative dose of prednisone (figure below):

Conclusion: The prevalence of MetS is high in premenopausal SLE patients and is mainly influenced by lupus therapy with prednisone or chloroquine rather than disease itself. Chloroquine use appears to decrease MetS prevalence even in patients on steroids.

Disclosure: L. Muniz, None; R. M. R. Pereira, None; T. Silva, None; E. Bonfà, None; E. F. Borba, None.

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Association of Coronary Artery Calcification with Brown and White Pericardial Adipose Tissue in SLE. Kelly J. Shields. Lupus Center of Excellence/Allegheny Health Network, Pittsburgh, PA.

Background/Purpose: Women with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD). We have shown that clinically CVD-free women with SLE have an increased volume of descending aortic perivascular adipose tissue, which is also associated with aortic calcification independent of overall adiposity. The relative volumes of brown (BAT) versus white adipose tissue (WAT) may also influence the development of exacerbated CVD. Typically, increased BAT has been associated with a leaner and healthier phenotype while increased WAT has been associated with an obese-like state. We hypothesized that greater pericardial adipose tissue (PAT) and WAT volumes will be associated with coronary artery calcification (CAC) in clinically CVD-free women with SLE.

Methods: Women participating in the “Heart Effects on Atherosclerosis and Risk of Thrombosis in SLE” (HEARTS) study were clinically CVD-free and diagnosed with SLE for at least 2 years. CAC was measured using electron beam computed tomography (EBCT) and quantified by Agaston scoring. The PAT (epicardial + paracardial adipose tissue) was quantified using commercially available software and attenuation values for overall adipose volume (–190 to –30 HU), WAT (–190 to –75 HU), and BAT (–75 to –30 HU). Logistic regression modeling for any CAC was used to evaluate associations. Models were adjusted for CVD risk factors (age, waist-to-hip ratio, menopausal status and hypertension) and circulating inflammatory markers (C3, C4 and CRP).

Results: The study included 156 SLE women and 46% (72/156) had any CAC. SLE women with CAC had higher circulating levels of C3 (p = 0.0002), C4 (p = 0.001), and CRP (p = 0.001). The WAT to BAT ratio (ttest = 0.35, p = 0.006) was significantly correlated with the extent of CAC. In unadjusted logistic regression models PAT (Odds Ratio/OR[95% CI], p-value: 1.02[1.01–1.03], <0.0001), WAT (1.03[1.01–1.04], <0.0001), and BAT (1.05[1.03–1.08], <0.0001) were significantly associated with any CAC. The three volumetric adipose measures maintained significance after adjusting for CVD risk factors (PAT (p = 0.006), WAT (p = 0.02), and BAT (p = 0.002)) and circulating inflammatory markers (PAT (p = 0.002), WAT (p = 0.007), and BAT (p = 0.005)).

Conclusion: Approximately half of the clinically CVD-free SLE women in this study had CAC. Traditional CVD risk factors do not explain the exacerbated CVD risk in the SLE population. We found that PAT and the relative WAT and BAT volumes were independently associated with any CAC even after adjustment for CVD risk factors and circulating inflammatory markers. Small visceral adipose depots surrounding the heart and vasculature may provide localized inflammation promoting CVD.

Disclosure: K. J. Shields, None.

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Cardiovascular Events Prior to or Early after Diagnosis of SLE. Murray E. Urowitz1, Dafna D. Gladman1, Nicole Anderson1, Dominique Blouin2 and Systemic Lupus International Collaborating Clinics (SLICC)2, 3.University of Toronto, Toronto Western Hospital, Toronto, ON, 2University of Toronto, Toronto Western Hospital (Coordinating Center), Toronto, ON.

Background/Purpose: A large multicenter multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. Previous studies have shown a history of cardiovascular events prior to diagnosis of systemic lupus erythematosus (SLE) and rheumatoid arthritis. This study describes the frequency of myocardial infarction (MI) prior to the diagnosis of SLE and within the first 2 years of follow-up.

Methods: An inception cohort of SLE patients from 31 centers in 12 countries has been assembled and followed at yearly intervals according to a standardized protocol between 2000 and 2014. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). MIs were reported and attributed on a specialized vascular event form. MIs were confirmed by one or more of the following: abnormal EKG, typical or atypical symptoms with EKG abnormalities and elevated enzymes (≥2 times ULN), or abnormal stress test, echocardiogram, nuclear scan or angiogram. Descriptive statistics were used.

Results: 31 of 1848 patients that entered the cohort had an MI. Of those, 23 patients had an MI occur prior to SLE diagnosis or within the first 2 years of disease. Of the 23 patients studied 60.3% were female, 82.6% were Caucasian, 4.3% Black, 8.7% Hispanic and 4.3% other. The mean age at SLE diagnosis was 52.5 ± 15.0 years. Of the 23 MIs that occurred, 16 MIs occurred at a mean of 6.1 ± 7.0 years prior to diagnosis and 7 occurred within the first 2 years of follow-up.

Table 1. Cohort Characteristics and CAD risk Factors at Baseline

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<th>Non-early MI Patients</th>
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<td>N</td>
<td>23</td>
<td>1825</td>
<td>0.0001</td>
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<tr>
<td>Sex (Female)</td>
<td>14 (60.9%)</td>
<td>1025 (90.1%)</td>
<td>0.0001</td>
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<tr>
<td>Age at SLE Diagnosis (years)</td>
<td>52.5 ± 15.0</td>
<td>34.5 ± 12.5</td>
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<tr>
<td>SLEDAI-2K</td>
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<td>5.35 ± 5.39</td>
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<tr>
<td>Anti-dsDNA</td>
<td>7.02 (31.8%)</td>
<td>659 (93.1%)</td>
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<td>C3/C4</td>
<td>822 (94.8%)</td>
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<td>0.31 (25%)</td>
<td>141/42 (19.0%)</td>
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<td>519/207 (63.9%)</td>
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<td>723 (38.8%)</td>
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<td>127/2028 (55.7%)</td>
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<td>75 (11.0%)</td>
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Conclusion: MI prior to or early in diagnosis of SLE may indicate earlier low grade disease activity not diagnosed or a concomitant alternative predisposition to AS and SLE.

Disclosure: M. B. Urowitz, None; D. D. Gladman, None; N. Anderson, None; D. Ibanez, None; S. L. L. C. C. (SLICC), None.

Heart Rate Variability: An Inflammatory Biomarker in Systemic Lupus Erythematosus.

Aikaterini Thanou1, Stavros Stavrakis2, John Dyer2, Stan Kamp3, Melissa E. Munroe1, David Albert3, Judith A. James1 and Joan T. Merrill1. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2University of Oklahoma Health Sciences Center, Oklahoma City, OK, 3AliveCor, Inc., San Francisco, CA.

Background/Purpose: Heart rate variability (HRV) is a marker of vagus nerve activity and can be easily obtained with minimal technical expertise in the outpatient setting, using software calculating the distance between consecutive R waves on the electrocardiogram tracing. Decreased HRV is strongly associated with cardiovascular morbidity and mortality, and measures of HRV have been inversely correlated with inflammatory biomarkers in the general population. The current study evaluates the relationship of HRV with clinical disease activity and cytokine pathways in patients with systemic lupus erythematosus (SLE).

Methods: 58 patients with SLE from the Oklahoma Lupus Cohort were evaluated at two visits with the stipulation that there must be at least mild/moderate disease activity at both visits (median 1 month from the baseline visit), there was a significant decrease in SLEDAI (average decrease 3.7 (SD 2.3)) and PGA (average decrease 2.3 (SD 1.0)) and PGA (average decrease 0.4 (SD 0.1)) compared to baseline. Change in HRV measures was negatively associated with change in the BILAG 2004 index (p=0.03). None of the disease activity indices were correlated with change in IL-6 levels (p>0.05 for each); however, the change in BLYS levels was positively associated with change in SLEDAI (p=0.03) and BILAG 2004 index (p=0.02).

Conclusion: These pilot findings suggest that HRV measures could provide a sensitive marker for lupus disease activity and improvement, and support a role for HRV as an easily measured, non-invasive, in-office procedure. Its relevance to specific clinical or immunologic phenotypes or potential utility as a treat to target endpoint remain to be further explored.

Disclosure: S. K. Tedeschi, None; H. Guan, None; A. Fine, None; B. L. Bermas, None; K. H. Costenbader, None.

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Disclosure: S. K. Tedeschi, None; H. Guan, None; A. Fine, None; B. L. Bermas, None; K. H. Costenbader, None.

Specific SLE Disease Manifestations in the Six Months Prior to Conception Predict Similar Manifestations during Pregnancy. Sara K. Tedeschi, Hong-shu Guan, Alexander Fine, Bonnie L. BERMAS and Karen H. COSTENBADER. Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Active SLE, in particular lupus nephritis, during the six months prior to conception is associated with disease flare during pregnancy. Previous studies, however, have not evaluated how other disease manifestations prior to conception are related to disease activity during pregnancy. We sought to investigate the relationship between SLE organ-specific disease activity in the six months prior to conception and organ-specific disease activity during pregnancy.

Methods: We identified SLE patients with >2 visits to our Lupus Center and ≥1 pregnancy lasting >12 weeks from 1990–2013, who had clinical and lab data available for the six months prior to conception and during pregnancy. All women had confirmed SLE by rheumatologist review for 1997 ACR Criteria for Classification. We collected data on: age, pregnancy outcomes, SLE medication use, history of nephritis, serositis (pleuritis, pericarditis), inflammatory arthritis, skin disease (malar rash, discoid lesions, photosensitivity), antiphospholipid antibody syndrome, hemolytic disorder (leukopenia, hemolytic anemia, thrombocytopenia), anti-dsDNA elevation, and low complement, both in the six months preceding and during pregnancy. We analyzed the data using Fisher’s exact tests.

Results: Among 1,127 women with SLE, 149 pregnancies occurred in 115 women. Mean age at SLE diagnosis was 23.8 (SD 6.8) years and at conception was 31.1 (SD 5.2) years; average SLE duration prior to pregnancy was 7.8 (SD 5.8) years; 8.7% were diagnosed with SLE during pregnancy. 68.7% were White, 14.8% Hispanic, 9.6% Black, and 7.0% Asian. During pregnancy the most common SLE manifestations were hematologic (15.4%), nephritis (10%), skin (9.4%), arthritis (6.7%), and serositis (4.7%). Activity of each of these SLE manifestations in the six months prior to conception was significantly associated with occurrence of the same manifestation during pregnancy. In contrast, patients without these clinical findings in the six months prior to pregnancy were unlikely to have activity in these organ systems during pregnancy. (Table 1)

Conclusion: Among women with SLE who had any organ system disease activity six months prior to conception, a large proportion had persistent symptoms of the same type during pregnancy. Those patients with quiescent organ-system manifestations six months prior to pregnancy were unlikely to become symptomatic during pregnancy. To our knowledge, this is the first study to reveal that organ-specific SLE manifestations, in addition to nephritis, in the six months prior to conception portend similar disease manifestations during pregnancy.

Table 1. Organ-specific SLE disease activity six months prior to conception and during pregnancy. N=149 pregnancies

<table>
<thead>
<tr>
<th>Disease Manifestation</th>
<th>Active during pregnancy</th>
<th>Inactive during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>4 (4%)</td>
<td>95 (96%)</td>
</tr>
<tr>
<td>Serositis</td>
<td>2 (2%)</td>
<td>97 (98%)</td>
</tr>
<tr>
<td>Skin</td>
<td>7 (7%)</td>
<td>92 (93%)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>12 (12%)</td>
<td>137 (137%)</td>
</tr>
<tr>
<td>Hematological Disorders</td>
<td>1 (1%)</td>
<td>148 (148%)</td>
</tr>
</tbody>
</table>

Disclosure: S. K. Tedeschi, None; H. Guan, None; A. Fine, None; B. L. BERMAS, None; K. H. COSTENBADER, None.

ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I: Pathways of Inflammation/Injury

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Protein Phosphatase 5 (PP5) Regulates Methylation Sensitive Gene Expression in CD4+ T Cells. Dipak R. Patel, Gabriela Gorelik and Bruce C. Richardson. University of Michigan, Ann Arbor, MI.

Background/Purpose: CD4+CD28- T cells are enriched in chronic inflammatory diseases like rheumatoid arthritis (RA) and lupus. They are cytotoxic and resistant to apoptosis. Compared to CD28+ cells, CD28- CD4 T cells over-express killer immunoglobulin-like receptors (KIRs) and other pro-
inflammatory molecules. These genes are regulated by DNA methylation, so they are over-expressed by CD4 T cells that are demethylated in vitro. This is a result of decreased signaling through the ERK and JNK pathways and, consequently, decreased activity of the DNA methyltransferase enzymes (DNMTs) responsible for DNA methylation. Protein phosphatase 5 (PP5) is a stress induced regulator of gene expression in multiple signaling pathways, including those involved in aging. It is expressed in CD4+CD28−, but not CD4+CD28+ T cells, and it inhibits both ERK and JNK signaling. We hypothesized that PP5 is over-expressed in CD4+ T cells in patients with RA and lupus, and that over-expressing PP5 in CD4 T cells from healthy donors will induce expression of methylation sensitive genes unique to CD4+CD28− T cells.

**Methods:** CD4+ T cells were isolated from healthy controls and patients, and PP5 mRNA was measured by RT-PCR. To study the effects of PP5 on gene expression, PBMCs from healthy donors were stimulated with phytohemagglutinin and cultured for 3 days with IL-2. CD4+ T cells were then isolated by negative selection, transfected (Amazk Nucleofector) with constructs encoding GFP and PP5 or GFP alone, and cultured 24–72 hours.

Expression of DNMT1 and methylation sensitive genes was assessed by RT-PCR in sorted CD4+GFP+ T cells. DNMT1 expression was measured 24 hours after transfection, and the other genes were analyzed 72 hours after transfection. Cell surface protein expression was measured by flow cytometry 72 hours after transfection.

**Results:** Compared to CD4+ T cells from healthy donors, PP5 mRNA is over-expressed in patients with lupus (1.97 fold change ±0.18 SEM, p=0.03) and RA (1.0±0.2, p=0.06). When transfected into CD4+ T cells from healthy donors, PP5 increased mRNA levels of KIR (2DL4 gene, 2.4±0.7, n=3, p=0.04), perforin (1.38±0.07 fold, p=0.03, n=3), CD11a (1.2±0.1 fold, p=0.06, n=3), CD70 (10.5±4.1 fold, p=0.03, n=3), and CD70 (10.5±4.1 fold, p=0.03, n=3). PP5 also increased the percentage of cells expressing surface KIRs (33±7% with control vs. 62±7% with PP5, n=7, p=0.01), CD70 (18.3±7% with control vs. 34±10% with PP5, n=3, p=0.06), and CD40L (15±6.1% with control vs. 27.3±9% with PP5, n=3, p=0.05). Finally, PP5 caused a corresponding 20±8% decrease (n=5, p=0.02) in DNMT1 mRNA expression.

**Conclusion:** CD4+CD28− T cells, which are enriched in lupus and RA, over-express pro-inflammatory methylation sensitive genes. These data demonstrate, for the first time, that PP5 contributes to the regulation of these genes (KIR, perforin, CD70, CD40L, and CD11a) in CD4+ T cells. PP5 is hypothesized to accomplish this by demethylating regulatory elements in the promoters for these genes, and this is currently being tested. PP5 expression is induced by oxidative and replicative stress, so it could provide a mechanistic link between those physiologic stressors and autoimmune disease flares.

**Disclosure:** D. R. Patel, None; G. Gorelik, None; B. C. Richardson, None.

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**UBE2L3 genotype Influences Plasma Cell Proliferation in Systemic Lupus Erythematosus By Regulation of NF-κB By The Linear Ubiquitination Assembly Complex.** Myles J. Lewis1, Simon Vyse3, Adrian M. Shields1, Sebastian Boeltz2, Patrick Gordon3, Timothy D. Spector2, Paul J. Lehner3, Henning Walczak4 and Timothy J. Vyse2. 1Queen Mary University of London, London, United Kingdom, 2King’s College London, London, United Kingdom, 3University of Cambridge, Cambridge, United Kingdom, 4Head of School of Medicine, University College London, London, United Kingdom.

**Background/Purpose:** Genome-wide association studies have identified a strong association between a single risk haplotype of the UBE2L3 gene and Systemic Lupus Erythematosus (SLE), as well as multiple autoimmune diseases (rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, psoriasis). UBE2L3 is an E2 ubiquitin-conjugating enzyme specific for RING/HECT hybrid or HECT E3 ligases. Linear ubiquitination is a newly described form of ubiquitination, whose only known function is controlling activation of NF-κB, mediated by the linear ubiquitination chain assembly complex (LUBAC).

**Methods:** UBE2L3 genotype data from GWAS in SLE was imputed up to 1000 Genomes level. UBE2L3 function was studied in vitro using standard molecular biology techniques in HEK293 cells, or ex vivo using B cells and/or monocytes from healthy individuals or SLE patients (NF-κB translocation by Imagestream, multicolour flow cytometry of B cell subsets) stratified by UBE2L3 genotype.

**Results:** Data from SLE GWAS, imputed to 1000 Genomes level identified rs140490 as the most strongly associated UBE2L3 SNP, located at −270bp of the promoter region (P=8.6×10−14; OR 1.30, 95%CI: 1.21−1.39). Microarray /western blot studies found that the rs140490 risk allele increased UBE2L3 expression in B cells and monocytes from PBMC. Overexpression of UBE2L3 in combination with LUBAC in HEK293-NF-κB reporter cell line led to a marked upregulation in NF-κB activity, which was abolished by dominant-negative mutant UBE2L3[C66S] RNAi blockade of UBE2L3 antagonised TNF signalling by inhibiting IκBα processing. Ex vivo human B cells and monocytes were isolated from genotyped healthy twins stimulated with CD40L or TNF respectively and NF-κB translocation quantified by Imagestream analysis. rs140490 genotype was correlated with both basal NF-κB activation in healthy human B cells, as well as the sensitivity of NF-κB to CD40 stimulation in B cells and TNF stimulation in monocytes. UBE2L3 expression was 3−4 fold elevated in B cells and monocytes in SLE compared to controls (P<0.001), with increased UBE2L3 expression in plasma cells from SLE patients compared to controls (P=0.01). UBE2L3 expression was significantly elevated in K4-67+ B cells consistent with a functional role in B cell proliferation. Consistent with the functional effect of UBE2L3 on CD40 driven NF-κB activation in human B cells, rs140490 genotype correlated with increasing plasmablast and plasma cell differentiation in SLE patients (P<0.001).

**Discussion:** Our study provides evidence to show that the UBE2L3 risk haplotype exerts a critical rate-limiting effect on TNF and CD40 activation of NF-κB in primary human cells, and that this effect is mediated through LUBAC. By tracking NF-κB nuclear translocation in B cells and monocytes from genotyped individuals, we have shown that the UBE2L3 risk variant amplifies both basal NF-κB activation and sensitivity of NF-κB to stimulation in ex vivo cells, leading to increased plasma cell proliferation in SLE.

**Disclosure:** M. J. Lewis, None; S. Vyse, None; A. M. Shields, None; S. Boeltz, None; P. Gordon, None; T. D. Spector, None; P. J. Lehner, None; H. Walczak, None; T. J. Vyse, None.

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**IRF1 Influences on Histone H4 Acetylation in Systemic Lupus Erythematosus.** Yiu Tak Leung1, Luhua Shi2, Kelly Maurer4, Li Song2, Zhe Zhang1, Michelle Petri3 and Kathleen E. Sullivan1. 1University of Pennsylvania, Philadelphia, PA, 2The Children’s Hospital of Philadelphia, Philadelphia, PA, 3University of Pennsylvania, Philadelphia, PA, 4Johns Hopkins University School of Medicine, Baltimore, MD.

**Background/Purpose:** Systemic lupus erythematosus (SLE) is the classical systemic autoimmune disease. Epigenetic processes, such as posttranslational histone modifications, can regulate gene expression without altering the underlying genomic sequence; these disease mechanisms that have had little attention in SLE to date. We previously reported that histone h4 acylation (H4ac) is globally increased across the genome in monocytes of SLE patients as compared to healthy controls using tiling array. Transcription factor motif analysis then found that 63% of genes with increased H4ac had potential interferon regulatory factor (IRF) 1 binding sites, associating this transcription factor in the dysregulated gene expression. In order to investigate how IRF1 interactions influence H4ac in SLE, we identified the specific hyperacylated H4 lysine residues, looked for histone acetyltransferases (HATs) and histone deacetylases (HDACs) dysregulation that may lead to the pathological hyperacetylation pattern and examined IRF1 associations with HATs and HDACs.

**Methods:** Flow cytometry for H4 lysine groups: K5, K8, K12 and K16 were run using isotype control H4Ac. H4Ac was defined in monocytes from 21 controls and 21 SLE patients, RNA-Seq was performed on monocytes from a different set of 8 controls and 8 SLE patients to look for an imbalance in HAT and HDAC expression; these imbalances were validated using real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). IRF1 influences on H4ac were evaluated in vitro using D54MG cells overexpressed with IRF1. IRF1 interactions with HATs and HDACs were studied using co-immunoprecipitation assays.

**Results:** Flow cytometry data showed that H4K5, H4K8, H4K12, and H4K16 acetylation were significantly increased in SLE monocytes. RNA-Seq results identified HDAC3 and HDAC11 with significantly decreased expression in SLE monocytes as compared to controls. HDAC3 can deacetylate all H4 lysine acetyl groups, preferentially acetylated H4K5 and H4K12. In contrast, the expression of PCAF, a HAT, was significantly increased in SLE monocytes as compared to controls. PCAF can place H4K5, H4K8, and H4K16 acetylation marks with a preference for H4K8. qRT-PCR data validated the HAT/HDAC expression patterns seen in the RNA-Seq studies. SLE monocytes had decreased gene expression levels of HDAC3 and HDAC11; PCAF had significantly higher gene expression in SLE than controls. IRF1-overexpressed in D54MG cells was associated with significantly increased H4K5 and H4K12 as compared to vector-only D54MG cells. While there was also some increase in acetylation at H4K16, no increase in acetylation was seen at H4K16 in IRF1-overexpressing D54MG cells. Co-immunoprecipitation studies using D54MG cells revealed IRF1 associations with PCAF, P300, CBP, Gcn5, Atf2, Hdac3 and Sirt1.
Conclusion: We hypothesize that IFR1 responds to alpha-IFN activation in SLE, and activated IFR1 recruits HATs, which then increases H4ac and leads to the chronic pathological gene expression in SLE. These studies have identified pivotal enzymes participating in the global hyper-acetylation in SLE.

Disclosure: Y. T. Leung, None; L. Shi, None; K. Maurer, None; L. Song, None; Z. Zhang, None; M. Petri, None; K. E. Sullivan, Immune Deficiency Foundation, 8, Baxter, 8, Up To Date, 8.

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Antimalariais Regulate TLR7/8 Mediated Macrophage Activation Via Epigenetic Modification at the TNFα Promoter.

Androo J. Markham1, Mark Halushka2, Cristina Guidiucci3, Robert M. Clancy4 and Jill P. Buyon1.

1New York University School of Medicine, New York, NY, 2John Hopkins Pathology, Baltimore, MD, 3Dynavax Technologies, Berkeley, CA.

Background/Purpose: Maternal anti-SSA autoantibodies contribute to the pathogenesis of congenital heart block by the formation of immune complexes (IC) comprised of Ro and ssRNA (hY3) which, via FcγR uptake, result in macrophage TLR signaling, a finding also applicable to other cell types and the pathogenesis of lupus in general. Accordingly, antagonists of innate cell drivers such as TLR7/8 and NF-κB would constitute a multi-target approach to the inhibition of proinflammatory and profibrotic mediators and subsequent organ injury. This study examined the role of TLR7/8 ligation and the modulatory effects of antimalariais on the epigenetic signature (methylation state) of histone 3 at lysine 4 (H3K4), a regulatory site in the promoter region of genes such as TNFα whose transcription is augmented by NFκB binding.

Methods: The approach included both in vitro and in vivo studies. The former employed TLR7/8 stimulated human macrophage cells including THP1 and peripheral blood monocytes and the latter for immunohistochemistry of autopsy tissue from the heart of a fetus dying with CHB and an age matched control.

Results: As expected, H3K4me2 (reflecting increased promoter activity) was expressed in both the CHB and control hearts. In the former, highly positive mononuclear infiltrates were identified in the AV nodal region. Based on these novel findings, in vitro experiments were initiated to examine the role of TLR7/8 ligation (hY3, surrogate for IC) on the epigenetic modification at histone 3 using broad-based and specific readouts, the latter for expression of TNFα and peripheral blood macrophages and the former immunohistochemistry of autopsy tissue from the heart of a fetus dying with CHB and an age matched control.

Conclusion: H3K4me2 (reflecting increased promoter activity) was expressed in both the CHB and control hearts. In the former, highly positive mononuclear infiltrates were identified in the AV nodal region. Based on these novel findings, in vitro experiments were initiated to examine the role of TLR7/8 ligation (hY3, surrogate for IC) on the epigenetic modification at histone 3 using broad-based and specific readouts, the latter for expression of TNFα and peripheral blood macrophages and the former immunohistochemistry of autopsy tissue from the heart of a fetus dying with CHB and an age matched control.

Disclosure: D. Andrade, None; M. Kim, None; L. P. Blanco, None; S. A. Karumanachi, Aggamin Pharmaceuticals, 1, Thermofisher, 2, Siemens Diagnostics, 3, Beth Israel Deaconness Medical Center, 7, G. Koo, None; P. M. Redecha, None; K. A. Kirou, None; A. M. Alvarez, None; M. J. Nulla, None; M. K. Crow, None; V. Abrahams, None; J. J. Kaplan, None; J. E. Salmon, None.

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The Second Messenger, Cyclic GMP-AMP Dinucleotide (cGAMP) and the Enzyme, Cyclic GMP-AMP Synthase (cGAS), Are Expressed in Systemic Lupus Erythematosus.


Background/ Purpose: The type I IFNs (IFN-α), are strongly associated with Systemic Lupus Erythematosus (SLE). It is generally considered that IFN-1 is induced by immune complexes (IC) containing (ribo)nucleoprotein antigens. However, this conclusion is based on in vitro studies and doesn’t address how IFN-I may be induced prior to the formation of IC. Cytosolic DNA induces IFN-I and other cytokines which are important for antimicrobial defense but can also trigger autoimmunity. Cyttoplasmic DNA frequently transduces signals via the adaptor protein, STING, and the transcription factor IRF3, however how cytosolic DNA is sensed in eukaryotic cells remains under intense investigation. Recently it was shown that a newly discovered enzyme called cyclic-di-GMP-AMP (cGAMP) synthase (cGAS) detects cytosolic DNA, synthesizes cGAMP which then acts as a second messenger to trigger a signaling pathway through STING and IRF3, resulting in production of IFN-β in mammalian cells. Our research aim is to determine whether the cGAS pathway could contribute to IFN I production in SLE.

Methods: cGAS and Interferon Stimulated Genes (ISGs) mRNA expression was quantified by quantitative PCR (qPCR). IFN3 phosphorylation was determined by anti-phospho-IRF3 antibody and western blot. GAMP levels were monitored by Selective Reaction Monitoring (SRM) with High Performance Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS/MS).

Results: When compared to normal controls (n=20), SLE patients (n=51) had a significant increase of the expression of cGAS (P=0.0045) in peripheral blood mononuclear cells (PBMC). cGAS expression positively correlated with
fibrosis in a murine scleroderma model. Tocilizumab (TCZ), an IL-6 inhibitor, was tested in the FaSScinate Clinical Trial in Patients With Systemic Sclerosis; Week 24 Data from a Phase 2/3 Trial. Safety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Clinical Aspects and Therapeutics I: Systemic Sclerosis, Advances in Therapy 874

Safety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis: Week 24 Data from a Phase 2/3 Trial. Dinesh Khanna1, Christopher P. Denton2, Jacob M. van Laar3, Angelika Jahreis4, Sabrina Cheng5, Helen Spotswood6, Jeffrey Siegel7 and Daniel E. Furst8 on behalf of the FaSScinate Clinical Trial in Patients With SSc9. 1University of Michigan Health System, Ann Arbor, MI, 2University College London Medical School, London, United Kingdom, 3University Medical Center Utrecht, Utrecht, Netherlands, 4Genentech, South San Francisco, CA, 5Roche Products Ltd., Welwyn Garden City, United Kingdom, 6University of California, Los Angeles, CA.

Background/Purpose: Systemic sclerosis (SSc) is a progressive, debilitating disease with limited treatment options. IL-6 has been implicated in disease pathogenesis. 1, 2 IL-6 receptor inhibitor prevented and reversed skin fibrosis in a murine sclerodermoid model. 3 Tocilizumab (TCZ), an IL-6 receptor antagonist, is under evaluation in the ongoing 2-year FaSScinate study, a randomized, double-blind, placebo-controlled trial. Wk 24 efficacy and safety data of TCZ in SSc pts are presented here.

Methods: Pts (≥18 y) with active SSc (1980 ACR criteria, ≤5-y disease duration, mRSS 15–40 units, and elevated acute-phase reactants) were randomized 1:1 to subcutaneous TCZ 162 mg or placebo (PBO) wkl for 48 wks. The primary end point was mean change in mRSS from baseline (BL) at wk 24, with patient and lung responses as secondary/exploratory measures.

Results: Eighty-seven pts (43 TCZ, 44 PBO) were enrolled. BL characteristics were similar between arms, including mean (SD) mRSS (TCZ, 26.4 [7.2]; PBO, 25.6 [5.9]). The primary end point, change in mRSS, and secondary end point, change in HAQ-DI, from BL to wk 24 are displayed in the Table. At 24 wks, a numerically favorable but not statistically significant effect of TCZ over PBO on mRSS was noted (TCZ, −3.9; PBO, −1.2; adjusted mean difference, −2.7 [95% CI −5.85, 0.45]). In addition, a numerically greater proportion of TCZ pts achieved clinically meaningful reduction in mRSS of ≥4.7. TCZ, 43.2% [16/37]; PBO, 26.3% [10/38]; p = 0.15. Fisher exact test). Exploratory analysis of change in forced vital capacity (FVC; liters) showed more PBO than TCZ patients (81% vs 50%) with progression of FVC decline (≥10%) (Table) and 27% of PBO pts vs 3% of TCZ pts with ≥10% FVC decline (p = 0.009, Van Elteren test). Adverse events (AEs) were reported in 88.4%20.9% of TCZ and 90.9%20.0% of PBO pts. Fewer noninfectious SAEs were reported in the TCZ arm (5 pts) than the PBO arm (10 pts). There were no serious AEs or infections (infection/inflammation SAEs were more common in TCZ than PBO pts (6 pts vs 1 pt). By system organ class, the following SAEs potentially indicative of SSc complications, were reported more frequently in the PBO than in the TCZ arm: cardiac SAE (TCZ, 0 pts; PBO, 3 pts), gastrointestinal SAE (TCZ, 0 pts; PBO, 2 pts), and renal SAE (TCZ, 0 pts; PBO, 2 pts). Three pts in the TCZ arm and 2 pts in the PBO arm discontinued due to AEs. One death occurred in each arm: 1 pulmonary infection in a TCZ pt on day 109 and 1 heart failure in a PBO pt 131 days after withdrawal.

Conclusion: In this phase 2 study, favorable trends in skin score for TCZ were detected though the primary skin score end point was not met. In addition, encouraging changes in FVC were noted. The ongoing double-blind and open-label phases of this trial will provide additional information.

References:

Table. Change From Baseline in mRSS, HAQ-DI, and FVC at Week 24 (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>TCZ</th>
<th>PBO</th>
<th>Difference (95% CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRSS</td>
<td>adjusted=4 mean (SD)</td>
<td>−3.9 ± 4</td>
<td>−1.2 ± 4</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>adjusted=4 mean (SD)</td>
<td>0.14 ± 4</td>
<td>0.12 ± 4</td>
</tr>
<tr>
<td>FVC (L) change ≤50% of baseline (n (%))</td>
<td>15 (50.0)</td>
<td>30 (81.1)</td>
<td>0.03 &gt; 0.25</td>
</tr>
<tr>
<td>FVC (L) decline ≥10% of baseline (n (%))</td>
<td>1 (3.3)</td>
<td>10 (27.0)</td>
<td>0.21 &gt; 0.05</td>
</tr>
</tbody>
</table>

HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent to treat.

Disclosure: D. Khanna, Actelion, Bayer, Biogen-Idec, BMS, Digna, Genentech/ Roche, Gilead, InterMune, Merc, Sanofi-Aventis, United Therapies, 5; Patient Health Organization, 6; Scleroderma Foundation, 6; C. P. Denton, Genentech-Roche, GSK, Actelion, Sanofi Aventis, Biogen-Idex, CSL Behring, 5; J. M. van Laar, Roche, UK, 2; Roche UK, 5; Genentech, Menarini, BMS, Abbott, Novartis, Tigenix, Pfizer, 8; A. Jahreis, Genentech/Roche, 3; S. Cheng, Genentech/Roche, 3; H. Spotswood, Roche Pharmaceuticals, 1; Roche Pharmaceuticals, 3; J. Siegel, Genentech/Roche, 3; D. E. Furst on behalf of FaSScinate Clinical Trial in Patients With SSc, AbbVie, Actelion, Amgen, BMS, Gilead, GSK, Novartis, Pfizer/Roche/Genentech, UCB, 2, AbbVie, Actelion, Amgen, BMS, Cytori, Janssen, Gilead, GSK, Novartis, Pfizer, Roche/ Genentech, UCB, 5, AbbVie, Actelion, UCB, 8.

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Treatment-Related Outcomes in Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: A Pooled Analysis of 12 Randomized Controlled Trials. Ronnie L. Rhee1, Nicole B. Gabler1, Amy Praestgaard1, Peter A. Merkel2 and Steven M. Kawut1. 1University of Pennsylvania, Philadelphia, PA, 2Vascularitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Recent studies have shown that therapies for pulmonary arterial hypertension (PAH) improve exercise capacity, but subgroup analyses suggest that these therapies may be less effective in patients with connective tissue disease (CTD-PAH). The aim of this study was to compare the effect of treatment on the change in six minute walk distance (Δ6MWD) and clinical events in CTD-PAH vs idiopathic PAH (IPAH).

Methods: A pooled analysis was performed on patient-level data from 12 Phase III randomized placebo-controlled trials of advanced therapies for PAH that were submitted to the FDA for approval. Outcomes for this analysis included Δ6MWD from baseline to 12 weeks, the occurrence of clinical worsening (defined as first occurrence of death, hospitalization for PAH, addition of other PAH medications, lung transplant, atrial septostomy, or worsening exercise capacity and/or functional class), and all-cause mortality. Missing 6MWD at 12 weeks was multiply imputed. A robust generalized estimating equation within a linear or logistic regression model was utilized using an exchangeable correlation structure and clustering on study trial. Effect modification of treatment assignment and diagnosis in terms of the functional class and baseline 6MWD was assessed. All regression models were adjusted for age, sex, race, drug class, baseline 6MWD, functional class, and baseline hemodynamics (right atrial pressure, pulmonary vascular resistance, and cardiac index).

Results: The study sample included 2,736 participants: 824 had CTD-PAH and 1,912 had IPAH. Patients with CTD-PAH were significantly older, more often female, and had a lower baseline 6MWD compared to patients with IPAH (Table 1). There was a significant interaction between treatment assignment and diagnosis in terms of the Δ6MWD, such that the treatment-related improvement in Δ6MWD was significantly less in CTD-PAH than in IPAH (difference-in-difference -11.3 meters, [95% CI -20.0, -2.6], p for interaction = 0.011). There was also greater treatment-associated reduction in clinical worsening and mortality in IPAH than in CTD-PAH (Table 2).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>CTD-PAH</th>
<th>IPAH</th>
<th>Δ6MWD (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 6MWD</td>
<td>375 ± 100</td>
<td>355 ± 100</td>
<td>0.011</td>
</tr>
<tr>
<td>Change in 6MWD</td>
<td>11.3 meters, [95% CI 20.0, 20.0]</td>
<td>20.0, [95% CI 20.0, 20.0]</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Disclosure: J. An, None; J. Woodward, None; R. Karr, None; T. H. Teal, None; K. B. Elkon, None.

ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Clinical Aspects and Therapeutics I: Systemic Sclerosis, Advances in Therapy
Sunday, November 16, 2014, 2:30 PM–4:00 PM
Conclusion: In clinical trials, treatment for PAH was less effective in CTD-PAH compared to IPAH in terms of increasing 6MWD, preventing clinical worsening, and possibly reducing the risk of death. The differential treatment response in CTD-PAH and IPAH supports the need for stratified analysis in future trials and suggests that a different pathophysiological process may exist in the two phenotypes of disease.

Table 1: Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>CTD-PAH (N = 824)</th>
<th>IPAH (N = 1,912)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54 ± 14</td>
<td>47 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>735 (89)</td>
<td>1,402 (73)</td>
<td>&lt;0.001</td>
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<td>Race, No (%)</td>
<td>480 (58)</td>
<td>1,155 (60)</td>
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<tr>
<td>White</td>
<td>33 (4)</td>
<td>54 (3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>311 (38)</td>
<td>703 (37)</td>
<td></td>
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<tr>
<td>WHO functional class, No (%)</td>
<td>374 (45)</td>
<td>847 (44)</td>
<td>0.599</td>
</tr>
<tr>
<td>I/I</td>
<td>450 (55)</td>
<td>1,065 (56)</td>
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</table>

Table 2: Risk of Clinical Worsening and Death Stratified by Diagnosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diagnosis</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>p for interaction</th>
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</thead>
<tbody>
<tr>
<td>Clinical Worsening</td>
<td>CTD-PAH</td>
<td>0.80</td>
<td>0.63–1.03</td>
<td>0.081</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>IPAH</td>
<td>0.51</td>
<td>0.40–0.65</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>CTD-PAH</td>
<td>1.73</td>
<td>0.75–4.00</td>
<td>0.198</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td>IPAH</td>
<td>0.66</td>
<td>0.27–1.60</td>
<td>0.356</td>
<td></td>
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</tbody>
</table>

Disclosure: R. L. Rhee, None; N. B. Gabler, None; A. Praegstad, None; P. A. Merkel, Genentech and Biogen IDEC Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5, S. M. Kawut, None.

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Sildenafil Attenuates the Fibrotic Phenotype in Systemic Sclerosis Skin Fibroblasts. Tomohiko Higuchi1, Yasushi Kawaiuchi1, Kae Takagi1, Akiko Tochimoto1, Yuko Ota1, Yoshihiro Katsumata1, Takahisa Gono2, Masanori Hanaoka1, Yuko Okamoto1, Hidenaga Kasawam1 and Hissashi Yamanaka1, 1Tokyo Women’s Medical University, Tokyo, Japan, 2Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease characterized by inflammation, vasculopathy and fibrosis. Tissue fibrosis directly contributes to mortality or quality of life. However, the effective therapy has not been established. Aberrantly activated fibroblasts in the affected area of SSc, which play a main role in the production and remodeling of collagen and other extracellular matrix components, is thought to be a key therapeutic target. Recent researches showed that stimulation of soluble guanylate cyclase (sGC) reverted fibrotic phenotype of SSc and other fibrotic disorders in vitro by increasing levels of intracellular cGMP (cGMP). The purpose of the present study is to assess the anti-fibrotic properties of cGMP in cultured fibroblasts from patients with SSc.

Methods: Skin fibroblasts were obtained from patients with diffuse cutaneous SSc. Intracellular cGMP levels were measured using a commercially available ELISA Kit. To increase the intracellular concentration of cGMP, sildenafil, an inhibitor of phosphodiesterase (PDE) 5, was added. Expression of PDE5 and alpha smooth muscle actin (aSMA) were analyzed by immunohistochemistry. Gene expressions related to profibrotic marker were evaluated by quantitative RT-PCR. Western blotting and ELISA were performed to investigate the effects of sildenafil on the downstream pathway of TGF-β.

Results: PDE5 expression on skin fibroblasts was confirmed by immunohistochemistry. Baseline cGMP levels in SSc skin fibroblasts were significantly higher than those in healthy skin fibroblasts. Sildenafil increased cGMP levels in a dose dependent manner in skin fibroblasts, and then our results indicated that sildenafil significantly decreased the expression of profibrotic genes, which were augmented by TGF-B1, including COL1A1, COL1A2, CTGF and ACTA2 in SSc skin fibroblasts. Conversely, these inhibitory effects of sildenafil were found to be weak in healthy skin fibroblasts. Also, we confirmed using immunohistochemistry that the protein levels of aSMA in SSc skin fibroblasts were down-regulated by sildenafil. Next, we explored the effects of sildenafil on...
the signal pathway of TGF-β. Sildenafil significantly reduced phosphorylation of p38 induced by TGF-β1, but did not affect phosphorylation of Smad3. In addition, sildenafil reduced Rho kinase activity.

**Conclusion:** We demonstrated that sildenafil attenuated the fibrotic phenotype of SSc skin fibroblasts induced by TGF-β1. This effect may be attributed by non-Smad signaling pathways, including MAPK and Rho kinase cascade. Sildenafil has been used for the treatment of SSc-associated pulmonary arterial hypertension and Raynaud phenomenon by its potent vasodilating effect. In addition, our findings would provide the evidence that sildenafil may have the potential to improve fibrotic lesions in SSc.

**Disclosure:** T. Higuchi, None; Y. Kawaguchi, None; K. Takagi, None; A. Tochimoto, None; Y. Ota, None; Y. Katsumata, None; T. Gono, None; M. Hanaoka, None; Y. Okamoto, None; H. Kawasumi, None; H. Yamanaoka, None.

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**Luminex and Autoantigen Microarray Analysis of Sera from Patients with Diffuse Cutaneous Systemic Sclerosis Reveals Changes Associated with Imatinib Mesylate Treatment.** D. James Haddon1, Hannah Wand2, Paul J. Utz1, Robert F. Spiera2, Jessica K. Gordon1 and Lorinda Chung1, 1Stanford University School of Medicine, Stanford, CA; 2Hospital for Special Surgery, New York, NY; 3Stanford University School of Medicine, Palo Alto, CA.

**Background/Purpose:** Tyrosine kinase inhibitors (TKIs), including imatinib mesylate, have been studied for the treatment of diffuse cutaneous Systemic Sclerosis (dcSSc). In a previously reported single center, open-label study of imatinib for dcSSc, a significant improvement in the modified Rodnan skin score (mRSS) was observed. In this study, we analyzed the patient serum samples collected during the trial by Luminex and autoantigen microarray to investigate the mechanism of action of imatinib in dcSSc, and to identify biomarkers that are predictive of response to imatinib.

**Methods:** Thirty patients who fulfilled ACR criteria for SSC, with dcSSc, were enrolled in the trial, and 24 completed 12 months of treatment with oral imatinib 400 mg daily. Serum samples were collected at intervention. Serum samples were collected at 1, 0, 6, 12, and 15 (post-treatment follow-up) months. Twenty-six patient serum samples were available for analysis at screening/baseline, 25 at 6 months, 20 at 12 months, and 15 at the follow-up time point.

**Results:** Luminex immunoassays were used to measure the levels of 44 cytokines, chemokines and growth factors in each serum sample in duplicate. Autoantigen microarrays were used to measure the levels of 30 autoantigens known to be associated with dcSSc, in parallel. Luminex and microarray results were analyzed by Significance analysis of microarrays (SAM), a statistical technique that uses permutation to adjust for multiple testing. SAM was used to identify Luminex analytes and autoantibodies that were present at significantly different levels: 1) in healthy controls vs. patients with dcSSc at baseline, 2) during treatment with imatinib vs. baseline; and 3) in the baseline samples of responders vs. non-responders. For this analysis, a decrease in mRSS ≥ 5, previously defined as the minimal clinically important difference, was considered a response to treatment.

**Results:** Luminex analysis identified 18 analytes that were present at significantly higher levels in the serum of patients with dcSSc than in healthy control serum, including previously reported factors IL-6, MCP-1, VEGF, IL-17 and MIP-1β (fold-change > 2, q < 0.001). Autoantigen microarray analysis revealed 7 autoantibodies present at significantly higher levels in dcSSc patient sera than in healthy control sera, including Scl-70 and RNA Pol III (fold-change > 1.5, q < 0.001). We observed significant reductions in 5 autoantibodies following 6 months of treatment with imatinib, including Scl-70 and RNA Pol III, compared to baseline (q < 0.001). Imatinib treatment was also associated with reductions in 8 Luminex analytes, including VEGF, IL-17, MCP-1, PDGF-AA, and PDGF-BB (q < 0.001). Levels of VEGF, IL-17, and MIP-1β were significantly higher in responders than non-responders at baseline.

**Conclusion:** Treatment with imatinib was associated with a reduction in the serum levels of VEGF and IL-17. Increased serum levels of VEGF, IL-17 and MIP-1β in dcSSc patients at baseline were associated with an increased likelihood of clinical improvement in MRSS with imatinib treatment. Investigation of the utility of the baseline levels of IL-17, VEGF and MIP-1β for patient stratification in the context of future randomized controlled trials of TKIs in SSC is warranted.

**Disclosure:** D. J. Haddon, None; H. Wand, None; P. J. Utz, None; R. F. Spiera, Novartis Pharmaceutical Corporation; 2. J. K. Gordon, None; L. Chung, None.

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**Efficacy of Autologous Hematopoietic Stem Cell Transplantation in Rapidly Progressive Systemic Sclerosis: Prolonged Remission of Disease Activity in a Long-Term Follow up.** Eleonora Zacara1, Domenico Sambataro2, Wanda Maglione3, Gianluca Sambataro4, Francesco Onida4, Claudio Annaloro5, Giorgia Saporiti2, Elena Tagliabue2, Agostino Cortelazzi2, Rosaria Giordano3, Claudia Vitali4 and Nicoletta Del Papa5, 1Osp. G. Pini, Milano, Italy; 2Istituto G.Pini, Milan, Italy; 3Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico-University of Milan, Milano, Italy; 4Istituto San Giuseppe, Lecco, Italy.

**Background/Purpose:** In the recent years, autologous hematopoietic stem cell transplantation (AH SCT) has been shown to represent an effective therapeutic option for patients (pts) suffering from rapidly progressive SSc, although the number of available clinical trials at present is relatively scant. Aim of the study was to retrospectively evaluate the efficacy of AH SCT in a long term in a number of patients with severe diffuse cutaneous SSc after a long lasting period of observation.

**Methods:** Since 2003, 18 pts affected by diffuse cutaneous SSc (male 5; female 13; median age 40 years, range 20 – 62), underwent AH SCT using positively selected CD34+ cells. Pts were eligible if they had a rapidly progressive disease, a modified Rodnan Skin Score (mRSS) > 14 and a clinical activity score > 3 (evaluated according to the European Scleroderma Study Group – ESSG), in the absence of major organ involvement. Mobilisation was performed with CTX 4000 mg/m2 given over two days and G-CSF 10 μg/m2/day. Conditioning regimen included CTX 50 mg/kg/day on days –5 to –2 and rabbit ATG 2.5 mg/kg/day on days –3 to –1. The major outcome variables were treatment safety and clinical response, in terms of mRSS and ESSG improvements. The long-term follow-up of organ dysfunction was evaluated by echocardiographic LEVF or PAPs, and functional respiratory parameters DLCO and VC.

**Results:** The median follow-up was of 37 months (range 6–138). Ninety-four % (17/18) of the pts demonstrated a beneficial clinical response with significant reduction of mRSS > 30% and ESSG at Month 6, and a further reduction of mRSS at year 1 of the most part of them was observed. The mean mRSS was 19.8 (SD + 5.3) at baseline, 9.3 + 4.6 at Month 6, 6.21 + 7.4 at year 1 and 3.0 + 2.2 at year 5; all the reductions were statistically significant (p < 0.001). The mean ESSG was 5.3 ± 0.85 at baseline, 2.1 ± 0.8 at Month 6, 2.0 ± 1.6 at year 1 and 1.5 ± 0.96 at Year 5; all the reductions were statistically significant (p < 0.0001). Organ involvement was rarely unchanged during follow-up: mean value of DLCO at baseline 65.0% + 19%, at Year 1 67.2% + 17.8% and at Year 2 58.0% + 14.7% (p=n.s); mean value of VC at baseline 81% + 23.6%, 82% + 15.7%, 89.2% + 26% (p=n.s). No echocardiographic changes were identified during follow-up. Two patients died during follow-up of SSc from pulmonary and cardiac complications due to the disease. One patient died from interstitial pneumonia at day + 65, leading to a TRM of 5.6% (1/18).

**Conclusion:** This study confirms that AH SCT in selected patients with rapidly progressive SSc results in sustained improvement of skin thickening and stabilisation of organ function up to 10 years after transplantation, so leading to a global clinical improvement, as showed by the persistent reduction in the ESSG clinical activity score. According to other experiences, TRM resulted reasonable, as a possible result of patients selection. These finding are in keeping with the view that AH SCT is effective in improving the active phase of SSc, while letting unchanged and stable the fibrosclerotic one. Further studies are needed to evaluate the importance of CD34 selection, the need of immunosuppressive therapy post-AH SCT and the best timing of HSCT in the treatment of SSc patients.

**Disclosure:** E. Zacara, None; D. Sambataro, None; W. Maglione, None; G. Sambataro, None; F. Onida, None; C. Annaloro, None; F. Saporiti, None; E. Tagliabue, None; A. Cortelazzi, None; R. Giordano, None; C. Vitali, None; N. Del Papa, None.

ACR Concurrent Abstract Session

Vasculitis I

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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**An Immunochip Study Confirms a Strong Contribution of HLA Class I and II Genes in the Susceptibility to Giant Cell Arteritis.** Francisco David Camarón1, Sarah Mackie2, José Ezequiel Martin1, John Taylor1, Augusto Vaglio3, Laura Bossini-Castillo4, Santos Castañeda5, María C. Cid6, José Hernández-Rodríguez2, Roser Solans2, Ricardo Blanco2, Lorenzo Beretta6.
DNA Methylation Analysis of the Temporal Artery Microenvironment Reveals a Robust T Cell Signature and Suggests a Role for TNF-a in Giant Cell Arteritis. Patrick S. Coit, Lindsey B. De Lott, Bin Nan, Victor M. Elnner and Amr H. Sawalha. University of Michigan, Ann Arbor, MI.

Background/Purpose: Giant cell arteritis (GCA) is a systemic large vessel vasculitis of unknown etiology. A hallmark of GCA is the presence of granulomatous inflammation of the arterial wall. The DNA methylation status of the arterial environment in GCA patients has not been previously elucidated. Here, we performed DNA methyl-ation profile of formalin-fixed, paraffin-embedded (FFPE) temporal artery tissue biopsies taken from GCA patients and age, sex, and ethnicity matched controls that presented with similar symptoms, but had normal temporal artery biopsies.

Methods: Temporal artery biopsies performed at the University of Michigan from 1988–2012 were reviewed. Twelve patients with non-equivocal histological evidence for GCA and twelve age, sex, and ethnicity matched controls that presented with similar symptoms, but had normal temporal artery biopsies were included in this study. All patients fulfilled the ACR classification criteria for GCA and were not taking steroids for more than 48 hours prior to biopsy. DNA was extracted from the affected portions of FFPE temporal artery tissue in GCA patients and from histologically-confirmed normal arteries in controls. Genome-wide DNA methylation status was evaluated using the Illumina HumanMethylation450 BeadChip Array, which covers 99% of RefSeq genes and over 485,000 methylation sites across the genome. Differentially methylated loci between affected and unaffected arterial tissues were identified, and subsequent bioinformatic analysis performed.

Results: We identified 156 unique hypomethylated CpG sites (853 genes) and 2754 hypermethylated CpG sites (1471 genes) in GCA patients compared to controls. Gene ontology enrichment analysis of hypomethylated genes revealed significant representation in T cell activation and differentiation pathways, including both Th1 and Th17 related cytokine gene signatures (Table 1). Other proinflammatory genes such as TNF, LTA, and LTB were significantly hypomethylated in the cellular milieu of GCA arteries. Of the hypomethylated CpG sites in TNF, which is a known genetic susceptibility locus for GCA, two are within 1500bp upstream of the transcription start site, while two CpG sites are in the gene body. In addition, other genetic susceptibility loci for GCA such as IFNG, PTNP22, and NLRP1 were also hypomethylated in this study. CCR7 which is expressed on mature DCs, was amongst the most hypomethylated genes in GCA, consistent with a previously described pathogenic role for mature DCs within GCA affected arteries. Gene ontology analysis of hypermethylated genes displayed enrichment for genes related to actin cytoskeletal arrangement and regulation of GTPase-mediated and Ras protein signal transduction.

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**Table 1. Biological Process Gene Ontology (GO) Terms Most Enriched Among Hypomethylated Genes in GCA Arterial Lesions**

<table>
<thead>
<tr>
<th>GO Term</th>
<th>GO Term ID</th>
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<tr>
<td>P value (Bonferroni)</td>
<td>P value (Bonferroni)</td>
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<td>TNF</td>
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<td>3.79E-12</td>
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<td>DNA methylation</td>
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<td>3.76E-26</td>
<td>2.16E-10</td>
<td>3.79E-12</td>
</tr>
</tbody>
</table>

**Conclusion:** DNA methylation profiling in GCA affected arteries revealed a robust T cell signature and identified key molecules that might help to better understand the pathogenesis of GCA.

**Disclosure:** P. S. Cot, None; L. B. De Lott, None; B. Nan, None; V. M. Elen, None; A. H. Sawalha, None.

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A Signature of microRNAs Overexpressed in Inflamed Temporal Arteries of Patients with Giant Cell Arteritis. Stefania Croci, Alessandro Zerbin, Luigi Boiard, Francesco Muratore, Alessandra Bisagni, Giulia Pazzola, Luca Cimino, Antonio Moramarco, Davide Nicoli, Enrico Farnetti, Bruno Casali, Alberto Cavazzia, Maria Parmegiani and Carlo Salvarani. Arcispedia S Maria Nuova, Reggio Emilia, Italy.

**Background/Purpose:** MicroRNAs (miRNAs) are small, non-coding RNAs that suppress gene expression at post-transcriptional level. miRNAs can regulate innate and adaptive immunity. Moreover, they have been found deregulated in various autoimmune diseases emerging as biomarkers and novel therapeutic targets. Giant cell arteritis (GCA) is an autoimmune inflammatory vasculitis affecting large and medium-sized arteries. Temporal artery biopsy (TAB) showing resident immune cells is the gold standard for the diagnosis of GCA. Nevertheless, a negative TAB does not rule out GCA and some patients receive a diagnosis of TAB-negative GCA, according to clinical and laboratory parameters. The present study aimed to identify novel therapeutic targets. miRNAs deregulated in GCA and to determine if miRNA levels might allow to discriminate between patients with GCA and those without.

**Methods:** 48 patients undergoing TAB for suspected GCA were included in the study and divided into 3 groups: GCA with positive TABs (n=23), GCA with negative TABs (n=7) and non-GCA with negative TABs receiving a different diagnosis (n=18). 1990 ACR classification criteria for GCA were satisfied in all GCA patients with positive TABs, in 6 of the 7 GCA patients with negative TABs and in none of the non-GCA patients. To identify candidate miRNAs deregulated in GCA, expression of 1209 miRNAs was profiled with a miRNA array (Ocean Ridge Biosciences, Palm Beach Gardens, FL) in inflamed TABs from 7 GCA patients versus normal TABs from 8 non-GCA patients. miRNAs showing a >2 fold, statistically significant differential expression with a false discovery rate <10%, were selected for further analysis. Their expression was validated by real-time PCR (QIAGEN, Milan, Italy) in different TAB samples as well as PBMCs and PMN cells isolated from GCA and non-GCA patients. To identify which cell type expressed miR-21 in TABs, in situ hybridization (Exiqon, Vedbaek, Denmark) was performed on FFPE tissue sections.

**Results:** 10 miRNAs emerged deregulated in inflamed TABs from GCA patients by a high throughput miRNA profiling assay. Subsequent real-time PCR confirmed that miR-146b-5p, -146a, -150 and -21 were significantly more expressed in TABs from GCA patients positive for a transmural inflammatory infiltrate. Negative TABs from GCA patients had a miRNA profile similar to negative TABs from non-GCA patients suggesting that miRNAs might be downstream inflammation. Expression of miR-146b-5p was particularly promising in a diagnostic perspective because it was possible to set a threshold level which correctly classified TABs as inflamed or normal. Within inflamed TABs, miRNA expression levels did not positively correlate with the load of infiltrating immune cells suggesting that miRNAs might be expressed by tissue cells. Indeed, in inflamed TABs, miR-21 was mainly expressed by spindle shaped cells of the media layer and stellate fibroblast-like cells of the intima layer. Moreover, miRNAs were expressed at comparable levels by circulating PBMCs and PMN cells from GCA and non-GCA patients.

**Conclusion:** miR-146a, -21, -150 and -155 and above all miR-146b-5p emerged as markers of inflammation in TABs from GCA patients, might be involved in GCA pathogenesis thus further investigated as therapeutics targets.

**Disclosure:** S. Croci, None; A. Zerbin, None; L. Boiard, None; F. Muratore, None; A. Bisagni, None; G. Pazzola, None; L. Cimino, None; A. Moramarco, None; D. Nicoli, None; E. Farnetti, None; B. Casali, None; A. Cavazzia, None; M. Parmegiani, None; C. Salvarani, Novartis Pharma AG, 2.

**883**

Accuracy of High Resolution MRI of Scalp Arteries for the Diagnosis of Giant Cell Arteritis: Results of a Prospective Study. Maxime Rheaume1, Ryan Rebell0, Christian Pognoux2, Simon Carette3, Marie Clements-Baker3, Violette Cohens-Halle1, David Doucette-Previle1, B. Stanley Jackson 5, Sam Salama3, George Ioannidis5 and Nader A. Khali1. Division of Rheumatology, St. Joseph’s Hospital, McMaster University, Hamilton, ON, 5Department of Radiology, St. Joseph’s Hospital, McMaster University, Hamilton, ON, 7University of Toronto, Toronto, ON, 7Queens University, Kingston, ON, 7Department of Surgery, St. Joseph’s Hospital, McMaster University, Hamilton, ON, 7University of Toronto, Toronto, ON, 7University of Toronto, Toronto, ON, 7Department of Pathology, St. Joseph’s Hospital, McMaster University, Hamilton, ON, 7St Joseph’s Healthcare Hamilton, Hamilton, ON, 7St Joseph’s Hospital, McMaster University, Hamilton, ON.

**Background/Purpose:** Temporal artery biopsy (TAB) remains the gold standard for the diagnosis of giant cell arteritis (GCA). It is invasive and its sensitivity is limited by segmental arterial involvement. We sought to determine the diagnostic accuracy of high-field MRI compared to TAB in patients with suspected GCA.

**Methods:** All patients referred for TAB at our center were approached for this study. A high-resolution 3T MRI of the scalp arteries was obtained before the TAB was performed. Arterial abnormalities on MRI were assessed according to a previously published grading scheme, evaluating mural thickness and enhancement based on multiplanar postcontrast T1-weighted spin-echo images. Diagnostic accuracy of MRI was evaluated by comparison with TAB results as a primary analysis. Secondary analyses included comparison to clinician diagnosis and ACR criteria.

**Results:** 191 patients were screened and 171 were included in the study. Exclusions were based on withdrawal of consent (n=11), contra-indication to MRI (n=2), non-diagnostic test (n=3, MRI, 2 TAB) or failure to obtain MRI (n=1). ACR criteria were met in 137 patients (80.1%). Physician diagnosis was available for 162 subjects, with 78 (48.2%) considered as GCA. The MRI showed abnormal scalp arteries in 60 patients (35.1%) while biopsy was positive in 31 (18.1%). MRI was positive in 29 of those 31 patients with positive TAB (Sensitivity 93.6%). MRI was normal in 109 of those 140 with negative TAB (Specificity 77.9%). Relative to TAB, the negative predictive value of MRI was 98.2%.

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Conclusion: High-resolution MRI detects biopsy-positive GCA with high sensitivity. A negative MRI is highly predictive of a negative TAB, such that patients with a negative MRI could safely be spared TAB. The significance of a positive MRI is not as well defined, and this should be the focus of future research.

MII: Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV)

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Biopsy</td>
<td>0.936 (0.780, 0.992)</td>
<td>0.779 (0.701, 0.844)</td>
<td>0.483 (0.332, 0.616)</td>
<td>0.982 (0.936, 0.998)</td>
</tr>
<tr>
<td>MRI</td>
<td>ACR (fulfilment of ≥3/5 ACR criteria)</td>
<td>0.394 (0.311, 0.484)</td>
<td>0.824 (0.701, 0.932)</td>
<td>0.900 (0.795, 0.962)</td>
<td>0.252 (0.175, 0.344)</td>
</tr>
</tbody>
</table>

Disclosure: M. Rheuma; None: R. Reblo; None: C. Pagnoux; None: S. Caturee; None: M. Clements-Baker; None: V. Cohen-Hallaleh; None: D. Doucette-Previle; None: B. S. Jackson; None: S. Salama; None: G. Ioannidis; None: N. A. Khalidi; None.

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Interleukin 6 Does Not Upregulate Pro-Inflammatory Cytokine Expression in an Ex-Vivo Model of Giant Cell Arteritis. Lorraine O’Neill1, Jennifer McCormick2, Wei Gao3, Conor Murphy4, Geraldine M. McCarthy5, Douglas J. Veale1, Ursula Fearon2 and Eamonn S. Molloy1. 1St. Vincent’s University Hospital, Dublin 4, Ireland, 2Translational Rheumatology Research Group, Dublin, Ireland, 3Royal Victoria Eye and Ear Hospital, Dublin, Ireland, 4Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Interleukin 6 (IL-6) is postulated to play a role in the pathogenesis of Giant Cell Arteritis. Several studies have demonstrated increased circulating IL-6 levels and upregulation of IL-6 in the temporal arteries of patients with GCA.

Multiple recent uncontrolled reports have noted improvements in clinical and laboratory parameters in patients with GCA treated with tocilizumab, an IL-6 receptor antagonist. However, persistent vascular inflammation has been reported in some cases.

The aim of this study was to examine the ability of IL-6 to induce pro-inflammatory mediators in ex-vivo temporal artery explant cultures.

Methods: 28 patients meeting 1990 ACR classification criteria for GCA were prospectively recruited. To directly examine the effects of IL-6 on pro-inflammatory mediators in GCA, ex-vivo temporal artery explant models were established.

Temporal artery explants were cultured in the presence or absence of recombinant human IL-6 (20 or 40 ng/ml) for 24 hours.

IL-6 mediates its effects through gp130 and the IL6 receptor. While gp130 is ubiquitous, the IL-6 receptor is limited to certain cells and therefore cells lacking the IL-6 receptor are unresponsive to the direct effects of IL-6. To overcome this, explants were co-cultured with IL-6 and its soluble receptor (sIL-6R).

Explant supernatants were harvested after 24 hours and assayed for INF-g, TNF, SAA, IL1b, IL 17, IL 8 and VEGF by ELISA. Of the cultured biopsies, 4 were snap frozen, protein was extracted and pSTAT3 expression assessed by Western Blot.

GraphPad Prism Ver 6.04 was used for statistical analysis. Results are presented as mean +/- SEM in pg/ml/mg of biopsy weight.

Results: Stimulation with IL-6 did not induce any of the pro-inflammatory mediators assayed. No differences were observed in the explants cultured in the presence or absence of the sIL6R or between those with a positive (n = 11) or negative (n = 17) temporal artery biopsy. Increasing the concentration of IL-6 to 40 ng/ml did not alter our findings.

Mean values of VEGF did increase following treatment with IL-6, even in the absence of sIL6R in keeping with the known ability of IL-6 to promote angiogenesis.

Western Blot analysis revealed increased expression of pSTAT3 in response to the combination of IL-6+sIL6R, but not IL-6 alone, suggesting that the addition of the sIL6R is necessary to induce signal transduction.

SAA * ng/ml/mg | 10.42 ± 4.31 | 7.45 ± 2.54 | 0.625
VEGF | 7.74 ± 3.45 | 107.3 ± 78.44 | 0.062

Conclusion: IL-6 stimulation of terminal artery explants from patients with GCA, at concentrations sufficient to activate STAT3 and up regulate VEGF, did not result in increased expression of key pro-inflammatory mediators. This data argues against a central role for IL-6 in driving vascular inflammation in GCA and raises the hypothesis that anti-IL6 based therapeutic interventions may have a lesser impact on vascular inflammation than on the systemic inflammatory syndrome in patients with GCA.

Disclosure: L. O’Neill; None: J. McCormick; None: W. Gao; None; C. Murphy; None; G. M. McCarthy; None: B. J. Veale; None: U. Fearon; None: E. S. Molloy; None.

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A 2-Week Single-Blind, Randomized, 3-Arm Proof of Concept Study of the Effects of Secukinumab (anti-IL-17 mAb), Canakinumab (anti-IL-1 b mAb), or Corticosteroids on Initial Disease Activity Scores in Patients with PMR, Followed By an Open-Label Extension to Assess Safety and Effect Duration. Eric L. Matteson1, Bhaskar Dasgupta2, Wolfgang A. Schmidt3, Carlo Salvarani4, Nagui Gendi5, Maury Galeazzi6, Sylvie Stitah7, Yue Li1, Marie-Anne Valentin5, Bolan Linghu5 and Stephen J. Oliver7.

Mayo Clinic, Rochester, MN, 2Southend University Hospital, Essex, United Kingdom, 3Immanuel Krankenhaus, Berlin, Germany, 4Arcispedale-Santa Maria della Misericordia, Reggio Emilia, Italy, 5Basildon & Thurrock University Hospital NHS Trust, Basildon, Essex, United Kingdom, 6Università di Siena, Siena, Italy, 7Novartis Pharma AG, Basel, Switzerland, 8Novartis Pharma AG, Cambridge, MA.

Background/Purpose: To assess the effects of a single dose of secukinumab or canakinumab in patients with new onset, untreated polymyalgia rheumatica (PMR).

Methods: In this single-blinded, double-dummy, randomized, active-controlled, parallel-group study, patients with PMR of >1 week duration were randomized 1:1:1 to receive single dose (3 mg/kg/body weight) of either secukinumab or canakinumab, or daily oral prednisone (PRED) at 20 mg a day. The primary endpoint was efficacy after 2 weeks, assessed by the PMR activity score (PMR-AS components: CRP, morning stiffness, ability to elevate arms; 100 mm VAS assessments for patient pain and physician global). Complete response was defined as >70% reduction in patient global assessment VAS compared with baseline, morning stiffness <30 min, and CRP <1.0 mg/dl. Partial response was defined as >50% reduction in patient global assessment VAS compared with baseline and morning stiffness <60 min. Patients treated with biologics failing to achieve criteria for either complete or partial response by Day 15 initiated treatment with PRED 20 mg/day. All patients receiving PRED underwent a scheduled taper after 2 weeks treatment. Patients were followed up to 154 days for safety and duration of treatment effects. Serum levels of IL-6 and VEGF were measured by ELISA.

Results: 16 patients (11 females) were randomized (secukinumab, n = 6, mean baseline PMR-AS 46.6; canakinumab, n = 5, mean PMR-AS 54.3; PRED n = 5, mean baseline PMR-AS 37.5). The primary endpoint was assessed in 13 patients (secukinumab, 6; canakinumab, 3; PRED, 4). PMR-AS reductions from baseline were seen in all patients at day 15: secukinumab = 52%; canakinumab = 65%; PRED 92%. By Day 15 no biologic-treated patients achieved complete response and only 1 patient in each biologic group achieved a partial response, whereas 1 patient in the PRED arm had complete response and 3 patients had partial responses. CRP reductions were most rapid in the PRED group and more consistent in patients treated with either PRED or secukinumab. In patients treated with PRED, rapid reductions were observed in mean VAS for physician global assessment and patients’ assessment of pain compared to only moderate or minimal effects in the secukinumab and canakinumab groups, respectively. PRED induced a rapid and consistent decrease in IL-6 while no consistent effects were noted in patients treated with biologics. Secukinumab induced rapid and consistent decreases in VEGF levels that were not observed in the other two groups. Patients in secukinumab (n = 4) and canakinumab (n = 3) groups who required switch to PRED with subsequent taper had a 40% and 35% lower monthly average steroid use, respectively, compared to the PRED group (n = 4) that had not been exposed to a biologic. All three study treatments were well-tolerated without SAEs or increased infections noted.
Conclusion: In this study PMR-AS reduced more rapidly by Day 15 in prednisone-treated patients than in patients receiving secukinumab or canakinumab. Patients receiving biologics followed by prednisone had overall lower cumulative steroid doses. The therapeutic effects of secukinumab and canakinumab in PMR remains uncertain and deserves further study.

Disclosure: E. L. Matteo, Novartis Pharma AG, 2; B. Dasgupta, Novartis Pharma AG, 2; W. A. Schmidt, Novartis Pharma AG, 2; Mundipharma, 2; C. Salvanes, Novartis Pharma AG, 2; N. Guidi, Novartis Pharma AG, 2; Roche Pharma AG, 2; UCB Pharma, 2; M. Galeazzi, None; S. Sittah, Novartis Pharma AG, 3; Y. Li, Novartis Pharma AG, 3; M. A. Valentini, Novartis Pharma AG, 3; B. Linghi, Novartis Pharma AG, 3; S. J. Oliver, Novartis Pharma AG, 1, Novartis Pharma AG, 3.

ARHP Concurrent Abstract Session
Exemplary Abstracts
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Measuring Rheumatoid Arthritis Remission: Which Index of Disease Activity Best Predicts Work Status? Nancy A. Baker1, Heather Eng2, Juan (June) Feng2, Jason Lyons2, Young Gil Hwang1, Kimberly P. Liang1 and Larry W. Moreland1. 1University of Pittsburgh, Public Health, Pittsburgh, PA, 2University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA.

Background/Purpose: Disease remission is the goal of treat-to-target initiatives in rheumatoid arthritis (RA). There are multiple indices to measure disease activity and remission status including those recommended by ACR and EULAR in 2011: the Simplified Disease Activity Index (SDAI) and a Boolean based definition (tender joint count, swollen joint count, C-reactive protein, patient global assessment ≤ 1). The choice of these measures was based on their predictive validity for radiographic damage and the Health Assessment Questionnaire (HAQ), outcomes which are focused on impairment and activity levels. Remission scores should be predictive of community participation, such as employment. As work disability is common for people with RA, it is particularly important that indices can accurately predict work status. This study evaluated each of five common indices of disease activity (Boolean, SDAI, Clinical Disease Activity Index [CDAI], Disease Active Score-28 joint count [DAS28], Routine Assessment of Patient Index 3 [RAPID3]) to identify the best predictor of work status.

Methods: In this cross-sectional study we extracted data on 511 working aged (≥65 year old) RA patients from the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) longitudinal registry based at the University of Pittsburgh. This registry, started in 2010 has enrolled 1,045 RA patients with over 7000 usual care clinic visits. Work status and index data are collected at most visits and we selected the most recent visit that contained information on both. Patients self-identified as “employed” were coded as such; all other categories were coded as not employed. We calculated the Boolean, SDAI, CDAI, DAS28, and RAPID3 scores and coded each patient as in remission/not in remission based on published cut-off scores (Figure 1). We completed 5 separate logistic regressions with work status as the outcome and each index as the predictor variable. Covariates were age, gender, remission duration, disease duration and the presence of any comorbidities (yes/no) measured through the Charlson score, which we dichotomized. We report the C-statistic, which is equivalent to the area under a ROC curve and allows us to judge how well each model discriminated between employed and not employed.

Results and Conclusion: In all models except CDAI, remission status was significantly associated with work status. While all models were moderately good at predicting work status (C-statistic range 0.66 to 0.77), the RAPID3 was the most accurate and the DAS28 and CDAI were the least. A score indicating remission on the RAPID3 would correctly identify that someone would or would not be employed 77% of the time. This superior accuracy may be related to the functional questions included in this index, whereas all other indices rely on symptoms and patient assessment of health without a functional component.

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The Impact of Inadequate Health Literacy on Disease Activity in Patients with Rheumatoid Arthritis. Maria Celeste Orozco1, Maria Florencio Marengo2, Christian A. Waimann1, Ana Inés Marcos3, Amelia Granel3, Sofía Veles2, Federico Zazzetti3, Juan C. Barreir3, Paula Kohan5, Oscar L. Rillo6, María Victoria Collado7, Graziela Gómez8, Ricardo V. Juárez9, Veronica Lencina7, Andrea D’Orazio7, Gustavo Rodriguez Gil9, Mariana Salcedo11 and Gustavo Citera1. 1Instituto de Rehabilitación Psicosfíca, Buenos Aires, Argentina, 2Hospital San Roque de Gonet, La Plata, La Plata, Argentina, 3Hospital Británico, Buenos Aires, Argentina, 4Hospital San Justo, Buenos Aires, Argentina, 5Hospital De Agudos Dr. E. Torn, Buenos Aires, Argentina, 6Hospital General de Agudos Dr. E. Torn, Buenos Aires, Argentina, 7Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, 8Instituto de Investigaciones Medicas de la UBA, Capital Federal, Argentina, 9Hospital Severo del Milagro, Salta, Argentina, 10Hospital Municipal de agudos Dr. Leonidas Lucero, Bahía Blanca, Argentina, 11Con-sulltorio Privado, San Nicolás, Argentina.

Background/Purpose: Health literacy is the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. It is being increasingly recognized as important determinant to health outcomes. Patients with low health literacy are less able to manage chronic conditions effectively. The aim of our study was to measure the level of health literacy in patients with Rheumatoid Arthritis (RA) and assess its association with clinical outcomes.

Methods: A multicenter cross-sectional study was conducted. Patient were recruited from 7 outpatient clinics including consecutive patients with diagnosis of RA according to American College of Rheumatology (ACR) 1987 criteria and/or ACR/European League Against Rheumatism (EULAR) 2010 criteria. Health literacy was assessed using the Test of Functional Health Literacy in Adults (S-TOFHLA) (0–36, 0 worst health literacy). Patients were categorized as having low or adequate health literacy using the standard cutoff (<23). Patient reported clinical outcomes included the Clinical Disease Activity Index (CDAI) and the Health Assessment Questionnaire (HAQ). We also collected data regarding patient demographics, comorbidities and treatment adherence - Adherence to treatment was assessed using the Compliance Questionnaire Rheumatology (CQR; 0 – 100, 0 low adherence). The association between health literacy and clinical/functional outcomes were evaluated using univariate and multivariate models adjusting by age, gender, educational level, disease duration and treatment adherence.

Results: Three hundred and thirty-eight patients were included, 84 % were female, mean age was 53 ± 12 years, disease duration 13 ± 10 years, CDAI 13 ± 11 and HAQ 1.00 ± 0.75. Mean S-TOFHLA score was 26 ± 12. Three hundred and two patients (76%) had adequate health literacy. These patients had significantly lower age (r = -0.22, p < 0.01), higher level of education(r = 0.40, p < 0.01), less number of comorbidities(r = -0.13, p < 0.01) and shorter disease duration(r = -0.14, p < 0.01). After adjusting for multiple confounders, patients with low level of health literacy showed significantly higher disease activity (b = 3.7, p < 0.01). Health literacy was not associated with HAQ (b = 0.14, p = 0.14). Using S-TOFHLA as continuous variables did not affect the results.

Conclusion: A quarter of patients with rheumatoid arthritis had inadequate health literacy, showing higher level of disease activity. Physicians
should recognize that literacy levels of their patients could affect clinical outcomes, and provide appropriate interventions to ease this burden.

Disclosure: M. C. Orozco, None; M. F. Marengo, None; C. A. Waizmann, None; A. L. Marcos, None; A. Grand, None; S. Velez, None; F. Zazzetti, None; J. C. Barreira, None; T. Uribe, None; M. Billo, None; M. D. R. Franco, None; G. Gómez, None; R. V. Jáurez, None; V. Lencina, None; A. D’Orazio, None; G. Rodriguez Gil, None; M. Salcedo, None; G. Citera, None.

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Background/Purpose: Costs associated with gout arc of growing interest due to its increasing prevalence, but quantifying those costs has been hampered by its co-occurrence with other highly prevalent, high-cost conditions. We estimated all-cause medical care expenditures and gout-attributable expenditures among US adults with gout age ≥18 years.

Methods: Using the 2005–2011 Medical Expenditure Panel Survey (MEPS), we identified adults with gout by the presence of ICD-9-CM 274. We estimated annual national total (aggregate) and mean per-person all-cause and gout-attributable expenditures overall and for four expenditure categories: ambulatory care (office-based and hospital outpatient); inpatient care; prescriptions; and other (emergency room visits, home health care, vision aids, dental visits, and medical devices). Gout-attributable expenditures were calculated using mults age regression models that adjusted for demographics (age, sex, race, Hispanic ethnicity, and education), health insurance coverage (any private, public only, or none), and a count of nine costly comorbidity conditions. All estimates are in 2011 US dollars.

Results: National total all-cause medical care expenditures among the 2.7 million adults reporting gout were $31.8 billion; mean per-person expenditures among US adults with gout were $11,663, compared to $4,643 for all adults. Across expenditure categories, all-cause mean per-person expenditures were: inpatient ($4,329), ambulatory care ($3,704), prescriptions ($2,497), and other ($1,133). National gout-attributable expenditures totaled $7.7 billion (mean per person = $2,805) and accounted for 24% ($7.7 billion/$31.8 billion) of all medical expenditures among US adults with gout. Mean per-person gout-attributable expenditures for inpatient ($1,488) and ambulatory care ($1,349) accounted for essentially all of the attributable expenditures. Attributable expenditures for prescription and other were less than $100 in magnitude and much less than the estimated error.

Conclusion: Mean per-person all-cause medical expenditures were more than 2.5 times higher among adults with gout compared to the entire adult population. Total annual national medical expenditures attributable to gout were $7.7 billion, accounting for almost one of four dollars spent for medical care of US adults with gout. The increasing prevalence of gout suggests increasing costs in the future. Raising awareness about recent therapies and guidelines to identify and treat gout at earlier stages and increase compliance may help moderate those costs.

Disclosure: M. G. Cisternas, None; L. Murphy, None; D. J. Pasta, None; E. H. Yelin, None; C. Helmick, None.

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Exercise, Manual Therapy, and Use of Booster Sessions in Physical Therapy for Knee OA: A Multi-Center Randomized Clinical Trial. G Kelley Fitzgerald1, Julie Fritz2, John Childs3, Gerard P. Brennan4, Douglas P. Landsittel5, Brett Neilson6, Alexandra Gil7 and J. Haxby Abbott8.1University of Pittsburgh, Pittsburgh, PA, 2University of Utah, Salt Lake City, UT, 3US Army-Baylor University, Schertz, TX, 4Intermountain Healthcare, Murray, UT, 5University of Pittsburgh, Center for Health Care Research Data Center, Pittsburgh, PA, 6Henry M. Jackson Foundation, Bethesda, MD, 7University of Otago, Dunedin, New Zealand.

Background/Purpose: There is need to improve the magnitude and duration of treatment effects of exercise therapy (ET) for patients with knee osteoarthritis (KOA). There is conflicting evidence that manual therapy (MT) can enhance the treatment effect magnitude of ET for pain and function. The use of booster treatment sessions have also been suggested to improve sustainability of these treatment effects, but evidence is lacking. The aims of the study were to: 1) determine if adding MT to ET programs would result in an additive treatment effect on pain and function, and 2) determine if use of booster treatment sessions would result in greater sustainability of these effects in patients with KOA.

Methods: Multi-center randomized clinical trial, including three clinical sites from different regions of the United States. 300 subjects (mean age = 58 ± 9 years; 199 female) meeting the ACR clinical criteria for KOA were randomly allocated to 1 of 4 groups; 1) ET- no booster, 2) ET + booster, 3) MT+EX-no booster, and 4) MT+EX + booster. Subjects not receiving booster sessions received 12 treatment sessions in 9 weeks. Subjects receiving booster sessions received 3 treatment sessions in 2 weeks then received 4 additional booster treatment sessions distributed over the remaining year. Primary outcome measure was the WOMAC total score. Secondary outcome measures included the numeric knee pain rating, the Timed Up and Go (TUG) test, the 30 sec. chair rising test, and the 40m walk test. Outcome measures were obtained at baseline, 9 weeks, and 1 year. Data was analyzed using a repeated measures linear mixed model of treatment effect and the treatment group by time interaction was performed, adjusting for treatment site location and bilateral knee involvement. Statistical significance was α = .05.

Results: The figure summarizes the WOMAC total scores at each time point. There were no statistical or clinically meaningful differences between treatment groups at either follow-up time point. There was no significant treatment group by time interaction. All treatment groups demonstrated meaningful changes in clinical outcome from baseline to the 9 week follow-up (within group effect sizes range = .69 to 1.2; percent change from baseline range = 37%–54%) which was also maintained over the 1 year follow-up period (within group effect sizes range = .70 to .85; percent change from baseline range = 37%–40%). Similar results were observed for all other outcome measures.

Conclusion: Adding MT to ET did not increase the magnitude of treatment effect and use of booster sessions did not exhibit superior sustainability of treatment effects over time. All four treatment approaches tested in this study yield moderate to large improvements in pain and function that were sustained over a one year period.

Disclosure: G. K. Fitzgerald, None; J. Fritz, None; J. Childs, None; G. P. Brennan, None; D. P. Landsittel, None; B. Neilson, None; A. Gil, None; J. H. Abbott, None.

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Test of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) 29-Item Profile in a Large Cohort of Rheumatic Disease Patients. Patricia P. Katz1, Sofia Pedro2 and Kaleb Michaud3.1University of California, San Francisco, San Francisco, CA, 2National Data Bank, Wichita, KS, 3University of Nebraska Medical Center and National Data Bank, Omaha, NE.

Background/Purpose: Patient-reported outcomes are routinely used in rheumatology research and clinical care. Yet, often outcomes cannot be compared across studies or diseases because a variety of measures are used in these assessments, and many important health domains are not assessed because of lack of measures or concerns about questionnaire burden. Further, many “traditional” patient-reported outcomes measures are available only in English, which is an increasingly limiting factor. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) consists of a group of patient-reported outcome measures that span a wide array of physical, social, and emotional health outcomes; are applicable across health conditions; and are available free of charge and in multiple languages. A test of the PROMIS measures has not been undertaken in patients with RA, OA, or...
fibromyalgia. This analysis presents an initial psychometric evaluation of PROMIS measures in a large cohort of these patients.

**Methods:** Data were from a subset of respondents to a single administration of a questionnaire that included the PROMIS 29-item profile. The sample included 528 individuals (RA: 323; OA: 109; fibromyalgia: 96). Using short questionnaires, the PROMIS-29 assesses 7 of the PROMIS health domains: Physical Function, Pain Intereference, Fatigue, Depression, Anxiety, Sleep Disturbance, and Ability to Participate in Social Roles. Each section was scored and converted to t-scores, with mean = 50 and SD = 10. Analyses examined correlations of PROMIS measures with scales measuring related constructs (SF-36 subscales, Health Assessment Questionnaire [HAQ]), and numeric rating scales for pain, fatigue, and sleep problems, for the total sample and within disease groups. Analyses also examined ability of PROMIS measures to discriminate among levels of satisfaction with health.

**Results:** PROMIS scales exhibited moderate (r = 0.7) correlations with most of the comparison measures, with some correlations slightly higher, indicating that similar constructs were being measured (Table 1). Results were similar for each disease group. All PROMIS scales discriminated among levels of satisfaction with health, yielding significant overall ANOVA results and significant non-parametric tests of trend (Table 2).

**Conclusion:** These PROMIS short forms exhibited strong psychometric properties. Use of PROMIS offers important expansions of current measures so that aspects of health, functioning, and quality of life that are important to patients can be included without increasing questionnaire burden.

### Table 1 Correlation of PROMIS Scales with Related Measures

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>PF</strong></td>
<td><strong>PI</strong></td>
<td><strong>PROMIS 29-Item Profile scales</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>SF-36 Physical Function</strong></td>
<td>0.83</td>
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<td><strong>SF-36 Role Physical</strong></td>
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<td><strong>SF-36 Role Emotional</strong></td>
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<td><strong>SF-36 Vitality</strong></td>
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<tr>
<td><strong>SF-36 Mental Health</strong></td>
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<td>0.67</td>
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<tr>
<td><strong>HAQ</strong></td>
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<tr>
<td><strong>NRS-pain</strong></td>
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<td></td>
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<tr>
<td><strong>NRS-fatigue</strong></td>
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<td></td>
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<tr>
<td><strong>NRS-clumsiness</strong></td>
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</table>

<sup>a</sup> For all PROMIS scales, higher scores reflect “more” of the construct being measured. E.g., Higher Physical Function scores reflect better functioning; higher Pain Interference scores reflect greater pain interference.

**Disclosure:** P. P. Katz, None; S. Pedro, None; K. Michaud, None.

### Table 2 PROMIS 29-Profile Scores<sup>a</sup> by Levels of Satisfaction with Health

<table>
<thead>
<tr>
<th>Satisfaction with health:</th>
<th><strong>PF</strong></th>
<th><strong>PI</strong></th>
<th><strong>PROMIS 29-Item Profile scales</strong>&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very satisfied (n=61)</td>
<td>48.0</td>
<td>52.7</td>
<td>48.0</td>
</tr>
<tr>
<td>Somewhat satisfied (n=173)</td>
<td>41.1</td>
<td>56.1</td>
<td>53.8</td>
</tr>
<tr>
<td>Neither satisfied nor dissatisfied (n=483)</td>
<td>37.9</td>
<td>61.4</td>
<td>57.9</td>
</tr>
<tr>
<td>Somewhat dissatisfied (n=139)</td>
<td>35.8</td>
<td>63.6</td>
<td>60.0</td>
</tr>
<tr>
<td>Very dissatisfied (n=89)</td>
<td>31.0</td>
<td>66.7</td>
<td>67.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Table presents mean scores for individuals in each satisfaction with health rating group. Differences were tested with ANOVA and non-parametric test for trend. All were significant p < 0.001.

**Disclosure:** K. D. Allen, None; D. Bongiorni, None; H. B. Bosworth, None; C. Coffman, None; S. Datta, None; D. Edelman, None; J. H. Lindquist, None; E. Oddone, None; H. Hoenig, None.

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Randomized Clinical Trial of Group Vs. Individual Physical Therapy for Knee Osteoarthritis. Kelli D. Allen<sup>1</sup>, Dennis Bongiorni<sup>1</sup>, Hayden B. Bosworth<sup>2</sup>, Cynthia Coffman<sup>3</sup>, Santanu Datta<sup>4</sup>, David Edelman<sup>5</sup>, Jennifer H. Lindquist<sup>6</sup>, Eugene Oddone<sup>7</sup> and Helen Hoenig<sup>8</sup>, <sup>1</sup>Durham VA Medical Center and University of North Carolina at Chapel Hill, Durham, NC, <sup>2</sup>Durham VA Medical Center, Durham, NC, <sup>3</sup>Durham VA Medical Center and Duke University Medical Center, Durham, NC.

**Background/Purpose:** Physical therapy (PT) is a key component of treatment for knee osteoarthritis (OA). There is a high demand for PT services in many healthcare systems, resulting in a need for evidence-based models for delivering PT in an efficient manner. A group-based approach to PT can extend services to more patients with lower staffing requirements than typical individual PT. The objective of this trial was to compare the effectiveness of a group-based patient program (GPT) with usual individual PT (IPT) for knee OA.

**Methods:** 320 patients with knee OA at the VA Medical Center in Durham, NC (mean age = 60, SD = 10; 88% male; 58% non-white) were randomized to either GPT or IPT. GPT included six 1-hour sessions, every other week, co-led by a physical therapist and PT assistant, with 8 participants per group. IPT, modeled after typical outpatient PT care for knee OA at the Durham VAMC, included two 1-hour visits with a physical therapist, 2-3 weeks apart. Both PT interventions included a home exercise program, as well as individual evaluations of functional limitations and needs for braces or assistive devices. GPT sessions also included exercise sessions supervised by the PT assistant. The primary outcome was the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC; range 0–96, higher scores indicate worse symptoms), and the secondary outcome was objective physical function (Short Physical Performance Battery; SPPB, range 0–20, higher scores indicate better function); both were assessed at baseline and 12-weeks, and WOMAC was also assessed at 24-weeks. Linear mixed models were used to assess the difference in improvement in outcomes between arms, adjusting for clustering of group sessions within the GPT arm.

**Results:** The median numbers of sessions attended for GPT and IPT were 5 (out of 6 possible) and 2 (out of 2 possible), respectively. At 12-week follow-up, WOMAC scores were 2.7 points lower in the GPT group vs. IPT [95% confidence interval (CI) = −5.9, 0.5; p = 0.10], indicating no meaningful difference in improvement between arms. However, mean total WOMAC scores declined −4.5 points from baseline across both arms combined [95% CI = −6.8, 2.2; p = 0.0001], indicating meaningful improvement. Similarly, for the WOMAC pain and function subscales and SPPB scores there was improvement across both arms at 12-weeks (p < 0.0001, p = 0.002, p = 0.02) but no difference in improvement between arms (p = 0.19, p = 0.12, and p = 0.37). At 24-week follow-up, WOMAC scores across both arms were 3.1 points lower compared to baseline [95% CI = −5.4, −0.7; p = 0.01], indicating some sustained improvement in both groups, with no difference between groups (p = 0.45).

**Conclusion:** Results of this study confirm that PT improves pain and functional outcomes in patients with knee OA. Outcomes did not differ substantially between GPT and IPT arms, suggesting that either is an effective means of delivering PT services for knee OA. The GPT approach in this study required less overall staff time per patient to deliver, and it could provide services efficiently to larger numbers of patients. Therefore it should be considered as a viable model for health systems to provide this service to patients with knee OA.

**Disclosure:** K. D. Allen, None; D. Bongiorni, None; H. B. Bosworth, None; C. Coffman, None; S. Datta, None; D. Edelman, None; J. H. Lindquist, None; E. Oddone, None; H. Hoenig, None.

**ACR Concurrent Abstract Session**

**Symptom Increase in Fibromyalgia Is Not Consistent with the Central Sensitization or Central Hyperresponsiveness Hypothesis.** Frederick Wolfe<sup>1</sup>, Brian T. Wallitt<sup>2</sup>, Johannes Rasker<sup>3</sup>, Robert S. Katz<sup>4</sup> and Winfried Häuser<sup>5</sup>, <sup>1</sup>National Data Bank for Rheumatic Diseases, Wichita, KS, <sup>2</sup>Washington Hospital Center, Washington, DC, <sup>3</sup>University Twente, Enschede, Netherlands, <sup>4</sup>Rush Medical College, Chicago, IL, <sup>5</sup>Klinikum Saarbrücken, Saarbrücken, Germany.

**Background/Purpose:** The current dominant hypothesis explains fibromyalgia (FM) as a centralized pain state in which the CNS originates or amplifies pain, which is then accompanied by fatigue, memory problems, and sleep and mood disturbances<sup>1</sup>. The often noted “pain-positive review of symptoms” is attributed to central hyperresponsiveness not to psychological factors or “somatization.”<sup>1</sup> Surprisingly, this explanation of non-pain symptoms has never been validated. As fibromyalgia and widespread pain (WP) have been accepted as evidence of the presence of central sensitization (CS), we used the widespread pain index (WPI), a non-symptom containing component of the polysymptomatic distress scale (PSD), to test whether the rate of increase in non pain symptoms as WP increased was greater in the presence of PSD defined fibromyalgia and WP than in their absence.

**Methods:** We studied 3,562 mixed rheumatic disease patients, and diagnosed FM by modified ACR FM criteria. To preclude bias because of the non-pain symptoms included in the PSD, we used WPI alone and as a surrogate for the PSD. We formed an ad hoc fibromyalgia symptom count...
(FSC) (0–19) by summing 19 non-pain related symptoms. We used linear splines and regression models to calculate separate slopes for symptom prediction at WPI levels between 0–6 and 7–19. An increase in the slope of the 7–19 WPI scores compared with the 0–6 WPI scores was accepted as evidence of the effect of CS.

Results: 96% of those with a WPI score ≥7 satisfied WP criteria, and FM was correctly classified in 89% (kappa 0.703). The FSC increased monotonically as WPI increased (Figure 1), and the slope for WPI 0–6 was 0.68 compared with 0.25 for 7–12 (P < 0.001). For each of the 19 symptoms examined, slopes were compared by odds ratios and were significantly lower in the 7–12 group (Table 1).

Conclusion: Our data show no increase in non-pain symptom slopes in subjects with high WPI. Instead, symptom increase is monotonic, and the rate of increase is greater at lower levels of WPI. Alternative hypotheses for increase in symptoms should include factors such non-CS pain and psychological variables.

References

Table 1. Odds ratios (OR) for rate of symptoms in WPI ≥7 compared with 0–6

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Variable</th>
<th>OR</th>
<th>Variable</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>0.85</td>
<td>Nausea</td>
<td>0.79</td>
<td>Trinitis</td>
<td>0.90</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.83</td>
<td>Paresthesias</td>
<td>0.81</td>
<td>Vision prob</td>
<td>0.83</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>0.88</td>
<td>Photosensitivity</td>
<td>0.86</td>
<td>Vomiting</td>
<td>0.87</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.85</td>
<td>Brusing</td>
<td>0.82</td>
<td>Alopecia</td>
<td>0.89</td>
</tr>
<tr>
<td>Dysnea</td>
<td>0.88</td>
<td>Heartburn</td>
<td>0.85</td>
<td>Anorexia</td>
<td>0.83</td>
</tr>
<tr>
<td>Hearing prob</td>
<td>0.87</td>
<td>Rash</td>
<td>0.92*</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>0.83</td>
<td>Reynaud’s</td>
<td>0.91</td>
<td>Constipation</td>
<td>0.84</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>0.84</td>
<td>Seizures</td>
<td>0.89*</td>
<td>Fever</td>
<td>0.84</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>0.77</td>
<td>Dysgeusia</td>
<td>0.82</td>
<td>Itching</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Not significant

Our data show no increase in non-pain symptom slopes in subjects with high WPI. Instead, symptom increase is monotonic, and the rate of increase is greater at lower levels of WPI. Alternative hypotheses for increase in symptoms should include factors such non-CS pain and psychological variables.

Background/Purpose: The polysymptomatic distress (PSD) scale is derived from variables used in the 2010 American College of Rheumatology (ACR) fibromyalgia (FM) criteria as modified for survey and clinical research. The scale is useful in measuring the effect of PSD over the full range of human illness, not just in those who are ACR criteria positive. However, no PSD scale categories have been defined to distinguish severity of illness in FM or in those who do not satisfy criteria. We analyzed the scale and multiple covariates to develop useful clinical categories for PSD and to further validate the scale.

Methods: Fibromyalgia was diagnosed according to the research criteria modification of the 2010 ACR fibromyalgia criteria. We used the 2012 German general population survey (N = 2445) to establish “normal” values. We then investigated categories in a large sample of patients with pain: 2732 with rheumatoid arthritis (RA), and developed categories by utilizing germane clinic variables that had been previously studied for severity groupings. By ACR definition, FM cannot be diagnosed unless PSD is at least 12.

Results: The mean PSD of those with FM in the General population was 16.2 and was 19.2 in the RA clinical sample. Based on population categories and regression analysis and inspections of curvilinear relationships in RA, we established PSD severity categories of None (0–3), Mild (4–7), Moderate (8–11), Severe (12–19) and Very severe (20–31). Categories were statistically distinct, and a generally linear relationship between PSD categories and covariate severity was noted (Table and figures). The thin line in the figures represents the distribution of PSD values.

Conclusion: The described PSD categories are clinically relevant and demonstrate FM type symptoms over the full range of clinical illness, not just in FM positive subjects. Although FM criteria can be clinically useful, no clear-cut distinction between FM (+) and FM (−) subjects can be seen in our data.

Table 1. Clinical variables according to PSD severity groups.

<table>
<thead>
<tr>
<th>PSD Group</th>
<th>PSD (0–3)</th>
<th>PSD (4–7)</th>
<th>PSD (8–11)</th>
<th>PSD FM (+) (12–19) FM (−) excluded</th>
<th>PSD FM (+) (20–31) FM (−) excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (0–10)</td>
<td>1.3</td>
<td>2.7</td>
<td>4</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Global severity (0–10)</td>
<td>1.4</td>
<td>2.8</td>
<td>3.9</td>
<td>5.2</td>
<td>6.3</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>0.4</td>
<td>0.8</td>
<td>1.1</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>PCS score (SF-36)</td>
<td>47.4</td>
<td>40.2</td>
<td>34.6</td>
<td>30.8</td>
<td>27.5</td>
</tr>
<tr>
<td>GAD Anxiety case (%)</td>
<td>1.3</td>
<td>3.4</td>
<td>6.8</td>
<td>22.3</td>
<td>30.6</td>
</tr>
<tr>
<td>PIQ-2 Depression case (%)</td>
<td>0.1</td>
<td>2.3</td>
<td>5.6</td>
<td>26.1</td>
<td>34.8</td>
</tr>
<tr>
<td>Regional Pain Scale (0–19)</td>
<td>0.8</td>
<td>2.6</td>
<td>5</td>
<td>8.2</td>
<td>16.3</td>
</tr>
<tr>
<td>Symptom severity (0–12)</td>
<td>0.9</td>
<td>2.8</td>
<td>4.3</td>
<td>7.2</td>
<td>8.2</td>
</tr>
<tr>
<td>ACR FM criteria (+) (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>PSD (0–31)</td>
<td>1.7</td>
<td>5.4</td>
<td>9.3</td>
<td>15.4</td>
<td>24.5</td>
</tr>
<tr>
<td>Widespread pain (%)</td>
<td>0.8</td>
<td>18.0</td>
<td>57.5</td>
<td>87.8</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Disclosure: F. Wolfe, None; B. T. Walitt, None; J. Rasker, None; R. S. Katz, None; W. Häuser, None.

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Polysymptomatic Distress Categories for Clinical and Research Use. Frederick Wolve1, Brian T. Walitt2, Johannes Rasker3, Robert S. Katz4 and Winfried Häsuer.1, National Data Bank for Rheumatic Diseases, Wichita, KS, 2Washington Hospital Center, Washington, DC, 3University Twente, Enschede, Netherlands, 4Rush Medical College, Chicago, IL, 5Klinikum Saarbrücken, Saarbrücken, Germany.

Background/Purpose: The polysymptomatic distress (PSD) scale is derived from variables used in the 2010 American College of Rheumatology (ACR) fibromyalgia (FM) criteria as modified for survey and clinical research. The scale is useful in measuring the effect of PSD over the full range of human illness, not just in those who are ACR criteria positive. However, no PSD scale categories have been defined to distinguish severity of illness in FM or in those who do not satisfy criteria. We analyzed the scale and multiple covariates to develop useful clinical categories for PSD and to further validate the scale.

Methods: Fibromyalgia was diagnosed according to the research criteria
Small Fiber Neuropathy in Women with Fibromyalgia. a Clinical-Pathological Correlation Using Confocal Corneal Biomicroscopy. Manuel Ramirez-Fernández1, Laura-Aline Martínez-Martínez2, Angelica Vargas-Guerrero2, Manuel Martínez-Lavín2, Everaldo Hernandez Quintela2 and Jorge Velazco-Caspia1. 1Asociación para Evitar la Ceguera en México, Mexico City, Mexico, 2Instituto Nacional de Cardiología, Mexico City, Mexico.

Background/Purpose: A consistent line of investigation proposes that fibromyalgia is a sympathetically maintained neuropathic pain syndrome (Semin Arthritis Rheum 2000;29:197). This view has been recently reinforced by several controlled studies describing decreased small nerve fiber density in skin biopsies of patients with fibromyalgia (Brain 2013;136:1857).

Small fiber neuropathy is a disorder of the peripheral nerves that primarily affects small somatic fibers and sympathetic fibers resulting in sensory changes and autonomic dysfunction. The cornea receives the densest small fiber innervation of the body. Confocal corneal biomicroscopy is a new noninvasive method to assess small nerve fiber pathology.

The main objective of this cross-sectional investigation was to assess the corneal small nerve fiber morphology in patients with fibromyalgia using confocal microscopy. The secondary objective was to correlate corneal nerve microscopic features with fibromyalgia severity parameters contained in several validated questionnaires.

Methods: We studied 17 female patients with fibromyalgia (mean age = 43 ± SD 5) and 17 age-matched healthy female control subjects. A central scan of the total corneal thickness was obtained with a confocal microscope (Confoscan 4, Fortune Technologies, Italy). A single ophthalmologist expert in corneal pathology evaluated stromal nerves morphology and thickness using the Navis v. 3.5.0. Software (NIDEK, Multi-Instrument Diagnostic System, Japan). Nerve thickness was defined as the mean between the widest and the narrowest portion of each analyzed stromal nerve. Nerve smoothness was defined as the difference between the widest and the narrowest portions of each analyzed stromal nerve.

Measurements were done without knowledge of the clinical diagnosis. All studied subjects filled out different questionnaires assessing fibromyalgia severity, including a neuropathic symptom questionnaire (LANSS).

Results: Corneal stromal nerves were easily identified as bright linear silvery structures. Patients with fibromyalgia had nerve thickness of 5.9 ± 2.2 micrometers (mean ± SD) significantly different from control's values (7.4 ± 2.4) p < 0.0001. The difference between widest and narrowest nerve diameter was also dissimilar in patients (1.5 ± 1.3) vs. controls (2.6 ± 1.5) p < 0.0001. Remarkably; when patients and controls were grouped together (n = 34), there was a negative correlation between corneal stromal nerve thickness and LANSS neuropathic symptoms questionnaire score (Spearman's r = -0.36, p = 0.03) as well as with tender points number (r = -0.38, p = 0.02), and other non-pain-related fibromyalgia symptoms.

Conclusion: Confocal biomicroscopy demonstrates that women suffering from fibromyalgia have thinner and smoother corneal nerve fibers when compared to healthy controls. When controls and patients are grouped together, there is a correlated continuum between the degree of corneal nerve pathology and fibromyalgia symptoms. Small fiber neuropathy may play a key role in fibromyalgia's pathogenesis.

Disclosure: M. Ramírez-Fernández, None; L. A. Martínez-Martínez, None; A. Vargas-Guerrero, None; M. Martínez-Lavín, None; E. Hernandez Quintela, None; J. Velazco-Caspia, None.

The Fibromyalgia Syndrome and Widespread Pain Frequency in Active Duty U.S. Service Members with Posttraumatic Stress Disorder. Bernard Hildebrand Jr. 1, Jay B. Higgs1, Douglas Williamson2, Edna Foa1, Patricia Resick3, Jim Mintz4, Antoinette Brundige5, Kevin Kelly5, Adam Borah5, Stacey Young-McCaughan5, Brett Litz5, Elizabeth Hembree2 and Alan Peterson2. 1San Antonio Military Medical Center, JBSA - Fort Sam Houston, TX, 2The University of Texas Health Science Center at San Antonio, San Antonio, TX, 3University of Pennsylvania, Philadelphia, PA, 4Duke University, Durham, NC, 5Rush Medical College, Chicago, IL, 6Taylor Hospital, Ridley Park, PA, 7National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: The Fibromyalgia Syndrome and Widespread Pain Frequency in Active Duty U.S. Service Members with Posttraumatic Stress Disorder (PTSD) and Afghanistan. Studies suggest the co-morbidity of PTSD and pain exacerbates somatic symptoms, and the relationship between PTSD and somatic symptom disorders, including the fibromyalgia syndrome (FMS), is a subject of much importance. The STRONG STAR Consortium offers a unique opportunity to study FMS in the context of a series of investigations of PTSD risk factors, features, and treatment methods in active duty personnel during a period of ongoing military conflict. We report the prevalence of FMS and widespread pain (WP) in pre-deployment, active duty US military service members and in post-deployment service members with PTSD.

Methods: Active duty US veterans of the wars in Iraq and Afghanistan enrolled in STRONG STAR Consortium studies were evaluated. A questionnaire screening for WP, symptom severity, symptom duration, and a prior diagnosis of a pain disorder was administered as part of the assessment battery for two treatment studies of PTSD patients and a prospective study assessing the effect of military deployment on PTSD development. The prevalence of WP and FMS were determined using 1990 ACR Criteria and the Wolfe modification to the 2010 ACR criteria, respectively.

Results: Of 4120 active duty military service members assessed pre-deployment, 118 (3%) met study criteria for the classification of FMS and 244 (5.9%) for WP. In a cohort of 181 service members with PTSD, 57 (31%) met criteria for FMS and 48 (27%) had WP. A separate cohort of 171 service members with PTSD identified 67 (37%) patients with FMS and 51 (30%) with WP.

Conclusion: The prevalence of FMS and WP was markedly elevated in active duty military service members seeking treatment for PTSD when compared to a sample of active duty personnel screened just prior to deployment. Further study may help answer questions regarding the interaction of FMS with PTSD and enable development of tailored therapies appropriate for US service members and veterans with PTSD, FMS and related disorders.

Disclosure: B. Hildebrand Jr., None; J. B. Higgs, None; D. Williamson, None; E. Foa, None; P. Resick, None; J. Mintz, None; A. Brundige, None; K. Kelly, None; A. Borah, None; S. Young-McCaughan, None; B. Litz, None; E. Hembree, None; A. Peterson, None.
Resting State Functional Connectivity Differs Between Chronic Fatigue Syndrome Patients and Healthy Controls. Jason Craggs¹, Charles Gay¹, Andrew O’Shea¹, Ricky Madhavan¹, Donald Price¹, Michael Robinson¹ and Roland Staud². ¹University of Florida, Gainesville, FL, ²Univ of Florida Med Ctr/HIMHC, Gainesville, FL.

Background/Purpose: Examining neural activity in the absence of task (i.e. resting state) is an active area of research. Functional connectivity, defined as correlations in BOLD signal between two brain regions, is a promising component of fatigue/pain research. Seed to voxel analyses are one approach used to estimate functional connectivity between brain areas. This approach takes the BOLD signal time course of a priori defined seeds and compares their signals to all other voxels in the brain. We determined brain areas of chronic fatigue syndrome (CFS) patients as seeds for connectivity analysis that demonstrated abnormal resting cerebral blood flow during arterial spin labeling (ASL) functional MRI.

Methods: CFS was determined using the CDC Criteria. 15 CFS patients (age = 50.5±13.0) and 12 HC (age = 49.2±12.2) were MRI scanned with a 3 Tesla Achieva during rest using a pseudo-continuous arterial spin labeling (pCASL) sequence. ASL data were corrected for rigid body motion and smoothed in SPMS. Label and control images were subtracted to create a perfusion time series. The perfusion time series was used to quantify cerebral blood flow (CBF) using the software asTBX. A mean CBF image was created which was normalized to MNI space and resampled into 2mm isotropic voxels. An independent samples t-test was used to examine voxel-wise differences in CBF between CFS patients and HC. Resulting t-maps were thresholded with a t-statistic > 4.0 and a cluster size > 120 mm³. 2 distinct clusters passed this threshold and were used to create seed masks for subsequent BOLD functional connectivity analyses. BOLD resting state data were slice-time corrected, re-aligned and resliced into 3mm isotropic voxels, co-registered to the anatomic volume, warped into MNI standard space and spatially smoothed. Data were spike-corrected to reduce the impact of artifacts using the post-processing Artifact Detection Tool. The final processing steps were then carried out using the functional connectivity toolbox Conn that implements the component-based noise correction method strategy for physiological and other noise source reduction, which included: Temporal (band-pass) filtering, and removal of several nuisance variables, such as CSF and white matter signal, rigid body motion parameters, and outlier data points.

Results: Significantly decreased blood flow was observed in the right parahippocampal gyrus of CFS patients [27.69 (6.22)] compared to HC [40.51 (7.89) (ml/100g/min)]. Subsequent analyses showed increased connectivity between the parahippocampal seed and the supramarginal gyrus of CFS patients compared to HC.

Conclusion: Our novel method of generating seeds for functional connectivity analyses, using multi-modal neuroimaging data, demonstrated increased connectivity between brain areas involved in memory and language processing of CFS patients.

Disclosure: J. Craggs; None. C. Gay; None. A. O’Shea; None. R. Madhavan; None. D. Price; None. M. Robinson; None. R. Staud; None.
Insurance Status and U.S. Region Associated with Placement of Permanent Vascular Access in Dialysis Patients with End-Stage Renal Disease Secondary to Lupus Nephritis. Laura Plantinga¹, Cristina M. Drenkard¹, Rachel Patzer¹, William McClellan¹, Stephen Pastan¹ and S. Sam Lim².

Background/Purpose: Prior data suggest sociodemographic and regional variability in various indicators of quality of end-stage renal disease (ESRD) care, both overall and in the SLE population, but, to our knowledge, no study has addressed the placement of a permanent vascular access prior to the start of hemodialysis in patients with ESRD secondary to lupus nephritis (LN-ESRD). We aimed to describe permanent vascular access placement among hemodialysis patients with LN-ESRD and to examine whether this placement differs by sociodemographic factors and across the 18 U.S. ESRD Networks, which are Centers for Medicare & Medicaid Services-defined regions that implement ESRD quality-of-care initiatives.

Methods: Among 5562 incident U.S. hemodialysis patients with LN-ESRD initiating treatment 7/05–9/11, we estimated the associations between permanent access placement (arteriovenous fistula or graft used or in place on first dialysis, vs. temporary catheter only) and race/ethnicity, insurance status, age, sex, and income. We computed incidence rates per 1000 person-years, used Adjusted Poisson models to identify the independent contribution of sex, age, race, and income to the incidence of TKA.

Results: Fewer than one-quarter (24.4%) of incident hemodialysis patients with LN-ESRD patients had a permanent vascular access placed at start of dialysis, compared to 36.0% of other ESRD patients. Hispanic LN-ESRD patients were less likely than their white counterparts to have a permanent vascular access (20.5% vs. 25.2%), but the association was not statistically significant after adjustment (OR=0.85; 95% CI, 0.69–1.05). Placement did not differ in black vs. white LN-ESRD hemodialysis patients. After adjustment, private, Medicaid, and other insurance were associated with equivalent likelihood of permanent vascular access, but having no insurance was associated with 38% lower likelihood of permanent vascular access among LN-ESRD patients (OR=0.62; 95% CI, 0.49–0.79). There was substantial, statistically significant Network-level variation in likelihood of permanent vascular access, with adjusted probabilities of permanent vascular access used or in place at first dialysis ranging nearly 2-fold, from 0.17 (Network 10, Illinois) to 0.33 (Network 16, Northwest).

Conclusion: The vast majority of LN-ESRD patients on hemodialysis are not initiating treatment with a permanent vascular access. LN-ESRD patients who are Hispanic or uninsured or who live in the Midwest or Southern California at the start of ESRD are less likely to have permanent vascular access. Targeted interventions to increase permanent vascular access among SLE patients with ESRD are warranted to prevent potential morbidity and mortality associated with temporary catheters.

Disclosure: L. Plantinga, None; C. M. Drenkard, None; R. Patzer, None; W. McClellan, None; S. Pastan, None; S. S. Lim, None.
Background/Purpose: Gout is the most common form of inflammatory arthritis and is caused by chronic hyperuricemia, leading to urate crystal deposition disease and subsequent intermittent flares and tophi development. ACR guidelines recommend treating to target SUA levels (<6 mg/dL, or, in some cases, <5 mg/dL as needed to control signs/symptoms). This study aimed to describe overall rates of SUA testing and differences in patient characteristics, comorbidities, treatments, and flare rates by SUA testing status.

Methods: Gout patients treated with urate-lowering therapy (ULT) were identified between Feb 1, 2011 and Jan 31, 2012 from the HealthCore Integrated Research Environment. Index event was considered to be the earliest of the following: a prescription for ULT; or a gout diagnosis (ICD-9 274.xx) or a claim for colchicine with ULT therapy in the year prior. Patients with <12 months pre- and post-index enrollment or with a diagnosis of cancer, evidence of hematologic cancer, tumor lysis syndrome, Lesch-Nyhan syndrome or juvenile gout, familial Mediterranean fever, or pregnancy in the pre- or postindex periods were excluded. Patient demographics and comorbid conditions were captured during the 12-month pre-index period. SUA laboratory testing, treatment characteristics, and overall gout control (SUA ≤6 mg/dL; no flares, no tophi) were examined during the 12 month post-index period. Target SUA level was ≤6 mg/dL. Flares were defined during the post-index period as either a claim for colchicine, or a healthcare visit recording gout together with ≥1 of the following within 1 week: joint aspiration/injection (corticosteroids), prescription of NSAIDs, corticosteroids, adrenocorticotropic hormone, or IL-1 antagonist.

Results: 50,602 ULT-treated patients met inclusion criteria (average age, 59; 82% male). During follow-up, 90% of patients received allopurinol, 6% (eubrostat, and 4% probenecid. SUA testing occurred in 47% of patients during 1-year follow-up. Those with SUA testing were younger (57 vs. 61 years) and had higher rates of colchicine use (23% vs 13%), hyperlipidemia (64% vs. 59%), and chronic kidney disease (15% vs 13%) compared to those without testing. Patients without SUA testing had higher rates of cardiovascular comorbidities: coronary artery disease (21% vs 17% in those with testing), angina (21% vs 16%), and peripheral vascular disease (10% vs 8%). A higher proportion of patients seen by a rheumatologist had testing compared with those not visiting a rheumatologist (75% vs 44%, respectively). Among patients with available SUA results (n=6649), 47% of subjects had SUA levels ≤6 mg/dL, and 30% achieved overall gout control.

Conclusion: Guidelines describe treating to target SUA as appropriate care. This study finds <50% of all gout patients treated with a ULT have SUA assessed at any time during a 12-month period. Most patients likely to have SUA assessments are younger, have more flares, or visit a rheumatologist. In patients with SUA assessment, <50% achieve SUA goal and less than a third achieve overall gout control. These findings suggest that contemporary gout care is suboptimal, leaving considerable room for improvement.


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Background/Purpose: Pediatric Rheumatology (PR) is among the smallest and least geographically accessible of the pediatric subspecialties. This problem may be addressed by utilizing the more extensive primary care provider (PCP) workforce, in combination with new technologies such as telemedicine. The objectives of this study were to 1) determine current PCP provision of medical services for children with JIA and 2) determine the willingness of these PCPs to provide services in the future.

Methods: Surveys were mailed to PCPs who had referred ≥2 patients to the University of Michigan Division of PR 2/2012-2/2014. Survey domains included the current provision of and willingness to provide medical services to children with JIA who are also followed by a pediatric rheumatologist.

Services assessed included administration of immunizations, performance of a focused joint exam, monitoring for the adverse effects of rheumatology medications, and making medication adjustments. Statistical analyses included proportions and chi square tests.

Results: After 2 of 3 planned mailings, 154/230 PCPs had responded (response rate=67%). The majority of PCPs reported that they already provide many of the assessed services, especially those that are typically performed for all of their patients, such as administering immunizations. Fewer PCPs reported performing services traditionally done by specialists, such as monitoring for adverse effects of medications or making dose adjustments (Figure 1). With the exception of changing medications without PR input, over 90% of PCPs reported willingness to provide the assessed services in the future (Figure 2).

Conclusion: This study found that the majority of PCPs already provide many of the assessed medical services for children with JIA and that an even larger majority are willing to provide these services in the future. Co-management between PCPs and PRs could benefit children and their families by limiting travel expenses and time missed from work and school, while promoting communication and collaboration between PCPs and PRs. The current practices and willingness of PCPs to provide services to their patients with JIA should be used to guide future co-management activities for PCPs and PRs.

Disclosure: A. Mroczek. None; G. Freed. None; M. Riebschleger. None.
period ("follow-up year"). Outcomes included all cause hospitalizations, SLE-related hospitalizations and emergency room (ER) visits. We used Poisson regression models to evaluate the impact of low adherence (average MPR<80%) on utilization outcomes in the follow-up year, adjusting for baseline age, sex, race/ethnicity, Charlson comorbidity index, SLE-specific risk index (Ward M, J Rheum, 2000) and number of SLE drugs taken.

Results: 15,955 patients with SLE were taking at least one immunosuppressive or anti-malarial drug and continuously enrolled in Medicaid over the two-year period. Mean age was 38.6 years (SD 11.3), 95% were female, and 39% were Black, 34% White, 16% Hispanic, 5% Asian, other, 1% Native. The average MPR during the baseline year was 49% (SD 30%). In the follow-up year, 28% had one or more hospitalizations, 17% SLE-related hospitalizations, and 49% ER visits. Lower adherence was associated with significantly increased risks of subsequent hospitalizations and ER visits, even after adjustment for sociodemographic factors, SLE risk index, comorbid disease, and number of SLE drugs taken (Table). ECR.

Conclusion: We found that lower adherence (MPR<80%) significantly increased risks of subsequent hospitalizations and ER visits in Medicaid beneficiaries with SLE. These results are consistent with past studies highlighting the importance of promoting medication adherence to improve health outcomes and decrease costs. Further research is warranted to gain a better understanding of how disease activity and severity influence this relationship.

Table Relationship between Adherence and Subsequent Hospitalizations and Emergency Room Encounters in U.S. Medicaid beneficiaries with SLE.

<table>
<thead>
<tr>
<th>Adherence in year one (MPR&lt;80%)</th>
<th>All-cause hospitalizations (IRR 95% CI)</th>
<th>SLE-related hospitalizations (IRR 95% CI)</th>
<th>Emergency Room visits IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral</td>
<td>1.40 (1.33, 1.54)</td>
<td>1.16 (1.25,1.46)</td>
<td>1.55 (1.48, 1.65)</td>
</tr>
<tr>
<td>Non-adherence in year one</td>
<td>(MPR&gt;80%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MPR=Medication Possession Rate; IRR= Incidence rate ratio. Poisson regression models were adjusted for baseline age, sex, race/ethnicity, SLE-specific risk index, Charlson comorbidity index and number of concomitant SLE medications. Each column represents a separate Poisson regression model.

Disclosure: J. Yazdany, None; C. H. Feldman, None; H. Guan, None; K. H. Costenbader, None.

ACR Concurrent Abstract Session Imaging of Rheumatic Diseases: Ultrasound
Sunday, November 16, 2014, 4:30 PM–6:00 PM

904 Ultrasound Synovitis Reflects Synovial Inflammation at a Histopathological Level. Nora Ng, Stephen Kelly, Frances Hruby, Maria DiCicco, Viola Roche, Rebecca Hands, Michele Bombardieri and Costantino Pitzalis. William Harvey Research Institute, Queen Mary University of London, London, United Kingdom.

Background/Purpose: Ultrasound (US) is widely used by rheumatologists to assess inflammatory burden on patients with inflammatory arthritis. Some studies have shown that US measures of inflammation reflect certain aspects of histological synovitis in a heterogeneous groups of patients with rheumatoid arthritis (RA). Little work has been done to describe this relationship in an early arthritis population. Our aim of this study is to investigate, at a single joint level, the correlation of US synovitis with histological synovial inflammation before and after treatment initiation in a homogenous cohort of patients with early RA.

Methods: Data was collected from 54 patients with early RA (fulfills 1987 ACR classification, symptom onset<12 months). Patients were naïve to both disease modifying anti-rheumatic drugs (DMARD) and to steroids. All patients underwent a core data set assessment including clinical, biochemical, imaging and an US guided minimally invasive synovial biopsy of the most inflamed joint. Patients were then initiated on DMARD according to standardised protocol. A repeat assessment and US guided biopsy was performed at 6 months follow up. US images of the joint are scored using a semi quantitative score (0–3). Sections of paraffin embedded synovial tissue received immunohistochemical staining for CD3, CD20, CD68, CD68sland CD138 and these parameters were graded in a semiquantitative fashion (0–4). Spearman’s rho was used to correlate scores at each time point.

Results: At baseline, US power doppler (PD) was significantly correlated with histological markers of inflammation - CD3 (r=0.43, p<0.05), CD20 (r=0.46, p<0.01), CD68 (r=0.37, p<0.05), and with inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (r=0.4, p<0.05). After 6 months of therapy, most of these correlations were still present, most notably with CD68sl (p<0.05). Interestingly, we also found that a fall in US PD in response to treatment at 6 months is associated with a fall in CD68sl (r=0.50, p<0.005) and a fall in DAS28 (r=0.40, p<0.05).

Conclusion: US PD has long been recognised as an accurate reflection of disease activity in inflammatory arthritis. Our results have shown that US PD also reflects synovial inflammation at a histopathological level. The association of US PD, CD68sl and DAS28 supports the current opinion that Power Doppler US is a biomarker for treatment response and reflects both clinical and histological markers of disease activity in patients with RA.

Disclosure: N. Ng, None; S. Kelly, None; F. Humpy, None; M. DiCicco, None; V. Roche, None; R. Hands, None; M. Bombardieri, None; C. Pitzalis, None.

905 First Step in the Development of an Ultrasound Joint Inflammation Score for Rheumatoid Arthritis: A Data Driven Approach. Anna-Birgitta Aga1, Hilde Berner Hammer1, Inge C. Olsen2, Till Uhlig3, Tore K. Kvien4, Désirée van der Heijde5, Elisabeth Lie1, Espen A. Haavardsholm6 and the Arctic study Group1, 7Diakonhjemmet Hospital, Oslo, Norway, 2Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The use of ultrasonography (US) in rheumatoid arthritis (RA) is rapidly increasing. Currently, there is no consensus regarding which joints and tendons should be systematically assessed. Validity, including comprehensiveness, and responsiveness must be weighted against feasibility. Our objectives were to develop candidate sets for assessment of US joint inflammation through a data driven approach using data from early RA patients, and then perform initial validation in an established RA cohort.

Methods: Between January 2010 and June 2013 patients (pts) were included in one of two cohorts: Early RA (DMARD-naïve pts with RA of <2 yrs symptom duration fulfilling 2010 ACR/EULAR classification criteria), and established RA (pts starting or switching biologic DMARDs). An extensive US examination was performed by experienced sonographers using a validated grey-scale (GSUS) and power Doppler (PDUS) semi-quantitative scoring system with scores 0–3 for GSUS and PDUS in each of the following 36 joints and 4 tendons: MCP 1–5, PIP 2–3, radiocarpal, distal radioulnar, intercarpal, elbow, knee, talocrural, MTP 1–5, extensor carpi ulnaris and tibialis posterior tendons, bilaterally. An US atlas was used as reference1. We performed principal component factor analyses (PCA) in the early RA US data to identify joint groups with high internal correlation, and selected candidate joint/tendon sets based on these analyses. We assessed the loss of information compared to the full score by R² from linear regression analysis. Finally, the candidate sets were validated in the established RA cohort.

Results: A total of 439 patients were included. 227 with early and 212 with established RA; 62% vs. 77% anti-CCP pos, mean(SD) age 51(14) vs. 52(13) yrs, DAS28 4.7(12.1) vs. 4.7(14.1), median(25–75 percentile) 28-SJC 3(11–11) vs. 52(10–10), disease duration 0.5(0.2–9) vs. 8(3–15) yrs, mean(95% CI) 36-joint GSUS score 23(21–25) vs. 28(25–30) (p=0.003), 36-joint PDUS score 11(10– 12) vs. 13(11–15) (p=0.20). Nearly 17,000 individual joints/tendons were assessed. We identified 9 groups based on PCA in the early RA data, presented in table 1. Comparisons between the candidate sets and the total GSUS and PDUS scores in the early RA cohort as well as validation in the established RA cohort are presented in table 2.

Conclusion: We used a data driven approach to develop candidate sets of joints/tendons to be assessed by GS and PD US, and the resulting reduced score retained most of the information from the total score of 40 joints/ tendons. Unilateral reduced scores explained 78% to 85% of the total score, while bilateral reduced scores explained 89% to 93% of the total score. The candidate scores performed equally well in a validation cohort of established RA. Our results show that a reduced US assessment may efficiently contribute to disease assessment in RA. Further validation in longitudinal RA cohorts and data on responsiveness are needed.

1Hammer HB et al. ARD 2011

Table 1: 9 joint/tendon groups with correlating scores based on principal component factor analysis of the GSUS and PDUS scores in early RA

| Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Group 7 | Group 8 | Group 9 |
How Long Does Sonographic Joint Activity Continue in Clinically Remittive Joints of Patients with Rheumatoid Arthritis? Miriam Gärtner, Farideh Alasthi, Gabriela Supp, Peter Mandl, Josef Smolen and Daniel Aleutah. Medical University of Vienna, Vienna, Austria.

Background/Purpose: Ultrasound (US) is sensitive for detecting tenosynovitis in patients with rheumatoid arthritis (RA). Synovial effusion and hypertrophy are evaluated by grey scale (GS), while hypervascularisation, can be measured using power Doppler (PD) signals. Both types of signals are highly sensitive, and may persist even in clinical inactivity. It is conceivable that such subclinical US signals may resolve if clinical inactivity of the respective joint is sustained, but this has not yet been shown during long-term follow-up.

It was the objective of this study to evaluate the persistence of subclinical US signals in previously clinically active joints, which have reached a state of continuous clinical inactivity.

Methods: We performed US imaging of 22 joints of the hands of RA patients, including GS and PD, each graded on a four point scale (0 = to last clinical activity, 1 = mild, 2 = moderate, 3 = marked). All joints with no activity by clinical assessment at the same time of the US examination were selected, and we identified the last point of clinical joint activity (swelling, tenderness, or both). The time between the last clinical joint activity and the current sonographic assessment in that joint was determined and persistence of subclinical US activity was estimated for all patients and all joints using time-to-event analysis.

Results: A total of 90 RA patients with 181 assessed joints were included in this study: 67.1% (1329) of the joints were positive on GS and 20.7% (410) showed PD signals. The mean ± SD number of joints showing signs of sonographic activity was: 15 ± 5 for GS, 5 ± 3.8 for PD.

The median (IQR) time between the last visit exhibiting clinical activity in a joint and the US assessment in the same joint was 3.6 (1.2;6.3) for joints with PD signals, and 3.5 (1.3;5.6) years for joints with GS signals.

If GS signals were ≥2 we found a significantly shorter time to the last visit with clinical activity compared to joints with GS=1 (median[IQR] 2.0 [0.6;2.6] vs. 3.9 [1.9;6.6]; p<0.001); for PD signals we saw the same trend (median[IQR] of 2.4 [0.5;5.3] for PD≥2 vs. 4.3 [1.0;6.2] for PD=1; p=0.066). In joints showing both highly positive GS and PD signals (both ≥2), the time to the last clinical activity was even shorter, with a median of 1.4 years. (Figure 1)

Conclusion: We conclude that subclinical joint activity is long lasting in RA joints in clinical remission, but resolves over time. The latter is indicated by a shorter period from last clinical activity for strong signals (PD≥2, GS≥2) as compared to weak signals (PD≤1, GS≤1).

Disclosure: M. Gärtner, None; F. Alasthi, None; G. Supp, None; P. Mandl, None; J. Smolen, None; D. Aleutah, None.

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Ultrasonographic Tenosynovitis Score Is Responsive to Biologic Treatment in Patients with Rheumatoid Arthritis. Hilde B. Hammer and Tore K. Kvien. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Ultrasound (US) is sensitive for detecting tenosynovitis in patients with rheumatoid arthritis (RA), where the synovitis can be assessed by grey scale (GS) and the increased vascularization by power Doppler (PD). The extensor carpi radialis (ECU) tendon in the wrist and the tibialis posterior (TP) tendon in the ankle are frequently involved in RA patients, and the tenosynovitis can be scored by use of a semi-quantitative (0–3) scoring system. The objective of the present study was to assess the involvement of ECU and TP tendons in patients with established RA as well as to explore the change in US scores of these tendons during treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Methods: A total of 181 RA patients (83% women, mean (SD) age 51 (13) years, disease duration 11 (9) years, 77% positive for anti-CCP) were examined when they started bDMARD (infliximab 10%, etanercept 43%, adalimumab 8%, golimumab 5%, certolizumab pegol 5%, rituximab 19%, abatacept 4% and tocilizumab 6%). All were examined at baseline and after 1, 2 and 3 months with US GS and PD of ECU and TP tendons bilaterally, all assessments performed by one sonographer (HBH) with Siemens Acuson Antares, Excellence version, using a 5–13 MHz probe with an optimized pre-setting of the machine for all examinations, laboratory and clinical assessments. The changes from baseline were assessed by use of paired samples T-test.

Results: Tenosynovitis was found in a high number of tendons at baseline (Table). The mean (SD) sum score of the four tendons was 2.7 (2.7) for GS and 1.6 (2.2) for PD, including 26% of the patients with no GS inflammation and 51% with no PD activity in any tendon. Mean (SD) baseline values for the clinical examinations were: ESR 28.6 (21.7), CRP 14.2 (20.6) and DAS28 4.6 (1.5). Both sum scores GS and PD decreased significantly from baseline to 1 month (p<0.001 and p=0.013, respectively), and both showed highly significant reduction after 3 months (p<0.001) (figure). Also ESR, CRP and DAS28 decreased already after 1 month (p<0.001 for all), as well as after 3 months (p<0.001 for all).

Conclusion: A large number of ECU and TP tendons were inflamed at baseline, and the sum scores of both GS and PD fell significantly already after 1 month. Since tenosynovitis in ECU and TP tendons are common in RA patients and responsive to change during bDMARD treatment, US of these tendons should be considered as candidates for inclusion in future US scores of RA patients.

Disclosure: M. Gärtner, None; F. Alasthi, None; G. Supp, None; P. Mandl, None; J. Smolen, None; D. Aleutah, None.

Table 2: Comparison of candidate joint/tendon sets for GSUS and PDUS assessment and the full 40-joint/tendon score in the early and established RA cohorts

<table>
<thead>
<tr>
<th>Modality</th>
<th>Candidate set of US joint inflammation</th>
<th>Side</th>
<th>Number of joints/tendons</th>
<th>Early RA</th>
<th>Established RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSUS</td>
<td>A1 Right</td>
<td>9</td>
<td>0.79</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>9</td>
<td>0.83</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>18</td>
<td>0.89</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B2 Right</td>
<td>11</td>
<td>0.85</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>0.85</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>22</td>
<td>0.93</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>PDUS</td>
<td>A1 Right</td>
<td>9</td>
<td>0.78</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>9</td>
<td>0.78</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>18</td>
<td>0.89</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B2 Right</td>
<td>11</td>
<td>0.83</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>0.81</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>22</td>
<td>0.92</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

1MCP 1, MCP 2, PIP 3, radiocarpal, elbow, MTP 1, MTP 2, and extensor carpi ulnaris and tibialis posterior tendons
2Same as candidate set A with addition of MCP 5 and MTP 5

Linear regression analysis with the total US score as dependent variable and the sum score of the candidate sets as independent variable: GSUS = grey scale ultrasonography. PDUS = power Doppler ultrasonography.

Discussion: A. B. Aga, None; H. B. Hammer, AbbVie, 2; I. C. Olsen, None; T. Ublig, None; T. K. Kvien, None; D. van der Heijde, None; E. Lie, None; E. A. Haavardsholm, AbbVie, Pfizer, MSD, Roche, UCB, 2; T. A. study Group, AbbVie, Pfizer, MSD, Roche, UCB, 2.

Ospedale Mauriziano, Turin, Italy. Italian Society for Rheumatology, Milan, Italy. A.O.U. S.Anna di Cona, Ferrara, Italy. L.Sacco University Hospital, Milan, Italy. Policlinico le Scotte, Siena, Italy. IRCCS Policlinico San Matteo, Pavia, Italy. Istituto di Cura Città di Pavia, Pavia, Italy. A.O. Sant’Andrea, Rome, Italy. A.O.U.P. Santa Chiara, Trento, Italy. Sapienza University of Rome, Rome, Italy. Orthopedic Institute Gaetano Pini, Milano, Italy. University of Siena, Siena, Italy. University Politecnica delle Marche, Jesi, Italy. Ospedale Infermi, Rimini, Italy. University of Padova, Padova, Italy. A.O.U. di Cagliari, Cagliari, Italy. Ospedale Civile Maggiore, Verona, Italy. University of Perugia, Perugia, Italy. Ospedale S Maria Nuova, IRCCS, Reggio Emilia, Italy. Istituto Clinico Humanitas, Rozzano, Italy. Moriggia-Pelascini, Gravedona, Italy.

Background/Purpose: Clinical remission is now an achievable goal in patients with rheumatoid arthritis (RA). Much has been done in order to better understand and define the concept of remission; in the field of ultrasonography (US) some studies have focused on joint tenosynovitis and its significance in terms of prognosis. In the literature, data on the prevalence of tenosynovitis in patients in clinical remission are scarce and its clinical and prognostic significance has not been studied yet. The objective of this study is to assess whether the US tenosynovitis is associated with a decreased risk of flare.

Methods: Sonographic Tenosynovitis Assessment in Rheumatoid Arthritis patients in Remission (STARTER) is a multicentre cohort study promoted by the Italian Society for Rheumatology (SIR) that includes 26 rheumatology centres recruited across Italy between Oct 2013 and Jun 2014. Ultrasonographers were trained and selected by an inter-reader reliability exercise against a reference standard using static images, setting to 0.7 one ad hoc weighted kappa as entry criterion. Only high level US machines and high frequency probes were allowed. Patients with RA and clinical remission (DAS28 or SDAI or CDAI) were eligible. All patients underwent full clinical evaluation and US examination (sonovisits (S-T) and sonosynovitis (-S). A 0–3 semiquantitative score of Grey Scale (GS-) and Power Doppler (PD-) was calculated for wrists, metacarpophalangeal, interphalangeal joints and extensor and flexor tendon sheaths. Flare was assessed using the flare questionnaire score ranging from 0 (no flare) to 10 (definite flare) [1], dichotomized at the median value (=3). The cross-sectional relationship between presence of GS-T/-S, PD-T/-S were evaluated by logistic models, and presented as odds ratios (OR) and 95%CI, both crude and adjusted for pre-specified confounders.

Results: A total of 408 RA patients in clinical remission were included in the analyses: 103 (25.4%) men, mean (SD) age 56.4 (13.5), median (IQR) disease duration 7.1 (3.7–13.5) years, median (IQR) remission duration 12 (8–28) months, RF positive 249/360 (69.2%), mean (SD) DAS28 2.1 (0.8), median (IQR) HAQ 0.125 (0.0–0.375), on DMARDs 300 (73.5%), on biologics 161 (39.5%), on glucocorticoids 170 (43.8%).

GS-T was present in 198/372 (53.1%) patients, PD-T in 88/372 (23.7%), while GS-S was present in 270/368 (73.4%) patients and PD-S in 171/372 (45.5%). The association between US variables and flare is reported in the Table.

<table>
<thead>
<tr>
<th>Outcome: flare questionnaire &gt;3</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted* OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey Scale Tenosynovitis</td>
<td>1.05 (0.69, 1.58)</td>
<td>1.09 (0.68, 1.75)</td>
</tr>
<tr>
<td>Power Doppler Tenosynovitis</td>
<td>2.11 (1.29, 3.45)</td>
<td>2.29 (1.29, 4.07)</td>
</tr>
<tr>
<td>Grey Scale Synovitis</td>
<td>1.09 (0.68, 1.74)</td>
<td>0.88 (0.50, 1.56)</td>
</tr>
<tr>
<td>Power Doppler Synovitis</td>
<td>1.60 (1.05, 2.43)</td>
<td>1.48 (0.91, 2.40)</td>
</tr>
</tbody>
</table>

*Age, sex, disease duration, remission duration, mono/dualtreated, comorbidities, RF, ACPA, DMARDs, biologic, glucocorticoids (oral and injections), NKASs.

Using absence of PD-T and PD-S as reference, PD-S alone showed an adjusted OR (95% CI) of 1.45 (0.82, 2.58), PD-T alone 3.84 (1.33, 11.08) and both PD-T and PD-S 2.55 (1.27, 5.10).

Conclusion: Power Doppler tenosynovitis is independently associated with patient reported flare more strongly than synovial indexes. US-tenosynovitis is a promising feature to identify patients in remission at higher risk of flare.


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A Diagnostic Protocol for Giant Cell Arteritis (GCA) Using Ultrasound Assessment. Jennifer Piper1, Ana Sofia Serafim1, Cristina Ponte1, Surjeet Singh2, Bhaskar Dasgupta2, Wolfgang A. Schmidt2, Eugene McNally3, Andreas P. Diamantopoulos3, Andrew Hutchings3 and Raashid Luqmani8. 1University of Oxford, Oxford, United Kingdom, 2Sciences, Oxford, England, 3Southend University Hospital, Essex, United Kingdom, 4Immanuel Krankenhaus, Berlin, Germany, 5Oxford University, Oxford, United Kingdom, 6Hospital of Southern Norway Trust, Kristiansand, Norway, 7London School of Hygiene and Tropical Medicine, London, United Kingdom, 8Oxford NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom.

Background/Purpose: Ultrasound (US) has not yet superseded temporal artery biopsy as a diagnostic test. This may reflect poor consistency of the scanning technique, due to the lack of a standardised scanning protocol. We have developed a standardised protocol which was implemented in a prospective study of 857 participants: 439 healthy controls and 418 patients with suspected GCA (Temporal Artery Biopsy versus Ultrasound, TABUL). We assessed each patient for evidence of typical ultrasound features of GCA: the presence of a halo surrounding the vessel wall, stenosis or occlusion of the vessel.

Methods: A detailed scanning protocol was developed for all cases and controls. We recorded the presence or absence of ultrasound features of GCA in each segment of each temporal artery (common, parietal, frontal proximal and frontal distal) and both auxiliary arteries. Sonographers were asked to acquire video and static images for each patient to ensure accuracy of findings. The sonographer measured and documented: halo diameter (based on a normal range of up to 0.3 mm for the temporal artery and up to 1.0 mm in the auxiliary artery) and length; pulse Doppler measurements prior to and within a stenosis (confirmed if the highest maximum systolic velocity was over twice the lowest maximum systolic velocity) and arterial occlusion. Each study site sonographer was required to be proficient in the protocol by scanning at least 10 healthy controls, passing an online test showing normal and abnormal scans (pass mark >75%) and scanning a patient with ultrasound evidence of active GCA.

Results: The US scanning protocol was started by 33 sites, with only 22 sites completing the training in 6.7 months [range 0.2 – 16.4 months]. A total of 439 controls were scanned across 31 sites (1 sonographer covered 3 sites). The online test was passed by 39 sonographers (multiple sonographers at some sites) with an average of 2 attempts [range 1–4]; 22 sonographers successfully scanned an active GCA patient, validated by the expert panel. The longest delay in completing the training was due to difficulty in recruiting a patient with active GCA (not case), which was necessary for each site prior to it joining the main study. Common issues encountered were a lack of time away from clinical duties completing the training was due to difficulty in recruiting a patient with active GCA.

We have created a bank of 857 sets of consistently recorded US images of temporal and auxiliary arteries from 418 patients with suspected GCA and 439 healthy controls. Expert review of the first 263 suspected patients has confirmed positive US findings of GCA in 100 patients and no US evidence in 163 cases.

Conclusion: Quality and accuracy are imperative for the clinical use of ultrasound data in the diagnosis of GCA. We have developed an effective training program and scanning protocol which ensures consistency and proficiency. The methodology can be adapted and extended to allow for additional arterial assessment, including carotid, vertebral and subclavian arteries, extending the value of a structured approach. We recommend the TABUL study scanning protocol as the standard approach for diagnosis of GCA using ultrasound.

Disclosure: J. Piper, None; A. S. Serafim, None; C. Ponte, None; S. Singh, None; B. Dasgupta, None; W. A. Schmidt, None; E. McNally, None; A. P. Diamantopoulos, None; A. Hutchings, None; R. Luqmani, None.

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The Selective Sphingosine-1- Phosphate Receptor 1/5 Modulator Siponimod (BAF312) Shows Beneficial Effects in Patients with Active, Treatment Refractory Polymyositis and Dermatomyositis: A Phase IIa Proof-of-Concept, Double-Blind, Randomized Trial. Katalin Danko1, Jiri Vencovsky2, Ingrid E. Lundberg3, Anthony A. Amato4, Chester V. Oddis5, Maria Molnar6, Antonette Mallari Moher7, Laurence Colin8, Florian Mueldershausen9, David Lee10 and Peter Gergely11. 1University of Debrecen, Hungary, Debrecen, Hungary, 2Charles University, Prague, Czech Republic, 3Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, 4Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, 5University of Pittsburgh, Pittsburgh, PA, 6Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary, 7Novartis Institutes for the Definition of Disease Research Unit (former employee), Basel, Switzerland, 8Novartis Pharma, Basel, Switzerland, 9Novartis Institutes for Biomedical Research, Basel, Switzerland.

Background/Purpose: Polymyositis and dermatomyositis (PM/DM) comprise a heterogeneous group of chronic inflammatory muscle diseases where infiltration of lymphocytes in the skeletal muscle plays a key pathogenic role. BAF312 (siponimod), an oral sphingosine-1-phosphate (S1P) receptor 1/5 modulator may be efficacious in inflammatory myopathies by inhibiting lymphocyte trafficking from secondary lymphoid organs to the muscle. A randomized, double-blind, placebo-controlled, multi-centric, partial cross-over Phase IIa Proof of Concept study was conducted to evaluate the safety, tolerability and efficacy of BAF312 in patients with PM/DM.

Methods: Eighteen patients with clinically active PM/DM who had responded inadequately to conventional treatment were randomized to receive 10 mg BAF312 or matching placebo (1:1) once daily for 12 weeks. The 10 mg dose was reached by a dose up-titration regimen over 10 days to minimize bradycardia, a common adverse effect of the S1P1 receptor modulator class. Following the placebo-controlled Period 1, all patients received 10 mg BAF312 for an additional 12 weeks in Period 2. No immunosuppressives but oral corticosteroids at a stable dose (max. 20 mg prednisone/day) were allowed as concomitant medication. Key outcomes were safety and efficacy as assessed by the responder rate according to the Definition of Disease Assessment of Improvement (DDAI) and the IMACS (International Myositis Assessment Study Group) clinical response, 12-weeks. Further investigation of the PD effect of BAF312 is warranted.

Results: Eighteen patients were enrolled into this trial and 16 patients received BAF312 either in Period 1 and/or Period 2. Overall, BAF312 was safe and well tolerated with no significant bradycardia observed. Four serious adverse events occurred in three patients, all in the Placebo group. Fourteen patients were evaluable for the efficacy analysis. The observed responder rates at week 12 were 4/7 (57%) for BAF312 and 1/7 (14%) for placebo using the IMACS definition of improvement. A Bayesian analysis of the IMACS responder status at week 12 yielded a probability of 0.96 that BAF312 is superior to Placebo. The PD effect of BAF312 (i.e., decrease in absolute lymphocyte count) was confirmed in all subjects receiving BAF312, with a mean decrease by >75% after 4 weeks of treatment.

Conclusion: Considering disease heterogeneity and low sample size, firm conclusions should not be drawn, but further investigations of BAF312 as a new treatment modality for patients with refractory PM/DM are warranted. Although disease heterogeneity and low sample size prevent definite conclusions, further investigations of BAF312 as a new treatment modality for patients with refractory PM/DM are warranted.

Disclosure: K. Danko, None; J. Vencovsky, Novartis Pharma, 5; I. E. Lundberg, Novartis Pharma, 5; A. A. Amato, None; C. V. Oddis, Novartis Pharmaceutical Corporation, 5; M. Molnar, None; A. Mallari Moher, None; L. Colin, Novartis Pharma, 3, Novartis Pharma, 3; F. Muellershausen, Novartis Pharma AG., 3; D. Lee, Novartis Pharma, 1, Novartis Pharma, 3; P. Gergely, Novartis Pharma, 1, Novartis Pharma, 3.

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Bioluminescent Imaging of Histidyl-Transfer RNA Synthetase-Induced Myositis Reveals Early-Phase Involvement of NF-Kb-Mediated Inflammation. Nicholas A. Young1, Lai-Chu Wu1, Michael Bruss1, Wael N. Jarjour2 and Dana P. Ascherman3. 1The Ohio State University Wexner Medical Center, Columbus, OH, 2Miami VAMC, Miami, FL.

Background/Purpose: The idiopathic inflammatory myopathies represent a group of autoimmune diseases that target muscle as well as...
extra-muscular organs, leading to significant morbidity and mortality. Among the most common specific autoantibodies associated with these disorders is Anti-histidyltRNA synthetase (HRS: Jo-1), which defines a subgroup of patients with clinical features. In order to further advance targeted therapies, we have modified a previously established model of HRS-induced myositis to highlight the potential role of NF-kB activation in early stages of disease.

**Methods:** BALB/C-Tg(NFkB-RE-luc)-Xen mice, which contain a firefly luciferase cDNA reporter gene under the regulation of 3 kb responsive binding sites, were injected intra-muscularly with 50 ml of recombinant murine HRS (5 mg/ml) affinity purified following amplification in a bacterial expression system. Inflammation was determined by measuring whole-body bioluminescent signals using the Xenogen in vivo imaging system (IVIS 200). The emitted photons from injected muscle were quantitated for each mouse at time zero and at 2 and 4 weeks. At 5 weeks post-HRS injection, mice were sacrificed; sections of injected as well as non-injected muscle tissue were then paraffin embedded and stained by H&E for histological analysis.

**Results:** NFkB-RE-luc mice inoculated with recombinant HRS developed a robust inflammatory response at the 2 week time point. This statistically significant inflammatory response measured by IVIS photon quantification was most pronounced at the site of injection, but did extend beyond this area in some mice (see figure). NF-kB activation subsided after 4 weeks, with residual bioluminescent signals approaching those induced by injection with PBS alone. Despite this apparent reduction in NF-kB activity, however, histologic analysis of HRS-injected muscle tissue revealed significant endomyositis inflammatory infiltrates at these later time points.

**Conclusion:** This novel application of NF-kB-regulated luciferase mice establishes a system that may facilitate therapeutic drug development for myositis through longitudinal analysis of candidate NF-kB inhibitors in different strains expressing the NF-kB-luciferase transgenes. However, because our results suggest that NF-kB-mediated signaling pathways primarily impact early stages of disease in this model system, alternative therapeutic targets must be sought for more temporally advanced disease; thus underscoring the need for phase-specific treatment in idiopathic inflammatory myopathy.

**Disclosure:** None.

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**Table 1. Final Myositis Response Criteria Model**

<table>
<thead>
<tr>
<th>Core Set Measure</th>
<th>Improvement score for each level of CSM</th>
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<tbody>
<tr>
<td>MD Global Absolute % Change</td>
<td></td>
</tr>
<tr>
<td>Up to &lt;=5%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5% up to &lt;=15%</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;15% up to &lt;=25%</td>
<td>15</td>
</tr>
<tr>
<td>&gt;25% up to &lt;=40%</td>
<td>17.5</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>20</td>
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</table>

<table>
<thead>
<tr>
<th>Patient Global/Parent Global Absolute % Change</th>
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</thead>
<tbody>
<tr>
<td>Up to &lt;=5%</td>
<td>0</td>
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<td>7.5</td>
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<tr>
<td>&gt;40%</td>
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</table>

<table>
<thead>
<tr>
<th>MMT/CMA Absolute % Change</th>
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<td>Up to &lt;=2%</td>
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<tr>
<td>&gt;2% up to &lt;=10%</td>
<td>10</td>
</tr>
<tr>
<td>&gt;10% up to &lt;=20%</td>
<td>20</td>
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</tbody>
</table>
HAQ/CHQ Absolute % Change

<table>
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<tr>
<th>Cut point on total improvement score</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20%</td>
<td>27.5</td>
<td>32.5</td>
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<tr>
<td>20% to 50%</td>
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<tr>
<td>&gt; 50%</td>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>10</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Total Improvement Score is sum of score achieved in each CSM.

Conclusion: In patients with asymptomatic or mildly symptomatic moderate CK elevation, the main etiology is lipid lowering medicines but in a substantial proportion the etiology remains unclear. In older patients and patients with lower CK at baseline it is more likely that CK normalizes in follow-up; patients without weakness as the main symptom at baseline were more likely to become asymptomatic at follow-up. These are encouraging findings that can help rheumatologists counsel these patients on their long term prognosis.

Disclosure: L. Kirillova, None; A. Tacang, None; A. Berger, None; T. M. Harrington, None; A. Bill, None.

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A Predictive Model of Disease Outcome in Rituximab-Treated Myositis Patients Using Clinical Features, Autoantibodies, and Serum Biomarkers

Jeanette Olazagasti1, Cynthia S. Crowson1, Molly S. Hei1, Consuelo Lopez de Padilla2, Rohit Aggarwal2, Chester V. Oddi2 and Ann M. Reed1

1Mayo Clinic, Rochester, MN, 2University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Develop predictive models of early (8 week) and late (24 week) disease outcomes using clinical features, autoantibodies, and serum biomarkers in patients with refractory myositis treated with rituximab.

Methods: In the Rituximab in Myositis (RIM) trial, all subjects (76 with adult dermatomyositis, 76 with adult polymyositis and 48 with juvenile dermatomyositis) received rituximab (2 doses on consecutive weeks) with half the patients receiving drug at baseline and half receiving drug 8 weeks later. Using start of treatment as baseline, serum samples (n=177) were analyzed at baseline and after 8 and 24 weeks after rituximab. Potential predictors included the following baseline features: clinical features, serum muscle enzymes, interferon gene score, autoantibodies (anti-synthetase n=28, TIF1-g n=19, Mi-2 n=28, SRP n=21, NXP2 n=18, non-myositis association n=24, undefined autoantibody n=9), and cytokines/chemokines measured by multiplexed sandwich immunoassays (Meso Scale Discovery) (type-1 IFN-inducible [IP-10, I-TAC, MCP1], Th1 [IFNγ, TNFα, IL2], Th2 [IL4, IL5, IL10, IL12, IL13], Th17 [IL6, IL17, ILβ] and regulatory cytokines [IL10, TNFa, MIP-1α, MIP-1β]). Our primary definition of response to treatment was based on absolute change from baseline to 8 weeks and 24 weeks in physician global assessment (CGA) and, half on VAS, and 6-minute walk test, and, half on VAS and extramascular VAS. Multivariable linear regression models were developed using stepwise variable selection methods.

Results: Preliminary models were built with good predictive ability both for change in physician global assessment and muscle disease activity at 24 weeks (R-square=0.41 and 0.40, respectively). The model for change in physician global assessment included the following baseline clinical and lab features: muscle disease activity, physician global assessment, and I-TAC (Table). The model for change in muscle disease activity included baseline physician global assessment, skeletal disease activity, I-TAC and IFNγ. Similarly, a predictive model was built with excellent predictive ability (R-square=0.67) for change in extramuscular disease activity at 24 weeks. This model included the following baseline clinical and lab feathers: constitutive, skeletal and extramuscular disease activity by VAS, and MIP-1β and Mi-2. We also built models from baseline to 8 weeks but their predictive ability was inferior compared to those for 24 weeks (R-square=0.3).

Conclusion: Changes in disease activity over time following treatment with rituximab in patients with refractory myositis can be predicted. These models could be clinically useful to optimize treatment selection in these patients.

Disclosure: L. Kirillova, None; A. Tacang, None; A. Berger, None; T. M. Harrington, None; A. Bill, None.

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Long Term Outcomes of Patients with Moderate Creatine Kinase (CK) Elevation Seen in a Rheumatology Clinic. Lyudmila Kirillova, Abraham Tacang1, Andrea Berger, Thomas M. Harrington1 and Andronicos Bili

1Geisinger Health System, Danville, PA, 2Center for Health Research, Geisinger Health System, Danville, PA.

Background/Purpose: Asymptomatic or mildly symptomatic patients with moderate creatine kinase (CK) elevation are commonly referred to rheumatologists. In patients without a clearly established diagnosis, the significance of the CK elevation and long term outcomes are unclear and there is lack of data to help rheumatologists to counsel these patients. The purpose of this study was to examine the outcomes of patients with moderate CK elevation of unclear etiology and identify possible predictors of CK normalization and symptom resolution.

Methods: Retrospective chart review of asymptomatic or mildly symptomatic patients with moderate CK elevation (250–1000 U/L) CK elevation who were referred to a rheumatologist for that reason, in a tertiary health system. Patients with known inflammatory myopathy, elevated troponin, cardiovascular disease, epilepsy or rhabdomyolysis were excluded. Patients with an established diagnosis within the first two visits with the rheumatologist were also excluded. Comparisons between groups were tested using two-sample t-tests, Wilcoxon rank sum tests, or Kruskal-Wallis test, and Pearson’s chi-square or Fisher’s exact tests, as appropriate.

Results: 62 patients were included of which 67.7% were male, 95.2% Caucasian, with median CK 368 U/L at baseline, median highest CK 602 U/L and median follow up of 7 years (interquartile range 5 to 8 years). At the end of the observation period, 2 patients (3.2%) were diagnosed with inflammatory myopathy. 36 patients (58.1%) were thought to have elevated CK due to medications (mostly cholesterol lowering medications), 5 patients (8.1%) were classified as "other" (race, exercise) causes and for 19 (30.6%) patients there was no established cause for the elevated CK. There were no differences between the outcome groups regarding demographics, median CK or symptoms at baseline. In 27 patients (43.5%) CK normalized at follow-up. Patients with normalized CK were older (median age 66 vs. to 56 years, p=0.03) and had lower CK levels (median CK 306 vs. to 403 U/L, p=0.009) at baseline compared to patients whose CK remained elevated. Of the 56 patients with symptoms at baseline 28 (50%) became symptom-free at follow-up; absence of muscle weakness was associated with resolution of the symptoms in follow-up (92.3% vs. 67.9%, p=0.026). In the 36 patients with CK elevation due to medications, CK normalized in 19 (52.8%) and symptoms subsided in 20 (55.6%) patients at follow-up. In the 19 patients with CK elevation of unknown etiology, CK normalized in 6 (31.6%) and symptoms subsided also in 6 (31.6%) patients at follow-up.

Disclosure: L. Kirillova, None; A. Tacang, None; A. Berger, None; T. M. Harrington, None; A. Bill, None.

914

A Predictive Model of Disease Outcome in Rituximab-Treated Myositis Patients Using Clinical Features, Autoantibodies, and Serum Biomarkers

Jeanette Olazagasti1, Cynthia S. Crowson1, Molly S. Hei1, Consuelo Lopez de Padilla2, Rohit Aggarwal2, Chester V. Oddi2 and Ann M. Reed1

1Mayo Clinic, Rochester, MN, 2University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Develop predictive models of early (8 week) and late (24 week) disease outcomes using clinical features, autoantibodies, and serum biomarkers in patients with refractory myositis treated with rituximab.

Methods: In the Rituximab in Myositis (RIM) trial, all subjects (76 with adult dermatomyositis, 76 with adult polymyositis and 48 with juvenile dermatomyositis) received rituximab (2 doses on consecutive weeks) with half the patients receiving drug at baseline and half receiving drug 8 weeks later. Using start of treatment as baseline, serum samples (n=177) were analyzed at baseline and after 8 and 24 weeks after rituximab. Potential predictors included the following baseline features: clinical features, serum muscle enzymes, interferon gene score, autoantibodies (anti-synthetase n=28, TIF1-g n=19, Mi-2 n=28, SRP n=21, NXP2 n=18, non-myositis association n=24, undefined autoantibody n=9), and cytokines/chemokines measured by multiplexed sandwich immunoassays (Meso Scale Discovery) (type-1 IFN-inducible [IP-10, I-TAC, MCP1], Th1 [IFNγ, TNFα, IL2], Th2 [IL4, IL5, IL10, IL12, IL13], Th17 [IL6, IL17, ILβ] and regulatory cytokines [IL10, TNFa, MIP-1α, MIP-1β]). Our primary definition of response to treatment was based on absolute change from baseline to 8 weeks and 24 weeks in physician global assessment (CGA) and, half on VAS, and 6-minute walk test, and, half on VAS and extramascular VAS. Multivariable linear regression models were developed using stepwise variable selection methods.

Results: Preliminary models were built with good predictive ability both for change in physician global assessment and muscle disease activity at 24 weeks (R-square=0.41 and 0.40, respectively). The model for change in physician global assessment included the following baseline clinical and lab features: muscle disease activity, physician global assessment, and I-TAC (Table). The model for change in muscle disease activity included baseline physician global assessment, skeletal disease activity, I-TAC and IFNγ. Similarly, a predictive model was built with excellent predictive ability (R-square=0.67) for change in extramuscular disease activity at 24 weeks. This model included the following baseline clinical and lab features: constitutive, skeletal and extramuscular disease activity by VAS, and MIP-1β and Mi-2. We also built models from baseline to 8 weeks but their predictive ability was inferior compared to those for 24 weeks (R-square=0.3).

Conclusion: Changes in disease activity over time following treatment with rituximab in patients with refractory myositis can be predicted. These models could be clinically useful to optimize treatment selection in these patients.

Disclosure: L. Kirillova, None; A. Tacang, None; A. Berger, None; T. M. Harrington, None; A. Bill, None.

Background/Purpose: Patients with polymyositis (PM) and dermatomyositis (DM) may have an increased risk of myocardial infarction (MI), similar to other connective tissue diseases. However, no relevant data are scarce to date. We estimated the future risk and time trends of MI to other connective tissue diseases. However, no relevant data are scarce to other connective tissue diseases. However, no relevant data are scarce to date.

Methods: Our data include all visits to health professionals and all hospital admissions, investigations (1990–2010) for all individuals. We conducted a retrospective matched cohort study. Ten controls matched by birth year, sex and calendar year were randomly selected from the general population for each case. Outcome: Newly recorded MI events during follow up from hospitalization (ICD-9-CM 410 or ICD-10 code: I21). In addition, we defined death from MI based on the death certificate diagnostic codes, including out of hospital deaths (ICD-10 code: I21). We calculated incidence rate ratios (IRR) overall and stratified by disease duration. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) adjusting for relevant confounders. Sensitivity analyses were conducted to assess for unmeasured confounders.

Results: Among 431 with PM (59% female, mean age 59.9 years) and 352 with DM (65% female, mean age 55.7 years) the corresponding incidence rate ratio (IRR) for MI were 8.14 (95% CI: 4.62–13.99) and 3.80 (95% CI: 1.89–7.09) respectively (see table). Overall, the highest IRRs for MI were in the first year after PM diagnosis (IRR = 12.65, 95% CI: 5.11–31.65) as well as DM diagnosis (IRR = 6.32, 95% CI: 1.66–21.03). The risk of MI remained statistically significant in the fully adjusted models (hazard ratios = 3.78 (95% CI 2.05–6.95) and 6.54 (95% CI: 2.73–15.67), respectively) (see table). Our results remained statistically significant after adjusting for the potential impact of an unmeasured confounder.

Conclusion: The results of this large truly general population-based study indicates an increased risk of MI in people with PM (four fold) and DM (seven-fold) particularly in the first year after diagnosis, suggesting that inflammation plays a key role in the pathogenesis of MI. Our results support the need for increased monitoring for cardiovascular disease and risk modification to prevent this potentially fatal complication in patients with DM and PM.
transient to placebo. These data suggest that the treatment effects observed with Romi are further augmented by follow-on treatments like DMAb.

Osteoporosis Center, Portland, OR. 4Leiden University Medical Center, Leiden, Netherlands, 5University of British Columbia, Vancouver, BC, 6Center for Clinical and Basic Research, Ballerup, Denmark, 7Amgen Inc., Thousand Oaks, CA.

Background/ Purpose: Osteonecrosis of the jaw (ONJ) is a rare but serious adverse event of some antiresorptive therapies, including denosumab (DMAb), and invasive oral procedures and events (OPEs) are suggested to be an important risk factor (Ruggiero, J Oral Maxillofac Surg 2009). The incidence of positively adjudicated ONJ in the DMAb bone loss clinical program is rare (between ≥1 and <10 per 10,000). In this study, we assessed the occurrence of invasive OPEs through Year 5 of the ongoing, 7-year FREEDOM Extension (EXT) trial.

Methods: In FREEDOM, women were randomized to receive DMAb 60 mg SC or placebo every 6 months for 3 years. Those who missed ≥1 dose of investigational product and completed the Year-3 visit were eligible for the open-label FREEDOM EXT; women in the EXT long-term group (N = 2343) received DMAb in FREEDOM and EXT, and women in the EXT cross-over group (N = 2207) received placebo in FREEDOM and DMAbs in EXT. Women who reached the EXT Year-3 visit were asked to chronicle their history of invasive OPEs (eg, dental implants, tooth extraction, natural tooth loss, or scaling or root planing [extensive subgingival cleaning]) during the EXT. Every 6 months thereafter, women were asked to document their oral health history since the last visit. Jaw surgery information was collected starting from month 30 of the EXT.

Results: The majority of women (78%) participated in the survey. Over 5 years of the EXT, 42.4% of these women reported an invasive OPE; the incidence of the 5 individual OPEs reported was similar between groups (Table). ONJ incidence was 0.4% (71/1500 subjects) in women reporting invasive OPEs and 0.05% (1/2036 subjects) in women reporting no invasive OPEs. The actual number of invasive OPEs may be underestimated due to limited capture of OPEs in medical charts and due to subjects’ recall bias of events that occurred in the first 3 years of the EXT. During the EXT (Years 1–5), the exposure-adjusted incidence of ONJ was 4.2 per 10,000 patient-years. Of the 8 ONJ cases, 6 have resolved, 1 is ongoing and continues to be followed, and the final outcome of 1 is unknown, as consent was withdrawn.

Conclusion: While invasive OPEs were common in this group of DMAb-treated women with postmenopausal osteoporosis, ONJ incidence was low. Invasive OPEs will continue to be queried prospectively in the EXT to characterize the long-term background rate.

### Table: Summary of Invasive Oral Procedures and Events

<table>
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<tr>
<th></th>
<th>FREEDOM Extension Years 1–5</th>
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<tbody>
<tr>
<td></td>
<td>Long-term (N = 2207)</td>
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<tr>
<td>Age at EXT baseline in years, mean (SD)</td>
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</tr>
<tr>
<td>Any invasive oral procedure or event, n (%)</td>
<td>763 (41.8)</td>
</tr>
<tr>
<td>Scaling or root planing</td>
<td>500 (27.4)</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>387 (21.2)</td>
</tr>
<tr>
<td>Dental implant</td>
<td>88 (4.8)</td>
</tr>
<tr>
<td>Natural tooth loss</td>
<td>59 (3.2)</td>
</tr>
<tr>
<td>Jaw surgery</td>
<td>11 (0.6)</td>
</tr>
</tbody>
</table>

N = Number of subjects who received ≥1 dose of investigational product in FREEDOM Extension and responded to ≥1 era event questionnaire related to FREEDOM Extension. n = Number of subjects with ≥1 invasive oral procedure or event.


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Evaluation of Invasive Oral Procedures and Events in Women with Postmenopausal Osteoporosis Treated with Denosumab. Results from the Pivotal Phase 3 Fracture Study Extension Nelson B. Watts1, John T. Grbic2, Michael McClung3, Socrates Papapoulos4, David Kendler5, Christence S. Teglbjaerg6, Lawrence O’Connor7, Rachel B. Wagman8, Eric Ng9, Nadia S. Daizadeh1 and Pei Ran Ho2. 1Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH. 2Columbia University, New York, NY. 3Oregon Osteoporosis Center, Portland, OR. 4Leiden University Medical Center, Leiden, Netherlands, 5University of British Columbia, Vancouver, BC, 6Center for Clinical and Basic Research, Ballerup, Denmark, 7Amgen Inc., Thousand Oaks, CA.

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Findings from Denosumab (Prolix®) Postmarketing Safety Surveillance for Serious Infections. W. Golden1, D. B. Crittenden1, M. Uhart1, R. B. Wagman1, C. Stehman-Breen1, S. Papapoulos2 and N. B. Watts3. 1Amgen Inc., Thousand Oaks, CA, 2Leiden University Medical Center, Leiden, Netherlands, 3Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH.
Background/Purpose: Prolia has marketing authorization in the EU, US, Canada, Japan, and over 40 countries or administrative districts worldwide for the treatment of postmenopausal women with osteoporosis at high/increased risk for fracture. As part of pharmacovigilance activities, Amgen Global Safety (AGS) continually assesses postmarketing adverse events reported by health care providers, patients, and other sources. Spontaneous adverse event reports, while often with insufficient information, are the cornerstone of safety surveillance programs and help detect rare and serious adverse drug reactions. Here we characterize the Prolia postmarketing experience for serious infections, including opportunistic infections.

Methods: A cumulative analysis of all non-clinical trial postmarketing serious infection reports (defined as those leading to ER visit or hospitalization) for Prolia in the AGS Database was conducted as of May 10, 2014 from solicited and spontaneous sources. Using postmarketing exposure estimates, we calculated overall reporting rates over time as well as cumulative rates for several serious infection subtypes, including opportunistic infections. Each infection subtype includes ≥1 related MedDRA Preferred Terms (PTs).

Results: Cumulatively through May 10, 2014, the total estimated post-marketing Prolia exposure was 1,963,794 patient-years (p-ys). There were 1,232 postmarketing reports of serious infection. The top 5 most frequently reported PTs were pneumonia (236), urinary tract infection (166), cellulitis (145), diverticulitis (59), and sepsis (59). Time to onset after the first dose of Prolia (reported for 305 cases) was highly variable, ranging from 1 to 916 days (mean 156, median 82.5). Among the 7 reported cases of endocarditis, only 2 were confirmed by echocardiography; both cases had confounding factors. The reporting rate of overall serious infection has decreased over time since product registration (first reporting period in 2010: 153 cases/100,000 p-ys; current reporting period in 2014: 57 cases/100,000 p-ys). Cumulative reporting rates of serious infection subtypes were low (Table) and below the background rates estimated from insurance claims data. Few cases of opportunistic infections were reported and included herpes zoster (32 cases; 1.6 cases/100,000 p-ys), unspecified fungal infections (10 cases; 0.5 cases/100,000 p-ys), and mycobacterium tuberculosis (5 cases; 0.3 cases/100,000 p-ys).

Conclusion: Recognizing the limitations of postmarketing safety data, these data suggest that reporting rates of serious infections decreased over time, and rates of events reported are lower than estimated background rates. The benefit/risk profile for Prolia remains favorable. Ongoing safety surveillance programs and help detect rare and serious adverse drug reactions.
Background/Purpose: Osteoporosis in men is an important clinical problem, associated with significant morbidity, mortality and societal expense. Men with osteoporosis represent between 20 and 25% of all osteoporotic patients and men are at greater risk of death following a hip fracture. Odanacatib (ODN), a selective inhibitor of cathepsin K, is currently being investigated as a treatment for osteoporosis. In a Phase II study in postmenopausal women, treatment with ODN 50mg once-weekly resulted in increases in bone mineral density (BMD) vs. baseline at the lumbar spine (LS) (11.9%) and total hip (TH) (5%) over 5 years. In this 2-year Phase III study safety and efficacy of ODN in the treatment of men with osteoporosis was investigated.

Methods: This was a double-blind, randomized; placebo controlled 24-month trial. Men ≥40 and ≤95 years of age with idiopathic osteoporosis or osteoporosis due to hypogonadism were enrolled. Inclusion criteria included a LS or hip (TH, femoral neck (FN) or trochanter) T-score of ≤−2.5 to ≤−4.0 without prior vertebral fracture or ≤−1.5 to ≤−4.0 with one prior vertebral fracture. Participants were randomized (1:1) to 50mg ODN or PBO orally once-weekly, and all received vitamin D supplements (total intake including food of 1000IU/day) and calcium supplements (total intake including food of ~1200mg daily). The primary outcomes were the effect of ODN versus PBO on LS BMD assessed by DXA versus PBO at 24 months and safety and tolerability. Secondary outcomes included changes in BMD at the TH, FN, trochanter sites, and bone turnover markers (u-NTx, s-CTx, s-PINP and s-BSAP).

Results: A total of 292 men were randomized and received at least one dose of study medication. The average age was 68.8 years, and 5.8% had total testosterone levels below 250ng/dL. BMD increases from baseline at 24 months in the ODN group at the LS and all 3 hip sites (TH, FN and trochanter) were 6.9%, 1.9%, 1.7% and 2.8% respectively, and all were greater vs. PBO (LS, TH and trochanter p<0.01; FN p=0.008). ODN significantly decreased (vs. PBO) the bone resorption markers u-NTxCr and s-CTx (68% and 77%, both p<0.001) and also decreased bone formation markers, s-PINP and s-BSAP (16% and 8%, p=0.001 and p=0.019 respectively) compared to PBO at 24 months. The between group decrease of bone formation markers was maximal at 3 months, after which levels returned towards baseline by 24 months. The adverse events and overall safety profile were similar between ODN and PBO.

Conclusion: In this study, ODN increased spine and hip BMD in osteoporotic men. Changes in bone turnover markers suggest that ODN treatment decreases bone resorption while producing relatively small decreases in bone formation by the end of the study. ODN is a promising potential therapy for the treatment of osteoporosis in men.

Disclosure: E. Orwoll, Merck Human Health, 2; S. Adami, Amgen, Eli-Lilly, Abbagen, Roche, Merck, 5; N. Binkley, Merck Pharmaceuticals, 2, Merck Human Health, 5; R. Chapurlat, None; B. Langdale, Merck, Amgen, Lilly, S. Doleckyj, Merck Human Health, 1, Merck Human Health, 3; H. Giezek, Merck Pharmaceuticals, 1, Merck Human Health, 3; B. Scott, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; A. Santora, Merck Human Health, 1, Merck Pharmaceuticals, 3.

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Comparison of Infection Rates in Patients Receiving Denosumab, Denosumab + Biologics and Biologics Alone in a Suburban Rheumatology Clinic. Sajina Prabhakaran and Charles Pritchard. 1Drexel University College of Medicine, Philadelphia, PA, 2Drexel University College of Medicine, Willow Grove, PA.

Background/Purpose: Biologics including rituximab, abatacept and belimumab increase the risk of infection in patients. Denosumab, a RANK-ligand inhibitor used in the treatment of osteoporosis may theoretically make patients more susceptible to infections. RANK is a member of the tumor necrosis factor receptor (TNFR) superfamily and inhibition may impair mononuclear cell function. One pivotal trial showed an increase in cellulsitis and erysipelas in patients on denosumab. We used a retrospective chart review of a patients in a sole specialty rheumatology practice to evaluate the infection rates and hospitalizations of patients on the combination of biologics with denosumab, biologic agents alone, and denosumab alone.

Methods: We reviewed the charts of 136 patients, 50 patients who received biologics only, 50 patients who received denosumab alone and 36 patients who received both simultaneously over the past 4 years. Biologics studied included infliximab, tocilizumab, rituximab, belimumab, abatacept, adalimumab, and golimumab. The primary end-point was to determine if there was a greater risk of infection, hospitalization, complication or discontinuation of biologic and/or denosumab in the combined group versus the biologic alone. Percentage of incidence was calculated for each group and Chi-square and Fisher’s Exact tests were used for analysis. Relative risks were calculated to compare infection risks between groups.

Results: There was no difference found in the risk of infection between the groups that received both biologic and denosumab compared to biologic alone, RR = 1.24, 95% CI: 0.76–2.04. There were statistically significant increases in the risk of infection in the groups that received both biologic and denosumab compared to the group that received denosumab; RR=7.87, 95% CI: 2.49–24.9 and biologic alone compared to denosumab, RR=6.35, 95% CI: 2.66–15.2. However, these rates were higher in the combination group compared to the denosumab (19.4% vs 12.5%, p=0.038). Statistically significant increases in the risk of infection with increased duration of exposure to biologics (p<0.001) were also noted.

Conclusion: We did not find an increased risk of infection with the combination of denosumab and a biologic compared to a biologic alone. The rates of infection and hospitalization of patients in the combination group were not significantly different between biologic medications. Secondary characteristics also did not affect the compared rates of infection. The duration of exposure to denosumab did not affect the infection rate. There did not seem to be any increased risk of infection in patients on combination non biologic DMARDS and denosumab. In summary this retrospective small study from a sole specialty rheumatology practice did not show a statistical increased risk of infection combining a biologic with denosumab vs a biologic. Hence it appears to be relatively safe to combine denosumab with a biologic agent.

Disclosure: S. Prabhakaran, None; C. Pritchard, Genetech, Abbvie, 6.

A Potential Role for TLR4 Activation in Osteoarthritis Associated Pain. Rachel E. Miller1, Shingo Ishihara1, Phuong Tran1, Richard J. Miller2 and Anne-Marie Malfait1. 1Rush University Medical Center, Chicago, IL, 2Northwestern University, Chicago, IL.

Background/Purpose: Damage associated molecular patterns (DAMPs) result from cellular stress and extracellular matrix breakdown. They may contribute to osteoarthritis (OA) pathogenesis by promoting synovitis and cartilage degradation, via activation of pattern recognition receptors (PRR) on chondrocytes and synovial cells. We hypothesized that DAMPs play a direct role in OA pain through activation of dorsal root ganglia (DRG) neurons. We investigated the effects of three OA-associated DAMPs, S100A8, S100A4, and α2-macroglobulin (α2M) on cultured DRG cells.

Methods: DRG neurons (L3-L5) were isolated from adult C57BL/6 mice (wild type, Tlr4 null or Tlr2 null) and cultured prior to (1) MCP-1 stimulation or (2) Ca2+ mobilization assays. For stimulation assays, cultures were treated overnight with S100A8 (1 μg/ml), S100A4 (1 μg/ml) or α2M (50–100 μg/ml) and supernatants collected for MCP-1 ELISA. The pro-inflammatory cytokine MCP-1 is a key mediator of pain in murine experimental OA. For Ca2+ mobilization assays, cultures were loaded with a Ca2+ indicator dye and responses to S100A8 (1 μg/ml) or α2M (50 μg/ml) were recorded. Further, destabilization of the medial meniscus (DMM) or sham surgery was performed in 10-week old male C57BL/6 mice. Mice were euthanized 8 or 16 weeks later and L3-L5 DRG were harvested for culture, with or without the selective TLR4 antagonist, TAK242 (Tocris, 10 μM). 2-macroglobulin (2M) are mediated through TLR4 whereas 2M (50–100 μg/ml) were recorded. Further, stimulation assays, cultures were treated with 100μg/ml of IL-1. S100A8 was an equally potent inducer of MCP-1 (p<0.0001 compared to control), whereas S100A4 did not stimulate MCP-1 expression.

Results: Stimulation of DRG cultures with α2M resulted in a concentration-dependent increase of MCP-1 production, where 100μg/ml of α2M caused a 10-fold increase compared to unstimulated cells (p<0.0001). These effects are similar to those observed with IL-1. S100A8 was an equally potent inducer of MCP-1 (p<0.0001 compared to control), whereas S100A4 did not stimulate MCP-1 expression.

Results: Responses to α2M or S100A8 were unaltered in DRG cultures of Tlr2 null mice. In contrast, DRG cells from Tlr4 null mice did not produce MCP-1 in response to α2M, whereas the response to S100A8 was 50% suppressed, suggesting that the effects of α2M are mediated through TLR4 whereas S100A8 may use other receptors as well. This was confirmed using a selective TLR4 inhibitor in wild type (wt) DRG cultures.

8 and 16 weeks after DMM, unstimulated DRG cells produced increased amounts of MCP-1 compared to naïve and sham. Addition of TAK242 to the culture medium significantly reduced MCP-1 levels produced by DMM DRG.

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A Potential Role for TLR4 Activation in Osteoarthritis Associated Pain.
cells, suggesting that TLR4 contributes to MCP-1 production observed after DMM surgery.

Since DRG cultures contain glial cells in addition to sensory neurons, we studied direct effects of o2M and S100A8 on neurons through assessing Ca\(^{2+}\) mobilization responses. On average, 8% of wt DRG neurons responded to S100A8 and 23% responded to o2M, suggesting that DRG neurons can express excitatory receptors for these DAMPs. In T\(\beta\)null DRG, 6% of all neurons responded to S100A8 and none responded to o2M.

**Conclusion:** These studies suggest a potential role for DAMPs in DRG activation, which may contribute to OA pain. TLR4 plays an important role in these effects but other receptors may also be involved. Our results suggest that PRR may be a novel therapeutic target in OA associated pain.

**Disclosure:** R. E. Miller, None; S. Ishihara, None; P. Tran, None; R. J. Miller, None; A. M. Malfait, None.

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**Characteristics of Pain Flares in Knee Osteoarthritis.** Susan L. Murphy\(^1\), Angela K. Lyden\(^1\), Arnold Gammaitoni\(^2\), David A. Williams\(^3\), Daniel J. Clauw\(^1\), J. Ryan Scott\(^1\) and Kristine Phillips\(^3\). \(^1\)University of Michigan, Ann Arbor, MI, \(^2\)Zogenix, Inc, San Diego, CA, \(^3\)Univ of MI Hlth System-Lobby M, Ann Arbor, MI.

**Background/Purpose:** For inclusion in osteoarthritis clinical trials, participants often need to have a pain ‘flare’, usually defined as a pain increase over a period of time prior to study entry. Outside of clinical trial settings, there is no consensus regarding what constitutes a pain flare. The purpose of this study was to examine the pain flares and their impact on daily living.

**Methods:** 45 participants (64 + 10 years; 55% female) with knee osteoarthritis underwent a baseline clinic visit as part of a larger pharmaceutical trial. At this visit, symptom measures were collected and participants were trained in procedures to collect data using a wrist-worn accelerometer in a 7-day home monitoring period. Participants wore the Actiwatch-Score and entered ratings of pain severity (0–10 scale) eight times per day. They were also asked to provide information at the end of each day in a logbook. Participants were asked to provide a definition of a pain flare and used that definition to indicate in the logbook if they experienced a pain flare that day and what and where they were doing when it occurred. Pain variability was calculated as the standard deviation of the pain ratings over the 7 day period. We hypothesized that pain flares and pain variability would be strongly related.

**Results:** When asked to define ‘pain flare’, descriptors of ‘sharp’ and ‘increased pain’ were used by 50% and 21% of the sample respectively. Other descriptors included ‘intense/severe’, ‘electrical’ and various descriptors (e.g., twinge, stabbing, pulsation). Pain flares were most often described to be of short duration. During the home monitoring period, 77% of the sample experienced at least one pain flare and the mean was 2.2 ± 2.0. Pain flares were most strongly associated with their worst daily pain (r = .51), followed by weekly average pain severity (r = .42), pain interference on the Brief Pain Inventory (r = .39), and WOMAC pain scale (r = .37). When asked to describe what they were doing when a pain flare occurred, participants most frequently mentioned activity-related causes (stair climbing, walking, shopping), while very few mentioned stiffness due to inactivity or being awakened by night pain. Pain flares were not significantly associated with pain variability (r = .12) or with neuropathic pain as measured by the PainDetect (r = .09); however PainDetect was most strongly correlated with WOMAC Pain (r = .60), WOMAC Physical Function (r = .57), and BPI severity (r = .60).

**Conclusion:** Pain flares occurred frequently over a week for people with osteoarthritis, were of short duration, and were most often experienced during activities. Interestingly, pain flares were not associated with pain variability. Although pain flares and pain variability may be activity-related, WOMAC subscale, which asked about pain or function during activities, were most strongly associated with a neuropathic component to pain. These findings provide further insight into the pain experience for people with knee osteoarthritis. Pain flares appear to be characterized by researchers and individuals with knee osteoarthritis in a variety of ways suggesting the need for additional research in this area.

**Disclosure:** S. L. Murphy, None; A. K. Lyden, None; A. Gammaitoni, Zars Research, 3; D. A. Williams, Pfizer, Inc, 2; D. J. Clauw, None; J. R. Scott, None; K. Phillips, None.

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**Cortical Reorganization after Duloxetine Treatment-Related Pain Decrease in Knee Osteoarthritis.** Pascal Tetreault, Marwan Bali\(\text{\textregistered}\), Etienne Vachon-Presseau, Renita Evonne Yeasted, Thomas J. Schnitzer and A. Vania Apkarian. Northwestern University, Chicago, IL.
Background/Purpose: Structural brain properties of patients coping with chronic painful conditions are becoming better understood but knowledge on how pain treatment affects these properties is still sparse. Assessment of cortical modifications during chronic pain evolution now permits identifying regions critically involved in painful pathologies. In this study, we evaluate structural brain reorganization of knee osteoarthritic (OA) patients after four months treatment with duloxetine (DLX) or placebo (P).

Methods: OA patients (n=40) meeting standard inclusion/exclusion criteria were randomized to treatment at baseline (figure 1A) and meniscal tear score (0.40 versus 0.10, P = 0.012) in the medial tibiofemoral compartment. No significant difference in BML change was observed. In multivariable analysis, after adjustment for founders and these structural factors, offspring still had an elevated risk of worsening knee pain (OR = 2.22, 95%CI = 1.17 to 4.22), as well as each subscale apart for walking and standing (OR = 2.01 to 3.36, all P < 0.05).

Conclusion: Offspring with family history of knee OA have an increased risk of worsening knee pain and progression of knee cartilage and meniscal pathology but not bony structural changes suggesting that genetic factors may be independently involved in the pathogenesis of knee pain and facets of structural progression. Intriguingly, the change in knee pain was independent of structural factors suggesting this effect is mediated by factors outside the knee.

Disclosure: F. Pan, None; H. Khan, None; G. Ding, None; T. Winzenberg, None; J. Martel-Pelletier, None; J. P. Pelletier, None; F. Cicuttini, None; G. Jones, None.

926 Does a Family History of Total Knee Replacement for Knee Osteoarthritis Influence Knee Pain and Structural Progression? A Prospective Longitudinal Cohort Study.

Methods: Duloxetine and pain relief. We thus add modification in GMD in the left precentral gyrus, left middle frontal gyrus and bilateral ACC (figure 1A). Interestingly, when patients positively responded to their treatment, independent of compound received, difference in GMD was observed only in the left precentral gyrus (figure 1B). In addition, regions in the left middle frontopolar (figure 1C) and inferior temporal gyri showed GMD changes when DLX induced pain relief. We thus show that some cortical regions presenting GMD reorganization were shared temporally. However, we observed a significant volume decrease (p < 0.001). Following treatment, DLX responders had a borderline significant volume increase (p = 0.07); in contrast, placebo responders had a significant volume decrease (p < 0.05). Whole-brain voxel-wise VBM contrast (before – after treatment) revealed that DLX-treated patients underwent modification in GMD in the left precentral gyrus, left middle frontal gyrus and bilateral ACC (figure 1A). Interestingly, when patients positively responded to their treatment, independent of compound received, difference in GMD was observed only in the left precentral gyrus (figure 1B). In addition, regions in the left middle frontopolar (figure 1C) and inferior temporal gyri showed GMD changes when DLX induced pain relief. We thus show that some cortical regions presenting GMD reorganization were shared among all 4 groups studied, suggesting that a proportion of gray matter structural modification may be naturally occurring in time while other regional changes are directly related to treatment received.

Conclusion: Understanding how pharmacological treatment affects structural brain properties is important to assess drug efficacy and its potential deleterious effects. We herein show that pharmacological treatment of OA pain is affecting cortical reorganization in a way that is dependent on treatment, response and the interaction of both.

Disclosure: P. Tetreault, None; M. Baliki, None; E. Vachon-Presseau, None; R. E. Yeasted, None; J. T. Schnitzer, None; A. V. Apkarian, None.

927 Urate Crystal Induced Inflammation and Joint Pain Are Reduced in Transient Receptor Potential Ankyrin 1 (TRPA1) Deficient Mice – a New Potential Role for TRPA1 in Gout.

Methods: Does a Family History of Total Knee Replacement for Knee Osteoarthritis Influence Knee Pain and Structural Progression? A Prospective Longitudinal Cohort Study.

Methods: A total of 219 participants (mean age 48 years, range 29 to 61) with 115 offspring and 104 controls participated in this study. Knee pain was respectively assessed using a simple knee pain questionnaire at baseline and at 6 months, while knee structural progression over 8 to 10 years as compared to randomly selected controls with no family history of knee OA.

Methods: Duloxetine and pain relief. We thus add modification in GMD in the left precentral gyrus, left middle frontal gyrus and bilateral ACC (figure 1A). Interestingly, when patients positively responded to their treatment, independent of compound received, difference in GMD was observed only in the left precentral gyrus (figure 1B). In addition, regions in the left middle frontopolar (figure 1C) and inferior temporal gyri showed GMD changes when DLX induced pain relief. We thus show that some cortical regions presenting GMD reorganization were shared among all 4 groups studied, suggesting that a proportion of gray matter structural modification may be naturally occurring in time while other regional changes are directly related to treatment received.

Conclusion: Understanding how pharmacological treatment affects structural brain properties is important to assess drug efficacy and its potential deleterious effects. We herein show that pharmacological treatment of OA pain is affecting cortical reorganization in a way that is dependent on treatment, response and the interaction of both.

Disclosure: P. Tetreault, None; M. Baliki, None; E. Vachon-Presseau, None; R. E. Yeasted, None; J. T. Schnitzer, None; A. V. Apkarian, None.

927 Urate Crystal Induced Inflammation and Joint Pain Are Reduced in Transient Receptor Potential Ankyrin 1 (TRPA1) Deficient Mice – a New Potential Role for TRPA1 in Gout.

Lauri J. Moilanen, Mari Hamalainen, Lauri Lehtimaki, Riina Nieminen and Eeva Moilanen. The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland.

Background/Purpose: In the gout, monosodium urate (MSU) crystals deposit intra-articularly and cause painful arthritis. In the present study we tested the hypothesis that Transient Receptor Potential Ankyrin 1 (TRPA1), an ion channel mediating nociceptive signals and neurogenic inflammation, is involved in MSU crystal-induced responses in gout by utilizing three experimental murine models.

Methods: The effects of pharmacological selective inhibition (HC-030031) and genetic depletion of TRPA1 were studied in MSU crystal-induced inflammation and pain by using 1) spontaneous weight-bearing test to assess MSU crystal-induced joint pain, 2) subcutaneous air-pouch model resembling joint inflammation to measure MSU crystal-induced cytokine production and inflammatory cell accumulation, and 3) MSU crystal-induced paw edema to assess acute vascular inflammatory responses and swelling.

Results: Intra-articularly injected MSU crystals provoked spontaneous weight shift off the affected limb in wild type but not in TRPA1 knock-out mice referring to alleviated joint pain in TRPA1 deficient animals. MSU crystal-induced cell infiltration and accumulation of cytokines MCP-1, IL-6, IL-1beta, MPO, MIP-1alpha and MIP-2 in subcutaneous air-pouch was attenuated in TRPA1 deficient mice and in mice treated with the TRPA1 inhibitor HC-030031 as compared to control animals. Further, HC-030031 treated and TRPA1 deficient mice developed tempered inflammatory edema when MSU crystals were injected into the paw.

Conclusion: TRPA1 mediates MSU crystal-induced inflammation and pain in experimental models introducing TRPA1 as a potential mediator and a drug target in gout flare.
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A Multinational Study of the Epidemiology, Treatment and Outcome of Childhood Arthritis Preliminary Data from 6,940 Patients. Alessandro Consolaro1, Amita Aggarwal2, Troels Herlin3, Olga Vogougiouka4, Ruben Burgos-Vargas5, Ilonka Orban6, Nahid Shafaie7, Maria Trachana8, Lidia Rutkowska-Sak9, Ingrida Rumba-Rozenfelde10, Dimitrina Mihaylova11, Alberto Martini1 and Angelo Ravelli12. 1Istituto Giannina Gaslini, Genova, Italy, 2Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, 3Aarhus University Hospital, Aarhus, Denmark, 4P. A. Kyriakou Childrens Hospital of Athens University, Athens, Greece, 5Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, 6National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, 7Tehran University of Medical Sciences, Tehran, Iran, 8Aristotle University, Thessaloniki, Greece, 9Institute of Rheumatology, Warsaw, Poland, 10University of Latvia, Riga, Latvia, 11University Children Hospital, Sofia, Bulgaria, 12Istituto Giannina Gaslini and University of Genova, Genova, Italy.

Background/Purpose: The epidemiology of juvenile idiopathic arthritis (JIA) is known to be variable worldwide and the therapeutic approach to JIA is not standardized. Moreover, the availability of the novel and costly biologic medications is not uniform throughout the world, with possible significant impact on disease prognosis. The EPOCA study is aimed to obtain information on the frequency of JIA subtypes in different geographic areas, the therapeutic approaches adopted, and the disease status of children with JIA currently followed worldwide.

Methods: So far, 124 centers in 55 countries have agreed to participate in the study. Participation in the study was proposed to the pediatric rheumatology center of all countries belonging to the Pediatric Rheumatology International Trials Organization (PRINTO), and to several centers in the US and Canada. Each center was asked to enroll 100 consecutive JIA patients or, if less than 100, all consecutive patients seen within 6 months. Each patient received a retrospective and cross-sectional assessment. Parent- and child-reported outcomes were recorded through the administration of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Participating countries were grouped into 6 geographic areas.

Results: Currently, 6,940 patients from 41 countries have been entered in the web database. Comparison of data from the different geographic areas is presented in the table.

<table>
<thead>
<tr>
<th>Geographical Area</th>
<th>JIA Cases</th>
<th>JIA Controls</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>79</td>
<td>76</td>
<td>155</td>
<td>1.00</td>
</tr>
<tr>
<td>Asia</td>
<td>264</td>
<td>273</td>
<td>537</td>
<td>1.00</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2173</td>
<td>2273</td>
<td>4446</td>
<td>1.00</td>
</tr>
<tr>
<td>Latin America</td>
<td>795</td>
<td>815</td>
<td>1610</td>
<td>1.00</td>
</tr>
<tr>
<td>North America</td>
<td>243</td>
<td>243</td>
<td>486</td>
<td>1.00</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2465</td>
<td>2465</td>
<td>4930</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Conclusion: Patients seen in Western Europe have a younger age at onset and a greater prevalence of uveitis. Systemic arthritis is more common in Asian patients, whereas enthesis related arthritis is less frequent in African patients. Children from Africa and Eastern Europe have a higher level of disease activity and a lower frequency of inactive disease, and African and Latin American patients have a greater prevalence of articular damage. Biologic medication are administered more frequently in North America and less commonly in Asia.

Disclosure: A. Consolaro, None; A. Aggarwal, None; T. Herlin, None; O. Vogougiouka, None; R. Burgos-Vargas, None; I. Orban, None; N. Shafaie, None; M. Trachana, None; L. Rutkowska-Sak, None; I. Rumba-Rozenfelde, None; D. Mihaylova, None; A. Martini, None; A. Ravelli, None.

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Antibiotic Exposure and the Development of Juvenile Idiopathic Arthritis: A Population-Based Case-Control Study. Daniel B. Horton1, Frank I. Scott IV2, Kevin Haynes3, Mary E. Putt4, Carlos D. Rose2, James D. Lewis1 and Brian L. Strom1. 1Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 2Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA, 3Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, 4Rutgers Biomedical and Health Sciences, Newark, NJ.

Background/Purpose: Dysregulation of the human microbiome has been implicated in the development of several autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD). Moreover, antibiotic exposure has been linked with the development of IBD in children. This study aimed to determine whether early antibiotic exposure increases the risk of incident juvenile idiopathic arthritis (JIA) in a general pediatric population.

Methods: A nested case-control study was conducted using The Health Improvement Network, a United Kingdom population-based medical records database with comprehensive diagnostic and outpatient prescription data. Children with incident JIA diagnosed before age 16 were identified by validated diagnostic codes (positive predictive value 86%). Age- and sex-matched control subjects were randomly selected with incidence density sampling in a 10:1 ratio from general practices taking care of at least 1 child diagnosed with JIA. Eligible subjects needed to be registered within 3 months of their birthdate. Individuals with prior IBD, immunodeficiency, autoimmune connective tissue disease, or vasculitis were excluded. The association between antibiotic prescriptions and JIA diagnosis was determined by conditional logistic regression.

Results: There were 153 children diagnosed with JIA in the study population (table 1). Any antibiotic exposure was associated with an increased risk of developing JIA after adjusting for confounders (adjusted OR 2.6, 95% CI 1.5-4.6) (table 2). This risk increased with the number of prescriptions in a dose-dependent manner. These results did not significantly change when adjusting for the number or type of infections. Age of exposure did not significantly modify this association. The relationship between antibiotics and incident JIA was similar across different antibiotic classes, although use of non-bacterial antimicrobial agents (e.g., antifungal, antiviral) was not associated with JIA. In sensitivity analyses excluding data up to 12 months before the index date, the association between antibiotics and incident JIA did not substantively change.

Conclusion: Antibiotic exposure was associated with an increased incidence of JIA. This study implicates a role for antibiotic exposure in disease pathogenesis, perhaps mediated through alteration in the microbiome.

Table 1: Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>96 (63)</td>
<td>960 (63)</td>
<td>1056 (63)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age category</td>
<td>107 (70)</td>
<td>1070 (70)</td>
<td>1177 (70)</td>
<td>1.00</td>
</tr>
<tr>
<td>1-5 years</td>
<td>36 (23)</td>
<td>360 (23)</td>
<td>396 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-10 years</td>
<td>10 (7)</td>
<td>100 (7)</td>
<td>110 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>25 (15)</td>
<td>256 (15)</td>
<td>281 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Personal autoimmune disease</td>
<td>5 (3)</td>
<td>0 (0)</td>
<td>5 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>44 (29)</td>
<td>195 (29)</td>
<td>239 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any infection</td>
<td>142 (93)</td>
<td>1313 (86)</td>
<td>1455 (86)</td>
<td>0.02</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>125 (82)</td>
<td>1138 (74)</td>
<td>1263 (75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>37 (24)</td>
<td>394 (26)</td>
<td>431 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30 (20)</td>
<td>253 (17)</td>
<td>283 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>35 (23)</td>
<td>296 (19)</td>
<td>331 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>7 (5)</td>
<td>63 (4)</td>
<td>70 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>83 (54)</td>
<td>865 (57)</td>
<td>948 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total infections, median (QRR)</td>
<td>3 (1.4)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Antibiotic exposure was associated with an increased incidence of JIA in a large pediatric population. This study implicates a role for antibiotic exposure in disease pathogenesis, perhaps mediated through alteration in the microbiome.
Steady Level (p >0.04 mg/day) 5.48 (0.07, 31.01) 8.99 (1.24, 66.69) 2.48 (0.03, 17.44) 11.18 (1.72, 73.70)
Steady Level (p >0.03 mg/day) 0.32 (0.10, 1.29) 0.61 (0.09, 3.12) 0.81 (0.02, 2.60) 0.13 (0.03, 0.87)
Prior MTX treatment (no vs yes) 1.94 (0.75, 5.00) 2.78 (0.33, 21.33) 2.97 (0.44, 20.51) 1.77 (0.65, 4.80)
Prior anti-TNF treatment (no vs yes) 1.81 (0.82, 4.09) 3.62 (0.27, 51.00) 2.03 (0.01, 6.78) 3.44 (0.44, 33.77)
Values in bold are significant; *Significant in at least one time point

Conclusion: This exploratory analysis suggests that canakinumab-naıve patients with normal CRP (i.e. ≤10 mg/l) at Day 15, lower baseline steroid doses, low number of active joints, no prior NSAID use are most likely to achieve inactive disease up to 12 weeks.

Disclosure: H. I. Brunner, Novartis, Genentech, Pfizer, UCB, AstraZeneca, Bojen, Boehringer-Ingelheim, Regeneron, 5, Novartis, Genentech, 8, Novartis Pharma AG, 9; N. Ruperto, Abbott, AstraZeneca, BMS, Centocor Research & Development, Eli Lilly and Company, “Francesco Angelini”, Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuticals Inc... This exploratory analysis suggests that canakinumab-naıve patients with normal CRP (i.e. ≤10 mg/l) at Day 15, lower baseline steroid doses, low number of active joints, no prior NSAID use are most likely to achieve inactive disease up to 12 weeks.

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Table 2 Multivariable models

<table>
<thead>
<tr>
<th>Exposure associated with JIA</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>2.6</td>
<td>1.54.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Any antibiotic, by dose category</td>
<td>2.7</td>
<td>1.37.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Unexposed (reference)</td>
<td>3.1</td>
<td>1.65.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5–10 courses</td>
<td>3.8</td>
<td>1.97.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More than 5 courses</td>
<td>4.5</td>
<td>2.1.0</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Legend: IQR interquartile range. All statistics are expressed as n (%) unless otherwise stated. All p values were obtained from univariable conditional logistic regression models.

Background/Purpose: Systemic juvenile idiopathic arthritis (SIA), an interleukin-1ß (IL–1ß)-mediated autoinflammatory disease, is characterized by recurrent flares of active disease. Canakinumab (CAN), a selective, human, anti-interleukin-1ß monoclonal antibody, has been shown to be efficacious in the treatment of SIA (Ruperto et al. N Engl J Med 2012). The present study aimed to explore baseline demographics and clinical characteristics that are most predictive of response to CAN in CAN-naive SIA patients during the initial 12 weeks of therapy.

Methods: Data from 3 trials were pooled for this analysis. CAN-naive patients (pts; n=178) aged 2–19 years with active SIA were enrolled and received sc CAN 4 mg/kg/month. Predictors of response (according to aACR* 30, 70, and Inactive Disease [ID]) at Days (D) 15, 29, 57 and 85 were explored using univariate and multivariate logistic regression analyses. The candidate predictors (categorical variables) of CAN-response considered were: Age group, Gender, Prior NSAIDs (no/yes), Prior MTX (no/yes), Steroids (0, >0 ≤5 0.4; >4 mg/kg/day), Number of Active Joints (≤10, 11≤20, >20) and Joints with Limitation of Motion (≤10, 11≤20, >20), CRP (elevated/normal) at baseline and at D15. All candidate predictors with p<0.1 in univariate analyses were included in the multivariate analysis. *ACR response plus absence of fever.

Results: By Week 2 there was substantial clinical benefit with 102 pts responding to open-label canakinumab treatment 4mg/kg/4wks sc, maintained a minimum adapted ACR Pediatric criteria [aACR*] 30 for up to 32 weeks, and were steroid-free or had successfully reduced steroid dose reduction/discontinuation and reduces risk to experience a flare. We evaluated the maintenance of efficacy with continued canakinumab treatment in SIA patients during the blinded randomized treatment withdrawal part of a large phase III trial.

Methods: Patients 2–19 yrs of age with active SIA who had responded to open-label canakinumab treatment 4mg/kg/4wks sc, maintained a minimum adapted ACR Pediatric criteria [aACR*] 30 for up to 32 weeks, and were steroid-free or had successfully reduced steroid dose reduction/discontinuation and reduces risk to experience a flare. We evaluated the maintenance of efficacy with continued canakinumab treatment in SIA patients during the blinded randomized treatment withdrawal part of a large phase III trial.

Results: 100 pts were randomized to a canakinumab (n=50) or a placebo (n=50) group, of whom 26 (53%) and 27 (54%), respectively, had CID at the start of the randomization part. In the first 2 months, probability of maintaining aACR response was similar for both treatment groups. Thereafter, the probability of maintaining aACR response was greater in the canakinumab vs placebo groups. The median time to worsening in aACR level for patients in the placebo group was 141 days (95% CI: 85, 281), and could not be calculated for canakinumab as <50% of canakinumab group had a worsening in their aACR level by the end of this phase. The median duration of exposure

Table: Inactive Disease - Multivariate logistic regression analysis on 12-week data

<table>
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<th>Variable</th>
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<td>CRP at Day 15 (elevated vs normal)</td>
<td>0.23 (0.07, 0.75)</td>
</tr>
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<td>Number of active joints (11–20 vs &lt;11)</td>
<td>0.22 (0.05, 1.66)</td>
</tr>
<tr>
<td>Number of active joints (0 vs &gt;20)</td>
<td>2.54 (0.12, 55.70)</td>
</tr>
<tr>
<td>Prior NSAID treatment (no vs yes)</td>
<td>2.01 (0.71, 5.71)</td>
</tr>
</tbody>
</table>

Background/Purpose: Canakinumab, a selective, human, anti-interleukin (IL) –1ß monoclonal antibody, is approved for the treatment of systemic juvenile idiopathic arthritis (SIA) patients (≥2 years old). SIA is an IL–1ß-mediated autoinflammatory disease, which is characterized by recurrent flares of active disease. Canakinumab treatment in patients with SIA, allows for successful steroid dose reduction/discontinuation and reduces risk to experience a flare.

We evaluated the maintenance of efficacy with continued canakinumab treatment in SIA patients during the blinded randomized treatment withdrawal part of a large phase III trial.

Results: 100 pts were randomized to a canakinumab (n=50) or a placebo (n=50) group, of whom 26 (53%) and 27 (54%), respectively, had CID at the start of the randomization part. In the first 2 months, probability of maintaining aACR response was similar for both treatment groups. Thereafter, the probability of maintaining aACR response was greater in the canakinumab vs placebo groups. The median time to worsening in aACR level for patients in the placebo group was 141 days (95% CI: 85, 281), and could not be calculated for canakinumab as <50% of canakinumab group had a worsening in their aACR level by the end of this phase. The median duration of exposure

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for the canakinumab group was 221.5 days (range: 8–617 days). There was a statistically significant relative risk reduction of 51% for the canakinumab vs placebo group to experience a worsening in aACR level (HR = 0.49; 95% CI: 0.27, 0.90; p = 0.0131). CID was achieved by 31 (62.0%) vs 17 (34.0%) patients in canakinumab vs placebo at their last visit (OR = 3.4; 95% CI: 1.5, 8.0; p = 0.0020) and CRM was reached by 20 (40%) canakinumab and 2 (4%) placebo patients by the end of the study.

Conclusions: A greater proportion of SJIA patients who continued canakinumab treatment maintained/improved their aACR response, achieved CID and CRM than pts who discontinued canakinumab by being switched to placebo, demonstrating maintenance of efficacy with continued canakinumab treatment over time.


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MRP8/14 Serum Level As Predictor of Response to Starting and Stopping Anti-TNF Treatment in Non-Systemic Juvenile Idiopathic Arthritis. Janneke Anink1, Marijke H. Otten1, Lisette W.A. van Suijlekom-Smit2, Marion A.J. Van Rossum3, Koert M. Dolman3, Esther P.A. Hoppenrejs4, Rebecca ten Cate5, Simona Ursu6, Lucy R Wedderburn1, Gerd Hornfell8, Thomas Vogl8, Dirk Föll11, Johannes Roth9 and Dirk Holzinger11.

1. Erasmus MC Sophia Children’s Hospital’s, Rotterdam, Netherlands, 2. Emma Kinderziekenhuis Academic Medical Center, Amsterdam, Netherlands, 3. St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, 4. Radboud University Medical Center, Nijmegen, Netherlands, 5. Leiden University Medical Center, Leiden, Netherlands, 6. Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, 7. Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, 8. Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, 9. Institute of Immunology University of Muenster, Muenster, Germany, 10. University Children’s Hospital Muenster, Muenster, Germany, 11. University Hospital Muenster, Muenster, Germany.

Background/Purpose: Biological therapy has dramatically improved the treatment of patients with JIA. However, there is still a group of patients that shows a lack of clinical response to this treatment. Furthermore, when patients do respond to treatment with etanercept, it is unclear when they can discontinue this treatment. The use of robust predictive markers of response to identify individuals who are likely to respond to anti-TNF treatment (etanercept or adalimumab) and who are able to stop etanercept may provide guidance in optimizing treatment strategies. Our objective was to test the ability of baseline MRP8/14 serum levels to differentiate between responders and non-responders to anti-TNF treatment and to correlate longitudinal follow-up of this marker in response to treatment. A second objective was to test the ability of MRP8/14 to distinguish between patients who are likely to flare after discontinuing etanercept.

Methods: Samples were collected from 89 JIA patients (13 polyarticular rheumatoid factor (RF) positive, 33 polyarthritics RF negative, 24 extended oligoarthritics, 5 persistent oligoarthritics, 4 enthesis related arthritis, 10 psoriatic arthritis) included in the Dutch Arthritis and Biologics in Children Register, the German Registry for Biologics in Paediatric Rheumatology and Great Ormond Street Hospital for Children London treated with TNF blockers. The patients were categorized into responders (ACRpedi≥50) and/or inactive disease according to the Wallace) and non-responders (ACRpedi<50).

Serum concentrations of MRP8/14 complexes were measured by ELISA at start of biological treatment and if available also within 6 months after start of treatment. A flare was defined as having at least three of the following: VAS physician or patient ≥ 20 mm, ≥ 2 active joints, any worsening on the CHAQ and ≥ 30% worsening on ESR or limited joints. Non-parametric tests were used for analyses.

Results: Before initiation of etanercept treatment, responders (n = 71) showed significantly higher levels of MRP8/14 serum complexes compared to non-responders (n = 18) (p = 0.004, median in responders: 1490 ng/ml (IQR 1020–3323 ng/ml), median in non-responders: 788 ng/ml (IQR 442–1233 ng/ml)). No significant correlation was found between baseline MRP8/14 and JADAS10 disease activity. In non-responders MRP8/14 levels did not significantly change after initiation of treatment whereas levels decreased in responders (p < 0.001). Change in JADAS10 disease activity was significantly correlated to change in MRP8/14 levels (Spearman’s rho: 0.4, p = 0.03). Samples were available from 28 patients at the time of discontinuation of etanercept. Patients who flared within 6 months after the discontinuation of etanercept had higher MRP levels at discontinuation than patients who did not flare (p = 0.031, median 1025 ng/ml (IQR 588–1288 ng/ml) vs. 505 ng/ml (IQR 346–778 ng/ml)).

Conclusion: High levels of baseline serum MRP8/14 have prognostic value in predicting a subgroup of JIA patients who will respond well to anti-TNF treatment. Decrease of MRP8/14 after initiation of treatment is associated with response to treatment. High MRP8/14 serum levels at time of discontinuation of etanercept are associated with a higher chance to flare.

Disclosure: J. Anink, None; M. H. Otten, None; L. W. A. van Suijlekom-Smit, Pfizer Inc; 2. M. A. J. Van Rossum, None; K. M. Dolman, None; E. P. A. Hoppenrejs, None; R. ten Cate, Pfizer Inc; 2. Pfizer Inc, 5; S. Ursu, None; L. R. Wedderburn, None; G. Horneff, Abbvie, Pfizer, and Roche, 2; Abbvie, Novartis, Pfizer, and Roche, 8; T. Vogl, None; D. Föll, None; J. Roth, None; D. Holzinger, None.

933

A Multi-Center, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab in Pediatric Patients with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate. Week 48 Results: N. Tizabichaye1, C. R. Hermolinio2, G. R. Ruperto3, N. Tzabichaye4, Carine Wouters5, Violeta Vladislya Panaviene6, Vyacheslav Chasnyk7, Carlos Abud-Mendoza7, Ruben Cuttica8, Andreas Reiff9, M Maldonado-Velázquez9, Nadina Rubio-Pérez10, Ric Koos10, V. Keltsev11, Evgeny Nasonov12, Daniel Kingsbury13, M. Bandeira Earl Silverman14, F. Wellner-Hennemann14, A van Royen-Kerkhof15, Alan M. Mendelsohn16, Lilianne Kim17, Daniel Lovell18 and A Martini19. 1PRCSG, Cincinnati, OH, 2Istituto Gianna Gaslini, Genoa, Italy, 3PRINTO & PRCSG, Bramstedt, Germany, 4Asklepios Klinik Sankt Augustin, 5Carine Wouters, 6Violeta Vladislya Panaviene, 7Carlos Abud-Mendoza, 8Ruben Cuttica, 9Andreas Reiff, 10M Maldonado-Velázquez, 11Nadina Rubio-Pérez, 12Ric Koos, 13V. Keltsev, 14Evgeny Nasonov, 15Daniel Kingsbury, 16M. Bandeira Earl Silverman, 17F. Wellner-Hennemann, 18A van Royen-Kerkhof, 19Alan M. Mendelsohn, 20Lilianne Kim, 21Daniel Lovell and 19A Martini. 20PRCSG, Bramstedt, Germany, 4Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany; 5University Hospital Genthise, Leuven, Belgium; 6Novartis Pharma, Saint-Petersburg, Russia; 7Hospital Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosi, San Luis Potosi, Mexico; 8Hospital de Ninos Pedro de Elizalde, Capital Federal, Argentina; 9Children’s Hospital of Los Angeles, Los Angeles, CA; 10INTO, Genova, Italy; 11TIZ Gent, Genoa, Italy; 12Paediatric Rheumatology International Trials Organisation–IRCCS (PRINTO), Genova, Italy; 13State Institute of Rheumatology of RAMS, Moscow, Russia; 14Randall Children’s Hospital at Legacy Emanuel, Portland, OR; 15Hospital Infantil Puerco Principe, Curitiba, Brazil; 16Hosp for Sick Children, Toronto, ON; 17Department of Pediatric Immunology & Rheumatology, Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, Netherland; 18Janssen Research & Development, LLC., Spring House, PA; 19Division of Rheumatology, Cincinnati Children’s Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, OH; 20Istituto Gaslini-PRINTO, Genova, Italy.
Background/Purpose: To assess efficacy and safety of SC golimumab (GLM) in polyarticular pediatric juvenile idiopathic arthritis pts (aged 2 to <18 yrs) with active arthritis despite MTX for ≥3 months.

Methods: In GO-KIDS, a 3-part randomized double-blind, PBO-controlled, withdrawal trial in pts with active JIA with a polyarticular course (≥5 active joints) and disease duration of ≥ 6 months despite current MTX (10–30 mg/m²/wk). In Part 1 (wk0–12), all pts received open-label (OL) 30 mg/m² GLM SC(max 50 mg) q4wks with stable MTX dosage. In Part 2, wk16 pts with ACR JIA 30 response entered Part 2 (wk16–48). In Part 2, pts were randomized to continue GLM or switch to PBO q4wks. Upon Part 2 completion at wk48 or ACR JIA flare in Part 2, pts received OL GLM in Part 3. Primary endpoint was proportion of ACR JIA 30 responders at wk16 without a JIA flare in Part 2 using wk16 as baseline measurement. Secondary outcomes were ACR JIA 30/50/70/90 response rates and inactive disease rates at wk16 and wk48 by group and safety.

Results: 173 pts (Caucasian 87.9%, 75.7% females; age [median/ range] 12 yrs/2–17 yrs) with moderately active disease were enrolled (Table1); 19 (11%) were d/c in Part 1 (lack of efficacy n = 14; AE n = 4, withdrawal of consent n = 1). In Part 1, 151 of 173 (87.3%) achieved an ACR JIA 30 response and 36.1% inactive disease status (Table2). In Part 2, 154 pts were randomized (PBO n = 76; continued GLM n = 78). The trial did not meet primary endpoint, as at the end of Part 2 groups (PBO, GLM) relative to wk 0 (Table1 and 2). Through wk16, pts receiving GLM had a significantly increased the lymphatic pulse vs. IgG (2.63 ± 0.36 pulses/min), and MTX also induced an increase vs. saline (1.08 ± 0.36 pulses/min), although this effect was significantly lower than anti-TNF. Consistently, footpad clearance of ICG was measured via NIR-ICG imaging (Figure). As predicted, anti-TNF treatment significantly decreased normalized synovial IgG (0.87 ± 0.14 vs. 1.52 ± 0.16; p < 0.05), measured by CE-MRI. This decrease correlated with a lower power Doppler volume within the joint, in addition to a measure of anti-TNF and MTX treated mice compared to placebo treated (0.04 ± 0.01 vs. 0.20 ± 0.03 mm³ and 0.05 ± 0.01 vs. 0.18 ± 0.08 mm³, respectively; p < 0.05). Lymphatic pulse rate and clearance were measured via NIR-ICG imaging (Figure). As predicted, anti-TNF significantly increased the lymphatic pulse vs. IgG (2.63 ± 0.68 vs. 0.99 ± 0.36 pulses/min), and MTX also induced an increase vs. saline (1.38 ± 0.21 vs. 0.38 ± 0.38 pulses/min), although this effect was weaker than anti-TNF. Consistently, footpad clearance of ICG was higher in anti-TNF and MTX treated mice vs. placebo (64.5 ± 2.5 ± 0.08 vs. 30.84 ± 12.26 and 64.54 ± 2.6 ± 0.02 vs. 42.49 ± 2.6 ± 0.09, respectively; p < 0.05). To gain insight into the mechanism of lymphatic pulse restoration, TEM was performed on the lymphatic vessels. We found that placebo treated mice showed damaged lymphatic endothelial cells (LEC) and smooth muscle cells (LSMCs), while anti-TNF treated mice showed intact LECs and LSMCs apical to fibrotic tissue, suggestive of tissue repair. Interestingly, anti-TNF treatment resulted in a significant ~4-fold increase in monocyte numbers normalized to placebo vs. MTX (3.77 ± 0.77 vs. 1.08 ± 0.19 cells per PLN; < 0.05) via flow cytometry. We previously reported monocytes trafficking in different lymphatic vessels. Thus, these findings indicate a unique role of monocytes to the PLN from the inflamed joint.

Conclusion: These NIR-ICG, CE-MRI and flow cytometry results

### Table 1

| Values are median (interquartile range) At Baseline (All enrolled patients n = 173) | At wk16 (All randomized patients prior to randomization, n = 154) | At wk48 | PRO + MTX (n = 76) | GLM + MTX (n = 78) |
|---|---|---|---|---|---|
| Physicians global assessment of disease activity | 5.40 (3.00; 7.00) | 0.50 (0.00; 1.30) | 0.30 (0.00; 1.00) | 0.30 (0.00; 1.30) |
| Patients global assessment of well-being | 4.50 (2.00; 6.00) | 0.00 (0.00; 2.30) | 0.60 (0.00; 1.15) | 0.45 (0.10; 1.70) |
| Number of active joints | 12.00 (8.00; 18.00) | 1.00 (0.00; 3.00) | 1.00 (0.00; 3.00) | 0.00 (0.00; 3.00) |
| Number of joints with limited range of motion | 8.00 (6.00; 15.00) | 1.00 (0.00; 4.00) | 0.75 (0.00; 4.00) | 1.00 (0.00; 3.00) |
| Physical function by CHAQ | 0.04 (0.00; 1.00) | 0.25 (0.00; 0.75) | 0.15 (0.00; 0.65) | 0.00 (0.00; 0.65) |
| Methotrexate (mg/wk) | 15.00 (10.00; 30.00) | 15.00 (5.00; 30.00) | 15.00 (5.00; 30.00) | 15.00 (5.00; 30.00) |

### Table 2: ACR JIA response and flare rates

**PART 1 [WK 0–16]**

- Percentage of ACR JIA responders at end of Part 1 [WK 16] (n = 173)
  - JIA ACR 30: 87.3% (151)
  - JIA ACR 50: 79.2% (137)
  - JIA ACR 70: 65.9% (114)
  - JIA ACR 90: 36.4% (65)
  - Inactive disease: 36.1% (62)

**PART 2 [WK 16–48]**

- Percentage of ACR JIA 30 responders without flare in Part 2 (n = 154)
  - PRO + MTX (n = 76): 52.6% (40)
  - P = 0.41

- Percentage of ACR JIA 30 responders at wk48 (vs. wk40) by treatment arm Part 2* [PRO + MTX/ GLM + MTX]
  - JIA ACR 30: 95.9%/89.9%

- Inactive disease [PRO + MTX/GLM + MTX]
  - PRO + MTX (n = 76): 27.6% (21)
  - GLM + MTX (n = 78): 39.7% (31)

Clinical remission (PRO + MTX/ GLM + MTX)

- ACR JIA 30 53.4%/56.2%
- ACR JIA 50 78.1%/78.1%
- ACR JIA 90 59.0% (46)

* S415
demonstrate that anti-TNF increases lymphatic transport to a greater extent than MTX. Furthermore, our data suggest that the primary mechanism for monocyte (type 1 synoviocyte) removal from inflamed joints following anti-TNF treatment is through restoration of lymphatic pulse and cellular egress.

Disclosure: E. M. Bouta, None; I. Kuzin, None; K. de Mesy-Bentley, None; R. Wood, None; H. Rahimi, None; R. C. Ji, None; C. T. Ritchlin, Eli Lilly and Company, 9, Eli Lilly and Company, 5; T. denticola, and T. forsythia. Our study was designed to examine whether the induction of PD enhance arthritis in the collagen-induced arthritis (CIA) mouse model.

Methods: CIA-prone major histocompatibility congenic B10 RIII mice were used in the study. These were divided into four groups (n = 10 each). Group I mice were infected orally with a polybacterial mixture of P. gingivalis, T. denticola, and T. forsythia for 24 weeks. Mice in group II were also orally infected with a polybacterial mixture followed by administration of collagen II (CII) emulsified in complete Freund’s adjuvant (CFA) and boosted with CII in incomplete Freund’s adjuvant (IFA) to induce arthritis. Group III mice were sham-infected controls. Group IV mice were administered CII emulsified in CFA and IFA as collagen control. After 24 weeks of infection, mice were examined for development of PD as well as for RA clinical signs; systemic spread of the infection, matrix metalloproteinase 3 (MMP3) levels, cytokine expression, anti-CCP (cyclic citrullinated peptide) antibodies, and autoimmune signaling molecules. Further, the tissue sections from mouse ankle joints and paws were evaluated for the presence of periodontal bacteria by fluorescence in situ hybridization (FISH).

Results: Group I and II showed oral colonization/infection with all 3 bacteria (100%), higher levels of anti-bacteria IgG antibodies (P < 0.0005) and greater significant alveolar bone resorption (P < 0.0005) than the sham-infected (Group III) and collagen control mice (Group IV). Group II mice showed exacerbated clinical signs of arthritis (10/10), systemic spread of periodontal bacteria, and significant serum MMP3 levels (P < 0.05) compared to Group IV. In vivo tomographic imaging of infected + collagen treated mice using MMP3 fluorescent probe showed intense MMP3 activity (fluorescence intensity = 12) in arthritic lesions (4/4) compared to collagen control mice (fluorescence intensity = 5). Histopathology of infected + collagen treated mouse ankle joints showed higher levels of characteristic inflammatory cellular infiltration, destruction of articular cartilage, pannus formation, and bone distortion (6/6) compared to collagen control mice. FISH showed the presence of P. gingivalis in the ankle joints of infected + collagen treated mice.

Conclusion: This is the first study to examine a causal relationship between PD and RA using two established disease models in mice. This study provides direct evidence for a causal association between major periodontal pathogens/ PD and increased severity in induced arthritis.

Disclosure: S. Chukkapalli, None; M. Rivera-Kweh, None; I. Velsko, None; I. Bhattacharya, None; S. J. Calise, None; E. Chan, None; M. Sato, None; M. Kesavalu, None.

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A Unique Role for IL-18 Receptor-α in Monocyte Migration in RA and K/BxN Serum-Induced Transfer Arthritis

W. Alexander Sinson, Phillip L. Campbell, R. Jeffrey Rust, Gautam Edhayyan, Ray A. Ohran, Nicholas Lepore, Alisa E. Koch, David A. Fox and M. Asif Amin

Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, 2Department of Veteran’s Affairs and University of Michigan, Ann Arbor, MI.
Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by monocyte (MN) recruitment. Proliferative cytokines and their corresponding receptors play an important role in the progression of RA by increasing MN infiltration. Soluble IL-18 receptor-α (IL-18Rα) is highly expressed in RA synovial fluids (SFs), synovial tissues (STs), ST fibroblasts, and CD4+ T cells. In this study, we determined the contribution of IL-18Rα in the pathogenesis of RA.

Methods: Western blotting was performed to examine IL-18Rα expression or IL-18Rα-binding capacity (TNF-α flow cytometry). We performed MN chemoattraction in modified Boyden chambers to determine the role of IL-18Rα in MN migration in vitro. To examine MN homing in the context of RA, we employed an RA ST-severe combined immunodeficient (SCID) mouse chimera using RA SFs with or without IL-18Rα neutralizing antibody. We harvested RA ST after 48 hours and examined tissue sections by immunofluorescence. K/BxN serum transfer arthritis was performed in IL-18Rα null and wild type (wt) mice to determine the role of the IL-18Rα in arthritis and MN recruitment. Cytokine levels were determined by enzyme linked immunosorbent assays (ELISAs) in ankle homogenates of IL-18Rα null and wt mice.

Results: TNF-α stimulated normal human SFs showed a marked increase of IL-18Rα expression. After finding increased expression in IL-18Rα, we determined its role in MN migration. IL-18Rα partially mediates TNF-α and RA SF-induced MN migration, as anti-human IL-18Rα antibody significantly inhibited TNF-α and RA SF mediated MN migration in vitro (p<0.05). We further investigated the importance of IL-18Rα to MN migration in human RA by using the RA-SCID mouse chimera. RA SF injected into the chimeric human ST resulted in MN recruitment to the ST, which was decreased in the presence of mouse anti-human IL-18Rα, suggesting that IL-18Rα is essential in RA SF-stimulated MN migration in vivo. We determined the contribution of IL-18Rα in inflammatory arthritis by performing K/BxN serum transfer arthritis. IL-18Rα null mice were resistant to K/BxN arthritis, showing a significant decrease in ankle circumference compared to wt mice (p<0.05). Mouse ankles harvested on day 9 of maximal arthritis showed a significant decrease in MN migration in IL-18Rα null mouse joint sections compared to wt mice, as determined by staining for F4/80, a macrophage marker. To determine the mechanism of decreased MN ingress and defective arthritis in IL-18Rα null mice, ELISAs were performed for proinflammatory cytokines using mouse ankle homogenates. We found a >3 fold decrease in IL-1β levels in IL-18Rα null mouse ankles compared to wt mouse ankles (p<0.05), suggesting that the IL-18Rα is critical in inflammatory cytokine expression.

Conclusion: These studies suggest that IL-18Rα is inducible in MNs and plays an important role in MN migration in vitro and in vivo. IL-18Rα null mice have impaired MN recruitment and arthritis development in part due to decreased IL-1β. These results provide strong evidence that the IL-18Rα plays an important role in MN ingress in RA and in a rodent model of inflammatory arthritis and may be a novel therapeutic target for RA.

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C1q Is Mandatory for Disease Development in Experimental Arthritis and Expression of Its Receptor Correlates with Rheumatoid Disease Activity in Patients. Matthieu Ribon1, Julie Mussard2, Roxane Herve2, Marina Botto3, Marie-Christophe Boissier4 and Patrice Deckert4. 1INSERM UMR 1125, L2P, Université Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France. 2Imperial College, London, United Kingdom. 3INSERM UMR 1125, L2P, Université Paris 13, Sorbonne Paris Cité, Bobigny, France.

Background/Purpose: The complement system is a major effector mechanism of innate and adaptive immunity. It is activated in rheumatoid arthritis (RA) patients but the pathway involved remains unclear. RA is associated with the production of autoantibodies with some of them, anti-citrullinated protein antibodies, representing a diagnosis and even a prognosis marker. Antibodies are known to activate the complement system via the classical pathway in a C1q-dependent manner. But some models suggest C1q-independent pathways in arthritis. Therefore, we have investigated whether C1q is necessary for disease development in a mouse model of RA based on (auto)immunization and we have analyzed C1q receptor expression in patients.

Methods: Disease development was studied in the collagen-induced arthritis (CIA) mouse model. The impact of C1q was evaluated by comparing wild-type (WT) mice and C1q-knockout (KO) true littermates. Arthritis was followed by clinical score evaluation. Inflammation and bone destruction were estimated by histology. Anti-collagen antibody, C3a and blood cytokine levels were measured by ELISA and Lumitex B/T lymphocytes and neutrophils were analyzed by flow cytometry. Osteoclastogenesis was analyzed by culturing bone marrow cells with M-CSF/RANKL and then counting TRAP-positive multinucleated cells by microscopy. In addition, whole blood cells from healthy donors and RA patients were used to estimate their C1q binding capacity in vitro.

Results: C1q is absolutely required for arthritis development as C1q-KO mice did not develop clinical signs of arthritis in contrast to WT mice. Both WT and KO mice developed anti-collagen antibodies and particularly similar levels of pathogenic IgG2a anti-collagen antibodies. Moreover, neither inflammation nor joint destruction was observed in C1q-KO mice. Importantly, the level of complement activation, estimated by C3a production, was similar in WT and C1q-KO mice. Surprisingly, no statistical difference was observed between WT and KO mice regarding the percentage or the activation of lymphocytes and neutrophils in the blood, spleen and lymph nodes. As a recent study suggested that C1q might influence osteoclastogenesis in vitro, we have shown that C1q deficiency does not alter development of osteoclasts from CIA mice. The impact of C1q on cytokine secretion in vivo is currently being analyzed. In RA patients, we have shown that the percentage of neutrophils able to bind C1q is significantly and positively correlated with the disease activity estimated by the DAS28.

Conclusion: C1q-KO mice are protected from arthritis development and thus C1q plays a key role in the CIA model. Although the complement system is activated, the classical pathway cannot be compensated by the alternative/lectin pathways in this model. Our results strongly differ from those reported in the serum-transfer model where C1q is not necessary for disease development, suggesting that C1q might be involved at different steps, maybe before antibodies are produced, for example in the response to DAMPs. In patients, the expression of total C1q receptors by neutrophils reflects disease activity, supporting the potential role of C1q in RA.

Disclosure: M. Ribon, None; J. Mussard, None; R. Herve, None; M. Botto, None; M. C. Boissier, None; P. Deckert, None.

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Prenatal Methyl-Rich Diet Decreases Inflammation in Collagen Induced Arthritis. Sanjay Garg1, Dipak R. Patel2 and Raymond Yung2. 1University of Michigan, Ann Arbor, MI, Ann Arbor, MI, 2University of Michigan, Ann Arbor, MI.

Background/Purpose: Early-life nutrition can have a profound effect on late-life disease development. Most current studies focus on macro-nutrition (calorie, carbohydrate, fat, and protein), and much less is known about the role that early life micro-nutrition plays in diseases of adults. One notable exception is that prenatal folic acid supplementation dramatically decreases the incidence of spina bifida and other neural tube defects. In mouse models, supplementing ‘methyl donors’ in the diet of pregnant mice (dams) affects the incidence of diabetes and obesity in their offspring. These changes have been attributed to changes in the DNA methylation status of selected genes.

Previously, we have demonstrated that feeding dams a prenatal diet supplemented with methyl donors (MDS) during mating and pregnancy decreases the levels of selected CD4+ T cell pro-inflammatory chemokines and cytokines in F1 mice by changing the DNA methylation pattern of those genes. CD4+ T cells are critical in arthritis pathogenesis, and many of the pro-inflammatory cytokines and chemokines required for arthritis development are regulated by DNA methylation. Recent studies have shown that RA is characterized by a perturbed extracellular redox environment. Based on our preliminary data, we hypothesize that the prenatal MDS diet will decrease inflammation in the collagen-induced arthritis (CIA) model of RA by modulating redox metabolites and CD4+ T cell function.

Methods: Female DBA/2 mice received either a control diet or MDS diet during pregnancy and lactation. Pups born to these mice (F1 Control or F1 MDS) were maintained on those diets after birth and until they were weaned at 4 weeks. After weaning, all mice were fed a standard (NIH 31) diet. Arthritis was then induced, and paw swelling was measured. Cytokines and redox metabolites were measured in the serum at specified time points, and mice were sacrificed for in vitro analysis of CD4+ T cell function.

Results: Both F1-MDS and F1-Control mice developed arthritis 30 days after collagen injection, and the mean arthritis score was decreased by at least 2 points at day 45 after injection (p<0.05). At 55 days after injection, CD4+ T cells from F1-MDS mice expressed decreased levels of TNF-α (p=0.04), IL-17 (p=0.04), and IL-6 (p=0.02) protein. Levels of the chemokine CCR7 were also decreased.
in CD4+ T cells from F1-MDS mice (p=0.02). The serum redox potential in CIA mice is more oxidizing (−77 mV) than in non-CIA mice (−83 mV) (p<0.01). After CIA induction, the redox potential was maintained at a more homeostatic level (−85 mV) in F1-MDS mice, and the redox potential was more oxidizing (−77 mV) in F1-Control mice (p<0.01).

**Conclusion:** The pre-natal MDS diet decreases disease severity, as measured by paw swelling in the CIA model of RA. The diet caused decreases in serum levels of pro-inflammatory cytokines and expression of pro-inflammatory genes in CD4+ T cells. Many of these genes are methylation sensitive. These results demonstrate that a pre-natal diet enriched in methyl donors can decrease disease severity in a mouse model of RA.

**Disclosure:** S. Garg, None; D. R. Patel, None; R. Yung, None.

**ACR Concurrent Abstract Session Rheumatoid Arthritis - Clinical Aspects II: Remission and De-escalation of Therapy**

**Sunday, November 16, 2014, 4:30 PM–6:00 PM**

**940 Reducing Therapy in Rheumatoid Arthritis Patients in Ongoing Remission.** Judith Haschka1, Jürgen Rech1, Matthias Engebrecht1, Stephanie Finzel1, Michaella Reiser1, Axel J. Hueber1, Arnd Kleyer2, Hans-Peter Tony2, Martin Fleck1, Karin Meurer1, Wolfgang Ochs3, Jorg Wendler1, Hann-Martin Lorenz1, Hubert Nüßlein3, Rieke Alten4, Winfried Demary4, and Georg Schett1. 1University of Erlangen-Nuremberg, Erlangen, Germany, 2University Hospital Würzburg, Würzburg, Germany, 3ASKlepios Medical Center Bad Abbach, Bad Abbach, Germany, 4Rheumatology Practice Bamberg, Bamberg, Germany, 5Rheumatology Practice Bayreuth, Bayreuth, Germany, 6Rheumatology Practice Erlangen, Erlangen, Germany, 7University of Heidelberg, Heidelberg, Germany, 8Rheumatology Practice Nuremberg, Nuremberg, Germany, 9Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, 10Rheumatology Practice Hildesheim, Hildesheim, Germany.

**Background/ Purpose:** Due to improved therapeutic management a steadily increasing number of rheumatoid arthritis (RA) patients reach stable remission of disease. Data on withdrawal of medication after sustained remission are limited, though it is important for economic and safety reasons. The RETRO study represents a real-life study addressing different strategies of reduction of DMARD therapy in RA patients in disease remission. The aim of the study was to evaluate the possibility of tapering and even discontinuation of DMARD therapy in RA patients in stable long-lasting remission and to determine predictors for recurrence of disease.

**Methods:** RETRO is a phase 3, multicenter, randomized, controlled, open, prospective, parallel-group trial (EudraCT Number: 2009-015740-42). Patients, fulfilling the ACR/EULAR2010 criteria for RA with disease history of ≥12 months, were enrolled into the study if they were in clinical remission (DAS28-ESR < 2.6) at stable dose of DMARDs for more than 6 months. Patients on ≥1 conventional and/or biological DMARDs were included and randomized into two treatment arms: Arm 1 (control group) was continuing full-dose conventional and/or biological DMARD treatment for 12 months; arm 2 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 12 months and arm 3 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 6 months before entirely dropping DMARD. In case of recurrence of disease (DAS ≥ 2.6) the original therapy was restarted.

**Results:** 101 patients (61.4% females, 60% ACAP positive, 63% RF positive; 37.6% biologic therapy, 80.2% MTX, 7.9% other DMARDs) finished the one year endpoint: 38 patients in arm 1 (age 55.8±13.9y, disease duration 6.8±5.9y, remission 20.9±16.7mo), 36 patients in arm 2 (age 54.1±13.1y, disease duration 8.6±7.7y, remission 14.5±12.7mo) and 27 patients in arm 3 (age 54.8±12.3y, disease duration 5.6±7.0y, remission 17.6±19.5mo). Of 101 patients, 66.3% were still in remission at 12 mo. Trial arms 2 (38.9%, χ²(1)=5.0, p=0.036) and 3 (51.9%, χ²(1)=9.6, p=0.003) significantly differed from the control group (15.8% flare rate) with more patients flaring in reduction arms. However, there was no significant difference between the two reduction arms (χ²(1)=1.1, p=0.443). A multivariate logistic regression identified ACAP positivity (Wald χ²=4.5, p=0.03) and treatment reduction compared to the control group (arm2: Wald χ²=6.6, p=0.01, arm3: Wald χ²=8.8, p=0.003) as predictors for subsequent flares. Sex, disease duration, remission duration, age, RF, biologic DMARD and remission depth (defined by fulfilling Boolean remission criteria yes/no) failed to predict recurrence of disease in this study.

**Conclusion:** This study is a prospective real life treatment strategy study investigating the effect of reduction and discontinuation of DMARD therapy in RA patients in stable remission. Interestingly neither remission depth, nor disease duration at baseline or biological DMARD therapy predicted the recurrence of disease. Presence of ACAP but not RF was the only predictor for recurrence of disease. The data indicate that treatment reduction and even discontinuation is feasible in a subset of RA patients in stable remission.

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**941 Biologic De-Escalation in Rheumatoid Arthritis: Cost Savings and Clinical Success.** Tarun S. Sharma1, Lyudmila Kirillova2, Andrea Berger3 and Eric D. Newman4. 1Geisinger Medical Center, Danville, PA, 2Geisinger Health System, Danville, PA, 3Center for Health Research, Geisinger Health System, Danville, PA.

**Background/ Purpose:** Economic considerations and clinical risks of prolonged biologic use in Rheumatoid Arthritis (RA) have emerged as concerns. In this study, we measured the clinical outcomes and cost savings of biologic de-escalation in patients with well-controlled RA.

**Methods:** We reviewed the electronic health records of all RA patients treated with a biologic medication from 01/01/13 to 12/31/13 (n= 940) and evaluated biologic de-escalation (decreased dose, frequency, or discontinuation). Baseline demographics were recorded for all patients. Successful de-escalation was defined as a de-escalation where the dose of biologic on 12/31/13 was lower than the pre-de-escalation dose and the efficacy was maintained until 12/31/13. Flare was defined as addition or increase in dose of steroid or Disease Modifying Anti-Rheumatic Drug or a switch in the biologic medication. We compared the de-escalated and non-de-escalated groups, the outcomes of de-escalation, and financial benefits of de-escalation. Predictors of successful de-escalation were evaluated using two sample t or Wilcoxon rank sum tests for continuous variables and Pearson’s chi-square or Fisher’s exact tests for categorical variables.

**Results:** Of the 940 RA patients treated with biologics, 87 (9.3%) underwent biologic de-escalation. Successful de-escalation was achieved in 74 RA patients (85.1%) at the end of the study period. Using the CDAI (Clinical Disease Activity Index) to define disease activity, the de-escalated patients had a median duration of 501.5 days in low disease activity or remission prior to a de-escalation attempt. There was no significant difference in the baseline characteristics between the de-escalated and non-de-escalated patients, except the de-escalated patients were more likely to be RF positive (83.1% vs. 67.7%, p=0.015). Results of a univariate analysis showed that the successfully de-escalated patients were more likely to be on their biologic for ≥2 years prior to de-escalation (70.3% vs. 38.5%, p=0.054, marginal significance). The unsuccessful group was more likely to have a RA flare during the observation period (53.8% vs. 68.9%, p=0.001).

Cost Analysis of successful de-escalations revealed savings of $719,702 and projected annualized savings of $1,256,886 if the successfully de-escalated patients remained at their latest biologic dose for 1 year.

**Conclusion:** This is the largest observational study analyzing clinical outcomes and cost savings of biologic de-escalation in RA. In our cohort of 940 RA patients on a biologic in the year 2013, 85% of the de-escalations were successful. The only predictor of successful de-escalation was biologic use ≥ 2 years prior to de-escalation. Significant cost savings from biologic de-escalation were achieved. Biologic de-escalation in RA is a sound methodology for improving value of care delivery - maintaining clinical disease control while reducing cost.

**Disclosure:** T. S. Sharma, None; L. Kirillova, None; A. Berger, None; E. D. Newman, None.

**942 ACR/EULAR Remission in RA patients in Clinical Practice - Does Substitution of Patient Global with Pain Score Change Remission Rates? Data from the Danish Danbio Registry.** Merete Lund Hetland. The Danish Rheumatologic Database (DANBIO), Glostrup Hospital, Copenhagen, Denmark.

**Background/ Purpose:** Modern treatment strategy in RA aims at remission. In 2011, new ACR/EULAR remission criteria were published for patients with RA. Of four Boolean criteria, one is a patient-reported outcome:
The patient’s global score (PATGL), which reflects how much the disease affects the patient’s life at the present. It has been criticized that patient’s pain affects the patient’s life at the present. It has been criticized that patient’s pain affects the patient’s life at the present. It has been criticized that patient’s pain affects the patient’s life at the present.

Disclosure: M. L. Hetland

References:
(1) Lage-Hansen PR, et al. EULAR 2014, Abstract# THU0320

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Predict the Chance of Remission for Your RA Patient in Real Life. Till Uhlig1, Vibeke Norvang1, Elisabeth Lie1, Erik Rødevand2, Knut Mikkelsen3, Åse S. Lexberg4, Synøve Kalstad5 and Tore K. Kvien1. 1Diakonhjemmet Hospital, Oslo, Norway, 2, Olavs Hospital, Trondheim, Norway, 3, ReumaTilsynssykehuset, Lillehammer, Norway, 4, Vestre Viken Hospital, Drammen, Norway, 5, University Hospital of Northern Norway, Tromsø, Norway.

Background/Purpose: Clinical remission (REM) is the treatment target in rheumatoid arthritis (RA), and there are several composite REM criteria available. Knowledge on how disease duration affects REM in daily clinical practice, and whether predictors of REM depend on the method for assessment of REM, is limited.

Objective: To study the rates of REM after 3 and 6 months with DMARD treatment applying different criteria, and to study predictors of REM after 6 months.

Methods: Data from 4992 patients in the NOR-DMARD study, representing real life rheumatology practice, were analysed. All patients started on a synthetic or biological DMARD and had 6-month follow-up data available. Mean (SD) age was 54.6 (14.9) yrs, disease duration was 8.5 (7.9) yrs, 73.2% were females. Disease duration (mean 7.9 [9.6] yrs) was grouped into: <0.5 yrs (n=1229), >0.5–1 yr (n=321), >1–5 yrs (n=992), >5–10 yrs (n=750), and >10 yrs (n=1532).

The applied definitions for clinical REM were Disease Activity Score 28 (DAS28) <2.6, Simplified Disease Activity Index (SDAI) <3.3, Clinical Disease Activity Index (CDAI) <2.8, Routine Assessment of Patient Index Data (RAPID3, range 0–10) <1, and the Boolean ACR/EULAR REM definition (BOOL) <1, with additional BOOL for practical use (BOOLP) <1.

Results: Overall REM rates (%) after 3 (6) months were for DAS28 22.5 (26.0%), CDAI 8.3 (12.6%), SDAI 9.8 (14.9%), RAPID3 20.3 (21.3%), BOIL 8.7 (10.1%) and BOILP 10.3 (12.2%). Both at 3 and 6 months REM rates were highest for disease duration <0.5 yr for all six composite definitions (ANOVA all <0.001), varying from BOIL 12.5% (3 yrs) to DAS28 34.3% (6 mths), with lower rates and minor changes across higher disease duration groups.
Conclusion: In clinical practice REM within 6 months of start/change of therapy was most frequently achieved if baseline disease duration is < 6 months. REM at 6 months is further independently predicted by use of biologic DMARDs, lower age, higher education, non-smoking, absence of gender-matched control group (n = 40 vs. 27). The level of mostly diastolic HF was found 4–6-fold increased in active RA but only 2-fold increased in states of disease remission. We conclude that optimal control of RA and awareness for diastolic HF more than type of treatment are crucial for adequately addressing cardiovascular risk in RA patients.

Disclosure: T. Schau, None; M. Gottwald, None; C. Butter, None; M. Zaenker, None.

**ACR Concurrent Abstract Session**

**Rheumatoid Arthritis - Small Molecules, Biologicals and Gene Therapy II: Novel Therapies in Rheumatoid Arthritis - Early in Development**

Sunday, November 16, 2014, 4:30 PM–6:00 PM

**945**

**Disease Remission Reduces Risk of Heart Failure in Rheumatoid Arthritis Patients Independent of Treatment Strategy.** Thomas Schau1, Michael Gottwald2, Christian Butler1 and Michael Zaenker1. 1Cardiology Dept., Immanuel Klinikum Bernau Heart Center Brandenburg, Bernau, Germany, 2Immanuel Klinikum Bernau, Rheumatology Center Northern Brandenburg, Bernau, Germany.

**Background/Purpose:** Risk of heart failure (HF) is increased in patients with RA, however there is great variance in reported prevalence rates due to different diagnostic standards and underestimation of diastolic HF. Besides traditional risk factors, systemic inflammation and persistent RA-activity are thought to be independent contributors to increased HF risk. This study was to determine influence of RA-activity on prevalence of HF in a community-based RA-cohort compared to age- and gender-matched controls by using the European Society of Cardiology (ESC) diagnostic guidelines.

**Methods:** A prospective, cross-sectional study including 157 consecutively recruited RA-patients from our outpatient clinic during a 3 months period. Inclusion criteria were written consent and diagnosis of RA fulfilling European Society of Cardiology (ESC) diagnostic guidelines.

**Results:** The RA and control cohorts were comparable in age (mean (SD) 61 years (±13) vs. 59 (±12)) and gender distribution (67% vs. 69%). In RA, median HAQ was 1.1 (Interquartile range (IQR) 0.8–2.0), median DAS28 was 2.8 (IQR 2.0–3.4), with remission (DAS28 ≤2.6) in 45%, low disease activity (DAS28 2.6–3.2) in 25% and higher disease activity (DAS28 >3.2) in 30% of the patients. Prevalence of HF was significantly higher in RA vs. controls (38.2% vs. 5.6%, p < 0.001). Of all diagnosed HF, only 2 RA patients showed reduced ejection fraction. Comparing RA and control group, traditional risk factors were not significantly different except mean BMI (29.5 ± 5 vs. 27.2 ± 4, p < 0.001) and prevalence of hypertension (59% vs. 40%, p = 0.019). No significant differences were found for diabetes, chronic kidney disease, hyperlipidaemia. Subgroup analysis revealed 37% prevalence of HF in patients with DAS28 >3.2 (RR 5.7, p < 0.001 compared to controls), 30%

In patients with DAS28 2.6–3.2 (RR 4.6, p = 0.0015) and 13% in patients with DAS28-remission (RR 1.95, p = 0.264). In multivariate analysis adjusted for age and gender, remaining risk factors for HF in RA were DAS28 ≥2.6 (OR 3.4, 95% CI 1.3–9.8), RA-duration >10 years (OR 2.6, 95% CI 1.2–5.8), CRP median >10 mg/l (OR 4.8, 95% CI 1.1–21), and ESR >16 mm/h (OR 5.4, 95% CI 2.1–16). We found no influence of treatment type.

**Conclusion:** Compared to age and gender matched controls, prevalence of mostly diastolic HF was found 4–6-fold increased in active RA but only 2-fold increased in states of disease remission. We conclude that optimal control of RA and awareness for diastolic HF more than type of treatment are crucial for adequately addressing cardiovascular risk in RA patients.

Disclosure: T. Schau, None; M. Gottwald, None; C. Butter, None; M. Zaenker, None.
Efficacy and Safety of NCC0114-0006, an Anti-II–21 Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis. Juan D. Cañete1, Piotr Leszczyński2, Rikke Riisbø3 and Klaus S. Frederiksen3. 1Hospital Clinic of Barcelona, Barcelona, Spain, 2Department of Rheumatology and Rehabilitation, Poznan Medical University, Poznan, Poland, and 3Novo Nordisk A/S, Søborg, Denmark.

Background/Purpose: A phase 2, randomised, double-blind, placebo-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of NCC0114-0006 in patients with active rheumatoid arthritis (RA) on background methotrexate (MTX) therapy.

Methods: Patients (N=62; 82% female) with RA (mean duration 6.9 years; 77% RF positive; 82% anti-CCP positive; mean DSAS28-CRP 5.7) and on MTX (mean duration 3.9 years; mean dose 14.3 mg/week) were enrolled. Patients were randomised to i.v. NCC0114-0006 (12 mg/kg; n=41) or placebo (n=21); two doses given 6 weeks apart. The primary endpoint was change in DSAS28-CRP from baseline to Week 12. ACR 20/50/70 and EULAR response at Week 12, adverse events (AEs), changes in laboratory safety measurements, antibodies against NCC0114–0006 (ADAs) and pharmacodynamic (PD) parameters were also evaluated.

Results: There were no significant differences between treatment groups with respect to baseline. Four patients in the NCC0114-0006 group withdrew (3 withdrew informed consent, 1 lost to follow-up). A significant improvement in mean DSAS28-CRP was observed with NCC0114-0006 versus placebo at Week 12 (–0.65, p=0.04; Fig. 1), due largely to reductions in swollen and tender joint counts. The reduction in DSAS28-CRP at week 12 was supported by improved disease activity in terms of ACR20/50/70 and EULAR response, although these endpoints did not reach statistical significance. An expected increase in total (both free and antibody-bound) IL-21 levels after treatment with NCC0114-0006 was observed. While no change in absolute B cell numbers was observed at Week 1, about one third of patients treated with NCC0114-0006 had increased percentages of plasma cells, plasmablasts and short-lived plasmablasts, with decreased percentages of naïve B cells. They also showed increased transcript levels of Ig-Lambda light chain (IGLV7–43) and other plasma-cell signature genes in whole blood analysis. However, the DSAS28-CRP response in these patients was comparable to placebo and those who did not exhibit this B cell alteration. Nevertheless, following treatment, DSAS28-CRP and ACR-N outcomes appear to be related to baseline CTX-I – a marker of bone resorption – but not baseline DSAS28-CRP. In NCC0114-0006-treated patients, 43 AEs were observed in 22/41 (54%) patients, while 24 AEs occurred in 11/21 (52%) placebo patients. Four serious AEs occurred in 3 placebo patients. A higher number of patients reported infections (24% vs 10%) and skin disorders (12% vs 5%) in the NCC0114-0006 group versus placebo. No treatment-related ADAs were detected. No clinically significant changes were observed in laboratory safety parameters.

Conclusion: Treatment with NCC0114-0006 significantly improved DSAS28-CRP versus placebo at Week 12. Changes in B cell subsets detected at Week 1 may be due to altered distribution of homing of plasma cells/plasmablasts. No safety concerns were identified.
Safety and Efficacy of CF101 in Rheumatoid Arthritis Patients: A Phase II Study. 

**Method:** This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of CF101 1mg, administered orally twice daily to patients with active RA for 12 weeks. Primary efficacy endpoint was ACR 20 response at week 12, with all-cause dropouts considered as non-responders, in the Intent-To-Treat (ITT) population. Secondary efficacy included: ACR 20/50/70 by visit, RA for 12 weeks. Primary efficacy endpoint was ACR 20 response at week 12 (P <0.05). ACR 50/70 response at week 12 in patients with no prior systemic therapy, i.e., naive patients were significantly higher compared to the response of the whole patient population treated with CF101.

**Conclusion:** CF101 was very well tolerated and reached the primary endpoint in the current study demonstrating clear evidence of efficacy as a monotherapy for 12 weeks in patients with active RA.

**Disclosure:** A. J. Kivitz, None; A. Zubrycka-Sienkiewicz, Astellas, paid by ICON CRO, 9, Janssen, 9; Roche, UCB, Sanofi, 9, Merck, 9; S. R. Gutierrez-Ureña, None; J. Poiley, None; R. Kristy, Astellas, 3; K. Shag, Astellas, 3; J. P. Garg, Astellas, 3.

**Results:**

**Background/Purpose:** CF101, is a highly selective A3 adenosine receptor (A3AR) agonist, demonstrated safety and anti-inflammatory effect in Phase 2 clinical studies of rheumatoid arthritis (RA) and Psoriasis. A3AR has been defined as a biological predictive marker, based on a significant correlation found in a former Phase II study, between its over-expression at baseline and positive patients’ response to CF101 treatment.

**Methods:** This study was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of CF101 1mg, administered orally twice daily to patients with active RA for 12 weeks. Primary efficacy endpoint was ACR 20 response at week 12, with all-cause dropouts considered as non-responders, in the Intent-To-Treat (ITT) population. Secondary efficacy included: ACR 20/50/70 by visit, ITT, using non-responder imputation. Seventy-nine patients were enrolled for the study based on inclusion criteria: A3AR > from 1.5 units and were randomized for two groups receiving CF101 1 mg (n = 42), or Placebo (n = 37).

**Results:** CF101 achieved ACR20 of 48.6%, statistically significantly higher than in the Placebo group (25.0%) at week 12 (P<0.001). CF101 showed superiority in ACR50 and ACR70 values vs. placebo although not statistically significant, most probably due to the low number of patients. Interestingly, ACR20, ACR 50 and ACR 70 response rate at week 12 in patients with no prior systemic therapy, i.e., naive patients were significantly higher compared to the response of the whole patient population treated with CF101.

**Conclusion:** The proportion of patients experiencing any adverse event (AE) was similar for both groups (16.7% for the CF101 group and 16.2% for the Placebo group). Two AEs, RA and rash, were considered possibly related to CF101. The majority of AEs were considered to be mild.

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**Background/Purpose:** We carried out a phase I clinical trial of tolerising autologous peripheral blood DCs exposed to 4 citrullinated self-peptides (“Rheumavax”) in 29 HLA-DR shared epitope (SE)+ anti-citrullinated peptide antibody + DMARD-treated rheumatoid arthritis (RA) patients, of whom 18 received Rheumavax. This study aimed to evaluate immune biomarkers of treatment and of clinical response to Rheumavax.

**Methods:** Frozen peripheral blood mononuclear cells (PBMC) were analysed for T cell, B cell, monocyte and DC subsets by flow cytometry (FACS) at baseline, 6 days, 4, 8, 12 and 24 weeks after Rheumavax, and Luminex and ELISA assays were used to measure 108 serum analytes. PBMC were stimulated ex vivo for 5 days with each of the delivered citrullinated peptides, or with control citrullinated aggrecan peptide or tetanus toxoid antigens. Proliferation and cytokine production were measured. To identify relevant markers of change, we used sparse partial least squares linear multivariate approach, nonlinear regression, ANOVA and t tests.

**Results:** Median disease duration of recruited patients was 2 years. At baseline, 9 of 18 patients assigned to Rheumavax had an incomplete response to DMARDs with a swollen joint count (SJC) of at least 1; 9 had minimal disease activity. One patient after Rheumavax, SJC of patients with active disease at baseline reduced by a mean of 5 joints and SJC of those with inactive disease did not change. Immune effects of Rheumavax were first expected 6 days after administration. Using a multiple linear regression to model the effect of changes in PB cells at day 6 on clinical response, we found that reduction in the proportions of CD25+CD127+ activated CD4+ T cells and CD14loCD16- monocytes, and increased proportions of CD25-CD127-CD4+ naive cells, CD56+CD16+ NK cells and Foxp3+CD127loCD25hi Treg cells predicted the reduction in SJC 1 month after Rheumavax with R2 of 0.38 (p =0.001). Relative to controls, treated patients had an increased proportion of PB CD25+CD127-CD4+ induced Treg from 6 days until 8 weeks after Rheumavax. Specific increase in IL-10 production in response to delivered cit-peptides occurred ex vivo in 4 patients, increased Treg in 8 patients and an increase in IL-10 and Treg in 4 patients post-Rheumavax treatment. Reduction in 12 pro-inflammatory cytokines, chemokines and metabolic factors in serum discriminated the 1 month response in Rheumavax treated and untreated patients. Consistent with their clinical and inflammatory improvement, treated patients had an increased proliferative response to tetanus toxoid ex vivo within 6 days of Rheumavax.

**Conclusion:** These data suggest that autologous tolerising DCs exposed to citrullinated peptides improved disease control in RA patients with prior partial response to DMARDs through reduction in circulating activated T cells and dendritic cell precursors, induction of Treg and lytic NK cells, and suppression of systemic inflammation, thereby restoring regulatory balance and immune function.

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122 or of serum from subjects receiving ABT-122 was determined using an in vitro assay of inhibition of TNF- and IL-17-induced IL-6 production by human fibroblast-like synoviocytes (FLS), derived from RA patients.

**Results:** Following IV or SC administration there was no significant difference in the adverse event (AE) profile between subjects receiving ABT-122 or placebo. There were no serious AEs or premature discontinuations due to AEs reported in this study. No subject had an infusion reaction, systemic hypersensitivity reaction or an injection site reaction. No clinically relevant changes in laboratory parameters, vital signs, or ECG parameters occurred. All AEs were mild or moderate in intensity. The most frequently reported adverse event was upper respiratory infection for both subjects given CLZ occurred. All AEs were mild or moderate in intensity. The most frequently relevant changes in laboratory parameters, vital signs, or ECG parameters were balanced, including use of background MTX in 70% of pts, disease duration (3–5 yrs less in CLZ 100 and 200 mg arms).

The study primary endpoint was met, with ACR20 response rates significantly higher in the CLZ 100 mg arm vs PBO (52.4 vs 29.3%, p = 0.039) and numerically higher in the CLZ 25 and 200 mg arms (46.3 [p = 0.101] and 39.0% [p = 0.178], respectively) at Wk 16. The table shows secondary endpoints. ACR20/50/70 response rates were higher than PBO for all CLZ treatment arms at Wk 24, but no clear dose response was seen. Mean decreases from baseline to Wk 24 in DAS28 (CRP), HAQ-DI, the number of dactylitic digits and Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score were greater in all CLZ treatment arms compared with PBO. PASI75 response rates were 12.2% in the PBO arm and between 12.2 and 28.6% in the CLZ arms at Wk 24. Through Wk 24, the rates of serious adverse events (SAEs) were similar across PBO, CLZ 25 and CLZ 100 mg arms (4.9, 4.9 and 4.8%, respectively) and higher for the CLZ 200 mg arm (9.8%), which was associated with more discontinuations. No serious infections, tuberculosis, malignancies, gastrointestinal perforations or unusual SAEs, were observed during the study period. Consistent with IL-6 blockade, non-clinically significant liver enzyme elevations in reductions and platelets and neutrophil counts were observed in the 3 CLZ treatment arms.

**Conclusion:** Clazakizumab is effective in controlling clinical features of PsA such as arthritis, enthesitis and dactylitis, with modest skin benefits. The safety profile was acceptable and consistent with IL-6 blockade. This is the first demonstration of a beneficial effect of targeting IL-6 in PsA and further studies are warranted.

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**References:**


Sunday, November 16

IV375 SC) or 150 mg s.c. (10 IV3150 SC) every 4 wks from Wk 8.
PBO was given on the same schedules. Patients naı̈ve to anti-TNF
therapy (⬃70%) and those intolerant of or inadequate responders to
anti-TNF therapy (TNF-IR; ⬃30%), were stratified across groups.
Statistical analyses for the primary and multiple secondary endpoints
used non-responder imputation (binary variables), mixed-effects repeated measures model (continuous variables), and linear extrapolation
(radiographic data), following a pre-defined hierarchical hypothesis
testing strategy to adjust for multiplicity.
Results: Demographics and baseline characteristics were balanced
between groups. Both 10 IV375 SC and 10 IV3150 SC demonstrated
significantly higher ACR20 responses vs. PBO at Wk 24 (50.5% and
50.0% vs. 17.3%, respectively; P⬍ 0.0001 vs. PBO). All pre-specified
secondary endpoints, including dactylitis, enthesitis, SF36-PCS, HAQDI, DAS28-CRP, ACR50, PASI 75, PASI 90, and mTSS score were
achieved by Wk 24 and reached statistical significance; active dose
separated from PBO as early as Wk 1 for ACR20, DAS28-CRP, and
HAQ-DI. Drug exposure levels were similar in the secukinumab
groups up to the primary endpoint due to i.v. loading. Improvements in
all primary and secondary endpoints were sustained through Wk 52. At
Wk 52, ACR 20/50/70 responses, using an observed analysis, were
66.9%, 38.4% and 25.6% for 10 IV375 SC and 69.5%, 50.0% and
28.2% for 10 IV3150 SC. In both TNF-naı̈ve and TNF-IR groups,
secukinumab demonstrated superiority at Wk 24 in ACR20/50/70,
PASI 75/90, HAQ-DI, SF36-PCS, dactylitis and enthesitis at both
doses and the effect was maintained through Wk 52. Secukinumab
significantly inhibited radiographic structural joint damage at Wk 24
vs. PBO. AEs at Wk 16: 60.4% (10 IV375 SC), 64.9% (10 IV3150
SC) and 58.4% (PBO); non-fatal SAE rates: 2.5%, 4.5% and 5.0%,
respectively. Mean, median, and maximum exposures: 438.5, 456.0
and 721 days; AE/non-fatal SAE rates: 78.1%/8.6% and 82.4%/12.9%
in pts who received secukinumab 75 mg s.c. or 150 mg s.c.,
respectively, at any point in the study.
Table Summary of selected 24-week efficacy results
Week 24 Data
ACR20 (% responders)
ACR50 (% responders)
ACR70 (% responders)
DAS28-CRP (mean change from
BL) Overall (nⴝ606)
a
Dactylitis (presence of, %) Overall
(nⴝ324)
a
Enthesitis (presence of, %)
Overall (nⴝ372)

Secukinumab 10
mg/kg IV 3 75
mg SC

Secukinumab 10
mg/kg IV 3 150
mg SC

PBO

50.5*
30.7*
16.8*
–1.67*

50.0*
34.7*
18.8*
–1.62*

17.3
7.4
2.0
–0.77

43.3*

51.9*

84.5

51.2*

54.0*

87.2

*P ⬍0.0001 vs. PBO; aData from pts with dactylitis (n ⫽ 324) and enthesitis (n ⫽
372) at baseline. ACR, American College of Rheumatology response criteria; BL,
baseline; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; IV,
intravenous; pts, patients; SC, subcutaneous

Conclusion: In this first phase 3 trial to evaluate highly selective IL-17A
inhibition in pts with PsA, secukinumab provided rapid, clinically significant
and sustained improvements in signs and symptoms, and inhibited joint
structural damage. Secukinumab was well tolerated through 52 wks.
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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Provides
Significant and Sustained Inhibition of Joint Structural Damage in
Active Psoriatic Arthritis Regardless of Prior TNF Inhibitors or Concomitant Methotrexate: A Phase 3 Randomized, Double-Blind, PlaceboControlled Study. Désirée van der Heijde1, Robert B. M. Landewé2, Philip
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7
Novartis Pharma AG, Basel, Switzerland.
Background/Purpose: Approximately two-thirds of patients (pts) with
psoriatic arthritis (PsA) experience progressive joint damage associated with
varying degrees of disability. Here we present the 1-year effect of IL-17A
inhibition with secukinumab on radiographic progression in pts with active
PsA enrolled in a 2-year, multicenter, randomized, double-blind, placebo
(PBO)-controlled, phase 3 trial (FUTURE 1; NCT01392326).
Methods: 606 adults with moderate to severe PsA were randomized to
PBO or one of two secukinumab treatment arms: secukinumab 10 mg/kg i.v.
followed by 75 mg s.c. (10 IV375 SC) or 150 mg s.c. (10 IV3150 SC). All
pts were assessed for joint response at Week (Wk) 16 (based on ⱖ 20%
improvement in tender and swollen joint counts). PBO-treated pts were
re-randomized to secukinumab 75 or 150 mg s.c. at Wk 16 (non-responders)
or Wk 24 (responders). The van der Heijde total modified Sharp scores
(mTSS), and erosion and joint space narrowing (JSN) scores were determined
at baseline, Wks 16/24 (depending on response) and Wk 52. The effect of
secukinumab on radiographic progression from baseline to Wk 24 was
evaluated using a non-parametric ANCOVA model, with linear extrapolation
for pts who had x-ray assessments at Wk 16. Exploratory analyses assessed
the proportion of pts with no structural progression (defined as change from
baseline in mTSS ⱕ 0.5) and maintenance of this effect over time.
Results: The changes from baseline in mTSS, erosion and JSN scores
demonstrated that secukinumab-treated pts had significantly less progression from
baseline to Wk 24 compared with PBO-treated pts, regardless of whether pts had
received prior therapy with a TNF inhibitor, were on secukinumab monotherapy,
or were receiving concomitant methotrexate (MTX; Table). Inhibition of joint
structural damage was sustained with secukinumab through Wk 52. Analysis of
PBO pts who switched to secukinumab showed a greater mean change from
baseline in mTSS for the PBO group from baseline to Wk 24 (mean increase of
0.48) vs. the period from Wk 24 to Wk 52 when pts had been switched to
secukinumab (mean decrease of –0.03), providing additional support for efficacy.
Analyses of pts who had x-rays at both Wk 16/24 and 52 showed that the
proportion of pts who experienced no progression from randomization to Wk 24
vs. the period from Wk 24 to Wk 52 was consistently high in the secukinumab
groups: 92.3% vs. 85.8%, respectively, for 10 IV375 SC and 82.3% vs. 85.7%
for 10 IV3150 SC. In pts initially randomized to PBO, 75.7% had no
progression from randomization to Wk 24 and this increased to 86.8% for the
period from Wk 24 to Wk 52 following active treatment with secukinumab (P⬍
0.05).
Table
Radiographic progression at Week 24 by treatment group
Week 24 (Mean change
from baseline)
mTSS
Erosion score
JSN score

S424

Secukinumab
10 mg/kg IV 3 75
mg SC n ⴝ 202

Secukinumab
10 mg/kg IV 3 150
mg SC
n ⴝ 202

PBO
n ⴝ 202

0.02†
0.08†
†
–0.06

0.13†
0.04‡
0.10

0.57
0.35
0.23


Results: The biomarker subset included 150 patients (placebo: n=51; APR20: n=51; APR30: n=48). Subjects in the biomarker subset had significant decreases in circulating levels of IL-8, TNF-α, IL-6, MCP-1, and ferritin, representing components of pro-inflammatory innate Th1 immunity.

Conclusion: Treatment for APR for 4 to 24 weeks was associated with significant decreases in circulating levels of IL-8, TNF-α, IL-6, MCP-1, and ferritin, representing components of pro-inflammatory innate Th1 immunity.

Background/Purpose: A definition of minimal disease activity (MDA) in PsA was derived from the opinion of 60 PsA experts including fulfillment of ≥5 of the 7 following criteria: tenderness joint count (TJC) ≤5, swollen joint count (SJC) ≤5, patient global assessment of disease activity (PtGA) ≤5, patient global assessment of health (PtHAQ) ≤0.5, patient global assessment of pain (P GAP) ≤45, modified total Sharp score (mTSS) ≤24, and PASI ≤15. Patient global disease activity (PtGA) (VAS) ≤20, HAQ ≤0.5, and tender entheseal points ≤5 (1). The aim of this analysis was to describe the rate of MDA achievement over time and to assess the association between MDA achievement and DAS28 remission in PsA patients treated with anti-TNF in a routine clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for <6 months. Data from PsA patients treated with infliximab (enrolled in 2005–2013) or golimumab (enrolled in 2010–2013) who had available MDA information at baseline, 6 months, and/or 12 months were included. Improvement in patient parameters over time was assessed for statistical significance with the paired-samples t-test. Agreement between MDA and remission as defined by the DAS28 (≤2.6) criteria was assessed with the sensitivity, specificity, as well as the positive (PPV) and negative (NPV) predictive value.

Results: A total of 123 PsA patients with mean (SD) age of 50.5 (10.5) yrs and mean (SD) duration since diagnosis of 6.1 (7.3) yrs were included in this analysis, providing information from 340 assessments. At the time of enrollment, the mean (SD) TJC was 20.3 (9.7), SJC was 12.6 (7.7), HAQ was 0.52 (0.45), PtGA was 55.3 (44.0), mTSS was 45.3 (25.3), and PASI was 56.4 (25.2). By 6 mos of treatment, statistically significant (P<0.05) improvements were observed in all clinical and patient outcome parameters studied, which were sustained or further enhanced over 12 months of treatment.
The proportion of patients with MDA significantly increased from 12.3% at baseline to 45.0% after 6 months of treatment (P < 0.001), and 41.9% at 12 mos (P = 0.021). Similarly, DAS28 remission was observed in 15.9%, 47.8% and 45.1% of patients at baseline, 6 mos, and 12 mos, respectively. Using DAS28 as reference standard, sensitivity was 69.8%, specificity 93.0%, NPV 88.2%, and PPV 80.4%.

Conclusion: MDA has high discriminatory power for remission as defined by the DAS28 criteria, while being more rigorous than DAS28. Furthermore, treatment with anti-TNF is effective in inducing MDA in 45% of patients as early as 6 mos from treatment initiation.

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The 10-Year Follow-up of Nephritis Trial Comparing Azathioprine and Mycophenolate Mofetil for Longterm Immunosuppression of Lupus Nephritis. Farah Tamurou1, David D’Cruz2, Shirshel Sanghe3, Philippe Remy4, Carlos Vasconcelos5, Christopher Fiehn6, Maria del Mar Ayala Gutierrez7, Inge-Marielette Gillboe8, Maria Tektonidou9, Daniel Blockmans10, Isabelle Ravel11, Valeria De Looze12, Loge Guettay13, Ricard Cervera14 and Frédéric A. Houssiau15. 1Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Bruxelles, Belgium, 2Louis Coote Lupus Unit, St Thomas’ Hospital, London, United Kingdom, 3St Thomas’ Hospital, London, United Kingdom, 4Hôpital Henri Mondor, Créteil, France, 5Hospital Geral Santo Antonio, Porto, Portugal, 6ACURA Centre for Rheumatic Diseases, Baden-Baden, Germany, 7Hospital Regional Universitario Carlos Haya, Malaga, Spain, Malaga, Spain, 8Oslo University Hospital Rikshospitalet, University of Oslo, University of Iceland, 9Athens University Medical School, Athens, Greece, 10UZ Leuven, Leuven, Belgium, 11Onze-Lieve-Vrouwenkliniken, Aalst, Belgium, 12Hôpital Cochin, Paris, France, 13Hôpital Cochin, Université Paris V Descartes, Paris, France, 14Hospital Clinic de Barcelona, Barcelona, Spain, 15Université catholique de Louvain, Brussels, Belgium.

Background/Purpose: Very long-term data are rarely reported in lupus nephritis (LN) trials, despite their pivotal importance to detect late poor renal outcomes and to identify early prognostic markers. Here we report the 10-year follow-up of the MAINTAIN Nephritis Trial, a randomized European-based open trial comparing azathioprine (AZA) and mycophenolate mofetil (MMF) as maintenance therapy of proliferative LN.

Methods: 105 patients suffering from Class IV or V LN were randomly assigned to receive AZA or MMF after induction therapy with intravenous cyclophosphamide (CY) and intravenous (IV) cyclophosphamide (CY) (Euro-Lupus protocol; 6 × 500mg fortnightly). The primary endpoint was time to renal flare. After a mean follow-up of 48 months, we reported that 25 and 19% of patients experienced a renal flare in the AZA and MMF group, respectively (NS) (Houssiau et al, ARD 2010). In March 2014, we collected the 10-year data. Survival curves were drawn according to Kaplan-Meier method and statistically tested by logrank test. Other statistical methods were used as appropriate.

Results: Five patients died (3 MMF, 2 AZA), of whom 2 (1 MMF, 1 AZA) had reached ESRD. Two additional MMF patients developed ESRD. Out of the 105 patients, 41 suffered from at least one renal flare, without difference between the two groups (22 AZA, 19 MMF). Proteinuric and nephritic flares were equally distributed between groups. Time to renal flare (all, proteinuric and nephritic) did not differ (p = 0.77; p = 0.39; p = 0.50). Out of the 100 living patients, 13 were lost-to-follow-up. For the 87 remaining patients, the mean (± SD) follow-up was 115 (± 17) months. Additional IV CY was prescribed in only 17% of the patients, somewhat more frequently in the AZA group, although the difference was not statistically significant (p = 0.2). Further use of MMF in the AZA group and further use of AZA in the MMF group occurred in 33 and 26% of the patients, respectively. Patients were classified as good or poor longterm renal outcomes if their creatinine at last follow-up was ≤120% (n = 83) or >120% (n = 21) of baseline value, respectively. Interestingly, while their baseline 24-h proteinuria did not differ, patients with good longterm renal outcome had a much lower 24-h proteinuria at 3, 6 and 12 months compared to patients with poor outcome (p < 0.0001 by ANOVA). Results were similar if different definitions of poor longterm renal outcome were used (eGFR below 60ml/min/1.73m²BSA, creatinine ≥1.0mg/dl or ≥1.4mg/dl). The positive predictive value of a uPCR ratio <0.50mg/mg at 3, 6 and 12 months for a good longterm renal outcome was excellent (89, 90 and 92%, respectively). By contrast, the negative predictive value was low (21, 29 and 32%, respectively), since many patients without an early proteinuria drop also achieved a good longterm renal outcome.

Conclusion: The longterm follow up data of the MAINTAIN Nephritis Trial do not indicate that MMF is superior to AZA for renal flare prevention in a Caucasian population suffering from proliferative LN. Moreover, we...
confirm the excellent positive predictive value of an early proteinuria drop for longterm renal outcome.

**Disclosure:** F. Tamirou, None; D. D'Cruz, Aspreva/Vifor, 2. Roche Pharmaceuticals, 5; S. Sangle, None; P. Remy, None; C. Vasconcelos, None; C. Fiehn, None; M. D. M. Ayala Gutierrez, None; I. M. Gilboe, None; M. Tektonidou, None; D. Blockmans, None; R. Ravelingien, None; V. E. Guern, None; G. Depresseux, None; L. Guillemin, None; R. Cervera, None; F. A. Housiau, Roche Pharmaceuticals, 5, Aspreva/Vifor, 5.

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**Discoid Lupus Onset and Decrease Risk of Renal Disease in Patients with Systemic Lupus Erythematosus: Data from a Large Latin American Cohort.** Guillermo J. Pons-Estel1, Gaobin Bao2, Bernado Pons-Estel3, Daniel Wojdyna4, Veronica Saurit5, Alejandro J. Alvarellos6, Francisco Caiero7, Emilia I. Sato8, Enrique R. Soriano9, Lilian Tereza Costallat10, Oscar Neira11, Antonio A. Iglesias-Gamarr12, Gil Reyes Llerena13, Mario Cardiel14, Eduardo M. Acevedo-Vásquez15, Rossa Chacon16 and Cristina M. Drenkard17.

**Background/Purpose:** Early data derived from small selected samples suggest that discoid lupus erythematosus (DLE) is negatively associated with renal involvement in patients with SLE. Recent findings from two large transversal studies are controversial, and the prognosis value of DLE on renal disease remains unclear. We used a longitudinal design to examine whether DLE onset protects against the development of LN in patients with systemic lupus erythematosus SLE from a large multiethnic Latin-American cohort.

**Methods:** We studied SLE patients enrolled in GLADEL, an inception longitudinal cohort from 54 centers in 9 Latin American countries. The main predictor was DLE onset, which was defined as physician-documented DLE that occurred before the diagnosis of SLE. The outcome was time from diagnosis of SLE to LN during the followup. LN was defined by clinical or histological documentation of lupus glomerulonephritis or renal insufficiency secondary to LN. Kaplan-Meier analysis and Cox proportional hazard models were used to examine the association between DLE onset and time to LN.

**Results:** We examined 891 GLADEL SLE patients at risk (91% females and 56% non-Caucasians). The mean age at SLE diagnosis and mean duration of follow-up were 30.8 years (SD 12.6) and 4.3 years (SD 2.3), respectively. Overall, 56 patients had DLE onset, and 329 developed LN during the followup. LN was defined from the diagnosis of SLE to LN during the followup. LN was defined by clinical or histological documentation of lupus glomerulonephritis or renal insufficiency secondary to LN. Kaplan-Meier analysis and Cox proportional hazard models were used to examine the association between DLE onset and time to LN.

**Disclosure:** G. J. Pons-Estel, None; G. Bao, GlaxoSmithKline, 2; B. Pons-Estel, None; D. Wojdyna, None; V. Saurit, None; A. J. Alvarellos, None; F. Caiero, None; E. I. Sato, None; R. E. Soriano, None; L. T. Costallat, None; O. Neira, None; A. A. Iglesias-Gamarr, None; G. Reyes Llerena, None; M. Cardiel, None; E. M. Acevedo-Vásquez, None; R. Chacon, None; C. M. Drenkard, NIH, 2, GlaxoSmithKline, 2.

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**Allogeneic Mesenchymal Stem Cell Transplantation for Lupus Nephritis Patients Refractory to Conventional Therapy.** Dandan Wang, Huayong Zhang, Xuebing Feng and Linyou Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

**Background/Purpose:** Allogeneic mesenchymal stem cell transplantation (MSCT) has been shown to be clinically efficacious in the treatment of various autoimmune diseases. Here we analyzed the role of allogeneic MSCT to induce renal remission in patients with active and refractory lupus nephritis (LN).

**Methods:** This is an open-label and single-center clinical trial conducted from 2007 to 2010 in which 81 Chinese patients with active and refractory lupus nephritis were enrolled. Allogeneic bone marrow- or umbilical cord-derived mesenchymal stem cells (MSCs) were administered intravenously at the dose of one million cells per kilogram of bodyweight. All patients were...
then monitored over the course of 12 months with periodic follow-up visits to evaluate renal remission, as well as possible adverse events. The primary outcome was complete renal remission (CR) and partial remission (PR) at each follow-up, as well as renal flares. The secondary outcome included renal activity score, total disease activity score, renal function and serologic index.

Results: During the 12-month follow-up, the overall rate of survival was 95% (77/81). Totally 60.5% (49/81) patients achieved renal remission during 12-month visit by MSCT. Eleven of 49 (22.4%) patients experienced renal flare by the end of 12 months after a previous remission. Renal activity evaluated by BILAG scores significantly declined after MSCT (mean±SD, from 4.49±2.60 at baseline to 1.09±0.83 at 12-month) in parallel with the obvious amelioration of renal function. Glomerular filtration rate (GFR) improved significantly 12 months after MSCT (mean±SD, from 58.55±19.16 ml/min to 69.51±27.93 ml/min). Total disease activity evaluated by SLEDAI scores also decreased after treatment (mean±SD, from 13.11±4.20 at baseline to 5.48±2.77 at 12 month). Additionally, the doses of concomitant prednisone and immunosuppressive drugs were tapered. No transplantation-related adverse event was observed.

Conclusion: Allogeneic MSCT resulted in renal remission for active LN patients within 12 months visit, confirming its use as a potential therapy for refractory LN.

Disclosure: D. Wang, None; H. Zhang, None; X. Feng, None; L. Sun, None.

961 Outcome of Lupus Nephritis and Impact on Health Related Quality of Life: Results from an International, Prospective, Inception Cohort Study

John G. Hanly for the Systemic Lupus International Collaborating Clinics, Aidan O’Keeffe2, Li Su3, Murray B. Urowitz4, Juanita Romero-Diaz5, Caroline Gordon6, Sang-Cheol Bae7, Sasha R Bernatsky8, Ann E. Clarke9, Daniel J. Wallace10, Joan T. Merrill11, David A. Isenberg12, Anisur Rahman13, Ellen M. Ginzler14, Paul Fortin15, Dafna D. Gladman16, Jorge Sanchez-Guerrero17, Michelle A. Petr18, Ian Bruce19, Mary Anne Dooley20, D. J. Wallace, None; D. A. Isenberg, None; A. Rahman, None; E. M. Ginzler, None; P. Fortin, None; D. D. Gladman, None; J. Sanchez-Guerrero, None; M. A. Petr, None; I. Bruce, None; M. A. Dooley, None; R. Ramsay, None; C. A. Aranow, None; G. S. Alarcon, None; B. Fossey, None; K. Steinsson, None; O. Nived, None; G. Sturfel, None; S. Manzi, None; M. A. Khamashta, None; R. F. van Vollenhoven, None; A. Zoma, None; M. Ramos-Casals, None; G. Ruiz-Irastorza, None; S. Sam Lim, None; Thomas Stoll21, Murat Inanc22, Kenneth C. Kalunian23, Diane L. Kamen24, Peter Maddison25, Christina A. Peschken26, Sören Jacobsen27, Anca Askanase28, Jill P. Buyon29, Chris Theriault30, Kara Thompson31, and Vernon Farewell32.

Background/Purpose: LN occurred in 38.3% of SLE patients, frequently as the "renal disorder" (ACR classification criterion) and/or biopsy confirmation. Data included medications, estimated glomerular filtration rate (eGFR) and proteinuria (ePrU), end-stage renal disease (ESRD), SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). GFR states were defined: state 1 (eGFR: >60 ml/min); state 2 (eGFR: 30–60 ml/min); and state 3 (eGFR: <30 ml/min). Similarly, PrU states were defined: state 1 (ePrU: <0.25 gr/day); state 2 (ePrU: 0.25–3.0 gr/day); and state 3 (ePrU: >3.0 gr/day). HRQoL was determined by SF-36 subscale, mental (MCS) and physical (PCS) component summary scores. Statistical analyses included analysis of variance or equivalent t-tests, Chi-squared test, and regression and Kaplan-Meier curves.

Results: Of 1,827 SLE patients, 89% were female, 49.2% Caucasian with mean±SD age 35.1±13.3 years. At enrollment, mean SLE duration was 0.5±0.3 years. SLEDAI-2K was 5.4±5.4, SDI was 0.3±0.7. The mean follow-up was 4.6±3.4 years. LN occurred in 700/1,827 (38.3%) patients: 566 (31%) at enrollment and 134 (7.3%) during follow-up. It was more common in Hispanics (49.3%), African ancestry (39.9%) and Asians (36.8%) compared to Caucasians (20.3%) (p<0.001). Renal biopsies from 395 (56.4%) patients revealed ISN classes (%): I: 9 (2.4); II: 36 (9.5); III: 101 (26.8); IV: 163 (43.2); V: 121 (31.2) and VI: 3 (0.8); 21% of all LN had impaired renal function and 417/671 (62.1%) had proteinuria. Following LN the estimated 10 year incidence of ESRD was 10.1% (95%CI: 6.6%, 13.6%) and there was a higher risk of death (HR=2.98, 95%CI 1.48, 5.99, p=0.002). Patients with eGFR <60 ml/min at diagnosis had lower SF-36 PCS scores (p<0.01) and lower Physical function. Physical role and Bodily pain scores. Over time, patients with abnormal eGFR and ePrU had lower SF-36 MCS (p<0.02) scores compared to patients with normal values.

Conclusion: LN occurred in 38.3% of SLE patients, frequently as the initial presentation, in a large multi-ethnic inception cohort. Despite current standard of care, nephritis was associated with ESRD and death, and renal insufficiency was linked to lower HRQoL. New strategies are required to improve outcomes of lupus nephritis.

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A Systematic Review and Network Meta-Analysis of the Risk of Serious Infections with Immunosuppressive Drugs for Lupus Nephritis

Background/Purpose: To compare the risk of serious infections of immunosuppressive medications used for the treatment of lupus nephritis.

Methods: We performed an up to date systematic review and network meta-analysis (NMA) by performing an updated search for randomized trials of immunosuppressive medications for lupus nephritis up to September 2013 with the help of Cochrane and ACR librarians. We updated the data from the systematic review for the 2012 ACR lupus nephritis treatment recommendations and the published Cochrane Review on lupus nephritis. We abstracted data related to infections from these trials. Bayesian network meta-analyses (NMA) were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using Markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

Results: 31 RCTs with 2,442 patients provided data. There were twenty-five 2-arm, five 3-arm and one 4-arm trial. We found that tacrolimus was associated with significantly lower risk of serious infections compared to prednisone, cyclophosphamide, mycophenolate mofetil and azathioprine with a risk approximately one-third (Table 1). We also found that MMF-AZA (MMF followed by AZA) was associated with significantly lower risk of serious infections as compared to low dose CYC, high dose CYC or high dose prednisone, although this was based on fewer data (Table 1). Other differences between immunosuppressive medications did not reach statistical significance.

Conclusion: Tacrolimus and MMF-AZA combination were associated with lower risk of serious infections serious infections compared to other treatment options for lupus nephritis. These numbers can help patients make informed decisions about treatment options for lupus nephritis.

Table 1 Comparison of various drugs for the risk of infections in patients with lupus nephritis showing statistically significant results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio (95% CI)</th>
<th>Relative Risk (95% CI)</th>
<th>Risk Difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC PRED</td>
<td>0.30 (0.10, 0.86)</td>
<td>0.34 (0.11, 0.88)</td>
<td>-8.97 (-15.82, -1.46)</td>
</tr>
<tr>
<td>TAC CYC</td>
<td>0.34 (0.13, 0.87)</td>
<td>0.38 (0.14, 0.88)</td>
<td>-7.47 (-13.89, -1.26)</td>
</tr>
<tr>
<td>TAC MMF</td>
<td>0.35 (0.14, 0.82)</td>
<td>0.38 (0.16, 0.84)</td>
<td>-7.23 (-15.34, -1.53)</td>
</tr>
<tr>
<td>TAC AZA</td>
<td>0.28 (0.09, 0.81)</td>
<td>0.32 (0.11, 0.83)</td>
<td>-9.61 (-20.74, -1.73)</td>
</tr>
<tr>
<td>MMF-AZA CYC LD</td>
<td>0.09 (0.01,0.80)</td>
<td>0.12 (0.03,0.81)</td>
<td>17.42 (-42.84, -2.08)</td>
</tr>
<tr>
<td>MMF-AZA PRED HD</td>
<td>0.03 (0.00,0.59)</td>
<td>0.06 (0.01,0.64)</td>
<td>37.87 (-82.60, -3.54)</td>
</tr>
<tr>
<td>MMF-AZA CYC HD</td>
<td>0.07 (0.01,0.56)</td>
<td>0.09 (0.01,0.62)</td>
<td>22.74 (-46.47, -6.14)</td>
</tr>
</tbody>
</table>

Disclosure: J. Singh, Savient, 2; Takeda, 2; Degeneron, 5; Allergan, 5; A. Hossain, None; A. Koth, None; G. Wells, Novartis, Bristol-Myers Squibb, and Abbott, 5; Bristol-Myers Squibb, 2; Abbott Immunology Pharmaceuticals, 8; he is a member of the executive of OMERACT and of the Scientific Committee for the Ontario Biologics Research Initiative, 9.

Efficacy and Safety Study (ACCESS) to identify predictors of renal response at 6 months in patients with lupus nephritis.

Methods: 134 subjects with class III or IV lupus nephritis were randomized to low-dose intravenous cyclophosphamide (IVC) or low-dose IVC with abatacept. Renal response was assessed at 24 weeks. Complete renal response (CR) was defined as: urine protein-to-creatinine ratio (UPCR) <0.5; serum creatinine (Cr) normal, or if abnormal, within 25% of baseline; and adherence to steroid taper regimen. Partial renal response (PR) was defined as: >50% improvement in UPCR; with the same parameters for serum Cr and steroid taper as CR. For the purposes of this analysis, we defined renal response as a composite of CR and PR. We identified possible predictors of renal response, including baseline demographic, clinical, laboratory, and histologic characteristics, as well as clinical and laboratory data obtained within the first 3 months of therapy. We calculated univariate odds ratios (ORs) and 95% confidence intervals (CIs) for renal response for each putative predictor, in the sample as a whole and within each treatment arm. We then conducted a multivariable logistic regression analysis, including all significant predictors (defined as p<0.05) from the univariate regressions.

Results: Reduction in proteinuria by at least 25% by week 12 was the strongest predictor of CR or PR at week 24 (OR 8.1; p<0.05). Normalization of C4 and normalization of C3 and C4 by week 12 were also predictive of renal response at week 24 (ORs 4.5 and 4.6 respectively; p<0.05). Reduction in proteinuria by at least 25% and normalization of C4 remained significant independent predictors in the multivariate analysis (ORs 13.3 and 3.6 respectively; p<0.05). This was independent of the treatment arm. None of the baseline characteristics was predictive of renal response.

Conclusion: This study demonstrates that a reduction of at least 25% in proteinuria at 3 months and normalization of C4 levels at 3 months independently predict renal response to therapy with low-dose IVC, with or without abatacept, at 6 months in patients with lupus nephritis. This supports previous findings from the Aspreva Lupus Management Study (ALMS), although reduction in proteinuria was a stronger predictor in this analysis. In contrast to the ALMS analysis, we did not find that time since lupus nephritis diagnosis or baseline eGFR were predictors of renal response. Future studies should address these and other, novel biomarkers so that we can more accurately predict which patients will respond well to treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete and Partial Responders</th>
<th>Univariate model OR (95% CI)</th>
<th>Multivariate model OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥25% reduction in proteinuria from baseline</td>
<td>No</td>
<td>8.1 (2.8–23.7)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13.3 (2.3–75.7)</td>
<td>–</td>
</tr>
<tr>
<td>Normalization of C3</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.2 (0.8–5.8)</td>
<td>–</td>
</tr>
<tr>
<td>Normalization of C4</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.5 (1.4–14.1)</td>
<td>3.6 (1.0–12.9)</td>
</tr>
<tr>
<td>Normalization of C3 and C4</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.6 (1.1–18.3)</td>
<td>–</td>
</tr>
<tr>
<td>Normalization of anti-dsDNA antibody</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.7 (0.3–2.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

Disclosure: S. Goglin, None; D. Wofsy, None; M. G. Cisternas, None; M. Dall’era, None.

ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Pathogenesis, Animal Models and Genetics I

Skin Collagen Synthesis Rates Distinguish Between Early and Late Diffuse Scleroderma Patients. Claire Emerson1, Martin Decaris1, Michelle Gatmai1, Flora Luo1, Dan Holochwost, Simplicia Flora Cruz1, Thomas Angel1, Kelvin Li1, Marc Hellerstein1, Fredrick M. Wigley2, Scott Turner3 and Francesco Boin4. 1KineMed Inc., Emeryville, CA, 2Johns Hopkins University School of Medicine, Baltimore, MD.
Background/Purpose: The synthesis and degradation of extracellular matrix (ECM), particularly collagen, is one of the central mechanisms perturbed in scleroderma (SSc). Understanding the kinetics of this process can be of great value to define disease activity during the course of SSc and to develop better tools to assess with precision response to therapeutic interventions.

Methods: Using a stable isotope (deuteron) labeling method and a new kinetic proteomic approach designed to enrich for ECM, we assessed the turnover of collagen in the skin of SSc subjects. Moreover, we pursued the extraction of different collagen pools based on their solubility to measure kinetics of collagen subtypes and other matrix molecules. Three subpopulations were studied: limited (n = 6), diffuse early-active (n = 5) and diffuse late-stage SSc (n = 6). Subjects were given heavy water for 3 weeks prior to a skin biopsy. Protein, lipid and cell kinetics were measured and correlated to gene array and histology from adjacent biopsies.

Results: Total collagen synthesis rates (% new collagen after 3 weeks of labeling) were significantly higher in late-stage diffuse SSc subjects (5.052% ± 1.953) compared to early-active (1.986% ± 0.8226; p = 0.0031) or normal subjects (2.237% ± 0.6365; p = 0.0031) demonstrating that fibrotic tissue in these subjects undergoes active remodeling. The microarray data showed that the higher collagen synthesis detected in late diffused patients is significantly associated with the expression of genes involved with fibrosis and cell cycle. When compared to total collagen synthesis rates, kinetic analysis of individual collagen pools revealed that the guanidine soluble collagen (corresponding to recently synthesized uncross-linked collagen and immature matrix) represented a greater proportion of the total collagen pool in the late diffuse subjects that have more established fibrosis.

Conclusion: This study shows that cutaneous fibrosis in late-stage SSc is not a static hypodynamic scarring but rather undergoes active remodeling with a pool of newly synthesized, uncross-linked collagen. These data emphasize that the biological processes and pathogenetic networks driving SSc skin involvement likely change over time with the different stages of the disease.

Disclosure: C. Emerson, Kinemed, 3; M. Decaris, Kinemed, 3; M. Ghatan, Kinemed, 3; F. Luo, Kinemed, 3; D. Holochwost, Kinemed, 3; S. Flora Cruz, Kinemed, 3; F. Angel, Kinemed, 3; K. Li, Kinemed, 3; M. Hellerstein, Kinemed, 3; F. M. Wigley, None; S. Turner, Kinemed, 3; F. Boin, None.

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Blockade of TLR4 Signaling By TAK242 Ameliorates Experimental Organ Fibrosis. Swathi Bhattacharyya1, Wenxia Wang2, Zhenghuo Tamaki1, Yasuhiro Tsukimi2, Masashi Yamazaki2 and John Varga1. 1Northwestern University, Feinberg School of Medicine, Chicago, IL, 2Takeda Pharmaceuticals Company Limited, Kanagawa, Japan.

Background/Purpose: Our recent studies implicate innate immune signaling through Toll like receptor 4 (TLR4) in scleroderma pathogenesis. aberrant production and accumulation of the endogenous TLR4 ligand Fn-EDA drives TLR4-dependent persistent fibroblast activation and progressive fibrogenesis in scleroderma. The goal of these studies is to evaluate the antifibrotic potential of pharmacological TLR4 blockade in organ fibrosis.

Methods: For this study, we used TLR4 intracellular signaling inhibitor TAK242. The effect of TAK242 was investigated in normal dermal fibroblasts activated with TLR4 ligands or scleroderma fibroblasts by Western blot analysis, immunofluorescence and real-time qPCR; and in 3-D organotypic human skin equivalents reconstituted with scleroderma fibroblasts. The effect of TLR4 inhibition by TAK242 was examined in vivo by local subcutaneous injection of bleomycin (BLM) to induce dermal and pulmonary fibrosis in 6- to 8-week-old female mice (C57BL/6d).

Results: TAK242 treatment ameliorated dermal and pulmonary fibrosis and reduced the expression of pro-inflammatory and pro-fibrotic mediators in the skin of BLM-treated mice compared to vehicle-treated wild type control mice. Importantly, TAK242 induced the regression of pre-established organ fibrosis. In vitro, TAK242 abrogated TLR4-induced stimulation of collagen synthesis and myofibroblasts differentiation in explanted normal skin fibroblasts, and in constitutively active scleroderma fibroblast populating 3D skin equivalents. The antifibrotic effects of TAK242 were accompanied by reduced activation of TLR4 signaling.

Conclusion: Our results provide evidence that specific TLR4 inhibitor TAK242 attenuates organ fibrogenesis both in vitro and in vivo. These findings identify TAK242 as a potential novel strategy for breaking the cycle of progressive fibrosis in scleroderma and other fibrotic diseases.

Disclosure: S. Bhattacharyya, None; W. Wang, None; Z. Tamaki, None; Y. Tsukimi, None; M. Yamazaki, None; J. Varga, None.

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Adiponectin Is an Endogenous Anti-Fibrotic and Target in Systemic Sclerosis: Novel Link Between Fibrosis and Metabolism. Feng Fang1, Roberta G. Marangoni1, Xiangchun Zhou1, Wen Hong2, Boping Ye2, Asano Yoshiihide1, Shiniichi Sato1, Yuri Masui1, Chengjing Zhang1, Katja Lakota1, Jun Wei1, Monique E. Hinchcliffe5, Philipp Scherer5, Laszlo Otvo5 and John Varga1. 1Northwestern University, Feinberg School of Medicine, Chicago, IL, 2China Pharmaceutical University, Nanjing, China, 3University of Tokyo, Tokyo, Japan, 4University of Texas Southwestern Medical Center, Dallas, TX, 5Temple University, Philadelphia, PA, 6Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Systemic sclerosis (SSc) skin fibrosis is associated with attenuated cutaneous adipose tissue and adipogenic gene expression. Levels of the adipose-derived cytokine adiponectin (APN) and its receptors, are both reduced in SSc, and inversely correlated with extent of skin involvement. We investigated the role of APN in pathogenesis of skin fibrosis in mice with genetic APN gain- and loss-of-function, and determined the effects, mechanism and therapeutic potential of APN-derived synthetic peptides on the fibrotic process in vitro and in vivo.

Methods: Fibrotic responses were examined in human and mouse fibroblasts, skin organ cultures and 3D skin equivalents. Novel APN-derived peptides targeting APN receptors were designed and synthesized. Genetic and pharmacological manipulation of APN signaling was evaluated in mouse models of sclerodermia.

Results: Mice lacking APN developed exaggerated cutaneous fibrosis and intradermal adipose loss upon bleomycin challenge. In contrast, ΔGly-APN mutant mice that have 2-fold elevated levels of circulating APN were protected from fibrosis, and showed preferential expansion of intradermal adipose tissue. To directly evaluate the role of APN signaling in SSc fibrosis, recombinant APN, as well as synthetic APN-derived peptides were used. APN treatment of skin fibroblasts resulted in suppression of collagen synthesis, myofibroblast transformation and other fibrotic responses that were mediated via the energy-sensing enzyme AMP kinase. Synthetic APN-derived peptides targeting the APN receptors abrogated fibrotic responses in explanted fibroblasts, skin organ cultures and in 3D human skin equivalents. Daily treatment of mice with APN-derived peptides induced potent activation of AMP kinase in target organs in the absence of toxicity. Significantly, peptide treatment prevented, as well as reversed, bleomycin-induced cutaneous fibrosis.

Conclusion: We identified an important homeostatic role for the adipocyte-derived cytokine APN in negative regulation of collagen deposition and myofibroblast accumulation, highlighting a novel link between metabolism and skin fibrosis. Restoring impaired APN signaling in SSc (scleroderma) using synthetic APN-derived peptides might therefore represent a pharmacological approach to fibrosis therapy.

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Mir-145 Protects Against Skin Fibrosis in Vivo by targeting TGF-β Signaling. Serena Vettori1, Christian Beyer2, Matthias Brock3, Naoki Iwamoto4, Britta Maurer1, Michelle Trenkmann4, Astrid Jüngel1, Renate E. Gay1, Maurizio Calcagni2, Gabriele Valentini2, Steffen Gay1, Joerg H. W. Distler5 and Oliver Distler5. 1Zürich University Hospital, Zürich, Switzerland, 2Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, 3Division of Plastic Surgery and Hand Surgery, University Hospital Zürich, Zürich, Switzerland, 4Second University of Naples, Napoli, Italy.

Background/Purpose: In vitro, mir-145 exerts anti-fibrotic effects in systemic sclerosis (SSc) by downregulating TGF-β signaling. In turn, ectopic TGF-β downregulates mir-145 thereby optimizing TGF-β signaling pathways. In this study, we aimed to investigate whether therapeutic application of mir-145 could prevent fibrosis via regulation of TGF-β in vivo.

Methods: We used mir-145+/− (n = 7–8), and mouse models of dermal fibrosis induced by either bleomycin (n = 6) or by adenoviral overexpression
of constitutively active TGF-β receptor type I (n = 3). MiR-145+/− mice and wild type controls were also treated with intradermal bleomycin, while a subset of bleomycin-induced dermal fibrosis mice were simultaneously treated with intradermal injections of a synthetic miR-145 designed for in vivo transfection. Dermal thickness, myofibroblast count (α-SMA staining on paraffin-embedded skin sections), and collagen content (hydroxyproline assay) were analyzed as outcomes of skin fibrosis. The expression of miR-145 and of miR-145 targets, TGFBR2 and SMAD3, was analyzed in mice treated with the synthetic miR-145 and in the mouse model of skin fibrosis induced by the constitutive activation of TGF-β receptor type I by real-time PCR.

Results: We found that miR-145+/− mice were more sensitive to the effects of bleomycin than wild type controls, as shown by a stronger increase of dermal thickness (2.04 versus 1.7 fold), α-SMA count (4.4 versus 3), and collagen content (1.82 versus 1.34; all p < 0.01). According to the anti-fibrotic effects shown by miR-145 in vivo, we expected to counteract bleomycin effects in C57BL/6 mice by the simultaneous administration of synthetic miR-145. Indeed, all explored outcomes improved in these mice, as compared to controls injected with a synthetic miR-scrambled: dermal thickness reduced from 1.7 to 1.27 fold, α-SMA count from 3.7 to 1.9, collagen content from 3.6 to 2.9; all p < 0.01. MiR-145 expression in mice injected with the synthetic miR-145 increased by 37 fold (p < 0.01) confirming the efficiency of the in vivo transfection. Accordingly, the downregulation of the previously identified direct miR-145 targets, TGFBR2 and SMAD3, by 0.21 and 0.10 fold (p < 0.05) supports the hypothesis that the anti-fibrotic effects of miR-145 are mediated by the downregulation of these TGF-β signaling components. Finally, in mice overexpressing constitutively active TGF-β receptor type I, miR-145 was strongly down-regulated by 0.55 fold in fibrotic skin as compared to mock-transfected controls, confirming the existence of a regulatory feedback loop between miR-145 and TGF-β in vivo and further proving the relevance of the miR-145/TGF-β interaction in vivo.

Conclusion: Here we show for the first time that the therapeutic application of miR-145 protects against skin fibrosis in vivo, thus opening the road to new therapeutic targeted approaches to SSC and other fibrotic disorders. We also confirm on the in vivo level, that the anti-fibrotic effects of miR-145 are mediated by the downregulation of the TGF-β signaling components TGFBR2 and SMAD3, and that the abnormal miR-145 expression that is observed in SSC is dependent, at least in part, on activation of TGF-β.

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969 Priming of WNT Signalling during Fibrosis Is Mediated By TGF-β-Induced Axin-2 Downregulation. Justin Gillespie1, Emma C. Derrett-Smith2, Michael McDermott1, Paul Emery1, Christopher P Denton2 and Francesco Del Galdo3. 1Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, 2UCL Medical School Royal Free Campus, London, United Kingdom, 3Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is characterized by autoimmune activation, vasculopathy and tissue fibrosis. Recently, activation of the Wnt/β-catenin signaling pathway in SSc fibroblasts has been linked to the pathogenesis of SSc. However, the relative role of crosstalk between TGF-β and Wnt Pathways in SSc is still to be determined. Here we have aimed to evaluate the Wnt pathway in SSc fibroblasts and the effects of TGF-β on canonical Wnt signalling. The effects of TGF-β on canonical Wnt signalling were measured by western blotting or immunohistochemistry. Canonical Wnt signalling was evaluated by TOPFlash luciferase reporter activity.

Methods: Dermal fibroblasts from 3 early diffuse cutaneous (dc)-SSc patients and 3 healthy controls (HC) were stimulated with recombinant human (rh)TGF-β and/or rhWnt-3a. mRNA stability was investigated using actinomycin D. mRNA levels were quantified by qRT-PCR and protein expression was measured by western blotting or immunohistochemistry. Canoical Wnt signalling was evaluated by TOPFlash luciferase reporter activity.

Results: In basal conditions, SSc fibroblasts did not show any increase in TOPFlash reporter activity compared to HC. On the contrary, the expression of Axin2, a Wnt target gene and negative regulator of the Wnt pathway, was reduced at both mRNA (58%; P < 0.01) and protein levels. Indeed, SSc fibroblasts had an increased response to rhWnt-3a compared to HC fibroblasts (11.6 fold increase in TOPFlash activity and 2.5 fold in Axin2 mRNA vs. 4.2 fold and 1.8 fold, respectively, in HC). TGF-β treatment of HC fibroblasts decreased Axin2 expression to levels similar to SSc fibroblasts, both at mRNA (38.7%; p < 0.001) and protein levels. This effect was associated with a 3.7 fold increase in mRNA decay. Concordantly, TGF-β-RIL DeltaK transgenic mice displayed a reduced expression of Axin2-2 in the dermis. Similar to SSc, pretreatment of HC fibroblasts with TGF-β increased their responsiveness to Wnt-3a (16.1 vs. 7.7 fold increase in TOPFlash activity; P < 0.01). Depletion of Axin2 by siRNA was sufficient to mimic the effect of TGF-β pretreatment (P < 0.05). Accordingly, XAV939-mediated Axin2 stabilization ablated the Wnt-3a-induced canonical hyperactivation in ‘TGF-β primed’ fibroblasts.

Conclusion: TGF-β stimulation primes dermal fibroblasts to increase their responsiveness to Wnt ligand-induced canonical signaling. TGF-β mediates the downregulation of Axin2-2, which is required for canonical Wnt signaling hyperactivation in dermal fibroblasts. Our data suggest that the increased Wnt signaling observed in SSc is a consequence of TGF-β signaling and therefore targeting of the TGF-β pathway may also help to resolve the aberrant Wnt signaling observed in SSc.

Disclosures: J. Gillespie, None; E. C. Derrett-Smith, None; M. McDermott, None; P. Emery, None; C. P. Denton, None; F. Del Galdo, None.

**Part 1: Background/Purpose**
Infection has been increasingly reported in the literature as an environmental trigger inducing the development of anti-phospholipid antibodies or antiphospholipid syndrome in genetically predisposed individuals. We conducted a systematic review and meta-analysis of observational studies to evaluate the risk of developing positive antiphospholipid (aPL) antibodies following infection compared to controls and determine whether these antibodies are associated with any clinical consequences.

**Methods:** We conducted a literature search using Medline, Embase, Web of Science, and the Cochrane CENTRAL databases with no language restriction to identify observational studies reporting on patients who develop positive aPL antibodies after infection from inception up to October 2013. Two independent reviewers assessed the studies for inclusion and for quality, and extracted relevant data. We extracted data on the related infection, profile and prevalence of aPL antibody, and patient clinical outcomes. We performed a meta-analysis and estimated relative risks (RR) with 95% confidence intervals (CI) of developing antibodies after an infection compared to controls.

**Results:** From 2,257 unique citations, 320 publications met our inclusion criteria; from these, we selected 216 studies with controls to estimate risk. The most commonly reported infections were viral and bacterial. Compared to controls, patients with an infection had 10.9 times more likely to develop positive IgG anticardiolipin (aCL) antibodies after the infection (95% confidence intervals (CI) 5.6–21.2). The highest risk ratio (RR) was observed after infection with tuberculosis (47.5: 95% CI 3.0–753.8), Q fever (44.0; 95% CI 2.8–702.5), and Hepatitis C virus infection (21.4: 95% CI 3.6–127.1). After an infection with Epstein Bar virus individuals were 33 times more likely to develop positive IgM aCL (95% CI 1.9–856.2) compared to controls. The RR for developing lupus anticoagulant or anti-β2-glycoprotein-I (GPI) antibodies were 2.4 (95% CI 1.3–4.5), and 2.3 (95% CI 1.2–4.4), respectively. For studies without controls (104), the pooled incidence of positive IgG aCL after infection was 36% (95% CI 27%–45%). The highest incidence was found in individuals with human immunodeficiency virus (HIV) (51%: 95% CI 38%–63%). Development of clinical manifestations of aPL syndrome was reported in 52.3% of the included studies. The most common manifestations were thromboembolic events or pregnancy related complications, occurring in 23.1% of individuals.

**Conclusion:** Various viral and bacterial infections can frequently induce the development of aPL antibodies, and can cause thromboembolic manifestations fulfilling the diagnosis of APS.

**Disclosure:** N. Abdel-Wahab, None; M. A. Lopez-Olivo, None; S. Talathí, None; M. E. Suarez-Almazor, None.

**Methods:** The long-term efficacy of Pneumovax vaccination seems to be preserved among AIRD patients for at least 10 years and its long-term effect is not affected by the use of biologics while MTX might slightly impair it. The actual recommendation for revaccination after 5 years should be reconsidered.

**Disclosure:** A. Broyde, None; U. Arad, None; N. Madar-Balakinski, None; D. Paran, None; I. Kaufman, None; I. Litinsky, None; D. Levartovsky, None; I. Wigler, None; D. Caspi, None; O. Elkayam, None.

**Background/Purpose:** Many epidemiologic studies of systemic lupus erythematosus (SLE) mortality in the United States (US) utilize patient registries that are regional and may not be applicable to the general population. Our approach is to analyze comprehensive mortality data in the US over the past 43 years. We aimed to determine the variation of SLE and lupus nephritis (LN) mortality by race, gender, and geographic location.

**Methods:** Using county-level national mortality data from the National Center for Health Statistics from the period of 1968–2010 divided into 3 cohorts based on International Classification of Diseases codes for version 8 (1968–1978), 9 (1979–1998) and 10 (1999–2010), we estimated age-adjusted mortality rates (AMR) per 100,000 persons and stratified results by gender, race, and geographic locations. We selected cases where the underlying cause of death was SLE (734.1, 710.0, M32) and further identified LN cases to include glomerular disease and renal failure.

**Disclosure:** M. Abdel-Wahab, None; M. A. Lopez-Olivo, None; S. Talathí, None; M. E. Suarez-Almazor, None.
Results: Of the 93,245,807 death records reviewed, we identified 46,786 cases of SLE. AMR-SLE were 3–5-fold higher in females than in males: 0.628 (95% CI 0.613–0.644), 0.748 (95% CI 0.737–0.759), and 0.700 (95% CI 0.688–0.712) among females; and 0.162 (95% CI 0.154–0.170), 0.176 (95% CI 0.170–0.182) and 0.134 (95% CI 0.128–0.140) among males for the periods of 1968–1978, 1979–1998, and 1999–2010 respectively. Intriguingly, while the AMR-SLE decreased among white males (from 0.149 in 1968–1978 to 0.107 in 1999–2010), and remained stable among white females (0.496 to 0.499, p=0.7) over the last 43 years, it increased among black females and males (1.601 to 1.959 in females, p<0.0001; and 0.270 to 0.335 in males, p=0.004). Thus, black females had ~6-fold higher AMR-SLE than black males and ~10–18-fold higher than white males. To test whether differences in LN, a severe common manifestation of SLE, contributed to these differences, we analyzed mortality trends among 3,607 deaths (1999–2010) ascribed to LN. Black females had the highest AMR-LN at 0.473 (95% CI 0.445–0.501), which was ~5-fold higher than AMR-LN in black males and white females and 36-fold higher than in white males. Analyses of regional differences in AMR-LN showed even more dramatic racial trends, with black females living in the South census region with the highest AMR-LN of 0.507 (95% CI 0.468–0.547) and white males living in the Northeast census region with the lowest AMR-LN of 0.006, a 85-fold difference. While AMR-LN showed even more dramatic racial trends, with black females having the highest AMR-LN at 0.473 (95% CI 0.445–0.501), which was ~5-fold higher than AMR-LN in black males and white females and 36-fold higher than in white males. Increased deaths ascribed to LN in black females, particularly in southern states, might account for the profound racial differences in SLE outcome.

Conclusion: Overall SLE mortality has not substantially decreased from the 1968–1978 to the 1999–2010 periods, except in white males. In fact, SLE black females, particularly in southern states, might account for the profound AMR-LN and AMR-SLE trends. AMR-LN showed even more dramatic racial trends, with black females living in the South census region with the highest AMR-LN of 0.507 (95% CI 0.468–0.547) and white males living in the Northeast census region with the lowest AMR-LN of 0.006, a 85-fold difference. While no regional differences in AMR-LN were observed for black males, AMR-LN was higher in the South than in the Northeast for white males, white females, and black females.

Disclosure: E. Y. Yen, None; M. Shaheen, None; J. M. Woo, None; D. K. McCurdy, None; R. R. Singh, None.

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Relation of Pelvic Drop during Walking to Risk of Incident Medial Knee Osteoarthritis: The Multicenter Osteoarthritis Study

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Background/Purpose: To test whether pelvic drop (PD) is associated with radiographic knee osteoarthritis (OA). PD is a common gait deviation that is associated with increased knee loads and the risk of OA progression.

Methods: The Multicenter Osteoarthritis Study (MOST) consists of 1930 subjects without knee OA on either knee (56% women, mean age 59 years) at baseline, 186 knees developed OA (e.g., 144 with KL<2). We identified incident cases at 84 months as having Kellgren & Lawrence (KL) grade ≥ 2 and used KL scores measured at 24-month and 36-month visits to assess radiographic OA progression. Baseline BMI was categorized as ≤25 kg/m2 (i.e., overweight), and ≥30 kg/m2 (i.e., obese). We first assessed the total effect of BMI on KL grade worsening at Month 36 (Table). We then decomposed the effect into the indirect effect of BMI (i.e., the pathway through its effect on KL grade at Month 24) and the direct effect (i.e., the pathway not through its effect on KL grade at Month 24) (Figure), using marginal structural model mediation analyses. All analyses were adjusted for age, sex, knee injury, and education.

Results: Of 1930 subjects without knee OA on either knee (56% women, mean age 59 years) at baseline, 186 knees developed OA (e.g., 144 with KL=2). The total effect of BMI on OA progression at Month 36 is entirely through its effect on OA progression by decomposing its effect components (Figure) using mediation analyses.

Disclosures: E. K. Quinn, None; M. C. Nevitt, None; J. C. Torner, None; C. E. Lewis, None; D. T. Felson, None.

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Obesity Paradox in Osteoarthritis Progression – What Effects Are We Measuring? Qiong Louie-Gao1, Hyon K Choi1, David T. Felson1, Tuhtna Neogi1, Uyen Sa D.T. Nguyen1, Na Liu1, and Yaying Zhang1.

1Boston University School of Medicine, Boston, MA, 2University of Manchester, Manchester, United Kingdom.

Background/Purpose: While obesity is a well-established risk factor for incident knee osteoarthritis (OA), it has a null association with OA progression. Among various potential explanations for such a paradox, one is a lack of precision in the research question. While investigators are interested in the total effect of BMI on OA progression among OA patients, most studies have instead measured a direct effect of BMI in the general population (Figure). This is because in these studies, data on BMI were assessed prior to OA diagnosis, or BMI measured after OA diagnosis has remained mostly unchanged compared with that prior to OA incidence. We have demonstrated this potential mechanism underlying the paradoxical findings of BMI in OA progression by decomposing its effect components (Figure) using mediation analyses.

Methods: Knee radiographs were taken at baseline and each annual follow-up visit, and severity of knee radiographic OA was assessed using Kellgren/Lawrence (KL) criteria among participants in the Osteoarthritis Initiative. We identified subjects who had no OA on either knee at baseline (i.e., KL<2). We first assessed the total effect of BMI on OA progression at Month 36. Compared with those with BMI≤25, overweight and obese subjects had a 1.40 (95% CI: 1.13–1.73) and 1.95-fold (1.54–2.46) increased risk of KL grade worsening, respectively, after adjusting for potential confounders.

Conclusion: These findings do not confirm a longitudinal association between pelvic drop during walking and 2-year risk of incident medial knee OA. Previous reports of a cross-sectional association could indicate that pelvic drop is a frequent consequence of existing medial knee OA rather than an antecedent cause of incident knee disease.

Table. Relative Odds of Incident Medial Knee OA in Categories of Increasing Pelvic Drop during Walking

<table>
<thead>
<tr>
<th>Pelvic Drop during Walking</th>
<th>Cases</th>
<th>Controls</th>
<th>Adj* Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (≤ 0.1°)</td>
<td>135</td>
<td>135</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>0.1° to 0.7° men, &gt; 0.5° women</td>
<td>16 (30.2%)</td>
<td>37 (68.6%)</td>
<td>0.8 (0.3–1.9)</td>
</tr>
<tr>
<td>1.1° to 1.9° men, &gt; 1.2° women</td>
<td>17 (33.3%)</td>
<td>34 (66.7%)</td>
<td>1.0 (1.0–2.4)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, BMI, race, clinic site, and walking velocity.

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general population. To obtain the intended total effect of BMI on OA progression, one could use the change in BMI after OA diagnosis as an exposure for the outcome of OA progression.

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Background/Purpose: Chronic musculoskeletal pain (CP) is associated with reduced levels of physical activity (PA), however few studies have examined the prospective nature of CP on PA at the population level. The aim of this study is to examine whether CP independently predicts a reduction in PA.

Methods: Data are from the UK Biobank, a large prospective cohort designed to support investigation of risk factors for major diseases of middle and old age. More than 500,000 men and women aged 40–69 were recruited between 2006–2010 (baseline); approximately 20,000 repeat assessments were conducted between 2012–2013 (follow-up). Participants answered questions on health and lifestyle by touch-screen questionnaire. CP is defined as self-reported pain lasting at least three months either all over the body or related to the neck or shoulder, back, abdomen, hip or knee, as well as facial pain or headache. Questions on PA and sedentary behaviour were asked using a modified short-form of the International Physical Activity Questionnaire at baseline and follow-up. PA was categorized as low, moderate or high according to frequency/duration of moderate and vigorous activity; PA change was calculated and dichotomized into same or improved activity category or worsened activity category. Hours spent watching TV and in non-work computer use were combined to estimate time in sedentary behaviour. Descriptive, linear and logistic regression analyses were conducted on 14,391 men and women with complete data on a priori covariates (age, gender, ethnicity, highest educational attainment, work status at follow-up, change in BMI status, baseline self-rated health, self-reported depression at follow-up and time-to-follow-up).

Results: Mean length of follow-up was 4 years (range 2.1–6.5). 5,567 participants (39%) had CP at baseline. Of those without CP at baseline, 20% (n=1,793) had developed it at follow-up. At baseline, fewer individuals with CP were categorized with moderate or high levels of PA ($\chi^2=12.5, p=0.002$). Overall, the majority of participants maintained the same PA category, while 21% had an improved activity classification and 20% had a worsened activity classification. Individuals with CP at baseline were more likely to deteriorate in activity status, than those without, who were more likely to stay the same or improve activity status ($\chi^2=9.2, p=0.002$). This relationship remained in multivariate logistic regression after adjustment for covariates, with baseline CP predicting a negative change in PA category (OR: 1.13; 95% CI: 1.04–1.23). Individuals with CP spent more time in sedentary behaviour than those without CP ($B=0.07, 95\% CI: 0.01–0.13$) in linear regression analysis adjusted for covariates and baseline sedentary behaviour.

Conclusion: CP predicts a negative change in PA over an average four-year follow-up period. Given the prevalence and persistence of CP, attention should be given to supporting and encouraging physical activity so as to prevent deterioration of PA levels and the spiral of pain-related inactivity within middle-age and early old age adults with CP.

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ARHP Concurrent Abstract Session Osteoarthritis

Sunday, November 16, 2014, 4:30 PM–6:00 PM

976 Measurement Properties of the Health Assessment Questionnaire Disability Index (HAQ-DI) in Patients with Generalized Osteoarthritis (GOA). Nienke Cuperus1, Elien A.M. Mahler1, Thea Vliet Vlieland2, Thomas Hoogeboom1 and Cornelia H.M. van den Ende5. 1Sint Maarten-skliniek, Nijmegen, Netherlands, 2Leiden University Medical Center, Leiden, Netherlands, 3CAPRI school for public health and primary care, CCTR centre for Care Technology Research, Maastricht University, Maastricht, Netherlands.

Background/Purpose: The involvement of multiple joints is common in osteoarthritis (OA), often referred to as generalized OA (GOA). Individuals with GOA typically suffer from limitations of both upper and lower extremity function. However, existing instruments measuring functional limitations in OA focus on a specific localization; limiting their use in GOA. We hypothesized the Health Assessment Questionnaire Disability Index (HAQ-DI), originally developed for inflammatory arthritis, to be appropriate to measure functional limitations in GOA. Therefore we evaluated the measurement properties (content validity, construct validity and reliability) of the HAQ-DI in patients with GOA.

Methods: Data were used from a randomized clinical trial comparing the effectiveness of two multidisciplinary treatment program for patients with GOA. 137 patients completed a standardized set of questionnaires before and directly after treatment. The measurement properties of the HAQ-DI were assessed according the Consensus Based Standards for the Selection of health Status Measurement Instruments Checklist. Floor and ceiling effects for each HAQ-DI category at baseline were considered present if $>15\%$ of patients scored the worst (3) or best (0) possible score. For the content validity, 17 health professionals experienced with GOA were asked to judge the relevance of each HAQ-DI item. Construct validity was assessed by computing associations (Pearson r) between HAQ-DI scores and scores on other clinical (unrelated) measures. Reliability was assessed by Cronbach’s alpha and intra-class correlation coefficient (ICC). The minimal important change (MIC) score was calculated using an anchor based method.

Results: Of 137 patients (mean age 60(±8) years; (85%) female), 93% reported to have complaints in both the upper and lower extremities. Floor and ceiling effects were present: 20%-30% of patients reported the best possible score on the HAQ-DI categories eating, dressing and gripping; 16% reported the worst possible score on the category hygiene. The content validity was questionable since according to the health professionals the HAQ-DI encompasses 9 (out of 20) activities that are not relevant or too easy to perform for GOA patients. Construct validity was rated positive given the moderate to strong associations with related constructs and weak associations with unrelated constructs. Cronbach’s alpha was 0.90, confirming internal consistency and the ICC was 0.81, reflecting good reliability. The MIC was 0.25 points and the smallest detectable change was 0.60 indicating that important changes cannot be distinguished from measurement error in individuals.

Conclusion: The HAQ-DI showed a good construct validity and reliability to measure functional limitations in patients with GOA. Given the unsatisfactory content validity, we recommend an update of the HAQ-DI items when using the HAQ-DI in future clinical practice and research focusing on functional limitations in GOA. This update might also be worthwhile for RA and all other rheumatic diseases.

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Adequate management of osteoarthritis (OA) requires both medical and behavioral strategies. However, some recommended therapies are under-utilized in clinical settings, and there is low use of behavioral strategies among patients. Consequently, recommended therapies are under-utilized in clinical settings, and requires both medical and behavioral strategies. However, some methods are more effective than others in improving outcomes. The objective of this trial was to examine the effectiveness of a combined patient + provider intervention for managing OA in a primary care setting.

Methods: 300 patients with diagnoses of hip and/or knee OA at the VA Medical Center in Durham, NC (mean age = 61, SD = 11; 91% male, 50% non-white) were randomized to a combined patient + provider intervention for managing OA versus usual care. The 12-month, telephone-based patient intervention focused on weight management, physical activity and cognitive behavioral pain management. The provider intervention involved delivery of patient-specific recommendations for OA treatments (based on multiple sets of published guidelines and including non-pharmacological treatments such as physical therapy), delivered in the electronic medical record. The primary outcome was the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), including the overall score (range: 0–100) and pain and function subscales. Secondary outcomes were objective physical function (Short Physical Performance Battery; SPPB; range: 0–20), weekly hours of any exercise and moderate or greater intensity exercise (Community Healthy Activities Model Program For Seniors or CHAMPS questionnaire) and depressive symptoms (Patient Health Questionnaire; PHQ-9; range: 0–27).

Linear mixed models (LMM) were used to assess the difference in improvement in outcomes between the intervention and usual care groups, adjusting for clustering within physicians.

Results: At 12-month follow-up, WOMAC scores were 4.2 points lower in the intervention group vs. usual care [95% confidence interval (CI) = −7.2, −1.1; p = 0.008], indicating improvement in symptoms and function. The WOMAC function subscale was 3.4 points lower in the intervention group compared to usual care [95% CI = −5.7, −1.0; p = 0.005], but there was no significant difference in WOMAC pain subscales between groups (p = 0.12). SPPB scores were 0.6 points higher in the intervention group than the usual care group [95% CI = 0.1, 1.2; p = 0.02], indicating improvement in function. Weekly hours of exercise were also higher in the intervention group relative to the usual care group at 12-month follow-up: any exercise = 3.7 hours [95% CI = 1.5, 5.8; p = 0.001] and moderate or greater intensity exercise = 1.6 hours [95% CI = 0.3, 2.9; p = 0.02]. There was no significant difference in depressive symptoms in the intervention groups compared to usual care groups.

Conclusion: This combined patient and provider intervention improved physical function (self-reported and objectively assessed) and physical activity levels in patients with hip and knee OA. The telephone-based patient intervention is relatively low-cost and could be disseminated widely, and the provider intervention could be integrated in an automated manner within electronic medical record systems.

Disclosure: K. D. Allen, None; H. B. Bosworth, None; A. Jeffreys, None; C. Coffman, None; S. Datta, None; J. McDuffie, None; E. Oddone, None; J. Strauss, None; W. S. Yancy Jr., None.

S78

Socioeconomic Status Measures Are Associated with Increasing Pain, Stiffness and Physical Function Among Individuals with Knee and Hip Osteoarthritis. Rebecca Cleveland1, Jordan B. Renner1, Joanne M. Jordan2, and Leigh F. Callahan1. 1University of North Carolina at Chapel Hill, Chapel Hill, NC; 2University of North Carolina Department of Radiology, Chapel Hill, NC; 3University of North Carolina Dept of Epidemiology, Chapel Hill, NC; 4University of North Carolina, Chapel Hill, NC.

Background/Purpose: The determinants of disability progression (DP) among those with knee and/or hip osteoarthritis (OA) are not well known. Our aim was to explore whether socioeconomic status (SES) measures were associated with DP at follow-up (FU) in the Johnston County Osteoarthritis Project (JoCo OA).

Methods: Analyses were carried out among individuals with radiographic knee and/or hip OA (rOA) aged ≥45 years who participated in TIME 1 (T1: 1996–2000), which included those who entered the cohort during the original study enrollment who returned for their first follow-up, and new enrollees recruited for cohort enrichment. Follow-up was assessed at TIME 2 (T2 FU: 2006–2010). DP was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) which includes Pain, Stiffness and Physical Function Subscales. Definitions were developed as an increase from T1 to T2 FU of ≥10 in the WOMAC total score, or any increase in a subscale score. SES measures were education (no high school diploma [<HS] vs HS diploma or more [≥HS]), occupation (non-professional vs professional) and block group poverty (≥20% vs <20%). Odds ratios (OR) and 95% confidence intervals (CI) for associations between SES and DP were estimated using logistic regression simultaneously adjusting for other SES measures plus age, gender, hip and/or knee injury, BMI and smoking.

Results: There were 796 individuals with knee and/or hip rOA from T1 who returned at T2 FU. The mean age was 64.6 years, 66.3% were female, 30.7% African American, and mean BMI was 31.8 kg/m². At T2 FU, there was increased disability in 26.8% of individuals with knee rOA and 21.8% of individuals with hip rOA. Analyses including all individuals with knee and/or hip rOA showed that individuals with <HS education were more likely to have developed disability by T2 FU (OR = 1.86, 95% CI = 1.28–2.60) when compared with those ≥HS education (Table 1). Slightly stronger associations were seen when evaluating the effect of education among those with only knee rOA, where those with <HS education had nearly a three-fold increase in odds of having an ≥10 point increase in WOMAC score at T2 FU (OR = 2.86, 95% CI = 1.45–5.67). Among those with only hip rOA, having a non-professional occupation was associated with an increase in WOMAC disability, and block group poverty that narrowly missed statistical significance (OR = 1.96, 95% CI = 0.98–3.91). Across all subscales, education was consistently associated with all subscales among those with only knee rOA, and occupation was associated with subscales among those with only hip rOA.

Conclusion: We report that individuals with lower education and non-professional occupation were more likely to have DP from T1 to T2 FU, associations that remained after adjustment for other SES measures. Our results suggest that SES may have an influence on DP, findings which may help clinicians in developing personalized OA intervention programs for individuals with low SES measures.

Table 1 Adjusted1 odds ratios (OR) and 95% confidence intervals (CI) for the association between SES measures and WOMAC score increase between the first and second follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Knee and/or Hip rOA</th>
<th>Only Hip rOA</th>
<th>Only Knee rOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee and/or Hip rOA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>n=796</td>
<td>n=595</td>
<td>n=201</td>
</tr>
<tr>
<td>Education</td>
<td>1.96 (1.28–3.00)</td>
<td>1.95 (0.75–5.37)</td>
<td>2.64 (1.45–4.87)</td>
</tr>
<tr>
<td>Non-Professional Occupation</td>
<td>1.00 (0.74–1.39)</td>
<td>1.96 (0.98–3.91)</td>
<td>0.80 (0.45–1.51)</td>
</tr>
<tr>
<td>Block Group Poverty &gt;20%</td>
<td>1.07 (0.74–1.58)</td>
<td>1.26 (0.66–2.39)</td>
<td>1.02 (0.56–1.83)</td>
</tr>
<tr>
<td>Physical Function Increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC Total Increase ≥10</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
</tr>
<tr>
<td>Block Group Poverty &gt;20%</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
</tr>
<tr>
<td>Block Group Poverty &lt;20%</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
<td>1.00 (0.50–1.98)</td>
</tr>
</tbody>
</table>

1Mutually adjusted for education, occupation, poverty
2Additionally adjusted for age, gender, hip & knee injury, BMI and smoking
3Comparing <HS education vs ≥HS education
4Comparing non-professional occupation vs. professional occupation

Disclosure: R. Cleveland, None; J. B. Renner, None; J. M. Jordan, Algynomics, 5, Samumed, 5, Flexion, 5, ClearView Healthcare Partners, 5, Trinity Partners, LLC, 5; L. F. Callahan, None.

S979

Genome-Wide Association Study for Severe Radiographic Knee Osteoarthritis. Youfang Liu1, Michelle Yau2, Laura Yerges-Armstrong3, Braxton Mitchell1, Rebecca D. Jackson4, Marc C. Hochberg5, Shad Smith6, William Maixner7, Luda Diatchenko8 and Joanne M. Jordan. 1University of North Carolina, Chapel Hill, NC; 2Department of Pharmacology, University of Illinois at Chicago; 3Department of Medicine, University of Chicago; 4Department of Biostatistics, University of Michigan; 5Department of Rheumatology, Immunology and Allergy, University of Pennsylvania; 6Rheumatology & Immunology, University of North Carolina at Chapel Hill; and 7Department of Biostatistics, University of North Carolina at Chapel Hill.

Background/Purpose: The determinants of disability progression (DP) among those with knee and/or hip osteoarthritis (OA) are not well known. Our aim was to explore whether socioeconomic status (SES) measures were
Background/Purpose: Knee osteoarthritis (OA) is a heritable common joint disorder. In previously reported genetic studies, cases were usually defined with a radiographic Kellgren and Lawrence (KL) grade ≥2. Since more severe knee OA is more likely to have greater medical and public health impact, we searched for genetic variations associated with severe radiographic knee OA (rKOA) of KL grade 3 or 4.

Methods: Caucasian participants with knee radiographic grade from the Johnston County Osteoarthritis Project (JoCo) were included in this analysis. Cases were defined as the subjects with KL grade ≥3 in at least one knee, while the controls were defined as the subjects with KL grades = 0 in both knees. Genome wide genotyping was completed using the Illumina Infinium IM-Duo array and imputed into 2.5M using HapMap II Caucasian as the reference data. Genome-wide association analysis was performed using logistic regression with adjustment for age and sex, with and without additional adjustment for BMI.

Results: Of 672 participants [64% women, mean age = 64.2 (SD = 10.6), mean BMI = 30.3 (SD = 6.4)], 353 were cases and 319 were controls. Although no SNPs reached genome-wide significant p-values at 5E-8, we identified two SNPs with p-values less than 5E-06 in the model without BMI adjustment (table). After BMI adjustment, associations were attenuated but still statistically significant (table). Both SNPs, rs11196174 and rs11196175, are located in the TCF7L2 gene which encodes a T-cell specific transcription factor participating in the Wnt signaling pathway, which has been shown to be related to OA.

Conclusion: Two SNPs, rs11196174 and rs11196175, located in the TCF7L2 gene were associated with severe rKOA, supporting the possibility that the pathogenesis of severe rKOA may be through the Wnt signaling pathway. Further studies will need to validate this finding in other populations.

### Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Position</th>
<th>A1</th>
<th>A2</th>
<th>Freq</th>
<th>Chr</th>
<th>With BMI adjustment</th>
<th>With BMI adjustment</th>
<th>Beta</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCF7L2</td>
<td>rs11196174</td>
<td>G</td>
<td>A</td>
<td>0.69</td>
<td>10</td>
<td>114724086</td>
<td>0.82</td>
<td>0.70</td>
<td>9.2e-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs11196175</td>
<td>C</td>
<td>T</td>
<td>0.31</td>
<td>10</td>
<td>114766004</td>
<td>-0.81</td>
<td>0.96</td>
<td>6.0e-05</td>
<td></td>
</tr>
</tbody>
</table>

### Disclosure

Y. Liu, None; M. Yau, None; L. Verges-Armstrong, None; B. Mitchell, None; R. D. Jackson, None; M. C. Hochberg, None; S. Smith, Aligynomics, Inc.; W. Maiinker, Aligynomics, Inc.; L. L. Diatchenko, None; J. M. Jordan, Aligynomics, Inc.; S. Samumed, 5; Flexion, 5; ClearView Healthcare Partners, 5; Trinity Partners, LLC, 5.

### 980

Annual Medical Care Expenditures Among US Adults with Osteoarthritis, 2008–2011

Miriam G. Cisternas,1 Louise Murphy,2 David J. Pasta,3 Daniel H. Solomon4 and Charles G. Helmick5. 1M-Duo array and imputed into 2.5M using HapMap II Caucasian as the reference. Genome-wide association analysis was performed using logistic regression with adjustment for age and sex, with and without additional adjustment for BMI.

Results: Of 672 participants [64% women, mean age = 64.2 (SD = 10.6), mean BMI = 30.3 (SD = 6.4)], 353 were cases and 319 were controls. Although no SNPs reached genome-wide significant p-values at 5E-8, we identified two SNPs with p-values less than 5E-06 in the model without BMI adjustment (table). After BMI adjustment, associations were attenuated but still statistically significant (table). Both SNPs, rs11196174 and rs11196175, are located in the TCF7L2 gene which encodes a T-cell specific transcription factor participating in the Wnt signaling pathway, which has been shown to be related to OA.

Conclusion: Two SNPs, rs11196174 and rs11196175, located in the TCF7L2 gene were associated with severe rKOA, supporting the possibility that the pathogenesis of severe rKOA may be through the Wnt signaling pathway. Further studies will need to validate this finding in other populations.

### Table 2

<table>
<thead>
<tr>
<th>Mean(SD)</th>
<th>0 weeks</th>
<th>4 weeks</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand pain on activity</td>
<td>7.30 (1.61)</td>
<td>6.22 (1.99)</td>
<td>0.008</td>
<td>0.24</td>
</tr>
<tr>
<td>Hand pain at night</td>
<td>6.56 (2.10)</td>
<td>4.19 (2.20)</td>
<td>0.000</td>
<td>0.45</td>
</tr>
<tr>
<td>Hand function</td>
<td>7.22 (1.74)</td>
<td>5.55 (2.14)</td>
<td>0.011</td>
<td>0.44</td>
</tr>
<tr>
<td>MAP-HAND</td>
<td>25.33 (7.08)</td>
<td>24.03 (7.87)</td>
<td>0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>CFF</td>
<td>40.05 (12.04)</td>
<td>33.14 (13.10)</td>
<td>0.000</td>
<td>0.50</td>
</tr>
<tr>
<td>CFF Index (cmm)</td>
<td>6.84 (2.17)</td>
<td>6.44 (2.53)</td>
<td>0.05</td>
<td>0.14</td>
</tr>
<tr>
<td>CFF Middle (cmm)</td>
<td>5.72 (2.25)</td>
<td>5.29 (2.25)</td>
<td>0.03</td>
<td>0.17</td>
</tr>
</tbody>
</table>

### Conclusion

This study demonstrates, for the first time, that compression gloves used by people with HOA led to significant improvements in: pain during the day and night, stiffness, hand function and finger motion, with inconclusive results [1]. The commonest compression gloves provided in the UK are Isotoner gloves. The aim was to evaluate effects of compression gloves on hand pain, stiffness and function.

Methods: A pre-post-test trial was conducted. Participants were recruited from 10 Rheumatology Occupational Therapy (OT) departments; had a doctor diagnosis of HOA and no steroid injections or new/exchanged medication within the previous 4 weeks. Assessments at 0 and 4 weeks included: hand pain on activity and at night, hand stiffness (0–10 numeric rating scales; none to very severe); Measure of Activity Performance of the Hand (MAP-HAND, 2); Grip Ability Test (GAT, 3); and composite finger flexion to distal wrist crease (CFF). OT assessors were trained in standardised hand assessment procedures. Assessor inter-rater reliability (ICC,10) was good: CFF (0.76–0.93); GAT (0.98) [4]. All participants received bottoner ½ finger gloves. Data were analysed using paired t-tests and effect sizes calculated using eta-squared (values of 0.14 = large effect, 5).

Results: 30 people with HOA participated: 28 women, 2 men; average age = 61.23 (SD 8.35) years; time since diagnosis 4.71 (SD 6.47) years. (Right hand data presented below).

Disclosure: A. Hammond, Jobskin UK, 2, Promedics Orthopaedics Ltd, 2, Dowager Eleanor Peel Trust, 2; Y. Prior, None; V. Jones, None; M. Dooley, None; Y. Hough, None; A. Jacklin, None.
982
Identification of Potential SERUM Autoantibody Biomarkers in Rheumatic Diseases Using a New Generation of Protein Arrays. Lucia Lourido1, Juan Fernandez-Tajes2, Valentina Calamia1, Carolina Fernandez-Costa1, Beatriz Rocha3, Patricia Fernandez-Puente1, Jesús Mateos1, Carlos Fernandez-Lopez1, Natividad Oreiro-Villar1, Manuel Fuentes2, Francisco J. Blanco Garcia1 and Cristina Ruiz-Romero1.

Methods: Antibodies were detected using NAPPA constructed as previously described by Ramachandran et al. 2008, containing 80 sequence-verified full-length human genes obtained from the Center for Personalized Diagnostics at the Arizona State University (www.dnasu.org) and selected by their prediction for relevance in OA. The antibodies were also detected in synovial fluids by ELISA. The antibodies were then tested for immuno-reactivity using a protein expression system, NAPPA arrays were incubated in optimized conditions with 20 OA, 20 RA and 18 CTRL serum samples. The antibodies were detected using an antibody against human IgG and fluorescein labelled. Array images were obtained and processed by Genepix 4000B and Genepix Software 6.0. For data analysis, normalization across all the arrays was performed.

Results: Significant (p<0.05) 4 different autoantibodies against four different proteins have been observed in OA compared to CTRL samples. Of note, 2 of these proteins are related to the metabolism of ECM (CHST14, PCOLCE); the others are associated to cell adhesion (CD44) and bone mineralization (LEP). We also observed that IL6 autoantibody levels distinguished RA and CTRL samples. Most interestingly, this approach allowed the differential classification of RA and OA patients by the detection of 3 specific autoantibodies against proteins involved in cell proliferation (IGFBP4, IGFBP6); and bone mineralization processes (LEP). We also observed that IL6 autoantibody levels distinguished RA and CTRL samples. One of these proteins (LEP) was also increased in OA compared to CTRL samples.

Conclusion: We have identified the presence of specific autoantibodies in OA allowing to characterize differential autoantibody profiles between OA and CTRL patients and most interestingly, between OA and RA patients. These autoantibodies released to the serum might have a biomarker value to more accurate diagnosis and prognosis of OA patients in clinical routine.

Disclosure: L. Lourido, None; J. Fernandez-Tajes, None; V. Calamia, None; C. Fernandez-Costa, None; B. Rocha, None; P. Fernandez-Puente, None; J. Mateos, None; C. Fernandez-Lopez, None; N. Oreiro-Villar, None; M. Fuentes, None; F. J. Blanco Garcia, None; C. Ruiz-Romero, None.

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Identification of Annexin A2 as an Autoantigen in Rheumatoid Arthritis and in Lyme Arthritis. Ainalisa Pianta1, Elise E. Drouin2, Sheila A. Avikar2, Catherine E. Costello3 and Allen L. Steere1.

Methods: We have previously identified endothelial cell growth factor (ECGF) as the first autoantigen known to be a target of T and B cell responses in antibiotic-refractory or antibiotic-responsive LA. In this study, we continued to characterize the repertoire of naturally presented HLA-DR peptides in synovial tissue in patients with RA or LA. We have already reported that HLA-DR-presented peptides were eluted from synovia, identified by tandem mass spectrometry, synthesized, and tested for reactivity with the matching patient’s PBMC. Immunoreactive peptides or their source proteins were then tested for T cell reactivity by IFN-γ ELISPOT assay or for antibody responses by ELISA. All RA patients met the 2010 ACR/EULAR criteria for RA and the LA patients met the CDC criteria for Lyme disease.

Results: In one RA patient who lacked positive tests for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), one of 86 non-redundant HLA-DR-presented peptides identified from her synovial tissue induced her PBMC to secrete IFN-γ. The peptide was derived from the protein annexin A2 and others had shown that ~10% of RA patients make autoantibodies against this self-protein. We tested serum samples from our cohort of RA patients for anti-annexin A2 autoantibodies, and for comparison, from healthy control subjects or from patients with antibiotic-responsive or antibiotic-refractory LA. In our RA cohort, sera from 24% of 91 patients had antibody responses to annexin A2 that were >3SD above the mean value in healthy control subjects (Figure). Surprisingly, about 20% of the patients with antibiotic-responsive or antibiotic-refractory LA also had antibody reactivity with this autoantigen. In annexin A2-positive RA patients, the magnitude of antibody responses to ACPA or RF were less than in annexin A2-negative patients. Studies to look for linked T and B cell responses to annexin A2 are currently in progress in both the RA and LA cohorts.

Conclusion: We confirm that annexin A2, a phospholipid-binding protein that protects damaged endothelial cells, is a potential autoantigen in a subgroup of patients with RA. Moreover, we report for the first time that this protein may serve as an autoantigen in a subgroup of patients with LA. As with reactivity to ECGF, autoantibodies responses to annexin A2 in Lyme disease seem to occur as a part of the immune response to the infection, whereas additional factors, such as immune dysregulation, are required for refractory arthritis.
Apolipoprotein B Is a Target of T and B Cell Responses in a Subgroup of Patients with Lyme Disease. Kristi A. Koelsch1, Jacen Maier-Moore2, Kenneth Smith2, Christopher Lessard2, Astrid Rasmussen3, Bijl Kurien3, Umesh Deshmukh4, A. Darise Farris4, Judith A. James5, Kathy L. Moser Sivils4, R. Hal Scofield6 and Mark Coggleshall7. 1University of Oklahoma Health Sciences Center, Oklahoma City, OK, 2University of Texas at El Paso, El Paso, TX, 3Oklahoma Medical Research Foundation, Oklahoma City, OK, 4US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Borrelia burgdorferi-induced autoimmunity in affected joints has been hypothesized to be a contributing factor to antibiotic-refractory Lyme arthritis (ARL). Our prior study, which combined proteomics and translational research, identified endothelial cell growth factor (ECGF) as the first known target of T and B cell responses in ~20% of patients with antibiotic-refractory or antibiotic-responsive arthritis and in ~10% of patients with erythema migrans (EM), the initial skin lesion of the disorder. Using this same approach, we identified apolipoprotein B (ApoB) as another novel autoantigen in Lyme disease.

Methods: HLA-DR presented self-peptides were isolated from ARLA patients’ synovia, identified by tandem mass spectrometry, synthesized, and tested for reactivity with the matching patient’s PBMC using an IFN-γ ELISpot assay. Immunoreactive peptides and their full-length source proteins were then tested for T and B cell reactivity using large numbers of patient and control cells and sera. Samples from patients with antibiotic-responsive arthritis were seen prior to antibiotic therapy, when the infection was still active, whereas those from patients with antibiotic-refractory arthritis were collected after antibodies, during the presumed autoimmune phase of the illness. A nitrotyrosine body responses were quantified by ELISA.

Results: From the synovial tissue of one ARLA patient, 141 non-redundant HLA-DR-presented self-peptides were identified and tested. One peptide derived from ApoB caused significant secretion of IFN-γ by ELISpot. A total of 25 patients showed ~10–30% patients with early or late manifestations of Lyme disease had T cell responses to ApoB.

To look for linked T and B cell responses, patients’ serum samples were also tested for anti-ApoB IgG antibodies. By definition, none of the SS healthy control subjects had a positive response (defined as >3 SD above the mean value in these subjects) (Figure). In comparison, 5% of patients with EM and 12% of patients with concurrent arthritis had positive responses for anti-ApoB IgG autoantibodies. Compared with the EM group, the values were significantly higher in both arthritis groups (P < 0.0001), particularly in those with responsive arthritis, a group still actively infected.

Conclusion: We report for the first time that ApoB is a target of T and B cell responses in a subset of patients with Lyme disease. Although the molecular mechanisms are not yet known, B. burgdorferi, an organism with sequences for >100 lipoproteins and multiple membrane glycolipids containing cholesterol, may contribute directly to the development of this autoimmune response. As with reactivity to ECGF, autoantibody responses to ApoB seem to occur as part of the immune response to the infection, whereas additional factors, such as immune dysregulation, are also required for refractory arthritis.

Disclosure: K. A. Koelsch, None; J. Maier-Moore, None; K. Smith, None; C. Lessard, None; A. Rasmussen, None; B. Kurien, None; U. Deshmukh, None; A. D. Deshmukh, None; C. A. Burton, None; G. McHugh, None; C. E. Costello, None; A. C. Steere, ACR, NIH, Foundation.
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Integrated Comprehensive Analysis of Immune Cell Subsets and Serum Protein Profile Identifies the Role of Pre-Germinatal Center B Cells in Sjögren’s Syndrome Pathogenesis


Background/Purpose: Whole blood flow cytometric analysis and serum protein profiling were commonly utilized to characterize disease-specific alterations in a wide variety of autoimmune diseases. However, precise mechanisms underlying their pathophysiological conditions were still obscure because each experimental approach was carried out independently and not well integrated. Therefore, we performed comprehensive flow cytometric analysis by multi-colored staining in combination with serum protein profile to fully understand pathological aspects in rheumatoid arthritis (RA) and primary Sjögren’s syndrome (pSS).

Methods: Heparinized peripheral blood was collected from untreated RA patients (N = 51), pSS patients (N = 60), and healthy controls (N = 36). Fresh whole blood was immediately stained with fluorescent-labeled antibodies and analyzed with 3-laser, 8-color FACS equipment. Over a thousand of serum protein profile were also obtained with aptamer technology from Somalogic, Inc. Serum immunoglobulin concentrations were evaluated by ELISA and gene expression levels were analyzed using quantitative real-time PCR.

Results: Among over 40 immune cell subsets we investigated, surface IgD+CD38++ B cells, called pre-germinatal center B (pre-GC B), were significantly increased in both RA and pSS patients. Interestingly, serum IgG but not IgM and IgA was positively correlated with the number of pre-GC B cells in pSS but not RA, suggesting their distinct role in pSS pathogenesis. Consistent with this, GC-related serum proteins such as PD-L2, SLAMF2, and CD30 ligand were significantly elevated and correlated with pre-GC B in pSS but not RA. Furthermore, pre-GC B cells isolated from pSS patients exhibited higher GC-related gene expressions including XBP1 and BACH2 than those from healthy controls.

Conclusion: Our findings suggest possible role of pre-GC B in pSS pathogenesis through IgG production and germinal center formation. By integrating multi-parametric flow cytometric analyses, we identified a novel immune cell phenotype, indicating this strategy as a useful tool to highly impact on better understanding of autoimmune diseases.

Disclosure: Y. Kassai

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Novel Auto-Antigen in Aortic Aneurysms of Large Vessel Vasculitis

R. Farris, None; J. A. James, None; K. L. Moser Sivils, None; R. H. Scofield, None; M. Coggshall, None.

Background/Purpose: Large vessel aneurysms (LVAV) are a group of autoimmune diseases characterized by injury and anatomic modifications of large vessels that may include the aorta and its branch vessels. Disease etiology is unknown. Using samples from aorta root, ascending aorta and aorta arch surgical specimens, we sought to identify antigen targets within affected vessel walls in patients with LVAV, including giant cell arteritis (GCA), Takayasu’s arteritis (TA) and isolated focal aortitis (IFA).

Methods: Thoracic aorta aneurysm specimens and autologous blood were acquired from consenting consecutive patients in whom aorta reconstruction procedures were indicated. Aorta tissues from patients with both LVAV and age-, race- and gender-matched patients with non-inflammatory aneurysms, were lysed and resolved on SDS-polyacrylamide gels. Sera from study groups were used to probe antigen-antibody reactivity on western blots followed by MS analysis to identify antigen. A additional sera samples tested included sera from diseases including medium to small vessel vasculitis, sepsis etc.

Results: We found that patients with LVAV (n=17) produce antibodies to 14-3-3 proteins in the aortic wall, whereas patients with non-inflammatory matrix disorders (n=17) rarely do so. Most of the sera from other immune diseases were also negative. A nti-14-3-3 antibody production was demonstrated in all 3 forms of LVAV. In each, sera contained autoantibody that was sufficient to immunoprecipitate 14-3-3 protein(s) from the aorta lysates. A nti-bodies to 14-3-3 were not found in sera of additional controls. Three out of seven known isoforms of 14-3-3 were found to be upregulated in LVAV aortas. Most 14-3-3 Ag was found to co-localize within granulomas, chronic inflammatory cells and smooth muscle cells in LVAV.

Conclusion: This study is the first to utilize sterile, snap frozen tissue under sterile reconstruction surgeries in an attempt to identify non-specific proteins in LVAV. 14-3-3 protein(s) appears to be a novel auto-antigen in aortic aneurysms caused by LVAV. The precise role of these antibodies and 14-3-3 proteins in LVAV etiology and pathogenesis deserves further study.

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Serum CXCL13 As A Biomarker of Disease Activity and Severity in Rheumatoid Arthritis: Comparison with Acute Phase Reactants and the Autoantibody Profile

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Background/Purpose: The B cell chemoattractant CXCL13 has recently emerged as a new candidate biomarker of disease activity capable of identifying patients with persistent synovitis and worst radiographic outcomes in early rheumatoid arthritis (RA). However, whether CXCL13 reflects underlying disease processes or represents another non-specific marker of inflammation is currently unknown. The current study aimed at analysing the clinico-pathologic significance of serum CXCL13 in comparison to routine laboratory markers of disease activity and severity in patients with RA.

Methods: Baseline serum levels of CXCL13 were measured by colorimetric ELISA in 205 consecutive early untreated RA patients with disease duration <12 months (median 3 months, IQR 2-5.5). Disease activity was assessed by a comprehensive set of subjective, semi-objective and objective clinical features. Changes in CXCL13 levels were evaluated in 87 patients after 2 months of treatment with methotrexate and low-dose prednisone. An additional study population of 60 RA patients (n=22 with disease duration <12 months) in whom paired serum and synovial samples were collected on the same day was used to assess the pathologic correlates of circulating CXCL13.

Results: In cross-sectional analyses at baseline, CXCL13 was moderately correlated with the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (r=0.35 and 0.36 respectively, p<0.001). Similarly to acute phase reactants, CXCL13 correlated with overall disease activity as measured by the DAS28, in particular with physician-derived measures, as well as with ultrasonographic scores for Gray Scale and power Doppler signals. In contrast to ESR and CRP, no correlation was found with patient-derived measures and the DAS28, in particular with physician-derived measures, as well as with ultrasonographic scores for Gray Scale and power Doppler signals. In turn, 53.4% of ACPA(-) patients had CXCL13 <100 pg/ml. Similarly reduced levels were observed for RF. After 2 months of treatment, CXCL13 levels were not significantly changed from baseline, as opposite to the significant reduction observed for acute phase reactants (standardised response mean 0.04, 0.52 and 0.66 for CXCL13, ESR and CRP respectively). In paired serum and tissue samples, circulating CXCL13 was
significantly correlated with synovial CXCL13 protein (rho 0.30, p=0.04) and mRNA (rho 0.56, p=0.02) expression. Similarly to ESR and CRP, serum CXCL13 was related to synovial inflammatory features such as the degree of sublining macrophage infiltration (rho 0.34, p=0.01). Serum CXCL13, but not acute phase reactants, showed further correlation with the presence and density of large B cell aggregates (rho 0.28, p=0.03), expression levels of the B cell enzyme activation induced cytokine deaminase (AI(D) (rho 0.4, p=0.046), and the receptor activator of nuclear factor κB ligand (RANKL) osteoprotegerin (OPG) ratio (rho 0.72, p=0.006).

Conclusion: Serum CXCL13 in RA reflects an immunologically active and potentially persistent pattern of synovial inflammation beyond the levels of conventional inflammatory markers and the ACPA status.

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989 FcγR IIb Facilitates Rapid Internalisation of Rituximab (type1 anti-CD20 antibody) in B Cells from Patients with RA and SLE and Contributes to Less Efficient B Cell Lysis Than Type 2 Anti-CD20 Antibodies, in Vitro. Venkat Reddy1, Geraldine Cambridge2, David A. Isenberg3, Mark Craig4 and Maria J. Leandro5. 1Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom. 2Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom. 3Southampton University, Southampton, United Kingdom.

Background/Purpose: Incomplete B-cell depletion using rituximab (RTX) is associated with poor clinical response in some individuals with RA and SLE, in particular. However, the precise mechanisms of resistance to depletion with RTX (type1 anti-CD20 monoclonal antibodies, mAbs) are poorly understood. Improving depletion may augment clinical response. Newer mAbs such as GA101 (type2) are more potent than RTX at deleting malignant B cells.

Methods: We included 5 healthy controls (HC), 15 patients with RA and 16 with SLE. An in vitro autologous whole blood depletion assay was used to compare BHH2 (type2, glycosylated GA101) with RTX (type1) and B cell lysing potential of mAbs was defined as cytotoxicity index (CTI). Briefly, 100µl of heparinised blood was incubated with either RTX, BHH2 or without antibody, at a concentration of 1µg/ml at 37°C, 5% CO2 for 24 hours. Samples were analysed by flow cytometry for CD45 + lymphocytes, CD3 + T-cells and CD19 + B-cells. The CTI was calculated using the formula: CTI of mAb = 100 - [(number of B:T-cells in sample without mAb - number of B:T-cells with mAb) / number of B:T cells in sample without mAb] x 100. Surface fluorescence quenching assay using isolated B cells was performed to assess for the internalisation of mAbs. Paired “t” test or Mann-Whitney U test was used to compare groups, as appropriate.

Results: Whole Blood Depletion: BHH2 (type2 mAb) was significantly more efficient than RTX (type1 mAb) at lysing B cells, in vitro, in all groups. The mean±SD CTI of BHH2 vs RTX in HC was 65±13 vs 45±24 (p=0.04), in RA, 61±12 vs 28±18 (p<0.0001); and in SLE, 30±17 vs 13±10 (p=0.0002). This hierarchy of B cell susceptibility to lysis by RTX was noted with HC > RA > SLE. BHH2 lyses the RA cells as well as controls – i.e. it fully overcomes the defect in RA whereas it doesn’t in SLE.

Internalisation: We performed a surface fluorescence-quenching assay at 6 and 24 hours. At both time points, a significantly greater % of BHH2 was accessible on surface when compared with RTX, in all groups. The mean±SD % surface accessible mAbs, after 6 hours of incubation for BHH2 vs RTX was 72±6 vs 57±11, 68±8 vs 57±12 (p<0.005) and 71±10 vs 63±12 (p<0.005) whereas after 24 hours of incubation it was 47±15 vs 28±12, 45±25 vs 36±15 and 59±9 vs 42±14 (p<0.005 for all), for HC, RA and SLE, respectively. Prior incubation with AT10 (a mAb directed against FcγR IIb) significantly reduced internalisation of type1 mAbs to a greater extent than type2 mAbs, a mean reduction of 12% vs 4%, respectively (p<0.005). Further, a significant variability was noted between patients in the extent to which internalisation of RTX, but not BHH2, was reduced by AT10.

Conclusion: Type 2 anti-CD20 antibodies are more efficient than type1 (rituximab) at lysing B cells from patients with RA and SLE. B cells from patients with SLE may be less susceptible to lysis in vitro by rituximab when compared with B cells from patients with RA and healthy individuals. FcγR IIb facilitates rapid internalisation of rituximab, but not type2 mAbs, by B cells from patients with RA and SLE, which may contribute to its inferior ability to lyse B cells. This study provides a mechanistic basis for considering type2 mAbs for clinical use in RA and SLE.

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990 WITHDRAWN

991 The Alternative CD20 Transcript Variant Is Not a Factor for Resistance to Rituximab in Patients with Rheumatoid Arthritis. Cecile Ganouet1, Marina Deschamps2, Sandrine Marion3, Philippe Saas4, Gilles Chiocchia5, Christophe Ferrand6 and Eric Toussirot7. 1Etablissement Francais du Sang / Université de Franche Comté, Besançon, France, 2INSERM UMR1098 / Etablissement Français du Sang/ Université de Franche Comté, Besançon, France. 3Université Versailles Saint Quentin, Montigny le Bretonneux, France, 4INSERM UMR1098, Besançon, France, 5Rheumatology Department, University Hospital, besançon, France.

Background/Purpose: the identification of predictive factors for the response, or alternatively factors for resistance to biological agents is a relevant goal in the management of patients with rheumatoid arthritis (RA). Rituximab (RTX) is a chimeric monoclonal antibody directed against the membrane CD20 protein expressed by B cells. Predictive factors for good response to RTX therapy in RA have been previously determined, and included presence of rheumatoid factors and anti-CCP antibodies. A spliced mRNA transcript of CD20 (D393-CD20) has been observed in tumoral B cells from patients with lymphoma and leukaemia (1). This transcript is coding for a non-anchored membrane protein and its expression may be associated with resistance to RTX in patients with haematological malignancies.

Objectives: we previously reported that this alternative D393-CD20 transcript is not expressed in B cells and synovial tissue from patients with RA. In this study, we aimed to determine whether D393-CD20 is expressed by circulating B cells from patients with RA who are refractory to RTX and whether it could be a factor for non-response to this treatment.

Methods: we selected patients who did not respond to RTX treatment (EULAR response). 24 RA patients (21 F, age [mean ± SD]: 57.6 ± 11.2 years; disease duration: 8.7 ± 6.7 years, positive rheumatoid factors: 13/24; positive anti-CCP antibodies: 13/24) were evaluated. All the patients had concomitant MTX and low corticosteroids (< 10 mg/dl); 21/24, CD20 mRNA expression study was performed using RT-PCR assay allowing to discriminate full length CD20 (membrane CD20) from D393-CD20 transcripts. A more sensitive RT-PCR assay, using a specific primer spanning the splice fusion area was then used to detect specifically only the D393-CD20 transcript. This analysis was performed on peripheral blood B cells from patients with RA.

Results: RA patients had high disease activity at baseline (DA28: 5.8 ± 0.8). Disease activity remained elevated after one course of RTX 1000 mg x 2 (DAS 28 at week 24: 5.5 ± 0.8). Among the 24 RA samples, although full length CD20 expression was always detected, we were unable to detect D393-CD20, even with the more sensitive RT-PCR assay permitting to identify the spliced transcript form. We did not identify a subgroup of patients who display positive D393-CD20.

Conclusion: the present study showed that, on the contrary of leukemic or lymphoma B cells, RA B-cells from RA patients who did not respond to RTX do not express D393-CD20. This result, together with our previous data (lack of expression of this alternative transcript in cross-sectional analysis of RTX-naïve RA patients and in vivo tissue from patients) indicate that D393-CD20 in RA may only be a molecular marker of malignancies rather than a factor predictive to RTX responses in auto-immune diseases like RA.

1- Henry C et al., Blood, 2010;115:2420-9

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992 Differential Antigen-Presenting B-Cell Phenotype from Synovial Microenvironment of Rheumatoid Arthritis and Psoriatic Arthritis Patients. Estefania Armas-Gonzalez1, Ana Díaz-Martín1, María Jesús Domínguez-Luis2, María Teresa Arce-Franco3, Adela Herrera-García3, Vanesa
Background/Purpose: The systemic depletion of B cells induced by mabthera, a monoclonal antibody against human CD20, has shown to be an effective therapy for controlling disease activity in rheumatoid arthritis (RA), but not in psoriatic arthritis (PsA) patients. This strongly suggests that B cells play a different role in the pathogenesis of these diseases. It has been suggested that B cells participate in the pathogenesis of chronic synovitis through several mechanisms, including T-cell activation by acting as antigen-presenting cells.

Objective: To study the potential differences in antigen-presenting phenotypes of B cells present in the synovial microenvironment of RA and PsA patients.

Methods: The surface expression levels of CD27, CD23, class II molecules (HLA-DR, -DQ and -DP), CD40 and CD86 were assessed by double- or triple-staining flow cytometry on CD20+ cells from peripheral blood (PB) and synovial fluid (SF) of 13 RA and 15 PsA patients. Flow cytometry analysis data are presented as relative mean fluorescence intensity with respect to cells in PB, which was considered 100%. The expression of interferon-induced protein IFIT-4, which is involved in the differentiation of monocytes into dendritic cells, was assessed by quantitative RT-PCR in negatively immunoselected CD19+ B cells from SF and PB of RA patients.

Results: Analysing all the patients included in this study, the percentage of mononuclear CD20+ cells in SF (2.24±0.37%) was significantly lower than in PB (8.59±1.26%, p<0.01). When these data were compared in RA versus PsA patients, the percentages of CD20+ cells in PB and SF were similar in both range and tendency. B cells from SF of RA and PsA patients showed an activated phenotype (down-regulation of CD23) and seem to have had in both range and tendency. B cells from SF of RA and PsA patients showed an activated phenotype (down-regulation of CD23) and seem to have had in both range and tendency. B cells from SF of RA patients showed an increased expression of HLA-DR and -DQ in CD20+ cells from SF compared to PB in both RA (277.84±65.66; 262.20±108.81) and PsA (267.86±88.53; 311.08±116.65) patients. HLA-DR was also elevated in rheumatoid SF B cells (1009.48±355.70), although conversely, a significantly lower expression of this class II molecule was observed in SF from PsA patients (46.38±19.73). Surface expression of CD86 was higher in PB than in SF B cells from both pathologies (RA: 629.79±172.24; PsA: 326.46±138.77). CD40 expression was significantly lower in SF compared to PB in B cells from RA patients (66.31±12.71); however, this was not the case in PsA patients (243.76±71.18). Interestingly, CD20 surface expression was 35% lower in B cells (CD19+, CD138-) from SF with respect to PB in RA patients. Finally, qRT-PCR showed an approximate 5-fold increase in IFIT-4 mRNA content in B cells from SF compared to PB in RA patients.

Conclusion: These data show that B cells in the synovial microenvironment of RA and PsA patients show a differential phenotype respect to molecules involved in antigen presentation and co-stimulation, which suggest that B cells play a different role in the pathogenesis of these two pathologies. This could have implications for the understanding of the dissimilar clinical management of RA and PsA patients show a differential phenotype respect to

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Background/Purpose: The presence of anti-citrullinated proteins antibodies (ACAPAs) in RA is associated with aggressive disease phenotype and bone destruction. As synovial fibroblasts (SFs) are considered key players of both synovial inflammation and bone destruction in rheumatoid arthritis (RA), we studied the effect of ACAPAs on fibroblasts migration.

Methods: Human dermal fibroblasts (HDFs) were obtained from Promocell. SFs were isolated from synovial tissue of RA patients (RASFs) and from OA patients. ACAPAs positive and negative IgGs were separated from plasma of RA patients and monoclonal anti-citrullinated antibodies were generated from RA synovial fluid by single B-cells. Migration scratch assays were performed using either RASFs or HDFs to test the effect of ACAPAs, synthesized monoclonal antibodies and appropriate negative controls. The effect of a phosphatidyl inositol-3-kinase (PI3K) inhibitor (wortmannin) and a focal adhesion kinase (FAK) inhibitor (PF-573228) was tested. Light microscopy images were taken at baseline and after 6 hours incubation and analyzed using NIH ImageJ to calculate migration index. Cytotoxicity and proliferation assays were done in parallel with migration assays.

Results: ACAPAs but not control IgGs induced a 3.9±0.5 (mean±SD) fold increase in HDFS and 9.6±0.5 (mean±SD) fold increase in SFs from RA migration (p<0.05). PI3K but not FAK inhibition almost completely abolished ACAPAs effects, with minimal fold migration increase of 1.4±0.4 (mean±SD). No difference in either cytotoxicity or proliferation rate were observed between different treatments. One out of three different anti-citrullinated monoclonal antibodies displayed similar mig.

Conclusion: We describe a novel effect of ACAPAs, providing a link between synovial fibroblasts and the adaptive immune system. We further suggest that different fine specificities of ACAPAs might have distinct impact on disease pathogenesis.

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IL-7 Modulates B Cell Immunoglobulin Isotype Production and Increases B Cell Activating Factor of the Tumor Necrosis Factor Family (BAFF) in Synovial Fibroblasts from Osteoarthritis (OA) and Rheumatoid Arthritis (RA) Patients. Georg Pongratz, Stephan Kuhn, Madlen Melzer, Torsten Lowin and Rainer Straub. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Interleukin(IL)-7 is increased in synovial fluid from rheumatoid arthritis (RA) patients as compared to osteoarthritis (OA) patients and has been attributed a proinflammatory role, especially due to its well established influence on T cells. However, B cells and synovial fibroblasts (SFs) also possess functional IL-7 receptors and stimulation of IL-7 receptors on B cells increases disease severity in collagen-induced arthritis. However, the mechanisms involved in this proinflammatory effect are not known. We therefore wanted to further characterize the effect of IL-7 on B cell antibody production and on the production of B cell activating factor of the tumor necrosis factor family (BAFF) and IL-6 in synovial fibroblasts (SFs).

Methods: Naïve splenic mouse B cells were cultured in the presence of different activating stimuli (LPS, anti-IgM, anti-CD40, anti-CD40 + IL-4, antiCD40 + IFN-γ) in the absence or presence of IL-7 added at different timepoints (with the initial stimulus or three days after start of culture) and different concentrations (0.1, 1.0, 10 ng/ml). Levels of antibody isotypes (IgA, IgM, IgG1, IgG2a, IgG2b, IgG3, IgE) and light chains (lambda, kappa) were determined in supernatant by ELISA after 5 days. SFs were isolated from OA (n=15) and RA (n=17) knee joints and cultured in the presence or absence of IFN-γ at different concentrations (0.1, 0.5, 1.0, 5.0, 10, 50 ng/ml) to induce BAFF and IL-6 in the absence or presence of different concentrations of BAFF and IL-6. BAFF and IL-6 were determined in culture supernatants by ELISA.

Results: IL-7 shows a differential effect on B cell antibody production, depending on the co-stimulus used and the isotype analysed. Most prominent effects were observed when IL-7 was present from the beginning of B cell culture. IL-7 increased IgG2a (p<0.038), IgG3 (p<0.001), and lambda light chains (p=0.024) and decreased kappa light chains (p<0.001) in the presence of co-stimulant stimulation with IL-4 and anti-CD40. IL-7 further increased LPS-induced IgG3 (p<0.001) and IgE (p<0.001). IL-7 alone was able to induce IgG in B cells to some extent without any additional stimulus (p<0.001). IFN-activated BAFF was increased by IL-7 in a concentration dependent manner in RA (p<0.001) but not OA SFs (p=0.078).

Disclosure: V. Hernandez, None.

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Anti-Citrullinated Proteins Antibodies Promote Synovial Fibroblast Migration in Rheumatoid Arthritis. Meng Sun1, V. Jay Joshua2, Aase Hj Hensvold3, Sergiu Bogdan Catrina2, Lars Klareskog3, Vivianne Malmström2, Heidi Wåhåmaa2 and Anca I Catrina1. 1Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, 2Molecular Medicine and Surgery, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, 3Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The presence of anti-citrullinated proteins antibodies (ACAPAs) in RA is associated with aggressive disease phenotype and bone destruction. As synovial fibroblasts (SFs) are considered key players of...
under hypoxic conditions (O2 2%) both, RA (p=0.001) and OA (p=0.008) SFs increased IFN-induced BAFF production in the presence of IL-7 in a concentration dependent manner. In contrast, IFN-induced IL-6 was not altered in SFs in the presence of IL-7.

**Conclusion:** Effects of IL-7 on the B cell compartment in arthritis can be direct by modulation of isotype production or indirect by increasing BAFF production in SFs. Therefore, IL-7 not only plays a role in modulating T cells but also modulates B cell function in arthritis and therefore might be a valuable drug target.

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**Background/Purpose:** B-cells utilizing the VH-region immunoglobulin gene VH4-34 produce natural autoantibodies. The rat monoclonal antibody 9G4 recognizes B-cells with VH4-34-encoded B-cell receptors (9G4+ B-cells) and also secretes immunoglobulins. In healthy individuals, 9G4+ B-cells present in splenic marginal zones and tonsils are excluded from germinal centre (GC) reactions, whereas in autoimmune diseases such as systemic lupus erythematosus, 9G4+ B-cells expand in the post-GC memory compartment, suggesting defective 9G4+ B-cell censoring mechanisms. In rheumatoid arthritis (RA) patients, the distribution of tonsil 9G4+ B-cells is similar to healthy individuals, but only limited phenotypic analyses have examined 9G4+ B-cells in peripheral blood. The aim of this work was to perform an extensive phenotype characterization of 9G4+ B-cell subpopulations in peripheral blood in RA patients and healthy controls (HC).

**Methods:** Blood samples were collected from established RA patients (n=12) and age and sex-matched HC (n=15). Peripheral blood mononuclear cells were isolated by density gradient centrifugation and 9G4+ B-cells (gated in CD19+ B-cells) were characterized by flow cytometry. 9G4+ B-cell subpopulations were defined using combinations of IgD, CD27 and CD38. The expression of CD5, CD24, IgM, BAFF-R and CCR5 was analyzed in total 9G4+ B-cells. Statistical analysis was performed with Mann-Whitney test.

**Results:** The frequency of total 9G4+ B-cells in circulation was similar between RA patients and HC (median values: 3.83% and 4.68%, respectively). RA patients had a higher frequency of 9G4+ IgD+CD27+ B-cells than HC (p=0.04). No significant differences were found in other 9G4+ subpopulations based on IgD/CD27 classification, although there was a tendency for higher levels of 9G4+ switched memory B-cells (IgD-CD27+) in RA patients (p=0.08) and significantly lower levels of 9G4+ transitional B-cells (IgD+CD27+CD10+) in HC compared to RA (p=0.004). RA patients also had significantly lower levels of 9G4+ naïve B-cells (IgD+CD27+CD10+CD38−) (p=0.04) when compared to HC. A tendency for higher levels of 9G4+ post-GC memory B-cells (IgD+CD27−CD38+) was also observed in RA patients. Furthermore, BAFF-R expression was significantly increased in 9G4+ B-cells from RA patients (both frequency and mean fluorescence intensity values) compared to HC (p=0.04 and p=0.006, respectively). There was a significant decrease in levels of 9G4+ CD5+ B-cells (p=0.004) in RA patients, but no other significant differences were found in 9G4+ B-cells expressing CD24, IgM and CCR5.

**Conclusion:** B-cell subpopulations are activated in RA which can be significantly reduced by IL-6R and TNF-α inhibition in vivo. DNB cells are expanded in RA and IL-6R inhibition resulted in a reduced proportion of IgD+ DNB cells. IL-6R inhibition leads to a reduced mutational frequency and hot spot targeting in IgA, IgG as well IgM DN Ig receptors. The results are in accordance with a specific effect on DN memory B cells by in vivo IL-6R receptor inhibition.

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Memory B Cell Subtype Modulation in Patients with Rheumatoid Arthritis. Zafar Mahmood1, Marc Schmalzing2, Thomas Dörner3 and Hans-Peter Tony4.1University of Würzburg, Würzburg, Germany, 2Charité University Medicine Berlin and DRFZ, Berlin, Germany.

**Background/Purpose:** Memory B cells have been shown to play important roles in the pathogenesis of rheumatoid arthritis (RA). With the advent of B cell targeted therapies the modulation of memory B cells seems to be a prime target. Human peripheral memory B cells can be classified into three major subtypes by the phenotypic expression of CD27 and IgD: CD27+IgD+, CD27+IgD− and CD27−IgD− double negative (DN) memory B cells. We aimed in this study to analyze different subsets of memory B cells in patients with RA under cytokine inhibition.

**Methods:** Memory B cell subsets were phenotypically analyzed for activation (expressions of CD95 and ki-67) and their isotype profile using 10 color flow cytometry at baseline, week 12 and week 24 during cytokine inhibition. Single B cell PCR approach was used to study isotypes specific Ig receptors. Mann-Whitney U test was used for statistical analysis by using GraphPad Prism 5.

**Results:** Surface and intracellular staining of memory B cell subsets showed a significantly higher percentage of CD95 and ki-67 expression in RA (n=60) compared to healthy donors (n=20). During cytokine (IL-6 or TNF-α) inhibition, both CD95 and ki-67 expression was significantly reduced at week 12 and 24 in all 3 types of memory B cells. RA patients showed a significant relative expansion of DN IgD−/CD27− B cells with a mixture of IgA, IgG and IgM expression dominated by the IgG phenotype. During IL-6 receptor inhibition, IgA+ DN B cells decreased significantly from 25.1 (18.0–54.2) percent median (range) at 19.0 (4.8–51.1) at week 12 (P=0.0016) and 20.5 (4.6–38.3) at week 24 (P=0.0008) respectively with no remarkable change in relative IgG+ and IgM+ B DN B cells. In the postswitch compartment, IgA+ and IgG+ postswitch B cells were not influenced during IL-6R inhibition. Isotype specific analysis of rearranged Ig-R sequences from DN B cells revealed that mutational frequencies were highest in IgA+B cells followed by IgG+ and IgM+, respectively. During IL-6R inhibition, significantly reduced mutational frequencies in Ig-receptors of all DN isotypes at week 12, 24 and 1year (p<0.0001) were observed. A accordingly hotspot motif targeting was also decreased whereas CDR3 length increased during therapy.

**Conclusion:** Our study suggests that all three major memory B cell subsets are activated in RA which can be significantly reduced by IL-6R and TNF-α inhibition in vivo. DN B cells are expanded in RA and IL-6R inhibition resulted in a reduction of particularly IgA+ DN B cells. IL-6R inhibition leads to a reduced mutational frequency and hot spot targeting in IgA, IgG as well IgM DN Ig receptors. The results are in accordance with a specific effect on DN memory B cells by in vivo IL-6R receptor inhibition.

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Explore Translational Pharmacokinetics/Pharmacodynamics Response/Efficacy Relationship of a Novel Bruton’s Tyrosine Kinase Inhibitor in Rat Collagen-Induced Arthritis Model. Jie Zhang-Hooever1, Erica Lecese2, Kalyan Chakravarty3, Ian Kenmeyer3, Jos Lommerse4, Marianne Spatz5, Francois Gervais5, Raul Sivilla6, Jian Liu7, Ronald Kim7,8, Sachin Lohani7, Kevin Matthew Moneyny7, Joseph Kozlowski7 and Alexandra Hicks9.1Merck Research Laboratories, Boston, MA, 2EMerk & Co., Boston, MA, 3Merck Research Laboratories, Rahway, NJ.

**Background/Purpose:** A non-normal B cell activation is an essential part of autoimmune inflammation. B cell depletion is proven to be an efficacious treatment in RA patients as well as in preclinical rodent rheumatoid arthritis models. Bruton’s Tyrosine Kinase (BTK) is downstream of B cell receptor and critical in B-cell development and activation, making it a potential therapeutic target for autoimmune inflammatory diseases. Here we evaluated a novel and selective small molecule BTK inhibitor in disease mechanism and pharmacokinetics (PK)/pharmacodynamics (PD) models to understand the level and duration of compound exposure on activation biomarker PD effect that leads to efficacy.

**Methods:** Female Lewis rats were treated with the BTK inhibitor (3, 10, 30, 100 mg/kg PO QD) prophylactically starting from the day of immunization in the rat collagen induced arthritis (CIA) model. Disease severity was evaluated in life by measuring paw thickness and
clinical scores and terminal by micro-CT imaging of ankle and knee joints for bone erosion. The effect of the BTK inhibitor on B cells was evaluated by ex vivo whole blood B cell CD86 PK/PD assay. Blood was collected from rats at 0, 0.5, 4, 8, and 24 hours after compound dosing. B cells were stimulated in vitro in whole blood by crosslinking of BCR with dextran conjugated anti-IgD. A cytokine biomarker CD86 expression on B cells was quantified by flow cytometry. Rat plasma compound concentrations were determined by protein precipitation followed by liquid chromatography - tandem mass spectrometry. A PK/PD-CIA model was built linking the effect of compound exposure with CD86 biomarker expression in the ex vivo whole blood assay and paw inflammation in the rat CIA. PK was best described using a zero-order dissolution linked with a first-order absorption compartment and a concentration dependent elimination rate. For CD86 expression a direct-effect model was used. Paw inflammation in the rat CIA modeling was performed based on the assumption that the biomarker PD effect drove the disease inhibition.

**Results:** The BTK inhibitor showed an exposure-dependent suppression of joint inflammation in the rat CIA model with an EAUC of 56 uM.h, and blocking of CD86 upregulation in ex vivo whole blood B cell biomarker activation assay (IC50 = 918 nM). Micro-CT imaging revealed reduced bone erosion in both ankle and knee joints by the inhibitor, and the bone effect correlated well with the reduction on joint inflammation. The integrated PK/PD-CIA model was used to simulate the full range of target engagement by the inhibitor as measured by the CD86 assay. A good correlation between average CD86 inhibition over a 24 hour time period and the paw thickness inhibition in the rat CIA model was found. An average of 60% CD86 suppression led to a 90% suppression of disease development in the rat CIA model.

**Conclusion:** Selective and novel BTK inhibitor is efficacious in the rat CIA model. Pharmacological evaluation of compounds in disease mechanism and target pathway relevant PK/PD and efficacy models can provide valuable data in building a translational PK/PD/efficacy platform from preclinical in vitro and in vivo models to human diseases in drug discovery.


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β2-Adrenergic Receptor Signal Is Augmented in B Cells in the Course of Arthritis to Increase IL-10. Georg Pongratz, Clemens Wiest, Madlen Melzer and Rainer Straub. University Hospital Regensburg, Regensburg, Germany.

**Background/Purpose:** Splenic B cells from collagen-induced arthritis (CIA) mice react to a β2-adrenergic (AR) stimulus with increased IL-10 production and adoptive transfer of these cells decreases disease activity. However, B cells from unimmunized mice do not adequately increase IL-10. Therefore, we test the hypothesis that sensitivity to catecholamines changes during CIA. Furthermore, we wanted to test if human peripheral blood B cells from osteoarthritis (OA) and rheumatoid arthritis (RA) patients also increase IL-10 following a β2-adrenergic stimulus.

**Methods:** FACS to determine AR pathway related proteins (β2-adrenergic, G-protein coupled receptor kinase (GRK) 2, phosphorylated and unphosphorylated mitogen activated protein kinase p38, and cAMP responsive element binding protein (CREB)) in B cells at different timepoints during CIA. Unstimulated splenic B cells and B cells stimulated with terbutalin, a β2-AR agonist, were used. Human B cells were isolated from peripheral blood of patients with OA or RA and stimulated under different conditions with or without terbutalin. IL-10 protein level was determined by ELISA after 5 days of culture.

**Results:** In the course of CIA the percentage of β2-AR + B cells increased and stayed above baseline (ANOVA p<0.05). In contrast, the mean fluorescence intensity (MFI) as measure for the number of receptors per cell remained unchanged. MFI for GRK2 decreased and stayed low from day 6 p.i. (ANOVA p<0.001). The relative increase in phosphorylation of p38 (ANOVA p<0.001) and CREB (ANOVA p<0.001) following a β2-AR stimulus was augmented starting at day 18 p.i. with a maximum response at day 55 p.i. in the late phase of CIA. In human B cells, similar mechanisms are in place, because β2-AR stimulation of RA, but not OA B cells increased IL-10.

**Conclusion:** The current data show, that B cells become more sensitive to β2-AR stimuli in the course of CIA, possibly due to a decrease in GRK2 and increase in the percentage of β2-AR expressing splenic B cells. Increased catecholamine sensitivity might support B cell and IL-10 mediated anti-inflammatory mechanisms primarily in the late phase of CIA. A similar mechanism is observed in human peripheral B cells and might be used to improve treatment of autoimmune arthritis.

**Disclosure:** G. Pongratz. None; C. Wiest. None; M. Melzer. None; R. Straub. None.

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MiR-155 as An Epigenetic Regulator of B-Cell Activation in Rheumatoid Arthritis: In Vivo and In Vitro Evidences. Stefano Alivernini1, Barbara Tolusso2, Silvia Canestri3, Luca Petrica3, Clara Di Mario3, Elisa Gremese2 and Gianfranco Ferraccioli2. 1Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy; 2Division of Pathology, Catholic University of the Sacred Heart, Rome, Italy.

**Background/Purpose:** MicroRNAs (miRs) are a novel class of post-transcriptional regulators. miR-155 was shown to be a regulator of B cell biology in haematological diseases as well as in myeloid cells in Rheumatoid Arthritis (RA). The regulation of the transcription factor PU.1 by miR-155 is required for the production of high-affinity IgG1 antibodies. The aim of this study was to investigate the expression of miR-155 in B cells of RA patients and its association with synovial inflammation.

**Methods:** 31 RA patients underwent ultrasound guided synovial tissue (ST) biopsy. ST samples were categorized through Hematoxyline and Eosine staining as diffuse or aggregate pattern. B cells from peripheral blood (PB) and matched synovial fluid (SF) of RA patients (n=19) and PB of healthy controls (HC) (n=10) were isolated by CD19+ microbeads (Miltenyi). B-cell subsets were determined by Flow-Cytometry using IgD/CD27 classification and ZAP70 intracellular expression was assessed. IL-6 and BAFF levels in PB and SF were measured by ELISA. miR-155 expression was determined by qPCR on B cells from PB and SF and on ST of osteoarthritis (OA) (n=3), diffuse RA (n=5) and aggregate RA (n=5) patients. Finally, B cells from PB of HC (n=5) were isolated by CD19+ microbeads and cultured in RPMI with or without IL-6 (30 ng/ml), BAFF (20 ng/ml), IL-6+BAFF. Cells were collected after 24h, 48h and 72h to assess miR-155 and PU.1 expression by qPCR.

**Results:** 14(45,2%) RA patients showed an aggregate synovial pattern in ST. RA patients with an aggregate synovial pattern were more likely anti-CCP positive compared to RA patients with diffuse pattern (p=0.05). Moreover, anti-CCP plasma levels direct correlates with the synovial aggregate grade (r=0.38; p=0.01). IL-6 and BAFF levels were higher in SF than in PB of RA patients regardless to the synovial pattern (p=0.001 for both). CD19+/IgD-CD27- and CD19+/ZAP70+ cells were over-represented in PB of RA patients with an aggregate pattern (p=0.05 and p=0.04) compared to RA patients with a diffuse pattern. Moreover, anti-CCP+ RA patients showed higher percentages of CD19+/IgD-CD27- and CD19+/ZAP70+ in the PB (p=0.01 for both) compared to anti-CCP- RA patients. miR-155 was over-expressed in PB B-cells compared to matched PB B-cells (p=0.05) in RA patients. Moreover, anti-CCP+ RA showed higher miR-155 expression in PB B-cells compared to anti-CCP- RA patients (p=0.02) and HC (p=0.001). miR-155 was over-expressed in ST of aggregate RA compared to diffuse RA (p=0.03) and OA (p=0.03) patients respectively. Finally, IL-6 and BAFF in vitro stimulation of healthy B-cells induced an overexpression of miR-155 after 72h of incubation (p=0.04 and p=0.03). Consistently PU.1 was down-regulated after in vitro stimulation (p=0.01 and p=0.03).

**Conclusion:** This study indicates that miR-155 is over-expressed in B-cells of RA patients and is associated to anti-CCP positivity and to an aggregate synovial pattern. IL-6 and BAFF, that are over-expressed in the SF environment, induce in vitro an over-expression of miR-155 in B-cells. Thus, miR-155 may represent a key regulator of B-cells in RA patients with an activated memory phenotype.

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Pathogenic Role of CXCL Chemokine receptor 3-Positive B Cells in Bone Destruction of Rheumatoid Arthritis. Yuri Hirosaki, Hiroaki Niiro, Shunichiro Ota, Naoko Ueki, Hirofumi Tsuzuki, Kunkiko Noda, Yosikazu Jabbazadeh Tabrizi, Hiroki Mitoma, Yojiro Arinobu, Mitsuhiro Akahoshi, Hiroaki Akashi, Norio Morimoto and Koichi Kaku. Department of Medicine and Biostematic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Background/Purpose: B cells can function as potent effector cells by production of autoantibody, immune complex formation and inflammatory cytokines. Clinical efficacy of B cell depletion therapy underscores a pathogenic role of B cells in autoimmune diseases such as rheumatoid arthritis (RA). A recent study suggests that infiltrating B cells in the joints of RA express RANKL, which plays a key role in osteoclastogenesis and inflammatory bone loss. In the RA joints, abundant accumulation of B cells expressing chemokine receptor CXCR3 was also noted, however the role of these cells in bone destruction of RA remains to be established. In this study, we have sought to elucidate the relationship of RANKL- and CXCR3-expressing B cells and their role in osteoclast differentiation.

Methods: Levels of RANKL/CXCR3 mRNA and protein in B cells from peripheral blood of normal subjects and RA patients were evaluated using quantitative RT-PCR and flow cytometry, respectively. Highly-pure B cell subsets were isolated using cell sorter. To validate the functional significance of chemokine receptor CXCR3 was also noted, however the role of these cells in bone destruction of RA remains to be established. In this study, we have sought to elucidate the relationship of RANKL- and CXCR3-expressing B cells and their role in osteoclast differentiation.

Results: Without stimuli, freshly-isolated B cells only marginally expressed RANKL mRNA and protein. Combined stimulation of B cells with B-cell receptor (BCR) and CD40, mimicked as chronic inflammation stimuli, however, significantly induced RANKL expression. Among B cell subsets, switched-memory (CD27+IgD-) B cells, a normal counterpart of pathogenic B cells in the joints, expressed RANKL at the highest levels. Upon the same stimulation, the levels of joint-homing receptor CXCR3 increased from 30 to 80%, representing the activation of the Wnt pathway, but not plasma cell differentiation. Switched-memory B cells of RA patients expressed higher levels of CD80/CD86 than that of healthy control. In addition, highly-activated switched-memory B cells expressing CD80/CD86 double-positive B cells from RA patients expressed RANKL and CXCR3 at higher levels than those from normal subjects. Consistent with these findings, these subsets induced osteoclast formation as assessed by TRAP staining compared with other B cell subsets.

Conclusion: Our current findings shed the light on a pathogenic role of switched-memory B cells in bone damage associated with RA via production of RANKL, and regulation of CXCR3-expressing B cells may provide a novel strategy for the treatment for this devastating disease.

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Global Transcriptome Analysis in Osteoarthritic Cartilage Reveals Significant Differential Gene Expression and Associations with Histologic Disease Progression. Matthew T. Jeffries1, Madison Donica1, Anand Annan2, Michael Stevenson1, Mary Beth Humphrey2, Judith A. James2 and Amr H. Sawalha3. 1University of Oklahoma Health Sciences Center, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK, 3University of Michigan, Ann Arbor, MI.

Background/Purpose: Osteoarthritis (OA) is the leading cause of chronic disability affecting 40% of individuals over the age of 70 and costing $128 billion annually in the US alone. Little is known regarding changes in gene expression that occur regionally within these affected joints. Herein, we perform RNA-seq analysis of eroded and intact cartilage from human OA, and correlate transcript levels with histopathologic disease severity.

Methods: Six femoral heads were obtained at the time of hip arthroplasty for primary OA. Articular cartilage tissue samples were dissected from grossly affected and grossly normal areas of the same joints, flash frozen in liquid nitrogen, and RNA was extracted. A portion of these samples were also histologically examined for OA severity using modified Mankin scoring. Following confirmation of RNA quality (RIN value >6), samples were sequenced with the Illumina Truseq system on a MiSeq sequencer. Raw data were analyzed and mapped using the GeneSifter software package. Genes with GeneSifter quality score <1.0 were excluded. For categorical analysis, EdgeR p<0.01 with Benjamini-Hochberg q<0.1 and expression ratios >0.83 or <-1.2 between affected and normal tissues were considered significant. For correlations with histologic score, Pearson’s r >0.75 or <-0.75 with p<0.05 were considered significant. Gene ontology and pathway analysis was performed using the Ingenuity IPA platform.

Results: Categorical analysis identified 43 overexpressed and 313 underexpressed genes in eroded compared to intact cartilage. Both under- and overexpressed genes were overrepresented in the fibroblastic growth factor (FGF) signaling pathway (p=0.004). FGF2R2 was found to be overexpressed in eroded cartilage. The Wnt pathway genes, WNT11 (ratio 0.27) and WNT9A (ratio 0.45), and the STAT3 pathway was also overrepresented, including both under- and overexpressed genes (p=0.001). A top predicted upstream regulator differentially expressed genes was mir-9 (p=0.005), known to be associated with metalloproteinase production. Further, we

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identified 176 genes positively and 1591 genes inversely correlated with histopathologic score. Among these, the NFAT pathway was highly over-represented, including both positively and inversely correlated genes (24, p = 0.002). The Rig-I innate immunity pathway was also overrepresented among inversely correlated genes (p = 0.008), as were several genes related to chromatin remodeling (overall p = 0.009: HDAC1, r = -0.89, MECP2 r = -0.78, RBBP4 r = -0.82, SAP130 r = -0.81, SIN3A, r = -0.80).

Conclusion: Using RNA-seq we detected significant changes in gene expression in eroded compared to intact OA cartilage, as well as expression changes correlated with histologic disease progression in OA. Our data strongly suggest involvement of several signaling pathways, many of which are potential therapeutic targets for OA. This work reinforces the heterogeneity of the disease process and provides novel insights into OA pathogenesis.

Disclosure: M. A. J. Effrions, None; M. Donica, None; A. Aman, None; M. Stevenson, None; M. B. Humphrey, None; J. A. James, None; A. H. Sawalha, None.

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Proteomic Analysis of Connexin 43 Reveals Novel Interactors Related to Osteoarthritis. Raquel Gago-Fuentes1, Patricia Fernández-Puente2, Paula Carpintero-Fernández2, Jesús Mateos2, María Dolores Mayan2 and Francisco Javier Blanco3. 1Cartilage Biology Research Group, Rheumatology Division, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, 2Rheumatology Division, CIBER-BBN/ISCIII, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain.

Background/Purpose: We have previously reported that articular chondrocytes in tissue contain long cytoplasmic arms that physically connect two distant cells. Cell-to-cell communication occurs through connexin channels termed Gap Junction (GJ) channels, which achieve direct cellular communication by allowing the intercellular exchange of ions, small RNAs, nutrients and second messengers. The Cx43 protein is overexpressed in several human diseases and inflammation processes and in articular cartilage from patients with osteoarthritis (OA). An increase in the level of Cx43 is known to alter gene expression, cell signalling, growth and cell proliferation. The interaction of proteins with the C-terminal tail of connexin 43 (Cx43) directly modulates GJ-dependent and -independent functions. Here, we describe the isolation of Cx43 complexes using mild extraction conditions and immunopurification.

Methods: Cx43 complexes were extracted from human primary articular chondrocytes isolated from healthy donors and patients with OA. The proteomic content of the native complexes was determined using LC-MS/MS, and protein interactions with Cx43 were validated using western blot and immunolocalisation experiments.

Results: We identified >100 Cx43-associated proteins including previously uncharacterised proteins related to nuclear functions, RNA transport and translation. We also identified several proteins involved in human diseases, cartilage structure and OA as novel functional Cx43 interactors, which confirmed the importance of Cx43 in the normal physiology and structural and functional integrity of chondrocytes and articular cartilage. Gene Ontology (GO) terms of the proteins identified in the OA samples showed an enrichment of Cx43-interactors related to cell adhesion, calmodulin binding, the nucleolus and the cytoskeleton in OA samples compared with healthy samples. However, the mitochondrial proteins SOD2 and ATP52 were identified only in samples from healthy donors.

Conclusion: The identification of Cx43 interactors will provide clues to the functions of Cx43 in human cells and its roles in the development of several diseases, including OA.

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Elevated Levels of BMP2 Compensate for Loss of TGF-Beta in Articular Cartilage during Experimental Osteoarthritis. Esmeralda Blaney Davison1,2, Atjjan van Caam1,2, Arjen Blom1,2, Elly Vitters1,2, Miranda Bennink1,2, Wim van den Berg1,2, Fons van de Loos3 and Peter van der Kraan2. 1Radboud university medical center, Nijmegen, Netherlands, 2Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: We have demonstrated that TGF-beta signaling via Smad2/3 is drastically reduced in articular cartilage (AC) with age and loss of Smad2/3-signaling predisposed AC for OA. We additionally showed that TGF-beta inhibition reduces the proteoglycan (PG) content in AC. During OA BMP2 is elevated in chondrocytes surrounding AC lesions. However, the effect of this BMP2 on AC is unclear. Therefore, we investigated whether elevated BMP-2 could counteract the loss of TGF-beta signaling during OA.

Methods: We made a unique transgenic mouse expressing human BMP2 under control of the Col2a1 promoter only when exposed to doxycycline (Col2a1-rTA-BMP2). Functionality was tested on mRNA from AC, spleen and liver 72 hours after exposure to doxycycline-and standard diet (hBMP2 expression). We induced OA (DMM-model) while treating them with doxycycline-versus standard diet. To study the effect of losing TGF-beta activity, we intra-articularly injected an adenovirus overexpressing TGF-beta-inhibitor LAP (A-dLAP). Four weeks after DMM induction knee joints were isolated for histology. OA was scored based on cartilage damage (adapted OARSI score, 0–30) and PG-content was measured with digital image analysis of Safranin O staining in AC of the medial tibia.

Results: Doxycycline treatment clearly elevated hBMP2 mRNA in AC, but not in spleen and liver thereby confirming functionality of the transgenic mouse. Doxycycline exposure in Col2a1-rTA-BMP2 up to 8 weeks did not result in alterations in healthy AC. DMM induced a clear increase in OA-score (average of all DMM groups of 16.9 versus 2.5 in non-DMM), but this was not affected by elevated chondrocyte-specific BMP2. TGF-beta inhibition with LAP did not affect the OA-score either. However, TGF-beta inhibition during DMM significantly reduced the PG-content compared to DMM alone (18%). BMP2 did not affect the PG-content during DMM (figure). Nevertheless, the PG-depletion by inhibition of TGF-beta during DMM could significantly and nearly completely be counteracted by elevated chondrocyte-specific BMP2.

Conclusion: Our data show that in healthy AC and AC affected by OA in young animals BMP2 did not have detectible effects. However, when TGF-beta signaling was lost, a phenomenon occurring in aged individuals, this resulted in decreased levels of PG-content in AC during OA. In this setting, BMP2 compensated this PG loss. Therefore the elevated levels of BMP2 near OA lesions could be a reparative response of the AC, compensating age-related loss of TGF-beta signaling.

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Background/Purpose: Intensive articular cartilage deterioration and synovial fibrosis in joints are prominently pathogenic features of osteoarthritis (OA) knees. Epigenetic reactions in joint microenvironments are linked to the incidence of diseases, including OA. Previous research has identified histone hypermethylation of lysine 9 (H3K9me2) and histone hyperacylation of lysine 14 (H3K14ac) in OA. However, whether histone modifications, in particular demethylases and histone acetyltransferases, contribute to the joint destruction in OA is unknown.

Methods: We studied the OA cartilage gene expression, histone modifications and histone demethylases using a publicly available OA gene expression signature and independent OA data. We also studied the relationship between histone modifications and the OA joint destruction by comparing data from OA patients and controls.

Results: Histone modifications, including histone deacetylation (H3K14ac, H3K18ac), histone trimethylation (H3K27me3, H3K4me3, H3K27me2), histone dimethylation (H3K9me2, H3K20me2), and histone acetylation (H3K9ac, H3K27ac, H3K4ac, H3K18ac) were significantly associated with OA joint destruction. Furthermore, histone demethylases were significantly associated with OA joint destruction.

Conclusion: Our data indicate that histone demethylases, including KDM6A, contribute to joint destruction in OA. These findings suggest that histone demethylases may be therapeutic targets for the treatment of OA.
of OA knees. Histone lysine dimethylase KDM6A is an emerging epigenetic regulator contributing to tissue development and remodeling. This study was undertaken to investigate the biological roles of KDM6A in joint integrity of OA knees and decipher the epigenetic actions of KDM6A on methylation statuses of master cartilage regulator SOX9 promoter and histone 3 lysine 27 (H3K27) and metabolism of cartilage and synovial matrices in OA knee joints.

**Methods:** Mice with collagenase-induced OA knees were weekly administered with KDM6A inhibitor GSK-J4 or vehicle for 12 weeks. Gait profiles, fluorescence in vivo imaging and μCT. Quantitative RT-PCR, immunoblotting, methylation-specific PCR, and chromatin immunoprecipitation were performed to quantify mRNA, protein expression, methylation statuses and enrichments of SOX9 promoter and H3K27.

**Results:** Articular cartilage damage and synovial fibrosis were in conjunction with increased expression of KDM6A. KDM6B and decreased levels of SOX9 and methylated H3K27 in OA knee joints. Administration with KDM6A inhibitor GSK-J4 alleviated the deleterious effects of OA on gait characteristics (maximum contact intensity, area and print area of paws) and joint inflammation. It also improved subchondral bone microarchitecture (trabecular volume, thickness, number and cortical porosity) and bone mineral density of affected joints. Inhibition of KDM6A attenuated the adverse effects of OA on chondrogenic matrix expression, morphology and OAARS scores of articular cartilage, as well as mitigated nucleated cell infiltration, hypervascularization and fibrotic matrix accumulation in synovial compartments. Loss of KDM6A signaling restored methylation of CpG islands in SOX9 promoter and alleviated the OA-mediated inhibition of SOX9 mRNA transcription and protein levels. Treatment with KDM6A inhibitor also increased H3K27 methylation that reduced the enrichment of H3K27 to proximal promoter region of fibrogenic transcription factor AP-1 and proinflammatory gene expression in injured joint tissues.

**Conclusion:** KDM6A induces SOX9 promoter and H3K27 hypomethylation that deregulates SOX9 and AP-1 actions on articular cartilage integrity and synovium homeostasis in the pathogenesis of OA knees. Inhibition of KDM6A ameliorates the OA-mediated epigenetic dysfunction in cartilage and synovium, thereby protects against excessive joint remodeling. This study sheds emerging lights on epigenetic modulation of joint integrity in OA knees and synovium, thereby protects against excessive joint remodeling. This study sheds emerging lights on epigenetic modulation of joint integrity in OA knees and synovium, thereby protects against excessive joint remodeling.

**Disclosure:** None.

**1007 Markedly Increased Mesenchymal Stem Cell Activity in MRI Bone Marrow Lesions Compared with Non-Involved Bone in Osteoarthritic Hip**

**Background/Purpose:** We hypothesised that deficiencies in native bone marrow mesenchymal stromal cells (MSCs) are critical for bone and cartilage repair but the role of such cells in vivo in hip OA is poorly defined. Subchondral bone changes depicted as bone marrow lesions (BMLs) on MRI are intimately linked to joint remodelling and OA structural deterioration, suggesting potential aberrant MSC responses within such tissue. We hypothesised that deficiencies in native in vivo CD45-CD271+ MSC numbers and/or function contributed to BML pathophysiology and investigated BML and non-BML hip subchondral bone for numerical, topographic and in vitro functional differences.

**Methods:** Twenty femoral heads were obtained during total hip arthroplasty from subjects with primary hip OA that fulfilled the ACR criteria for hip OA. Ex vivo 3T MRI identified BML and non-BML regions from excised human hips. Immunophenotyping of BM-MSCs was performed by flow cytometry. The first half of each BML was cultured in low-density CFE in the presence of EDTA-decalcified to quantify trabecular bone area and cartilage thickness. Digital imaging was performed on 16 paired excisions using 92 manually defined morphologically homogenous regions containing cartilage and 188 regions containing only bone. The MSC frequency relative to total live cells was established using flow cytometry for the CD45+CD271+ phenotype. A colony forming unit-fibroblast (CFU-F) assay determined the number of MSCs per million cells. In vitro tri-lineage MSC differentiation assessed functional capacity of expanded CD271+ cells. MSC topography was examined using anti-CD271 IHC.

**Results:** Regions with a normal appearance of cartilage were closely associated with non-BML MSCs (p=0.01) compared to BML where most of the surface was damaged. Trabecular bone area was increased in BML regions (p=0.001). In 18/20 subjects, the proportion of native CD45+CD271+ MSC phenotype cells was higher in BMLs (Figure 1A, median 3.5-fold difference; p<0.001). This was confirmed using CFU-F assays (Figure 1B, 12/14 subjects, median 3.5-fold; p=0.013). Small differences were detected in MSC proliferation and mineralization capacities but not in their phenotype (<95% CD73+CD90+). We observed abundant CD271+ MSCs surrounding subchondral blood vessels near the cement line underlining cartilage lesions and in regions surrounding subchondral cysts, suggesting an accumulation and/or local proliferative MSC response to tissue injury (Figure 1C).

**Conclusion:** BMLs of OA femoral heads contain a higher proportion of MSCs with similar in vitro functional capacity compared to neighbouring joint.
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Autophagy Activation Protects from Mitochondrial Dysfunction in Human Chondrocytes. Beatriz Carames1, Paloma López de Figueroa2, M artín Lotz3 and Francisco J. Blanco4. 1Cartilage Biology Group. Rheumatology Division, INIBIC–A Coruña, SPAIN, A Coruña, Spain, 2Cartilage Biology group. Rheumatology Division, INIBIC–A Coruña, Spain, A Coruña, Spain, 3The Scripps Research Institute, La Jolla, USA, La Jolla, CA, 4Rheumatology Division, INIBIC–A Coruña, Spain, A Coruña, Spain.

Background/Purpose: Autophagy, is a key pathway of cellular homeostasis for removing damaged macromolecules and organelles, including mitochondria. Recent studies indicate that autophagy activation is defective in stasis for removing damaged macromolecules and organelles, including mitochondria.

Methods: Human chondrocytes were treated with Oligomycin (10 μg/ml), a mitochondrial respiratory chain (MRC) inhibitor of complex V. Mitochondrial function and cell death were evaluated by Flow Cytometry, Fluorescence Microscopy, and Immunofluorescence. Autophagy activation was analyzed by determination of LC3-II, a main marker of autophagy activation by Immunofluorescence and Western Blot. Autophagy activation was induced by mammalian target of rapamycin complex 1 (mTORC1) selective inhibitor Rapamycin (Rapa, 10 μM) and the dual mTORC1 and mTORC2 inhibitor Torin 1 (50 nM). Genetic deletion of Autophagy markers (sAtg5, sAtg6) was used to evaluate the role of autophagy in mitochondrial dysfunction.

Results: Mitochondrial dysfunction was induced by treatment with Oligomycin, which significantly decreased mitochondrial membrane potential (∆Ψm) (Oligo: 41.74 ± 7.59, expressed as % vs control; *p < 0.01). This was associated with increased intracellular ROS production (25.7 % vs. control; *p < 0.001 compared to control condition) and mitochondrial superoxide generation (29.61 % vs. control; *p < 0.001 compared to control condition). Furthermore, increased cell death by apoptosis was observed (Control: 11.35 ± 1.73; Oligo: 25.37 ± 6.767, *p < 0.05 vs. control). A autophagy activation determined by LC3-II was increased at short incubation times, perhaps acting as an early response to stress and then decrease in a time dependent manner.

Conclusion: Our data highlight the role of autophagy as a critical protective mechanism against mitochondrial dysfunction. Pharmacological interventions that enhance autophagy may have chondroprotective activity in cartilage degenerative processes such as OA.

Disclosure: B. Carames, None; P. López de Figueroa, None; M. Lotz, None; F. J. Blanco, None.

Table 1. ICRS Macroscopic Scores and ICRS Visual Histological Assessment Scale

<table>
<thead>
<tr>
<th>Group</th>
<th>ICRS Macroscopic Score</th>
<th>P value*</th>
<th>ICRS VHAS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>2.5 ± 0.5</td>
<td>&lt;0.001</td>
<td>3 ± 1.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Group 2</td>
<td>7 ± 2.1</td>
<td>&lt;0.05</td>
<td>14 ± 0.5</td>
<td>&lt;0.005</td>
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<tr>
<td>Group 3</td>
<td>5 ± 2.3</td>
<td>&lt;0.01</td>
<td>12 ± 2.2</td>
<td>&lt;0.01</td>
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<tr>
<td>Group 4</td>
<td>12 ± 1.2</td>
<td>17 ± 1.5</td>
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</tr>
</tbody>
</table>

*p value indicated comparison of Group 4 with other groups.

Conclusion: This short term in vivo study demonstrated that when administered at the site of microfracture, scSOX9 was able to induce hyaline cartilage regeneration in situ in combination with microfracture for cartilage repair in a rabbit model.
reparative tissue with features of hyaline cartilage and significantly improved the outcome of cartilage repair by microfracture. These data suggest combination of microfracture with scSOX 9 has great potential being translated into a therapy for cartilage repair and therapy for OA.

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Background/Purpose: Sympathetic nerve fibers play an important role in bone and tissue homeostasis of joints. However, sympathetic nerve fibers are able to switch their phenotype and respective neurotransmitter machinery from sympathetic to cholinergic. This transition was shown in developing sweat glands, in the peristome and in failing heart tissue. This is crucial since strong anti-inflammatory effects have been described for the α7nicotinic acetylcholine receptor as well as for the cholinergic co-transmitter vasoactive intestinal peptide (VIP). We studied connective tissue obtained from the knee and finger joints of osteoarthritis (OA) and rheumatoid arthritis (RA) patients and tested possible transition requirements in an in-vitro model with murine sympathetic ganglia.

Methods: Knee synovial tissue samples obtained from 44 OA and 21 RA patients and connective tissue as well as bone tissue samples from interphalangeal finger joints obtained from seven OA and five RA patients were stained for tyrosine hydroxylase (TH, noradrenergic fibers), vesicular acetylcholine transporter (VACHT, cholinergic fibers) and VIP (cholinergic fibers). Sympathetic ganglia were obtained from newborn C57B16 mice and double-stained for TH and VACHT after a co-culture period of two days with osteoclast progenitors attained from the femoral and tibial bone marrow from adult healthy and arthritic mice. Supernatants from osteoclast progenitors were tested for possible transition factors. Whole RNA isolated from the respective osteoclast progenitors was screened via microarray analysis in order to identify possible candidate transition factors.

Results: In connective tissue sections from human finger joints, VACHT but not VIP positive cholinergic nerve fibers were more present in OA than in RA patients. In knee synovial tissue no significant difference in the appearance of cholinergic (VACHT and VIP) nerve fibers was found. The ratio of VACHT/TH immunoreactivity of sympathetic ganglia in coculture with osteoclast progenitors from healthy mice was elevated compared to experiments with osteoclast progenitors from arthritic mice. Leukemia inhibitory factor (LIF), a known transition factor from the glycoprotein 130 cytokine family, is present in low concentrations in supernatants from osteoclast progenitor cells but did not induce transition. Microarray analysis showed upregulation of several candidate molecules (biglycan, fibronectin, LIF, periostin, tenascin-C, tensin-1, TIMP-1) in the transcriptome of osteoclast progenitors from healthy mice compared to arthritic (n = 3 vs. 3, mean fold change >2.0, p < 0.01).

Conclusion: In humans and mice, catecholaminergic-to-cholinergic transition is possible in less inflamed tissue of the joint but not in highly inflamed arthritic tissue.

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Fibroblast Growth Factor-2 and Its Receptor Antagonists in Osteoarthritis.

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Background/Purpose: The fibroblast growth factor (FGF) family represents an interesting group of molecules which are involved in the regulation of connective tissue development and metabolism. FGF-18 has promising effects also in articular cartilage whereas FGF-2 seems to signal through different cellular receptors and its role in osteoarthritis (OA) remains unknown in many aspects. In the present study we investigated the presence and effects of FGF-2 in OA joints by assessing the associations of FGF-2 with cartilage degrading matrix metalloproteinase (MMP) enzymes and with the synthesis of the major cartilage matrix components aggrecan and collagen as well as by investigating the effects of FGF receptor antagonists.

Methods: Synovial fluid and cartilage samples were obtained from 98 OA patients undergoing total knee replacement surgery (60 females and 37 males, BMI 30.9 ± 0.6 kg/m², age 69.8 ± 10.0 years; mean ± SEM). FGF-2 concentrations in the synovial fluid and cartilage culture medium were measured by immunoassay. The effects of FGF-2 and its receptor antagonists on the production of MMP-1, MMP-13, aggrecan and collagen II were investigated in cultures of primary human OA artrocytes. The study was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland and it was carried out in accordance with the Declaration of Helsinki. The patients gave their written informed consent, and their diagnosis was confirmed to fulfill the ACR classification criteria for osteoarthritis.

Results: FGF-2 was present in OA synovial fluid and released into the culture media from cartilage samples obtained from OA patients. Interestingly, FGF-2 concentrations correlated positively with the concentrations of MMP-1 (r = 0.414, p < 0.001) and MMP-13 (r = 0.362, p < 0.001) (Fig. 1) in the cultures of OA cartilage. Further, FGF-2 up-regulated the production of MMP-1 and MMP-13, and down-regulated the expression of aggrecan and collagen II, in human OA chondrocyte cultures. More importantly, FGF receptor antagonists AZD4547 and NVP-BGJ398 (10–300nM) down-regulated the production of MMP-1 and MMP-13 and up-regulated the expression of aggrecan and collagen II in a concentration dependent manner, and not only in the presence but also in the absence of exogenous FGF-2.

Conclusion: The present results suggest that, in contrast to its growth factor like effects in some other conditions, FGF-2 induces catabolic and anti-anabolic effects in osteoarthritis. Moreover, FGF-receptor antagonists showed promising beneficial effects on the balance of catabolic and anabolic mediators within OA cartilage.

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Marie-Charlotte Laguillon1, Alice Courties1, Xavier Houard1, Martine Auclair1, Alain Sautet2, Bruno Feve1, Jacqueline Capeau1, Francis Berenbaum2 and Dominique Mubashshir3. 1Institute Clément Ader, Paris, France, 2AP-HP, Saint-Antoine Hospital, Rheumatology Department and DHU i2B, Paris, France, 3AP-HP, Saint-Antoine Hospital, Orthopaedic Surgery Department, Paris, France.

Background/Purpose: Recent epidemiological studies have suggested an association between type 2 diabetes/hyperglycemia and osteoarthritis (OA) but experimental evidences are lacking (1). We aimed i) to decipher the impact of a high glucose environment on chondrocyte activation ii) to compare the production of pro-inflammatory mediators by OA cartilage explants derived from diabetic (db) or non-db patients.

Methods: Primary cultures of chondrocytes from new-born mice were stimulated for 24h and 72h with/without IL-1β (5 ng/mL) under a normal (5.5 mM) or a high (25 mM) glucose environment. Glucose uptake by cells was measured.

Figure 1. Levels of FGF-2 released by human OA cartilage correlated positively with the levels of MMP-1 (A) and MMP-13 (B).
analyzed by incorporation of radioactive 2-deoxyglucose. Osmotic stress was assessed by adding mannitol. Gene expression and release of pro-inflammatory mediators (IL-6, COX2/PGE2) were analyzed by RT-qPCR, ELISA and EIA, respectively. Oxidative stress was assessed by the measurement of reactive oxygen species (ROS) by fluorescent DCFDA and production of NO by Griess reaction. To address the role of high glucose and oxidative stress on chondrocyte activation, cells were pretreated with cytochalasin B (1 μM), a glucose transporter inhibitor, or treated with a specific inhibitor of the polyol pathway (Epalrestat, 10 μM), a specific mitochondrial antioxidant (Miotempo, 50 μM) or a NO synthase inhibitor (L-NAME, 5 mM). Ex vivo, pro-inflammatory mediators (IL-6, PGE2) release in 24h-conditioned media of IL-1β-stimulated OA cartilage from db and non-db patients was measured by ELISA/EIA.

Results: In vitro, at 72h, the expression and release of IL-6 and COX2/PGE2 were dramatically increased in the presence of IL-1β in high glucose as compared to normal glucose concentration by 5.6- and 3- fold (IL-6 mRNA and protein, respectively), 8- [COX2] and 3.6-fold [PGE2] (n=5, p = 0.03 for all analyzes). Glucose uptake was also transiently increased by IL-1β at 72h (n=3). M. anotillon experiments ruled out the hypothesis of an osmotic stress due to high glucose (n=3). High glucose environment under IL-1β stress increased ROS and NO production (2.1- and 1.9-fold, respectively; n=5, p = 0.04 and p = 0.03). Cytochalasin B significantly decreased the induction of IL-6 mRNA (-40%; n=6, p = 0.02). L-NAME significantly decreased the release of IL-6 and PGE2 (-40% and -78%, respectively; n=5, p = 0.04) as did Epalrestat (-49% for mRNA IL-6 and -55% for COX2; n=3), and as did Miotempo (IL-6: -69% and COX2: -90%; n=2).

Conclusion: High glucose exposure sensitizes chondrocytes to IL-1β activation via increased glucose uptake, oxidative stress and polyol metabolic pathway leading to a sustained chondrocyte pro-inflammatory phenotype. Such results are in accordance with an increased sensitivity to inflammatory stress of OA cartilage of db patients. These results strengthen the hypothesis that diabetes could be a trigger for the initiation and/or the severity of OA.


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1013 Mitochondrial Function Is Impaired in Human Knee Osteoarthritic (OA) Chondrocytes and Improved By Pharmacologic AMPK Activation Via SIRT1 and PGC-1α. Ru Bryan1; Yun Wang2; Xianlian Zhao3; Martin Lotz2; Robert Terkeltaub3.1VA Medical Center/University of California San Diego, San Diego, CA, 2VA Medical Center/UCSD, San Diego, CA, 3VAMC, San Diego, CA, 4The Scripps Research Institute, La Jolla, CA, 5VA Medical Center/University of California San Diego, San Diego, CA.

Background/Purpose: Chondrocyte mitochondrial abnormalities have been identified in OA, and have the potential to mediate disease progression by promoting oxidative stress and inflammation-driven cartilage matrix catabolism. AMPK (AMP-activated protein kinase) and the NAD⁺-dependent protein deacetylase SIRT1 are cellular energy bio-sensors recently implicated in cartilage tissue homeostasis. In chondrocytes, AMPK promotes mitochondrial biogenesis. Overexpression of SIRT1 or PGC-1α impairs mitochondrial biogenesis and function. Therefore, we hypothesize that pharmacologic activation of AMPK improves mitochondrial function via SIRT1 and PGC-1α in human knee OA chondrocytes.

Methods: We studied cultured human knee chondrocytes from both normal and OA donors (passage 1) with and without the selective AMPK pharmacologic- activator A-769662, or overexpression of SIRT1 or PGC-1α via transfection. Phosphorylation and expression of AMPKα, expression of SIRT1, PGC-1α, and expression of PGC-1α were examined by Western blot analysis. Mitochondrial DNA copy number was determined by the ratio of cytochrome c oxidase I (COX1) mitochondrial gene and 18S rRNA (nuclear gene) by quantitative PCR. Mitochondrial mass was measured by MitoTracker Green FM staining. Oxygen consumption and intracellular ATP level were measured.

Results: In comparison with normal chondrocytes, human OA chondrocytes (grade III and IV) exhibited reduced oxygen consumption (P = 0.03), decreased intracellular ATP level (P = 0.019), and less mitochondrial biogenesis indicated by decreased mitochondrial DNA content (P = 0.001) and mitochondrial mass, decreased expression of NRF1, NRF2 and TFAM, as well as decreased expression of respiratory complexes I, II and III. These differences were linked to reduced phosphorylation of AMPKα and expression of SIRT1 and PGC-1α, and increased acetylated PGC-1α in OA chondrocytes. Stimulation of human OA chondrocytes with A-769662 increased phosphorylation of AMPKα and expression of SIRT1 and PGC-1α, and decreased acetylation of PGC-1α. A-769662 also increased oxygen consumption (P = 0.003), intracellular ATP level (P = 0.015), and mitochondrial biogenesis. Overexpression of SIRT1 or PGC-1α in chondrocytes also induced increased mitochondrial biogenesis.

Conclusion: Both mitochondrial oxidative phosphorylation and mitochondrial biogenesis are impaired in human knee OA chondrocytes. AMPK activation improved the observed impairments of mitochondria in OA chondrocytes, and did so via SIRT1 and PGC-1α. These findings provide a novel molecular mechanism by which pharmacologic activation of AMPK has translational potential to inhibit progression of cartilage degradation in OA via restoration of chondrocyte mitochondrial biogenesis and function.

Disclosure: R. Bryan; None; Y. Wang; None; X. Zhao; None; M. Lotz; None; R. Terkeltaub; None.

1014 Harpagide, a Low Molecular Weight Natural Product, Suppresses IL-1α-Induced IL-6 Expression By Blocking the Activation of p38 MAPK and Transcription Factors CEBPα and AP-1 in Primary Human Osteoarthritis Chondrocytes. Abdul Haseeb1; Tariq Haqgi2.1Northwest Ohio Medical University (NEOMED), Rootstown, OH, 2Northeast Ohio Medical University, Rootstown, OH.

Background/Purpose: There is growing evidence that shows the involvement of IL-6 in cartilage degradation during OA. Significant correlation between IL-6 levels in serum as well as synovial fluid and OA severity has been reported. IL-6 stimulates the expression of MMP-13 and inhibits the expression of type II collagen. Harpagide is a low molecular weight compound isolated from the secondary roots of Harpagophyllum procumbens (Hp). In the present study we used an in vitro model of inflammation in OA to investigate the therapeutic potential of Harpagide in OA.

Methods: Primary human chondrocytes were isolated from the unaffected cartilage obtained from OA patients who underwent total knee arthroplasty. Human OA chondrocytes were cultured and pre-treated with Harpagide (500 μM) and then cultured with and without IL-1β (5 ng/ml). Chondrocyte viability was assayed using Trypan blue exclusion assay. Secreted levels of IL-6 in the culture supernatants were quantified by ELISA. Total RNA levels and phosphorylation levels of CEBPα and AP-1 in human OA chondrocytes were measured by Western blot analysis using specific antibodies. Nuclear extracts were prepared and used to study the effect on the nuclear localization and activation of NF-κB, CEBPα and AP-1 in OA chondrocytes by Western blotting and DNA binding activity. IL-6 mRNA levels were quantified using the TaqMan assays. Data were derived using Origin 6.1 software and P < 0.05 was considered significant.

Results: Harpagide had no effect on OA chondrocyte viability in vitro. Treatment of primary human OA chondrocytes with IL-1β markedly stimulated the mRNA expression of IL-6 and protein secretion in the culture supernatants which was inhibited significantly (p < 0.05) by pre-treatment with Harpagide. Harpagide did not inhibit the IL-1β-induced degradation of IκB and the activation of NF-κB but suppressed the IL-1β-triggered nuclear localization and activation of CEBPα and AP-1 in human OA chondrocytes. The IL-6 levels and phosphorylation levels of CEBPα and AP-1 in human OA chondrocytes were measured by Western blot analysis using specific antibodies. Nuclear extracts were prepared and used to study the effect on the nuclear localization and activation of NF-κB, CEBPα and AP-1 in OA chondrocytes by Western blotting and DNA binding activity. IL-6 mRNA levels were quantified using the Taqman assay. Data were derived using Origin 6.1 software and P < 0.05 was considered significant.
also identify a novel mechanism of IL-6 suppression which bypasses the activation of NF-κB. These data provide strong evidence with mechanistic details in support of the possible use of Harpagide as a therapeutic choice to prevent/retard the progression of OA.

**Background/Purpose**

**Methods**

**Results**

**Conclusion**

Disclosure: A. Haseeb, None; T. Haqqi, None.

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**Mir-9/MCPIP1 Axis Mediated Regulation of IL-6 Expression in Osteoarthritis Chondrocytes.** Tarig Haqqi1, Abdul Haseeb2 and Mohammad Shahidul Makkii2. 1Northeast Ohio Medical University, Rootstown, OH. 2Northeast Ohio Medical University (NEOMED), Rootstown, OH.

**Background/Purpose:** Post-transcriptional regulation of cytokine expression is important for maintaining tissue integrity. MCPIP1 was identified as a novel protein, which destabilizes inflammatory cytokines mRNAs via their 3' UTR. IL-6 has recently gained attention because of its high levels in synovial fluid in Osteoarthritis (OA) and ability to induce high levels of MMP-13 in OA. In the present study, we determined whether MCPIP1 regulates IL-6 expression and evaluated the role of miR-9/MCPIP1 axis in the regulation of IL-6 in human OA chondrocytes.

**Methods:** Human chondrocytes were prepared from OA cartilage by the enzymatic digestion. Taqman assays were used for gene expression analysis using RNA isolated from cultured primary chondrocytes or from damaged or smooth regions of OA cartilage or RNA immunoprecipitation (RIP). RNA fluorescent in-situ hybridization (ISH) for IL-6 and MCPIP1 expression was performed using RNA scope. Transfection was done using Amaxa kit. Knockdown experiments were performed using Trilissenc-27 human siRNA. For RIP, lysates from IL-1β-stimulated chondrocytes were incubated overnight with anti-MCPIP1 antibody or with isotype control IgG followed by RNA purification.

**Results:** MCPIP1 expression was low in damaged cartilage compared to smooth cartilage while the expression of IL-6 was high in damaged cartilage and low in smooth cartilage, suggesting that lower expression of MCPIP1 may be contributing to the excessive expression of IL-6 in OA. Expression of miR-9 predicted by Targetscan to bind the seed sequence in MCPIP1 mRNA was high in damaged cartilage compared to smooth cartilage and was also upregulated by IL-1β in OA chondrocytes. Over expression of miR-9 mimic or inhibitor in OA chondrocytes altered the expression of MCPIP1 and IL-6. IL-1β-mediated induction of IL-6 was initially low in OA chondrocytes but was significantly accelerated 8 h post-stimulation. On the other hand, expression of MCPIP1 was high initially in IL-1β-stimulated OA chondrocytes but started to decline 8 h post-stimulation. Overexpression of wild type MCPIP1, but not of mutant MCPIP1, in OA chondrocytes reduced the expression of IL-6 mRNA and protein significantly (p<0.05). Importantly, siRNA-mediated knockdown of MCPIP1 elevated the IL-6 mRNA expression in OA chondrocytes. TaqMan analysis of the immunoprecipitated mRNAs showed that anti-MCPIP1 antibody pulled down larger amount of IL-6 mRNA than control IgG antibody did thus demonstrating the binding of MCPIP1 with IL-6 mRNA in OA chondrocytes.

**Conclusion:** In this study for the first time expression of MCPIP1 and miR-9 in human OA cartilage and chondrocytes is shown. The data also demonstrate mir-9/MCPIP1/IL-6 interactions and provide evidence of miR-9/MCPIP1 axis as an important regulator of IL-6 expression in OA.

Disclosure: A. Haseeb, None; M. Shahidul Makkii, None.

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**BMP9-Induced pSmad1/5/8 Signaling and Chondocyte Hypertrophy Are Effectively Inhibited by TGFβ1.** Arjan van Caam, Esmeralda Blaney Davidson, Ellen W. van Goffen, Wim B. van den Berg and Peter M. van der Kraan. Radboud university medical center, Nijmegen, Netherlands.

**Background/Purpose:** Osteoarthritis is characterized by degradation of articular cartilage. TGFβ-supersignaling via Smad phosphorylation (pSmad) plays a crucial role in cartilage maintenance. Two distinct pSmad pathways exist: pSmad5/8 and pSmad2/3. pSmad2/3 induces matrix formation and protects cartilage against deleterious processes like chondocyte hypertrophy and IL-1 signaling. In contrast, pSmad5/8 is linked to chondocyte hypertrophy and expression of the main cartilage degrading enzyme: MMP-13. Recently a very potent pSmad5/8 inducing ligand has been identified: BMP9. BMP9 is produced by the liver and circulates in high levels. Over 60% of all BMP activity in serum can be attributed to BMP9, showing...
the abundance of this BMP. In this study we investigated the effect of this potent pSmad1/5/8 inducing ligand, BMP9, on chondrocyte phenotype. Furthermore, because of pSmad2/3's importance in chondrocyte homeostasis, we studied the interaction between BMP9-signaling and TGFβ1-induced pSmad2/3 signaling.

**Methods:** In this study, primary bovine chondrocytes were used. BMP9-induced Smad phosphorylation was detected after 1 h and 2 h using Western Blot. Subsequently, BMP9-induced gene expression was measured up to 24 h using real-time qPCR. Biological activity of pSmad2/3 was measured using the (CAGA)12-luc reporter assay, which produces luciferase in response to pSmad3. Cellular hypertrophy was investigated by culturing chondrocytes 1 week in the presence of growth factors and analyzing gene expression of hypertrophy markers.

**Results:** In primary bovine chondrocytes, BMP9 stimulation in doses upwards of 50 pg/ml induced pSmad1/5/8, which was reflected in expression of the Smad2/5/8 response gene bID1. Remarkably, BMP9 doses of 1 ng/ml and higher also induced pSmad2, but, expression of the pSmad3 response gene βSerpine1 was not induced. Co-stimulation of chondrocytes with BMP9 and a low dose TGFβ1 (0.1 ng/ml) reduced BMP9-induced pSmad1/5/8 and, surprisingly, enhanced TGFβ1-induced pSmad2. After 24 hours, this interaction was reflected in mRNA levels, as co-stimulation increased expression of the pSmad2/3 responsive genes: βSerpine1, bIDfb1 and bIDm7 and decreased expression of bID1. Furthermore, BMP9 also synergistically enhanced biological activity of TGFβ1 in the CAGA12-Luc reporter assay. The uniqueness of this synergy between BMP9 and TGFβ1 was illustrated by co-stimulation of chondrocytes with TGFβ1 and two other BMPs important in chondrocyte biology: BMP2 and BMP7, which showed that both these BMPs do not synergize with TGFβ1 on Smad2/3p. As a more long term effect, BMP9 induced chondrocyte hypertrophy after one week of stimulation, as indicated by upregulation of Alkaline phosphatase and Col10a1, however, addition of 0.1 ng/ml of TGFβ1 inhibited this BMP9-induced hypertrophy.

**Conclusion:** Our results show that BMP9 potently induces pSmad1/5/8 and its downstream gene expression in chondrocytes. In long term culture this results in induction of chondrocyte hypertrophy. However TGFβ1 can potently inhibit this hypertrophy. Possibly, this runs via the observed but yet unexplained pSmad2/3 enhancing interaction between both growth factors, which is unique for BMP9 compared to BMP2 or BMP7.

**Disclosure:** A. van Caam, None; E. Blaney Davidson, None; E. W. van Geffen, None; W. B. van den Berg, None; P. M. van der Kraan, None.

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Targeting the Bone-Driven Metabolic OA Phenotype By a Novel Dual Amylin Calcitonin Receptor Agonist, KBP-056.

**Background/Purpose:** Osteoarthritis (OA) may be segregated into different disease phenotypes based on disease drivers; cartilage damage, joint inflammation or subchondral bone remodelling. Each phenotype may require targeted treatments. Patients with a bone-driven OA may particularly benefit from a treatment with anti-resorptive and chondroprotective properties. Salmon calcitonin (sCT), a hormone acting through CT and amylin receptors, have in multiple preclinical models been demonstrated to improve bone homeostasis and attenuate joint destruction, in part through the anti-resorptive property. In addition, sCT have recently been shown to have a positive effect on obesity and diabetes, which may benefit certain OA subjects. Several Dual Amylin Calcitonin Receptor Agonists (DACRAs) have been characterized through a larger screening program; KBP-056 was found to be particularly interesting for OA, by showing higher potency for the receptors than sCT. The objective of this study was to investigate the in vivo effect of KBP-056 on bone and cartilage turnover, as well as metabolic health.

**Methods:** Male Sprague Dawley rats (Taconic, Ry, Denmark) were given HFD for 10 weeks before they were treated with defined doses of KBP-056 (0.025, 1.25, 5.5, 10 mg/kg) or vehicle as subcutaneous injections. Blood was collected from overnight fasted rats immediately at baseline, 3 and 24 hours after first treatment. Rats were treated for 8 weeks. Body weight was recorded weekly. Biomarkers of bone and cartilage degradation were assessed in the blood using the ELISA sCTX-I (bone resorption) and CTX-II (cartilage degradation), CTX-I and -II were reported as fold of baseline levels, as means with standard error of mean (SEM) and compared using two-way ANOVA assuming normal distribution. Significance levels: *P < 0.05, **P < 0.01, ***P < 0.001. In addition, a similar study was performed using ovariectomy (OVX)-meniscectomy (MNX) Sprague Dawley rats.

**Results:** Serum levels of both CTX-I and -II decrease significantly 3 hours after treatment with KBP-056, even at the lowest dose tested (P < 0.05, fig. 1). Moreover, a dose-dependent response by CTX-I still remained 24 hours after treatment, suggesting increased potency. KBP-056 caused a 19% vehicle-corrected weight reduction for two highest doses at the end of the experiment. A similar weight reducing effect was observed in OVX-MNX rats.

**Conclusion:** The data presented here clearly indicate a protective effect of KBP-056 on both bone and cartilage in vivo, when evaluated by biochemical markers. Furthermore, KBP-056 has demonstrated positive effects on metabolic health (cause a weight decrease), and may therefore represent a possible treatment opportunity for bone-driven OA, with an unhealthy phenotype (e.g. high BMI). Many further studies are needed to match the optimal treatment opportunity with the right OA patient for a personalized health care approach for OA.
Age-related abnormalities (loss of T-cell reactivity, development of autoantibodies, activation of inflammatory mechanisms) may be synergising with senescence and inflammageing (as suggested by the increased frequency of IRC in some OA patients) may therefore play a role in OA in addition to their implication in healthy ageing.

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Changes in Peripheral Blood Immune Cell Composition in Osteoarthritis. Agata Burska1, Mark Campbell2, Rafi Raja2, Dylan White1, Paul Emery3, Philip G. Conaghan1 and Frederique Ponchel1. 1Leeds Institute of Rheumatic and Musculoskeletal Medicine, Translational Research in Immunemediated Inflammatory Diseases, the University of Leeds, Leeds, United Kingdom, 2NIHR-Leeds Mucosal and Musculoskeletal Medicine, Translational Research in Immune-mediated Inflammatory Diseases, the University of Leeds, Leeds, United Kingdom, 3NIHR-Leeds Mucosal and Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, 4Leeds Institute of Rheumatology and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Mucosal and Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: Healthy ageing and the occurrence of the common age-related disease osteoarthritis (OA) result from varying degrees of interaction between many determinants (genetic, lifestyle). Immunosenescence and inflammageing are features of the ageing immune system. Age-related abnormalities (loss of T-cell reactivity, development of autoantibodies, activation of inflammatory mechanisms) may be synergising with structural defects of the musculoskeletal system aiding the development of OA. We aimed to determine if abnormalities of blood immune cell composition are associated with OA, beyond the defects already associated with age.

Methods: Blood samples were collected from 120 healthy controls (age range 18–69) to establish variations associated with age and 120 OA (age range 49–80). We examined loss or acquisition of age-related changes in blood composition. B-colours flow cytometry was performed to establish the frequencies of: CD4/CD8, B, NK-cells. Naive and regulatory T and B-cell were subsequently analysed and cells with an abnormal phenotype identified in Rheumatoid arthritis is direct relation with inflammation (IRC phenotype).

Results: Flow cytometry was performed on all 240 samples (only 20 HC and 45 OA were analysed for B-cells) and demonstrated, as expected, very little change in lineage representation associated with age in health with; no change for NK, CD4, and B-cells, weak decline in CD8 (rho = −0.300, p = 0.019) and increase in NKT (rho = 0.315, p = 0.012). In contrast phenotyping T and B-cells showed clear age-related changes with reduction of naive CD4 T-cell (rho = 0.817, p < 0.0001), Regulatory T-cells increased (rho = 0.401, p < 0.0001) whereas B-reg reduced (rho = −0.658, p = 0.002). IRC were not related to age.

In OA, differences were observed. NK, CD4 and B-cells were not related to age but in OA, NK cells were positively correlated (rho = 0.350, p < 0.0001), CD4 (rho = −0.318, p = 0.001) and B-cells (rho = −0.260, p = 0.006) negatively. The NKT correlation with age was maintained in OA (rho = 0.817, p < 0.0001), CD4 (rho = −0.315, p = 0.001) whereas B-reg reduced (rho = −0.658, p = 0.002). IRC were not increased with the exception of ~20 patients.

Conclusion: This analysis of the immune cell composition of the blood of OA patients suggests that immune dysfunction is present in OA above what is directly related to ageing. Immunosenescence and inflammageing (as suggested by the increased frequency of IRC in some OA patients) may therefore play a role in OA in addition to their implication in healthy ageing.

Disclosures: D. Reker, Nordic Bioscience Diagnostic, 3; S. T. Hjuler, Nordic Bioscience Diagnostic, 3; K. Andraassen, Nordic Bioscience Diagnostic, 3; M. A. K Larsen, Nordic Bioscience Diagnostic, 3; AbbVie Inc., 5; K. Henriksen, Nordic Bioscience Biomarkers and Research, 3; A. C. Bay-Jensen, Nordic Bioscience Holding A/S, 1, Nordic Bioscience Diagnostic, 3.

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Transhyretin and Amyloid in Cartilage Aging and Osteoarthritis. Yukio Akasaki1, Oscar Alvarez-Garcia2, Natalia Reixach3, Joel Buxbaum4 and Frederique Ponchel1. 1Leeds Institute of Rheumatic and Musculoskeletal Medicine, Translational Research in Immune Mediated Inflammatory Diseases, the University of Leeds, Leeds, United Kingdom, 2Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 3NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, 4Leeds Institute of Rheumatology and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Mucosal and Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: Deposition of amyloid is a common aging-associated phenomenon and a key factor in the pathogenesis of several aging-related diseases. Osteoarthritis is the most prevalent joint disease and aging is its major risk factor. Although amyloid deposits appear to be prevalent in OA-affected joints, their composition and effects on cell and tissue function are unknown. Transhyretin (TTR) is an amyloidogenic protein. Point mutations in the TTR gene cause familial amyloidotic polyneuropathy and cardiomyopathy. Wild-type TTR can also assemble into amyloid deposits and this may be facilitated by oxidation, or the presence of sulfated glycosaminoglycans. This study addressed TTR deposition in aging and OA-affected knee cartilage and effects of TTR on chondrocyte function.

Methods: Amyloid deposition in normal and OA human knee cartilage was determined by Congo-red staining and polarized light microscopy. TTR in cartilage and synovial fluid was analyzed by immunohistochemistry and western blotting. TTR gene expression in chondrocytes was studied by quantitative PCR and RNA sequencing. Effects of wild type and mutant TTR were studied in normal human chondrocyte cultures with measurements of cell viability and OA-related gene expression.

Results: There was no amyloid deposition in young normal cartilage. In contrast, 58% (7/12) of aged normal cartilage and 100% (12/12) of OA cartilage samples had Congo red staining. TTR was detectable in all OA and a majority of aged but not in young normal cartilage and predominantly located at the cartilage surfaces. TTR is not produced by chondrocytes at substantial levels and synovial fluid levels are similar in normal and OA affected knees. In chondrocytes, TTR induces cell death, the expression of proinflammatory cytokines and extracellular matrix degrading enzymes. This was observed for the amyloidogenic but not for the non-amyloidogenic TTR mutant. Effects of TTR on cell viability and gene expression are mediated by activation of TLR4 signaling and MAP kinases.

Conclusion: These findings are the first to suggest that TTR amyloid deposition may not represent an inconsequential aging-related phenomenon but contribute to cell and extracellular matrix damage in articular cartilage.

Disclosures: Y. Akasaki, None; O. Alvarez-Garcia, None; N. Reixach, None; J. Buxbaum, None; Y. Iwamoto, None; M. K. Lotz, None.
Background/Purpose: The synovial lining tissue consists of fibroblast-like synoviocytes (FLS) and monocyte-derived macrophage-like synoviocytes (MLS) within a self-built meshwork of dense extracellular matrix (ECM) components. FLS are thought to direct ECM synthesis, assembly and degradation. Whether FLS themselves or the ECM network serve as guiding structures for MLS migration is incompletely understood. Thistempted us to study the dynamics of synovial tissue modelling under steady state and inflammatory conditions using a three-dimensional in-vitro model of the synovial tissue.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. CD14+ monocytes (Mo) were isolated from peripheral blood. FLS and Mo were labeled with fluorescent membrane dyes and cultured in spherical extracellular matrix micromasses with an average size of 1.5 mm for up to two weeks. Second harmonic generation (SHG) was used for the visualization of collagen fibers. For stimulation experiments, micromasses were cultured in medium containing 10 ng/ml of tumor necrosis factor (TNF). Cell migration was monitored in individual micromasses by real-time confocal/multil-photon microscopy.

Results: The formation of a FLS network was observed within 3–7 days and coincided with the detection of collagen fibers that colocalized with FLS. The majority of Mo was found to be in close contact with the FLS network with low tendency for migration. A minor fraction of Mo displayed a directed cell movement with an impressive maximum speed of up to 15 μcm/min. Rapid Mo migration occurred in intimate contact with FLS but did not necessarily follow FLS network boundaries. In addition, we observed the formation of Mo cell clusters that co-localized with collagen fibers in the absence of FLS. The addition of TNF i) increased the frequency and size of Mo cell clusters and ii) prolonged the overall mobility of Mo.

Conclusion: The 3D synovial tissue culture system allows for monitoring and analyzing the dynamics of synovial lining modelling. Both, FLS and Mo appear to cooperate in the organization of the synovial lining tissue with subtle migration patterns of Mo in relation to the organized synovial lining architecture. Ongoing experiments address molecular mechanism(s) of Mo – FLS interaction in order to identify potential targets for future therapeutic intervention in arthritis.

Disclosure: B. Wang, None;
Leptin Production By Osteoarthritis Synovial Fibroblasts: Stimulation By Glucocorticoids and Mineralocorticoids through the Glucocorticoid Receptor and GILZ (Glucocorticoid-Induced Leucine Zipper) Protein. Olivier Malaise, Biserka Relic, Sophie Neuville, Edith Charlier, Dominique De Seny and Michel G. Malaise. GIGA Research - University of Liège - CHU of Liège, Liège, Belgium.

Background/Purpose: Osteoarthritis (OA) is a metabolic disorder for which leptin is playing a catalytic role on cartilage. In mice, obesity due to impaired leptin did not cause OA. In vitro, we have previously shown that OA synovial fibroblasts (SF) produced leptin, hypothesizing that they were also able to contribute to intra-articular levels of leptin. The glucocorticoid prednisolone strongly induced leptin and leptin receptor (Ob-R), suggesting a deleterious involvement in the metabolic component of OA.

Aldosterone, a mineralocorticoid, is found in OA synovial fluid and is involved in systemic metabolic regulation. First, we will study the mineralocorticoid’s influence on leptin and Ob-R expressions, and determine whether leptin and Ob-R are glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) dependent.

Glucocorticoid-induced Leucine Zipper (GILZ) protein, induced by glucocorticoids, is an anti-inflammatory mediator in inflammatory models. Links with leptin are unknown, but GILZ’s overexpression decreases adipogenic properties of prednisolone, with an unchanged endogenous or TNF-related modulation. Moreover, CpdA and TGF-β, that did not induce GILZ in OA SF, did not induce leptin.

(4) GILZ inhibition with shRNA did not modify the anti-inflammatory properties of prednisolone, with an unchanged endogenous or TNF-α-induced IL-6 reduction opposite to the control.

Conclusion: (1) Both prednisolone and aldosterone induced leptin and Ob-R through GR but not MR: mifepristone (GR antagonist), but not eplerenone or spironolactone (MR antagonists), reduced both prednisolone- and aldosterone-induced leptin and Ob-R. GR silencing with shRNA confirmed these results.

(2) GILZ was induced by prednisolone and aldosterone. Similarly to leptin, stimulations with GR or MR antagonists and GR silencing showed that both leptin and Ob-R inductions were GR-dependent: leptin and GILZ shared similar modulations. Moreover, CpdA and TGF-β, that did not induce GILZ in OA SF, did not induce leptin.

(3) GILZ was involved in prednisolone- and aldosterone-induced leptin and Ob-R, with a significant dose-response decrease when GILZ was down-regulated with shRNA.

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Disclosure. M. Ramirez, None; J. Potvin, None; D. Ramirez, None; A. M. Reginato, None.

ACR/ARHP Poster Session B
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis
Monday, November 17, 2014, 8:30 AM - 4:00 PM

Hematopoietic Cell Kinase (HCK) As a Novel Regulator of Fibroblast-like Synoviocyte Function in RA. Ying Wang, Deega Hammaker, David L. Boyle, Toshio Yoshizawa and Gary S. Firestein. "UCSD, La Jolla, CA, "University of California San Diego, La Jolla, CA, "University of California at San Diego School of Medicine, La Jolla, CA, "Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background/Purpose: Fibroblast-like synoviocytes (FLS) are key mediators of inflammation and joint damage in rheumatoid arthritis (RA) through the production of cytokines and matrix metalloproteinases (MMPs) as well as invasion into extracellular matrix. The search for potential kinases that target FLS for RA led to hematopoietic cell kinase (HCK) as a candidate target. HCK is a member of the Src tyrosine kinases and is primarily expressed by myoid cells. HCK deficiency reduces the migration of M-CSF- and RANKL-induced murine bone marrow mononuclear cells in vitro, indicating that it might play a role in cell migration. However, its expression in mesenchymal cells is not defined, and nothing is known about HCK function in synoviocytes. To determine if HCK is a potential therapeutic target in RA, we evaluated HCK expression and function in RA FLS. These studies show that HCK is an inducible gene in RA FLS that regulates key pathogenic functions, thus allowing an inhibitor to target its effects primarily at sites of inflammation.

Methods: FLS were obtained from RA and osteoarthritis (OA) patients undergoing joint replacement surgery and used from passage 3 through 9. Three separate cell lines were studied for each experiment. To study HCK expression in FLS, RA and OA FLS were serum starved and treated with medium, IL-1β (2ng/ml) or TNF (50ng/ml) for various times. mRNA levels between MUS crystal and chondrocyte may contribute to cartilage damage in gout. The objective of this study was to investigate the effect of increasing concentrations of MUS crystals on chondrocyte function and differentiation.

Methods: Primary chondrogenic cell line (ATDC5) were cultured in a 1:1 mixture of DMEM/F12 medium containing 10% FBS, Insulin-Transferrin-Selenium and incubated with increasing concentrations of endotoxin-free MUS crystals at increasing concentrations (0.01, 0.025, 0.05 and 0.1 ng/ml) for 4, 7, and 14 days respectively. Purification of total cellular RNA for real time PCR was performed from ATDC5 at different time points. Real-time quantitative PCR was performed on specific extracellular matrix genes, transcription factors and metalloproteinases. Aclan-blue and Alizarin red S staining was performed at selected time point of ATDC5 cells exposed to different MUS concentration.

Results: MUS crystals have a negative effect in the function and differentiation of ATDC5 chondrogenic cell lines. The ability of chondrocyte to produce matrix protein assessed by relative mRNA expression of aggrecan and type II collagen was reduced in chondrocytes following culture with MUS crystals and correlated with Alcan-blue staining. The expression of chondrogenic gene expression was found to correlate with Runx 2. Expression of Ihh, and MMP-13 was increased and confirmed by western blotting (1-way ANOVA p<0.05). Furthermore, the expression of degradative enzymes such as A dams4 and A dams5 was also increased contributing to the cartilage degradative process.

Conclusion: Long-term culture of MUS crystals with chondrogenic cell line ATDC5 impairs the function and differentiation of chondrocytes. MUS crystal’s stimulate expression of Ihh and MMP-13 contributing to the development of osteoarthritis.

References:

Disclosure. M. Ramirez, None; J. Potvin, None; D. Ramirez, None; A. M. Reginato, None.
were determined by qPCR. For functional studies, we used a novel selective small molecule HCK inhibitor, with an IC50 of approximately 7nM. IL-6 and MMP expression were measured by qPCR. MTT assays were performed to determine PDGF-induced proliferation. Apoptosis was induced by H2O2 stimulation and MTT assay. For cell migration, scratch assays were performed on PDGF-stimulated FLS monolayers. The data were analyzed using student’s t test and one way ANOVA.

Results: HCK mRNA levels were very low under basal conditions in culture. IL-1 and TNF increased HCK expression, with maximal introduction at 24 hr by 734- and 65-fold, respectively. TNF-induced IL-6 expression was decreased by 39% in cells treated with 1 μM of the HCK inhibitor (p = 0.025). MMP3 expression was also inhibited by 50-15% (p = 0.03) and 41-12% (p = 0.026) after the stimulation with IL-1p and TNF, respectively. The small molecule HCK inhibitor (1 μM) significantly reduced PDGF-induced FLS growth by 93-32% on day 3 (n=3 RA FLS, p = 0.001), and 81-19% on day 7 (p = 0.001). The compound had no effect on H2O2-induced apoptosis, suggesting that the effect on cell growth was due to decreased proliferation rather than increased cell death. HCK inhibition impaired PDGF-induced migration by 83-31% (p = 0.04).

Conclusion: HCK was induced by IL-1β and TNF in RA FLS. HCK blockade decreased cytokine production, MMP production, proliferation, and cell migration in FLS. Because the gene is minimally expressed in resting cells, its main effect would be in cells at the site of inflammation. Therefore, HCK could be a promising therapeutic target for RA that can regulate pathogenic behavior in a site and event specific manner.

Disclosure: Y. Wang, None; D. Hammer, None; D. L. Boyle, None; T. Yoshizawa, Ono Pharmaceutical Co., Ltd.; S. G. Firestein, None.

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ADAM-10 Plays Monocyte Migration and Adhesion in Rheumatoid Arthritis Synovial Fibroblasts. Takato Isozaki1, Sho Hisi2, Shinichi Nishimi2, Aki Maekawa3, Mayu Satō2, Nao Oguro2, Shinya Seki2, Yoko Miura3, Yusuke Miwa4, Koei Oh1, Yoichi Toyoshima3, Masanori Nakamura3, Katsunori Inagaki3 and Tsuyoshi Kasama1. 1Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, 2Showa University of Med, Shinagawa-ku Tokyo, Japan, 3Showa University School of Med, Tokyo, Japan.

Background/Purpose: ADAM-10 is a transmembrane metalloprotease that mediates the shedding of extracellular matrix proteins and cell surface receptors. In RA, ADAM-10 expression is upregulated in vivo and in vitro, and ADAM-10 siRNA inhibited RA synovial fibroblasts (SFs) migration in vitro and in vivo. However, the role of ADAM-10 in monocyte adhesion is unknown. We investigated whether ADAM-10 mediates monocyte adhesion to RA SFs.

Methods: RA SFs were transfected with siRNA against ADAM-10. In order to determine that ADAM-10 mediates monocyte adhesion, RA SFs showed a 56% (p = 0.025) inhibition of COX-2 metabolite of RA SFs compared to sham-depleted controls. Adhesion of THP-1 to ADAM-10 transfected RA SFs showed a 34% (p = 0.001) inhibition of thrombin-1 (THP-1) induced adhesion. The COX-2 inhibitor, nimesulide (n = 0.01), significantly decreased COX-2 expression. The COX-2 inhibitor reversed the effects of THP-1 adhesion.

Results: Upregulation of target receptors.

Conclusion: Under hypoxic conditions, Endocannabinoids increase the efficacy of endocannabinoids through ADAM-10 and induce COX-2 expression. This might be important in RA where low oxygen and COX-2 inhibition are necessary to fully exploit the therapeutic potential of endocannabinoids. This might be important in RA where low oxygen and abundant cytokine expression up-regulate COX-2 in the joint. In addition, pro-inflammatory cytokines increase the efficacy of endocannabinoids due to upregulation of target receptors.

Disclosure: T. Isozaki, None; S. Hisi, None; S. Nishimi, None; A. Maekawa, None; M. Satō, None; O. Oguro, None; S. Seki, None; Y. Miura, None; Y. Miwa, Tanabe-Mitsubishi, 2, Wyeth Pharmaceuticals, 2, Chugai, 2, Abbott Immunology Pharmaceuticals, 2, Asteras, 2, Ono, 2, Bristol-Mayer Squibb, 2; K. Oh, None; Y. Toyoshima, None; M. Nakamura, None; K. Inagaki, None; T. Kasama, None.

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Anandamide and Related Eicosanoids Decrease the Production of Pro-Inflammatory Cytokines in Synovial Fibroblasts By a COX-2-Dependent Mechanism: Involvement of Calcium and TRP Channels. Torsten Lowin1, Tanja Spåth 2, Angelika Graeber1 and Rainer Straub1. 1Laboratory of Exp. Rheumatology and Neuroendocri-Immunology, University Hospit-ality Regensburg, Regensburg, Germany, 2Laboratory of Exp. Rheumatol-ogy and Neuroendocri-Immunology, Regensburg, Germany, 3University Hospital Regensburg, Regensburg, Germany.

Background/ Purpose: Endocannabinoids are immunomodulatory lipid compounds that act on cannabinoid receptors type 1 and 2 but also on transient receptor potential (TRP) channels. Their action is terminated by FAAH, one major enzyme responsible for endocannabinoid degradation. COX-2, however, also degrades endocannabinoids, and products from this reaction are pro-inflammatory. This study studied a potential mode of action for the anti-inflammatory effects of endocannabinoids in synovial fibroblasts from RA and OA donors. Furthermore it is investigated how pro-inflammatory cytokines alter the responsiveness of synovial fibroblasts to endocannabinoids.

Methods: COX-2 and cytokines were detected by ELISA. ERK 1/2, p38, CREB and c jun phosphorylation was assessed by proteome profiler analysis and cell-based ELISA. Cannabinoid receptors 1 and 2, TRPA1, TRPV1 and COX-2 were detected by western blotting and cell-based ELISA. The XCELLigence system was used to determine EC50 values for CB1/CB2, TRPV1 and TRPA1 with/without cytokine stimulation.

Results: The endocannabinoid arachidonylethanolamide (anandamide, AEA) and related eicosanoids palmitoylethanolamide (PEA), oleyl ethanolamide (OEA) and N-arachidonylglycine (NAGy) reduced TNF-induced production of IL-6, IL-8 and MMP-3. The effects of AEA, OEA and PEA were significantly enhanced by addition of the COX-2 inhibitor nimesulide but not by FAAH inhibition. The effects of all compounds tested were not inhibited by CB1 or CB2 antagonism but were blocked by TRPV1 and TRPA1 antagonists in RASFs and OASFs. In the case of AEA, COX-2 inhibition reversed the effects of TRPA1 antagonism. Quantification of CB1, CB2, COX-2, TRPV1 and TRPA1 revealed a significant stimulatory influence of pro-inflammatory cytokines and hypoxia on observed protein levels. Furthermore, high AEA concentrations (>1μM) induced cell death only when combined with the intracellular calcium chelating agent BAPTA-AM. Analysis of intracellular signaling pathways revealed an inhibitory effect of AEA on p38 and ERK1/2 phosphorylation after TNF stimulation.

Conclusion: Under hypoxic conditions, Endocannabinoids promote an anti-inflammatory phenotype in RASFs and OASFs by activating/desensitizing TRPV1 and TRPA1. As a consequence, MAP kinase signaling is reduced as demonstrated after AEA treatment. Furthermore, COX-2 and FAAH inhibition are necessary to fully exploit the therapeutic potential of endocannabinoids. This might be important in RA where low oxygen and abundant cytokine expression up-regulate COX-2 in the joint. In addition, pro-inflammatory cytokines increase the efficacy of endocannabinoids due to upregulation of target receptors.

Disclosure: T. Lowin, None; T. Spåth, None; A. Graeber, None; R. Straub, None.

1030
ABT-122, a Novel Dual Variable Domain (DVD)-Ig™, Targeting TNF and IL-17, Inhibits Peripheral Blood Mononuclear Cell Production of GM-CSF and Decreases Lymphocyte Expression of CXCR4 in Healthy Subjects. Melanie Ruzeck1, Donna Conlon1, Hekkia Mansikka2, Robert Padley1 and Carolyn Cuff1. 1AbbVie, Inc, Worcester, MA, 2AbbVie, Inc, North Chicago, IL.

Background/ Purpose: TNF and IL-17 contribute to the pathogenesis of several inflammatory disorders and are known to induce chemokines and cytokines, including chemokine (C-X-C motif) ligands 1 (CXCL1), 5 (CXCL5), and 8 (CXCL8), chemokine (C-C motif) ligand 2 (CCL2), IL-1b, IL-6, G-CSF, and GM-CSF. In addition, the CXCL12 chemokine receptor, CXCR4, is reported to be coordinately regulated by TNF and IL-17. As these factors play a role in the pathogenesis of several
autoimmune diseases, greater clinical responses in patients may be possible with dual neutralization of TNF and IL-17. ABT-122 is novel DvD-Ig<sup>+</sup> molecule targeting both human TNF and IL-17 cytokines and is currently in clinical trials. The aim of this study was to determine the biologic response to ABT-122 in healthy volunteers based on known activities of TNF and/or IL-17 in humans.

**Methods:** Twenty-four healthy subjects were administered a single dose of ABT-122 (1.3 mg/kg subcutaneously) in a Phase I trial. PBMCs were collected prior to ABT-122 administration at baseline and at days 7, 15, 35 and 57 post dosing and cryopreserved. Thawed PBMCs were either analyzed directly by flow cytometry for chemokine receptors CXCR1, CXCR4, and CXCR5, or stimulated with LPS. Supernatants from the LPS cultures were analyzed by multiplex analysis (MAPx, Millipore EMD) for CXCL8, CXCL1, CXCL5, CCL2, IL-1β, IL-6, IL-10, G-CSF, and GM-CSF.

**Results:** A single dose of ABT-122 administered to healthy volunteers resulted in a 4-fold lower production of GM-CSF through day 5. Compared with baseline from LPS-stimulated PBMCs, CXCR4 expression also decreased on B cells, T cells, and monocytes at day 7 compared with baseline with average reductions of 54%, 41%, and 20%, respectively. Decreases in CXCR4 on B cells persisted to day 15 (24%) and day 36 (18%). As GM-CSF and CXCR4 are reported to be synergistically regulated by IL-17 and TNF, these results suggest dual neutralization by ABT-122. Consistent with known activities of anti-TNF agents in RA patients, there were 2.5-fold elevations in the anti-inflammatory cytokine IL-10 and significant 9–12% decreases in CXCR5 expression on T cells following administration of ABT-122. Other chemokine/cytokine responses to LPS stimulation and expression of CXCR1 were unchanged after ABT-122.

**Conclusion:** The changes observed in expression of GM-CSF and CXCR4 in healthy subjects with dual neutralization of TNF and IL-17, demonstrate pharmacodynamic activity of ABT-122 DvD<sup>+</sup> protein consistent with the known combinatorial activities of TNF and IL-17. Notably, the effects of ABT-122 on these analytes were demonstrated in healthy volunteers, thus these changes likely reflect modulation of the in vivo homeostatic activities of TNF and IL-17 in the absence of disease. These data further support the rationale that ABT-122 can be used to evaluate the therapeutic potential of dual IL-17 and TNF blockade in patients with disorders driven by these two cytokines.

Disclosure: M. Ruzek, Abbvie; 1, A. Walsh, 2, A. Beamer, 3, A. Sudini, 4, D. Leaman, 5; K. Maers, 6, K. Sudini, 7, D. Leaman, 8.

**1031**

**Induction of Pro-Apoptotic Noxa Expression By Ursolic Acid Sensitizes Rheumatoid Arthritis Synovial Fibroblasts to Apoptosis: A Role of Mir-181a.** Salahuddin Ahmed<sup>1</sup>, Laura Walsh<sup>2</sup>, Anil Singh<sup>3</sup>, Maria Beamer<sup>2</sup>, Kuladeep Sudini<sup>2</sup> and Douglas Leaman<sup>2</sup>. 1Washington State University, Spokane, WA, 2University of Toledo, Toledo, OH.

**Background/Purpose:** In rheumatoid arthritis (RA), the paucity of pro-apoptotic protein Noxa in RA-FLS may significantly contribute to the resistance of synovial fibroblasts (FLS) to apoptosis. In the present study, we evaluated the expression of pro-apoptotic protein Noxa in RA-FLS using a potent anti-inflammatory pentacyclic triterpenoid uroacic acid (UA) triggers apoptosis and studied the underlying mechanism.

**Methods:** Effects of UA (2.5–10 μM) on human RA-FLS morphology and cell viability were determined by microscopy and a colorimetric MTT/H<sub>2</sub>OTetrazolium (MTT) assay. Western blotting was used to evaluate the apoptosis signaling mediators, Noxa, and Mcl-1 expression.

**Results:** UA (2.5–20 μM) decreased the cell viability of RA-FLS in a dose-dependent manner. Importantly, UA (10 μM) selectively induced Noxa expression within 3 h to ~2–3 fold in RA-FLS (p<0.05; n=4). Induction of Noxa led to the consequent downregulation of Mcl-1 expression and apoptosis by 24 h of UA treatment (p<0.05; n=3). The inhibition of Mcl-1 expression by UA resulted in the sensitization of RA-FLS to TRAIL-induced PARP cleavage and apoptosis. Overexpression of Noxa using a plasmid vector targeting UA was effective in making RA-FLS susceptible to apoptosis. Using a siRNA method to block Noxa expression, we found that the RA-FLS apoptosis-inducing activity of UA was significantly blocked suggesting that UA induced apoptosis in RA-FLS primarily through Noxa upregulation. Confirmatory studies using WT and Noxa<sup>−/−</sup> BMK cells showed that UA efficiently induced apoptosis in WT cells but had no effect in Noxa<sup>−/−</sup> counterparts (p<0.01; two independent experiments). Interestingly, transfection of stably expressing Noxa in Noxa<sup>−/−</sup> BMK cells restored the apoptosis inducing capability of UA. MicroRNA array analysis showed a significant decrease in RA-FLS mir-181a expression, a miRNA known to facilitate apoptosis, by ~30% as compared to the normal FLS (p<0.05). We also found that UA (5–10 μM) was capable of inducing mir-181a expression in RA-FLS as compared to the non-stimulated samples suggesting that UA-induced Noxa expression and consequent apoptosis in RA-FLS may be mediated epigenetically via upregulation of mir-181a.

**Conclusion:** Our novel findings indicate that inducing Noxa expression by UA in RA-FLS effectively induces apoptosis and this effect is partly mediated through mir-181a. Thus, developing therapeutic strategies that can selectively upregulate Noxa and/or modulate mir-181a to induce apoptosis in RA-FLS may have potential therapeutic application for the treatment of RA.

Disclosure: S. Ahmed, None; L. Walsh, None; A. Singh, None; M. Beamer, None; K. Sudini, None; D. Leaman, None.

**1032**

**Neutralization of IL-17 A Mediated Kidney Pathology Associated with Immune-Complex Mediated Autoimmune Glomerulonephritis.** Pathra Biswas<sup>1</sup>, Kritika Ramani<sup>1</sup>, Kelly M. Mears<sup>2</sup>, Anna Huppier<sup>3</sup> and Sarah L. Gaffen<sup>1</sup>. 1University of Pittsburgh, Pittsburgh, PA, 2University of Pittsburgh, Pittsburgh, PA.

**Background/Purpose:** Immune complex mediated autoimmune glomerulonephritis (AGN) is often a fatal clinical manifestation of systemic lupus erythematosus. In recent years, pro-inflammatory cytokines in the nephritic kidney appear to contribute to the pathogenesis of AGN. The inflammatory cytokine network that drives renal pathology is poorly understood. IL-17, the signature cytokine of T-helper 17 (Th17) cells, which promotes autoimmune pathology in a variety of settings, is beginning to be identified in kidney diseases as well. However, the role of IL-17 and the consequence of blocking IL-17 in the pathogenesis of AGN have not been elucidated.

**Methods:** We took advantage of a prototypic mouse model of AGN, where glomerular injury is induced by generating an autoimmune response against rabbit anti-mouse glomerular basement membrane serum. In this model, development of AGN is an inevitable consequence of glomerular injury induced by immune-complex deposition, recapitulating many features of lupus nephritis. Accordingly, wild type (WT) and IL-17 receptorA<sup>−/−</sup> (IL-17RA<sup>−/−</sup>) mice were subjected to AGN and evaluated for the development of kidney pathology over a period of 14 days. We also test the therapeutic efficacy of neutralizing IL-17 in AGN induced WT mice.

**Results:** We showed that IL-17RA signaling is critical for the development of renal pathology. Despite normal systemic autoantibody response and glomerular immune-complex deposition, IL-17RA<sup>−/−</sup> mice exhibit diminished influx of inflammatory cells and kidney specific expression of IL-17 target genes correlating with disease resistance in AGN. IL-17 enhanced the production of pro-inflammatory cytokines and chemokines from tubular epithelial cells. Finally, we were able to show that neutralization of IL-17<sup>−/−</sup> mediated renal pathology in wild type mice following AGN.

**Conclusion:** These results clearly demonstrated that IL-17RA signaling significantly contributes to renal tissue injury in experimental AGN. Additionally, it also suggested that blocking IL-17<sup>−/−</sup>LR signaling may be a promising therapeutic strategy for the treatment of AGN associated with SLE, which may have ramifications in other autoimmune kidney disorders.

Disclosure: P. Biswas, None; K. Ramani, None; K. Mears, None; A. Huppier, None; S. L. Gaffen, None.

**1033**

**Stat3 Promotes IL-10 Expression in SLE T Cells through Trans-activation and Chromatin Remodeling.** Christian Hedrich<sup>1</sup>, Thomas Rauer<sup>2</sup>, Sokratis Apostolidis<sup>3</sup>, Alexandros P. Grammatikos<sup>4</sup>, Noe Rodriguez<sup>5</sup>, Christina Ioannidis<sup>6</sup>, Vasilios C. Kytaris<sup>7</sup>, Jose C. Crispin<sup>8</sup> and George C. Tsokos<sup>9</sup>. 1Children’s Hospital, Dresden, Germany, 2BIDMC, Harvard Medical School, Boston, MA, 3BIDMC, Boston, MA, 4Beth Israel Deaconess Medical Center, Boston, MA, 5Beth Israel Deaconess Medical Center/Boston Medical School, Boston, MA.

**Background/Purpose:** IL-10 is an immune-regulatory cytokine that is expressed by a wide range of cells and tissues. It plays a central role in the
Therapeutic Potential of Targeting Sialic Acid Modified Receptors in Osteoarthritis. Maria Dolores Mayan1, Paula Carpintero-Fernández1, Raquel Gago-Fuentes1, Marta Varela-Eirin1, Gary S. Goldberg2 and Francisco Javier Blanco3. 1Cartilege Biology Research Group, Rheumatology Division, INIBIC-Hospital Universitario De La Coruña, A Coruña, Spain, 2Department of Osteological Medicine, School of Medicine, Stratford, Canada, 3Department of Molecular Biology, School of Osteopathic Medicine, Stuttgart, Germany.

Background/Purpose: Glycosylated proteins are essential components of the extracellular matrix (ECM) of cartilage and contribute to the maintenance of its function. A shift from α-2,6- to α-2,3-linked sialic acids of glycoproteins modifies the binding ability of proteins to substrates, influencing cellular anchoring and affecting signal transduction. Intriguingly, the predominance of α-2,3-sialylation of chondrocytes glycoproteins was associated with the pathophysiology of rheumatic diseases including rheumatoid arthritis (RA) and osteoarthritis (OA). A highly O-glycosylated protein with α-2,3-sialic acid, involved in the induction of inflammation and tissue repair, is the transmembrane mucin receptor named Podoplanin (PDPN). The present study aimed to assess the effect of specifically targets a-2,3-sialic acid residues with a lectin-based drug (MASL) on chondrocyte dedifferentiation and cartilage breakdown processes.

Methods: For immunofluorescence and immunohistochemistry assays, in situ cartilage was fixed and frozen immediately using Tissue-Tek O.C.T. and isopentanol in liquid nitrogen. Primary cells in monolayer culture were fixed with formaldehyde for optical microscopy assays. 4mm cartilage punches were prepared from cartilage explants that were cut in the operating room immediately after surgery and cultured in DM EM with 0.1% FCS. Chondrocytes were isolated from articular cartilage and cultured in DM EM with 15% FCS. Cell viability was evaluated by the colorimetric MTT assay. Cell adhesion and growth was assessed with fibrinogen-coated well plates and Wound Healing Assay Kit. Reactive oxygen species levels were measured by DCFH-DA and by flow cytometry. RNA was isolated with TRIzol® Reagent and analyzed by Real-Time RT-PCR.

Results: The treatment of chondrocytes with 400 and 720 nM of MASL did not affect cell viability, adhesion or growth. To mimic pathological conditions, cells and cartilage explants were treated with 5 μM oligomycin. Treatment of chondrocytes with oligomycin did not affect cell viability but increased ROS levels over 10 fold and MMP3, IL-6 and COX2 mRNA levels over 3-10 folds. The treatment of cells with MASL effectively protected chondrocytes from ROS production when incubated in the presence of oligomycin. Moreover, oligomycin induced the expression of inflammatory cytokines including IL-6 and COX2, and this induction was reverted by treatment with nanomolar concentrations of MASL. 5 μM/μL of oligomycin for 7 days decreased safranin uptake and disrupted the ECM structure of cartilage punches as evidenced by ulceration increasing lacunae space. However, the presence of 400 nM of MASL prevented the cartilage destruction and inhibited COX2 and MMP3 induction by oligomycin treatment. Immunohistochemistry assays revealed that OA cartilage contained significantly higher levels of PDPN protein in comparison with cartilage from healthy donors.

Conclusions: This study demonstrates that physiologically relevant concentrations of MASL protect chondrocytes from detrimental effects of ROS, inflammatory cytokines and MMPs and preserve chondrocyte phenotype and articular cartilage structure under pathological conditions.
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Synergism Between GM-CSF and IL-17 Causes Enhanced Joint Pathology Via the Production of IL-6 and IL-23.

Tateishi, None; Walgreen, None; 1037

Kawasaki, None; M. Bennink, None; Monique M. Helsen, Liduina van den Bessel1a, Ian P. Wicks, Wim B. van den Berg1, Fons A. van de Loo1 and Marije I. Koenders1. 1Radboud university medical center, Nijmegen, Netherlands, 2The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

Background/Purpose: T-helper-17 (Th17) cells are important mediators of inflammatory diseases, and are the main pathogenic cell type in many animal models of autoimmunity. Recent studies highlight a surprising role for T-cell derived granulocytemacrophage colony stimulating factor (GM-CSF) in the pathogenicity of Th17 cells. We examined the mechanism by which interleukin 17 (IL-17) and GM-CSF contribute to cartilage- and bone damage of synovial joints during experimental arthritis, and investigated their potential additive and synergistic effects to provide a rationale for combination therapy in auto-inflammatory conditions.

Methods: Collagen-induced arthritis (CIA) was elicited in DBA/1J mice. Neutralizing antibodies to IL-17 and/or GM-CSF were administered after onset of disease for 14 days. Arthritis progression was followed by macroscopic scoring of the paws (maximum score of 12 per mouse). In addition, the effect of local over-expression of IL-17 and/or GM-CSF was studied by adenoviral transfection in naive knee joints. Joint pathology was studied by X-ray and histology, and Luminex and QPCR were performed to determine cytokine and chemokine expression.

Results: Combined therapeutic treatment of mice early after the onset of CIA ameliorated disease progression. Macrophage joint inflammation was significantly reduced, from a total score of 5.6±0.4 for mice treated with isotype control antibodies to 2±0.6 for mice treated with combination therapy. Treatment with anti-IL-17 or anti-GM-CSF alone resulted in scores of 3.4±0.5 and 3.5±0.4, respectively. Simultaneous blocking of GM-CSF and IL-17 was also the most effective treatment in the prevention of radiological bone damage and histological cartilage destruction.

To provide further insight in local additive or synergistic effects of IL-17 and GM-CSF, overexpression of IL-17, GM-CSF or the combination was achieved with adenoviral vectors. Inflammatory infiltrate and cartilage- and bone damage developed in all groups from day 1 after adenoviral transfer, with the most severe effect observed in the combination group. On day 7, partial destruction of joint architecture was apparent in knee joints after combined overexpression of IL-17 and GM-CSF. Overexpression of GM-CSF alone induced IL-17, which production was elevated by IL-17. Interestingly, overexpression of IL-17 alone caused a clear increase in synovial IL-6 production (179±63pg/ml), which was dramatically enhanced in the presence of GM-CSF (1.9±0.4ng/ml). In addition, a strong synergistic effect of combined overexpression was seen on the Th17 differentiation factor S458.

Conclusion: Our results demonstrate that the combined presence of IL-17 and GM-CSF causes aggravated joint damage through synergistic effects on inflammatory mediators in the synovial joints. In view of the moderate success of therapeutic IL-17 or GM-CSF blockade in rheumatoid arthritis, combined inhibition of IL-17 and GM-CSF might be an interesting alternative option for RA patients that do not fully respond to inhibition of the separate cytokines.

Disclosure: A. E. M. van Nieuwenhuijze, None; D. M. Roeleveld, None; B. Walgreen, None; M. Bennink, None; M. M. Helsen, None; I. P. Wicks, None; W. B. van den Berg, None; F. A. van de Loo, None; M. I. Koenders, None.

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Anti-MDA5 Antibody Associated Myositis Compared to DM Patients: A Distinct Muscular Pattern Associated with a Shared IFN Signature.

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Background/Purpose: Anti-MDA5 auto-antibodies are thought to be specifically associated with dermatomyositis (DM). Nevertheless anti-MDA5 auto-antibody positive patients (MDA5+ DM) predominantly suffer from extra-muscular involvement with severe interstitial lung disease, and arthritis. Further, skin lesions may be atypical with skin ulcers and mechanics’ hands. Importantly, clinical signs of myopathy are rather mild or absent and morphology and immunology of skeletal muscle tissue has not been studied yet. Thus, the previously described characteristic ‘IFN signature’ in classical DM may not be found in MDA5+ DM patients. We aim to describe the histological pattern of the skeletal muscle and the intrinsic immune response in MDA5+ DM patients.

Methods: Muscle specimens were subjected to conventional staining and immunohistochemical analysis to describe muscle fibers, vessel morphology and inflammatory features. Morphometry of vessels was performed using image software on digitally completely scanned slides and by electron microscopy. A panel of six interferon stimulated genes (ISGs) (OAS1, OAS3, IRF15, MX1, RIG1 and MDA5), involved in the IFN immune response were tested by quantitative PCR in muscle biopsie (results expressed as normalized fold change relative to a normal muscle). The median fold change of the six ISGs, was used to create an IFN score. Results: Compared to anti-MDA5 auto-antibody negative DM patients (based on ENMC criteria). Serum level of IFN-α was tested using a biossays.

Results: In MDA5+ DM patients (n=9) the mean MRC-score (five score) of the weakest muscular group was 4.5±0.5 and CK levels were 498±809 IU/l. Muscle biopsies (n=10) were analyzed compared to MDA5- DM patients (n=7). Histological analysis showed that anti-MDA5+ patients did not present the classical feature of perifascicular fiber atrophy. Inflammation was focal in the perimysium and mainly perivascular but significantly less intense as it is shown by density scores of CD45+ leukocytes (35.8±28 vs. 5.9±7.6 cells/mm²; p=0.05). MHC-class I staining was also less intense and more focal compared to MDA5- DM patients who harboured a diffuse staining pattern with a perifascicular re-inforcement. MDA5+ DM patients did not show signs of capillary loss since the capillary density was 279±17.7/mm² vs. 340.9±16.5/mm² (p=0.05) in MDA5- DM patients. In the same line the frequency of enlarged capillaries (diameter >10μm) was decreased (3.8±1.1% vs. 13.9±2.3%). Tubulero-bulbar formations were observed in only 50% of MDA5+ patients, but in all cDM patients. In MDA5+ DM patients a strong up-regulation of ISGs expression was observed with QPCR values ranging from 74.5±17.2 to RIG1 to 1107±406 for ISG15 even though, the IFN score was less increased than in controls (139.5 vs 634; p=0.005). Finally IFN-α serum levels were increased in all active MDA5+ DM patients (n=2).

Conclusion: These results show that myositis in patients with anti-MDA5 Ab positivity shows a distinct morphological pattern compared to MDA5- DM patients, but is associated with an IFN signature as well, underlining the importance of this pathway in the pathogenesis of both entities.

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Macrophage-Fibroblast Crosstalk Pathways Amplify RA Joint Pathology.


Background/Purpose: Macrophages and synovial fibroblasts represent key cellular drivers of RA. The goal of this study was to define how the complex cellular programs of macrophages and fibroblasts crossregulate within an inflammatory setting and potentially perpetuate pathologic responses. Previously, we have shown that soluble synovial fibroblast products...
suppress the macrophage TNF-induced Type I Interferon response. Here through a next-gen sequencing transcriptomic analysis, we describe on a global scale how the macrophage TNF-a response is reshaped by synovial fibroblast factors, ultimately converting classic anti-inflammatory/resolution pathways into programs that feedback to support fibroblast growth and function. Furthermore, macrophages isolated directly from RA synovium indeed activate a subset of these gene expression networks, suggesting these macrophage-fibroblast crosstalk pathways represent novel therapeutic targets.

Methods: Human blood derived macrophages and human RA synovial fibroblasts were co-cultured in transwell plates and treated with TNF for 2 days. The transcriptomes of both cell types were analyzed by RNA sequencing (RNA-seq). Pathway analysis programs identified macrophage responses specifically controlled by synovial fibroblasts, as well as identified candidate soluble crosstalk mediators. Cellular STAT3 activity was monitored by Western blot detection of phospho-STAT3 levels and by qPCR analysis of STAT3-dependent genes, while the soluble mediators responsible for inducing differential STAT3 responses were confirmed with neutralizing antibodies in the culture media.

Results: Synovial fibroblasts modified specific programs within the macrophage inflammatory response, impacting 30% of TNF-regulated genes. Pathway analysis demonstrated fibroblast factors largely transformed macrophage lipid programs and induced growth factor responses, including genes known to promote wound healing activities and growth of fibroblasts. Interestingly, while TNF-a alone induced an anti-inflammatory STAT3 response, TNF-a combined with fibroblast factors blocked this resolution response and instead diverted STAT3 activity towards mitogenic and metabolic pathways. Furthermore, initial analysis of synovial macrophages isolated directly from RA synovium revealed a subset of the crosstalk pathways identified in the in co-culture system including specific growth factor responses.

Conclusion: We propose the combination of inflammatory and fibroblast-derived factors found in the RA synovium drive macrophages into an unresolved novel macrophage phenotype that in part functions to feedback and support synovial fibroblast pathologic activity.

Disclosure: L. T. Donlin, None; J. Ding, None; L. B. Ivashkiv, None.

1039 Interleukin-20 Is Triggered By TLR Ligands and Associates with Rheumatoid Arthritis Disease Activity. Ladislav Senolt1, Klara Prajzlerova2, Hana Hulejova3, David Vejgl and Karel Pavelka1 and Jiri Vencovsky1.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation and subsequently joint damage with systemic manifestations. Interleukin-20 (IL-20) has been previously identified as a pro-inflammatory cytokine that may be implicated in the pathogenesis of chronic inflammatory diseases, particularly RA (1). Recently, phase 2a trial (2) demonstrated that treatment with anti-IL-20 monoclonal antibody significantly reduced disease activity in seropositive patients with RA. Therefore, the aim of the current study was to characterize the role of IL-20 in patients with RA.

Methods: The levels of serum and synovial fluid IL-20 were measured by ELISA assay in 34 patients with RA (25 female) and 35 patients with OA (19 female). Disease activity was assessed based on the Disease Activity Score of 28 joints (DAS28). The expression of IL-20 in synovial tissue samples from patients with RA (n=5) and OA (n=7) were determined by immunohistochemistry. Secretion of IL-20 was analysed in human peripheral blood mononuclear cells (PBMCs) isolated from blood of patients with RA (n=8).

Results: The expression of IL-20 was significantly up-regulated in RA compared with OA synovial tissue, particularly in the lining (2.6±0.65 vs 0.93±0.19; p=0.003) as well as in the inflammatory infiltrates of the sublining layer (2.2±0.57 vs 0.37±0.36; p=0.005). The levels of IL-20 in synovial fluid were significantly higher in patients with RA compared to those with OA (86.3±87.5 vs 41.9±43.3 pg/ml; p=0.01). IL-20 production from PBMCs was induced by Poly I:C (TLR-3 ligand) (p=0.0001) and LPS (TLR-4 ligand) (p=0.0008), but not with pro-inflammatory cytokines such as TNF-a (p=0.09) or IL-1 (p=0.74).

In contrast to local sites of inflammation, serum levels of IL-20 in RA patients were comparable to those in OA patients (41.7±48.7 vs 32.3±45.4 pg/ml; p=0.04), and significantly correlated with DAS28 (r=0.58; p=0.001) and anti-CCP levels (r=0.36; p=0.045). When adjusted for anti-CCP levels, correlation with DAS28 remained still significant (r=0.540; p=0.002).

Conclusion: Our data show that IL-20 is independently associated with RA disease activity and may be triggered by TLR ligands at local sites of inflammation. A association between IL-20 and anti-CCP levels may, at least partially, explain disease activity improvement after the treatment with anti-IL-20 monoclonal antibody in seropositive RA patients.


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1040 Dysregulated Serum Interleukin 16 Concentration Associated with Clinical Disease Activity in Patients with Rheumatoid Arthritis Is Efficiently Corrected By Immunological Intervention. Atsuko Murata1, Katsuya Suzuki1, Yoshiaki Kassai2, Takahiro Miyazaki3, Rimpei Morita4, Akihiko Yoshimura4 and Tsutomu Takeuchi1. 1Keio University School of Medicine, Tokyo, Japan, 2Takeda Pharmaceutical Company, Fujisawa, Japan, 3Takeda Pharmaceutical Company Limited, Kanagawa, Japan, 4Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: IL-16 is a chemoattractant factor that evokes massive infiltration of mononuclear cells in the synovial tissue in patients (pts) with rheumatoid arthritis (RA). IL-16 concentrations are elevated in RA synovial fluid and also sera. However, the effect of current pharmaceutical intervention on this key cytokine and its association with clinical outcome are not fully understood. The purpose of this study was to clarify the effects of various treatments on IL-16 and the role in RA pts.

Methods: The study enrolled consecutive RA pts who met the 1987 or 2010 RA classification criteria as well as pts with primary Sjogren’s syndrome (pSS) and healthy controls (HC). Serum IL-16 and other proteins’ concentrations in these groups were measured by quantitative proteomics assay using nuclear acid aprotamers. Levels of IL-16 in RA pts were measured at baseline and 12 weeks after treatment with MTX or three different biologics (infliximab (IFX), tocilizumab (TCZ), and abatacept (ABT)). Statistical differences were assessed using two-tailed t-test.

Results: Serum IL-16 concentration was significantly increased in pts with untreated active RA (n=28) compared to the HC (n=30, p<0.0001) and pSS (n=30, p=0.0001) groups. IL-16 was positively correlated with serum anti-CCP (r=0.70, p=3.5E-05) in pts with untreated RA, but only weakly and negatively correlated with MMP-3 in pts with pSS (r = -0.31, p=0.095). IL-16 was significantly decreased during treatment for RA for 12 weeks in all 86 RA pts (Figure). On stratification, IL-16 was decreased in the MTX- (n=31), TCZ- (n=17) and ABT-treated (n=16) patients compared with the untreated RA pts (n=28). p = 0.0004 for all comparisons.

Disclosures: L. B. Ivashkiv, None.
groups, but did not change in the IFX-treated group (n=22). Regarding clinical disease activity, the decrease in IL-16 was positively associated with DAS28-CRP in the MTX (R = 0.48, p = 0.007), A BT (R = 0.60, p = 0.001), TCZ (R = 0.52, p = 0.06) groups. Furthermore, the decrease in IL-16 was positively correlated with a decrease in serum CRP in the MTX (R = 0.48, p = 0.007) and A BT (R = 0.54, p = 0.03) groups, which indicates a stronger association with CRP in the composite measure, except for the TCZ group. MM-P3 in the MTX, IFX and TCZ groups was also significantly decreased at 12 weeks. In contrast, the decrease in IL-16 with treatment was not correlated with that of MMP-3, unlike the case with untreated RA at baseline.

Conclusion: Treatment with MTX, TCZ and A BT for active RA ameliorated the dysregulation of serum IL-16. This correction was correlated with decreases of clinical disease activity and CRP, except for TCZ, but not correlated with MMP-3. The directional change in serum IL-16 with different interventions, especially with TCZ, may indicate the need to revise molecular abnormalities in RA.


1041 Imaging the Role of Chemoattractants in Inflammatory Arthritis. Yoshishige Miyabe, Thomas T. Murooka, Chie Miyabe, Nancy Kim, Thorsten Mempel and Andrew D. Luster. Massachusetts General Hospital, Charlestown, MA.

Background/Purpose: Inflammatory arthritis, including rheumatoid arthritis, is characterized by neutrophil recruitment into the diseased joint. Our previous studies and the work of others have demonstrated important roles for several neutrophil chemoattractant receptors, including the G protein coupled receptors BLT1 and CCR2, and the complement receptor C5aR in a murine model of immune-complex mediated arthritis. However, the precise role for each chemoattractant in the process of neutrophil recruitment into the inflamed joint remains unclear.

Methods: Multiphoton intravital microscopy (MP-IVM) was used to study the migratory behavior of wild-type and chemoattractant receptor-deficient leukocytes in the joint in the K/BxN serum transfer model of inflammatory arthritis. LysM-GFP mice in which endogenous neutrophils and macrophages express GFP were also used in these studies. Following the transfer of arthriticogenic serum, MP-IVM was performed to analyze neutrophil migratory behavior in the joint on day 1 (early phase of arthritis) and day 7 (established arthritis). We also analyzed the ability of WT and chemoattractant receptor-deficient neutrophils to enter the joint in short term adoptive transfer and homing assays on days 1 and 7 following arthritogenic serum transfer using MP-IVM.

Results: Analysis of neutrophil migratory behavior revealed that the number of neutrophils adhering to blood vessels of the joint and subsequently infiltrating into the inflamed joint was markedly increased on day 7 following arthritogenic serum transfer in WT LysM-GFP mice, compared to day 1 following serum transfer and compared to control untreated WT LysM-GFP mice. In short term homing assays, both WT and BLT1-deficient neutrophils rolled along current vessels in WT and BLT1-deficient mice, whereas neither of following serum transfer but did not adhere or enter the joint. In contrast, adoptive transfer of WT and BLT1-deficient neutrophils on day 7 following serum transfer into WT mice revealed that the number of BLT1-deficient neutrophils that adhered to and subsequently migrated into the joint was dramatically reduced compared to WT neutrophils. Furthermore, neither WT nor BLT1-deficient neutrophils entered the joints of BLT1-deficient host mice on days 1 or 7 following serum transfer.

Conclusion: BLT1 plays an important role in both the adhesion and transmigration of neutrophil across blood vessels of the joint during immune complex induced arthritis.

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1042 IL-1β and TNF-α Promote Monocyte Viability through the Induction of GM-CSF Expression By Rheumatoid Arthritis Synovial Fibroblasts. Charles E. Brion, Stuart-Laffitte-Laffitte, Maria Alice Brion, Frederic Blanchard, Dominique Heymann and Benoit Le Groff. INSERM, UMR 957, Nantes, France.

Background/Purpose: Macrophages and synovial fibroblasts (SF) are two major cells implicated in the pathogenesis of rheumatoid arthritis (RA). They can interact in the synovial micro-environment to drive inflammation and bone destruction. The aim of our work was to investigate the effects of SF on monocyte viability and differentiation and to determine which factors were implicated in these effects.

Methods: SF were isolated from synovial tissue of 9 RA patients and CD14+ cells were magnetically isolated from healthy donors by MACS technology. SF conditioned media were collected after 24 hours of culture with or without TNF-α or IL-1β. After 3 days of culture with RA SF conditioned media, monocyte survival was assessed using a WST-1 viability test. To study the involvement of M-CSF, IL-34 and GM-CSF, their expression was quantified in RA SF by qPCR in RA synovial fluids by ELISA assay, and specific blocking antibodies were used in monocyte cultures. Macrophages polarization after culture with RA SF conditioned media was studied by flow cytometry. The cell surface markers analyzed were CD14, CD68, CD163 (M1), CD200R (M2a) and CD163 (M2c). A non-parametric test (Kruskall Wallis) was used to perform statistical analyses.

Results: SF conditioned media significantly increased monocyte viability compared to cells cultured in medium alone (p<0.001). This effect was stronger when using conditioned media from IL-1β or TNF-α pre-stimulated SF. Monocyte viability was significantly increased compared to M-CSF (p<0.005) and M-CSF and IL-34 blocking antibodies, alone and in combination, had no effect on monocyte viability induced by SF conditioned media. In contrast, blocking GM-CSF resulted in a significant decrease in monocyte viability by 30% when added to the stimulated SF conditioned media (p<0.001). The expression of GM-CSF by RA SF was stimulated by TNF-α and IL-1β and GM-CSF expression was quantified in RA SF conditioned media by qPCR, in RA synovial fluids by ELISA assay, and specific blocking antibodies were used in monocyte cultures. Macrophages polarization after culture with RA SF conditioned media was studied by flow cytometry. The cell surface markers analyzed were CD14, CD68, CD163 (M1), CD200R (M2a) and CD163 (M2c). A non-parametric test (Kruskall Wallis) was used to perform statistical analyses.

Disclosure: C. Darrieutort-Laffitte, None; M. A. Boutet, None; M. Chatelais, None; R. Brion, None; F. Blanchard, None; D. Heymann, None; B. Le Groff, None.


Background/Purpose: Total hip replacement (THR) is a highly successful treatment for degenerative arthritis, alleviating pain and restoring joint function in the vast majority of patients. However, inflammatory reactions to polyethylene wear debris resulting from fretting of metal-on-metal (MoM) implants can lead to implant loosening and revision surgery. To avoid the adverse effects of polyethylene wear products, metal-on-metal bearings were introduced. Recent studies, however, have revealed an alarming rate of early revision surgery related to the development of adverse local tissue reactions (ALTR)
characterized by extensive and rapid necrosis of soft tissue surrounding implants with metal-on-metal (MoM) or dual modular neck (DMN) designs. We have used chemokine/cytokine profiling of synovial fluid and serum and gene expression analysis of peri-implant tissue to identify biomarkers for early detection and to gain insights into the pathogenesis of ALTR.

**Methods:** Synovial fluid and serum was collected from ALTR and osteolysis patients at revision surgery, and cell-free aliquots were prepared and immediately frozen. Antibody arrays were used to identify selected chemokines and cytokines and results confirmed by ELISA. For gene expression profiling, total RNA was prepared from peri-implant tissue using Trizol. RNA integrity was verified using an Agilent Bioanalyzer, and then subjected to microarray analysis (Affymetrix U133 2.0). Results: were verified using real time PCR.

**Results:** Synovial fluid from ALTR patients demonstrated elevated levels of several chemokines and cytokines compared to those seen in osteolysis patients, including the interferon gamma inducible chemokines MIG/CXCL-9 and IP-10/CXCL10. Levels of these factors were generally higher in the DMN ALTR patients than the MoM ALTR patients. More modest elevations of these chemokines were found in ALTR serum samples. Microarray analysis revealed a unique ALTR gene expression profile that was absent in arrays prepared from peri-implant tissues from patients with osteolysis. Pathway analysis identified a unique chemokine/interferon signature that mirrored the protein profile of synovial fluid.

**Table 1** Mean (Standard Deviation) levels of selected proteins in the synovial fluid and serum (in pg/ml). p-values are for comparison to the osteolysis group.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Osteolysis</th>
<th>ALTR-MoM</th>
<th>p-value (MoM)</th>
<th>ALTR-DMN</th>
<th>p-value (DMN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial Fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>1.320 (1.96)</td>
<td>178.442 (120.307)</td>
<td>8.46 E-6</td>
<td>68.803 (68.867)</td>
<td>2.52 E-3</td>
</tr>
<tr>
<td>IP-10</td>
<td>1.884 (0.344)</td>
<td>100.137 (78.138)</td>
<td>9.32 E-5</td>
<td>32.829 (30.575)</td>
<td>2.02 E-3</td>
</tr>
<tr>
<td>IL-4</td>
<td>976 (786)</td>
<td>28.583 (28.481)</td>
<td>1.53 E-3</td>
<td>16.102 (21.768)</td>
<td>2.10 E-2</td>
</tr>
<tr>
<td>IL-8</td>
<td>6.621 (12.820)</td>
<td>64.172 (36.125)</td>
<td>2.21 E-3</td>
<td>54.338 (41.980)</td>
<td>1.32 E-3</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>273 (163)</td>
<td>592 (332)</td>
<td>1.48 E-3</td>
<td>456 (279)</td>
<td>0.033</td>
</tr>
<tr>
<td>IP-10</td>
<td>17.4 (8.8)</td>
<td>25.7 (29.5)</td>
<td>0.31</td>
<td>32.3 (31.6)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

**Conclusion:** Expression profiling of peri-implant tissues from ALTR patients reveals a unique chemokine/cytokine gene signature. The corresponding gene products are detectible in synovial fluid and serum, indicating their potential utility as biomarkers for early diagnosis and monitoring of patients at risk for ALTR. In addition, pathway analysis reveals up-regulation of genes involved in lymphocyte trafficking and activation, providing insights into disease pathogenesis and importantly identifies potential therapeutic targets to prevent this devastating complication.

**Disclosure:** E. Purdue

**Tertiary Lymphoid Organ Developmental Program: Divergent Paradigm of Lymphoid Organogenesis.** Saba Nayar1, Bridget Glaysher1, Joana Campos3, Jorge Caamano2, David W threats1, Kai Toellner1, Sanjiv Luther3, Mark Coles3, Christopher Buckley3 and Francesca Barone4. 1University of Birmingham, Birmingham, United Kingdom, 2University of York, York, UK, 3Losanne University, Epalinges, Switzerland, 4University of York, York, United Kingdom, 5The University of Birmingham, Birmingham, United Kingdom.

**Background/Purpose:** Tertiary lymphoid organs (TLOs) represent the histological hallmark of many immune-mediated inflammatory diseases. TLOs are characterized by a functional leukocyte aggregation and network of lymphoid-like stromal cells (LLSc). LLSc express lymphoid chemokines (CXCL13, CCL19, and CCL21), survival factors (BAFF and IL-7), lymphoid markers and adhesion molecules (gp38, RANKL, ICAM-1 and VCAM-1) that locally support lymphocytes survival and organization in ectopic sites areas.

**Methods:** We have used a combination of in vitro and in vivo approaches in two models of TLO formation to address the dynamic of stromal cell activation within TLOs.

**Conclusion:** We demonstrated that the acquisition of this lymphoid phenotype by the non-activated resident stroma requires a multistep process, fundamentally different from that responsible for secondary lymphoid organ formation. We showed that early, during TLO formation, IL-4 receptor engagement via IL-13 on quiescent tissue-resident fibroblasts induces LLSc priming and mediates the up-regulation of gp38 and lymphoid-associated adhesion molecules. Expansion of this activated lymphoid stroma requires IL-22/IL-22R mediated signaling. Lack of IL-22 or its receptor induces defective LLs proliferation, abrogation of CXCL13 expression and TLO involution. Finally we demonstrated that, similarly to secondary lymphoid organ, stabilization of the stroma to a functional lymphoid phenotype requires lymphocyte infiltration and lymphoblast beta expression. This work highlights critical differences between the embryonic program responsible for SLO formation and the inflammatory development of TLOs and unveils novel potential targets for TLO targeting.

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**1046 Modulatory Effect of Adiponectin on Apoptosis and Proliferation of Synovial Fibroblasts from Rheumatoid Arthritis Patients.** Wenfeng Tan1 and Miaojiang Zhang1. 1The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, 2the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA, 3the First affiliated hospital with nanjing medical university, nanjing, China.

**Background/Purpose:** We previously reported that adiponectin (AD) is highly expressed in the inflammatory joint of rheumatoid arthritis (RA)
patients and closely correlated with progressive bone erosion, but the mechanism remained largely unclear. Synovial fibroblasts from RA patients (RAFSs) have been suggested a unique characteristic of resistance to apoptosis that contributes to synovial hyperplasia, synovitis and bone erosion in RA. In this study, we tested the role of AD on apoptosis and proliferation in primary RAFSs.

**Methods:** RAFSs was treated with PBS in the absence and presence of AD (0.1, 1 or 10 \(\mu\)g/ml) for 4 h to 72 h and the frequencies of apoptosis cells were measured by flow cytometry. CCK-8 and direct microscopic count were also used to analyze the proliferation of RAFSs after stimulation with AD. Real-time PCR was used to test the expression of Bcl-2, Bax, p53, CDK4, PCNA, IL-6, IL-8 and MMP-3 mRNA in RAFSs. Western blot was used to test the protein expression of Bcl-2 and Bax and activation of signal transduction pathways.

**Results:** The frequencies of apoptosis cells were significant decreased in RAFSs after AD stimulation. AD could promote proliferation of RAFSs compared with untreated AD, a markedly increased CDK4 and PCNA mRNA expression and decreased level of p53 mRNA were observed in RAFSs treated with AD. The levels of IL-6, IL-8 and MMP-3 expression also significantly increased in RAFSs upon AD stimulation. Western blot indicated that AD could rapidly triggered p-Akt and p-ERK activity and then induced Bcl-2, but decreased Bax expression in RAFSs.

**Conclusion:** Our findings indicate that AD could affect apoptosis and proliferation of RAFSs via Akt and ERK pathway, suggesting a critical role of AD on disease progression in RA.

**Disclosure:** W. Yu, None; W. Tan, None; M. Zhang, None.

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**Type I and II Interferon Signatures in Sjögren’s Syndrome: Contributions in Distinct Clinical Phenotypes and Sjögren’s Related Lymphomagenesis.** Adriano Nezios, Fotini Gravani, Efstathia K. Kapsogeorgou, Michael Voulgarides, Haralampos M. Moutsopoulos, Mary K. Crow and Clio Mavragani. School of Medicine, University of Athens, Athens, Greece. General Hospital of Athens ‘G. Gennimatas’, Athens, Greece. School of Medicine, National University of Athens, Athens, Greece. Hospital for Special Surgery, New York, NY.

**Background/Purpose:** Both type I and II interferons (IFNs) have been implicated in the pathogenesis of Sjögren’s syndrome (SS). We aimed to explore the contribution of type I and II IFN signatures in the generation of distinct SS clinical phenotypes including non-Hodgkin’s lymphoma (NHL) development, a major SS complication.

**Methods:** Peripheral blood from SS patients (n = 31), SS patients complicated by lymphoma (SSL, n = 13) and healthy donors (HD, n = 30) were subjected to real-time polymerase chain reaction for interferon inducible genes. The same analysis was performed in minor salivary gland tissues (MSG) derived from 31 SS patients, 10 SSL patients and 17 sicca controls (SC).

**Results:** In peripheral blood and MSG tissues, overexpression of both type I and II IFIGs was observed in SS patients versus HD and SC, with a predominance of type I IFN signature in peripheral blood and a type II IFN signature in MSG tissues. SS patients with salivary gland enlargement, lymphopenia, anti-Ro/SSA antibodies and hypergammaglobulinemia exhibited higher type I IFN scores in peripheral blood compared to their counterparts without those features. Hypergammaglobulinemia was also associated with increased type II IFN scores in peripheral blood. In MSG tissues derived from SSL patients we observed lower IFN \(\gamma\)/IFN \(\alpha\) ratio in MSG tissues showed the best discrimination for lymphoma development, with an area under the curve of 0.88 (95% CI: 0.72–1.00, p-value: 0.001).

**Conclusion:** Discrete expression patterns of type I and II IFN signatures might be related to distinct clinical SS features and SS related lymphomagenesis.

**Disclosure:** A. Nezios, None; F. Gravani, None; E. K. Kapsogeorgou, None; M. Voulgarides, None; H. M. Moutsopoulos, None; M. K. Crow, None; C. Mavragani, None.

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**1048**

**Oncostatin M Suppresses Activation of IL-17/Th17 Via Suppressor of Cytokine signaling3 (SOCS3) Regulation in CD4+ T Cells.** Young Ok Jung, Seon Yoon Lee, Sung Yoon Lee, Mi-La Cho and Hea-Jin Son. Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea. Catholic University of Korea, Seoul, South Korea. Hallym University Sacred Heart Hospital, Gyeonggi-do, South Korea. Rheumatism Research Center, Catholic Institutes of Medical Science, The Catholic University of Korea, Seoul, South Korea.

**Background/Purpose:** Oncostatin M (OSM) is a pleiotropic cytokine that belongs to the interleukin(IL)-6 group of cytokines. High level of OSM was detected in synovium of rheumatoid arthritis (RA) patients but its exact role in arthritis perpetuation has not been elucidated. We evaluated the role of OSM in T helper 17(Th17) cell differentiation, the most important cells in arthritis development.

**Methods:** Collagen-induced arthritis (CIA) was induced in DBA/J mice. IL-2 immune complex(IC) were injected intraperitoneally three times at 2days intervals before 1st immunization. Severity of arthritis was assessed by clinical scoring of arthritis. CD4+ T cells were isolated by MACS and incubated in Th17 differentiation condition with and without OSM. The levels of cytokines were measured using ELISA. To analyze intracellular cytokine were analyzed by FACS. Subpopulations of T cells of spleens were assessed by confocal microscopy. The mRNA levels of OSM and signaling molecules were determined by RT-PCR and real time PCR. The protein levels were measured by Western blot. Suppressor of cytokine signaling3 (SOCS3) small interfering RNA(siRNA) was transfected by using the Amaxa 4D-nucleofector X unit (Lonza, Cologne, Germany).

**Results:** IL-21C treatment reduced the clinical arthritis score and OSM and SOCS3 were increased in splens of IL-21C treated mice. We observed that OSM suppressed Th17 cell differentiation and the levels of IL-17 and IL-21 were decreased in dose dependent manner in vitro. OSM time dependently increase the level of STAT3, STAT5 and SOCS3 in mRNA and protein levels. STAT21, the STAT3 inhibitor, abrogated the suppressive effect of OSM on Th17 differentiation. SOCS3 siRNA also abrogated the suppressive effect of OSM.

**Conclusion:** OSM was up-regulated spleens of IL-21C treated mice. OSM suppressed the Th17 cell differentiation and the inhibitory effects of OSM on Th17 cells were via SOCS3 regulation.

**Disclosure:** Y. O. Jung, None; S. Y. Lee, None; S. Y. Lee, None; M. L. Cho, None; H. J. Son, None.

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**1049**


**Background/Purpose:** Development of rheumatoid arthritis (RA) is associated with different genetic and environmental factors. We postulate that cow milk could be such an environmental trigger and a recent prospective study of Lu et al. (Arthritis Care Res 2014;66(6):802-9) suggests that frequent milk consumption is associated with reduced OA progression in women. Human breast milk contains many components to promote development of neonatal immune competence, such as cytokines, antibodies and immune cells. More recently, exosomes were identified in both bovine and human breast milk. Exosomes are small vesicles recently rediscovered as an important part of intercellular communication. Milk exosomes are known to carry immunoregulatory microRNAs and cytokines, thereby enhancing the antimicrobial defense in newborns. It is however unknown whether exosomes are present in commercial milk and whether they are bioactive.

**Methods:** By differential ultracentrifugation, followed by ExoQuick isolation, we isolated exosomes from commercial milk. NanoSight analysis was performed to estimate vesicle size (0120nm) and concentration (approx. 1013 exosomes per ml). The expression of milk-derived mRNA and microRNA was confirmed by RT-qPCR. Exosomes were acidified at a gastrointestinal pH2 to test their stability. Cellular uptake of PKH-67 labeled exosomes was analyzed by confocal microscopy and flow cytometry. TGFB levels were measured with a CAGA-fLuc reporter construct. Naïve T cells were cultured for 5 days with an inflammatory cocktail in the presence of milk exosomes, to induce Th17 differentiation. ROR-yt and IL-17 expression levels were determined by RT-qPCR.

**Disclosure:** W. Yu, None; W. Tan, None; M. Zhang, None.
**Results:** We found clear levels of messenger- and miRNAs (e.g. miR-let-7a, 124a) in cow milk exosomes. Sucrose gradient followed by electron microscopy revealed an exosome-like morphology. We showed cellular uptake of exosomes in vitro by murine macrophages. Splenic antigen presenting cells and non-phagocytic fibroblasts. To test the stability of these vesicles, we used a luciferase reporter assay to measure in vitro NFκB activation. A ciliation, up to gastric acid level kept the exosomes intact, and did not alter the inhibitory effect they had on NFκB activation. A 1μl TGFβ was detected using CAGA-fluc reporter cells and blocked by addition of anti-TGFβ1,2,3 antibodies. More importantly, incubation of naïve T cells with milk exosomes in the presence of an inflammatory cytokine cocktail induced significant Th17 differentiation.

**Conclusion:** We clearly showed that commercial milk contains stable exosomes, which are resistant to acidification. These vesicles can facilitate Th17 differentiation and could therefore play an important role in auto-immune disorders, such as rheumatoid arthritis. To our knowledge, this is the first study to show that commercial milk contains immunoregulatory exosomes with active TGFβ. Our data suggest that bovine milk-derived exosomes, carrying immunoregulatory cargo, could remain intact in the gastrointestinal tract and therefore reach the circulation. This warrants further research to determine their biological effect in both healthy individuals and patients with autoimmune diseases.

**Disclosure:** B. C. H. Pieters, None; O. J. Arnzt, None; M. G. A. Broeren, None; A. van Caam, None; P. M. van der Kraan, None; M. de Vries, None; F. A. J. van de Loo, None.

**1050**

**A Role for Purinergic Receptor Signalling in Basic Calcium Phosphate Crystal-Induced Inflammation.** Clare C. Cunningham1, Emma M. Corr2, Geraldine M. McCarthy3 and Aisling Dunne. 1Trinity College Dublin, Dublin 2, Ireland, 2Mater Misericordiae University Hospital, Dublin 7, Ireland.

**Background/Purpose:** Basic calcium phosphate (BCP) crystals are uniquely associated with osteoarthritides (OA). They are found in the majority of affected joints and closely correlate with the extent of joint destruction, suggesting a pathogenic role in driving disease. They have been shown to induce pro-inflammatory cytokine production and activate synovial fibroblasts. Released nucleotides such as ATP and UTP from osteocytes which then activate mechanical stress and activation of purinergic receptors drives the release of nucleotides such as ATP and UTP from osteocytes which then activate signalling pathways that can negatively impact bone remodelling. It has also been proposed that particulate matter such as alum and monosodium urate (MSU) crystals drive interleukin-1 production via ATP release and purinergic signalling. Furthermore, it has been reported that the P2Y6 receptor and its downstream signalling molecule phospholipase C (PLC) mediate the inflammatory responses induced by MSU crystals. In this study, we sought 1) to determine whether BCP crystals induce the release of ATP from murine macrophages and 2) to investigate the role of purinergic signalling in BCP-induced inflammation in order to identify novel targets for the treatment of BCP-related arthropathies, such as OA.

**Methods:** Murine macrophages were stimulated with BCP crystals over the course of 5 hours, and ATP release was measured using the ATPlight luminescence assay system. BCP crystals are known to drive IL-1β production in vitro. Therefore in order to investigate the role of purinergic receptors in BCP-induced cell activation, murine macrophages were primed with lipopolysaccharide, a toll-like receptor agonist prior to treatment with the broad-spectrum P2 receptor inhibitor oATP, the P2Y6-specific inhibitor MRS2578, or the PLC inhibitor U73122. Alternatively, siRNA was used to knock down the expression of P2Y6. The cells were then stimulated with BCP crystals and IL-1β production was quantified by enzyme linked immunosorbent assay (ELISA).

**Results:** We have found that physiological concentrations of BCP crystals (50μg/ml) induce the release of approximately 100 nM ATP by murine macrophages, a concentration sufficient to activate purinergic receptors. Inhibition of the P2Y6 receptor or PLC dose-dependently reduced IL-1β production following BCP stimulation, with full abrogation observed with the top dose of each inhibitor. Furthermore a 40% knockdown of the P2Y6 receptor led to an equal reduction in BCP-induced IL-1β production.

**Conclusion:** Based on these studies we propose that nucleotides released from BCP-activated cells act in an autocrine or paracrine manner via purinergic receptors to enhance BCP-induced inflammation. Released nucleotides may also act on neighbouring osteoblasts/osteoclasts to impact on bone remodelling.

**Disclosure:** C. C. Cunningham, None; E. M. Corr, None; G. M. McCarthy, None; A. Dunne, None.

**ACR/ARHP Poster Session B**

**Epidemiology and Public Health (ACR): Rheumatoid Arthritis and Systemic Lupus Erythematosus Outcomes**

**Monday, November 17, 2014, 8:30 AM-4:00 PM**

**1051**

**Rates of Renal Remission with Immunosuppressives in Lupus Nephritis: A Systematic Review and Network Meta-Analysis.** Jasvinder Singh1, Ahmed Kobt2, Amolqir Hossain3, Amy M. Oudano4 and George Wells4. 1University of Alabama at Birmingham, Birmingham, AL, 2University of Ottawa, Ottawa, ON, 3The University of Alabama at Birmingham, Birmingham, AL, 4University of Ottawa Heart Institute, Ottawa, ON.

**Background/Purpose:** To compare renal remission rates with immunosuppressives by performing a systematic review and network meta-analyses (NMA) of RCTs of lupus nephritis.

**Methods:** We performed a systematic review and NMA of randomized trials of patients with lupus nephritis, who were treated with immunosuppressives alone or in combination with other immunosuppressant or biologics (such as rituximab or belimumab) compared with another immunosuppressant with/without biologic or placebo. We compared the rates of complete renal remission or partial renal remission. Complete renal remission was usually defined as return to normal serum creatinine, urine protein ≤0.5 g/d, and inactive urinary sediment (<≤ 5 white blood cells per high-power field and ≤ 5 red blood cells per high-power field, and a reading of lower than 2+ on dipstick and absence of red cell casts). Partial remission was variably defined in the studies, with the most common definition of improvements in urinary parameters between 25–50%. Bayesian NMA were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using M markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

**Results:** 39 RCTs with 2,730 patients provided data; 35 were 2-arm RCTs and 4 were 3-arm RCTs. Comparisons showed that cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus (TAC), cyclosporine (CSA) and MMF + TAC were superior to prednisone alone in achieving renal remission (Table 1). Compared to MMF, CYC HD and PRED were less likely to lead to renal remission. Compared to AZA, TAC and MMF + TAC were superior. MMF + TAC was superior to MMF-AZA, CYC-AZA, CYC HD, CYC LD MMF + RTX and LEF in leading to renal remission.

**Conclusion:** Our NMA combined the ability of immunosuppressive medications and combinations to lead to remission (complete and/or partial) in RCTs of patients with lupus nephritis. Comparative effectiveness of medications is now available to assist treatment decision-making, with the caveat of trial heterogeneity and indirect comparisons.

**Table 1 Comparison of various drugs for the renal remission (complete or partial) in patients with lupus nephritis showing statistically significant results**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Odds Ratio (95% CrI)</th>
<th>Relative Risk (95% CrI)</th>
<th>Risk Difference % (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYC</td>
<td>PRED</td>
<td>2.0 (1.3, 3.0)</td>
<td>1.0 (1.0, 1.1)</td>
<td>29.7 (16.9, 40.7)</td>
</tr>
<tr>
<td>HMF</td>
<td>PRED</td>
<td>3.12 (1.5, 6.6)</td>
<td>1.79 (1.2, 2.7)</td>
<td>37.1 (19.4, 43.8)</td>
</tr>
<tr>
<td>TAC</td>
<td>PRED</td>
<td>1.39 (1.1, 1.8)</td>
<td>1.1 (1.0, 1.2)</td>
<td>22.0 (13.0, 31.7)</td>
</tr>
<tr>
<td>CYC</td>
<td>PRED</td>
<td>3.7 (2.5, 7.3)</td>
<td>1.4 (1.2, 1.7)</td>
<td>48.0 (32.2, 57.4)</td>
</tr>
<tr>
<td>CYC + HMF</td>
<td>PRED</td>
<td>2.78 (1.3, 5.6)</td>
<td>1.65 (1.1, 2.2)</td>
<td>57.0 (38.2, 70.7)</td>
</tr>
<tr>
<td>CYC LD</td>
<td>CYC</td>
<td>4.7 (3.8, 7.7)</td>
<td>1.3 (1.0, 1.6)</td>
<td>24.7 (17.4, 31.0)</td>
</tr>
<tr>
<td>PRED LD</td>
<td>CYC</td>
<td>3.02 (1.5, 5.7)</td>
<td>1.23 (0.95, 1.5)</td>
<td>18.8 (8.0, 29.6)</td>
</tr>
<tr>
<td>PRED</td>
<td>CYC</td>
<td>8.0 (4.1, 16.7)</td>
<td>0.25 (0.29, 0.75)</td>
<td>-48.0 (-51.7, -42.3)</td>
</tr>
<tr>
<td>CYC</td>
<td>PRED</td>
<td>0.0 (1.0, 2.5)</td>
<td>1.1 (0.97, 1.3)</td>
<td>-12.3 (-11.8, -4.1)</td>
</tr>
<tr>
<td>CYC</td>
<td>PRED</td>
<td>1.85 (1.2, 2.9)</td>
<td>1.0 (1.0, 1.0)</td>
<td>-120.0 (-120.9, -115.7)</td>
</tr>
<tr>
<td>CYC</td>
<td>MMF</td>
<td>4.4 (2.4, 8.0)</td>
<td>1.63 (1.36, 1.95)</td>
<td>53.8 (45.1, 62.9)</td>
</tr>
<tr>
<td>CYC</td>
<td>MMF</td>
<td>8.22 (7.0, 9.6)</td>
<td>1.0 (0.98, 1.0)</td>
<td>-5.8 (-12.1, 0.5)</td>
</tr>
<tr>
<td>CYC</td>
<td>MMF</td>
<td>0.87 (0.4, 1.7)</td>
<td>1.0 (0.87, 1.0)</td>
<td>-43.1 (-53.5, -32.8)</td>
</tr>
</tbody>
</table>

**S463**

Background/Purpose: Rheumatoid arthritis (RA) related comorbidities are major determinants of morbidity and mortality. Little is known regarding the trends in these conditions. The purpose of our study was to examine whether the risk of comorbidities in RA patients has changed in recent years.

Methods: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA in 1980–2007 and a comparison cohort of subjects without RA of similar age and sex were assembled and followed until the occurrence of new comorbidities has declined over time. This may indicate earlier recognition and improved management of comorbidities both in the RA and in the general population.

**Table 1:** Predictors of disease severity after 1 year

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>1 year HAQ &gt; 1 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>101 (ref)</td>
<td>90</td>
<td>2.35 (0.13, 0.94)</td>
</tr>
<tr>
<td>Weighted</td>
<td>&gt;3</td>
<td>34</td>
<td>0.48 (0.19, 1.56)</td>
</tr>
</tbody>
</table>

Conclusion: Self reported comorbid disease burden predicts disease activity and level of disability in an eRA cohort after 1 year of treatment. Weighting co-morbidity for severity and function do not increase the strength of association with 1 year outcomes in early RA. Adjusting for the confounding effects of co-morbidity is important when assessing response to treatment. Use of self reported co-morbidity questionnaires appear to be an acceptable method of quantifying co-morbidity in routine rheumatology outpatient departments.
Background/Purpose: To investigate the associations of rheumatoid factor (RF) and autoantibodies against citrullinated proteins (ACPA) with rheumatoid arthritis (RA) disease activity.

Methods: We analyzed the association of RF and ACPA on individual and composite measures of disease activity at baseline in four recent randomized controlled clinical trials (RCT) using stratified and matched analyses. Data included one RCT in early RA patients on rituximab, RTX; three on golimumab, GOL, in early and established populations.

Results: A total of 2,118 patients were analyzed in the four studies. In both, the RTX and the pooled GOL cohorts, RF- patients, regardless of ACPA status, had the highest levels of baseline disease activity, while ACPA+ patients had similar or lower disease activity than ACPA-, regardless of RF status (See Figure, using Simplified Disease Activity Index, SDAI).

Conclusion: The data suggest that the presence of RF rather than ACPA is related to higher disease activity. When matched for RF levels, ACPA+ had little influence on disease activity, if at all, with the tendency towards lower disease activity for ACPA+ patients.

Acknowledgement: We thank Roche and Janssen for providing anonymised patient level data from their clinical trials.

Disclosure: D. Aletaha: None; F. Alasti: None; J. S. Smolen: None.

1056 Factors Associated with Impairment on Quality of Life in Early or Established RA Patients. Dam Kim1, Yoon-Kyoung Sung1, Soo-Kyung Cho2, Sooyoung Won1, Miinkyung Han1, So-Yong Bang1, Hoon-Suk Cha1, Chang-Bum Choi1, Jung-Yoon Cho2, Won Tae Chung3, Seung-Jae Hong2, Jae-Bum Jun4, Y Jong OK Jung5, Jinseok Kim6, Seong-Kyu Kim7, Tae-Hwan Kim7, Tae-Jong Kim15, Eunmi Koh7, Choong Ki Lee8, Hyeseon Lee9, Joo-Hyun Lee9, Jaejoon Lee9, Jisoo Lee9, Sang-Hoon Lee10, Shin-Seok Lee10, Sung Won Lee10, Seung-Chol Shin11, Dae-Hyun Yoo12, Wan-Hee Yoo12, Boyoung Yoon13, and Sang-Chol Bae13. 1Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, 2Hanyang University Guri Hospital, Guri, South Korea, 3Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 4Catholic University of Daegu School of Medicine, Daegu, South Korea, 5Dong-A University Hospital, Busan, South Korea, 6Kyung Hee University, Seoul, South Korea, 7Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 8Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea, 9Ewha Womans University Mokdong Hospital, Seoul, South Korea, 10Chonnam National University Medical School, Gwangju, South Korea, 11Yeungnam University, Daegu, South Korea, 12IlSan Paik Hospital, Inje University, Goyang, South Korea, 13Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 14Ewha Womans University School of Medicine, Seoul, South Korea, 15Konkuk University Hospital, Seoul, South Korea, 16Chonnam National University Bundang Medical School, Gwangju, South Korea, 17Dong-A University Hospital, Busan, South Korea, 18Pusan National University Hospital, Daejeon, South Korea, 19Chungnam National University Hospital, Daejeon, South Korea, 20Chonbuk National University School of Medicine, Jeonju, South Korea, 21Inje University Ilsan Paik Hospital, Goyang, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disabling disease with significant impact on the quality of life (QOL) of patients. Since clinical features are different in RA patients according to the disease course, various factors might be influence on the low QOL depending on the phase of the disease. We aimed to explore the associations for factors to impairment on quality of life in either early RA or established RA patients.

Methods: A total of 5,361 RA patients in the KORean Observational study Network for Arthritis (KORONA) were included in this study. The EuroQol-5 dimension (EQ-5D) is a widely used generic QOL instrument, and it allows for negative utility values, which correspond to health states worse than death. We defined the worst QOL as EQ-5D score < 0, a state worse than death. We classified RA patients according to their disease duration: early RA patients (n = 714) as patients whose disease duration was less than 1 year and patients with longer disease duration formed the established RA patients (n = 4,647). The distribution of EQ-5D in both groups of early and established RA patients were compared, and the possible determinants for negative EQ-5D score in each group were explored using the logistic regression analyses.
Table 1. Determinants of health state worse than death (EQ-5D)<0 in early and established RA patients.

<table>
<thead>
<tr>
<th></th>
<th>Early RA (n=714)</th>
<th>Established RA (n=4,647)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00 (0.95–1.06)</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middile school or less</td>
<td>1.08 (0.31–3.76)</td>
<td>1.25 (0.77–2.05)</td>
</tr>
<tr>
<td>High school or more</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Income (X10^3 won)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2,000</td>
<td>2.83 (0.27–30.08)</td>
<td>1.46 (0.57–3.73)</td>
</tr>
<tr>
<td>2,000–4,999</td>
<td>2.52 (0.23–27.63)</td>
<td>1.56 (0.61–4.07)</td>
</tr>
<tr>
<td>≥5,000</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Regular exercise, (%)</td>
<td>1.41 (0.44–4.47)</td>
<td>0.66 (0.43–0.99)</td>
</tr>
<tr>
<td>Operation history due to RA, (%)</td>
<td>0.63 (0.06–6.24)</td>
<td>0.81 (0.52–1.26)</td>
</tr>
<tr>
<td>Fracture history, (%)</td>
<td>0.10 (0.32–3.65)</td>
<td>0.88 (0.57–1.38)</td>
</tr>
<tr>
<td>Sleep VAS (cm, mean=-SD)</td>
<td>1.02 (1.01–1.04)</td>
<td>1.01 (1.00–1.01)</td>
</tr>
<tr>
<td>Fatigue VAS (cm, mean=-SD)</td>
<td>1.04 (1.01–1.07)</td>
<td>1.03 (1.02–1.04)</td>
</tr>
<tr>
<td>DA25 (OR)</td>
<td>0.74 (0.46–1.20)</td>
<td>1.28 (1.00–1.65)</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>17.29 (5.06–50.15)</td>
<td>10.02 (7.05–14.25)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>0.64 (0.21–1.93)</td>
<td>1.21 (0.79–1.87)</td>
</tr>
</tbody>
</table>

Conclusion: This is the first study applying AVEm to RA pts. Results detected domains that are potentially modifiable and should be considered in clinical management. Resistance to stress and emotional issues should be predominantly targeted. Further study analyzes will address correlations to other study parameters and confounding factors. Thus, appropriate strategies that promote healthy personal attitudes and equip pts with adequate supporting coping skills that prepare them for the challenges at their daily work and should be developed.

Unrestricted grants: M inistry of Innovation, Science, Research and Technology of the German State North Rhine-Westphalia, Deutsche Rheuma-Liga e.V., supported by German LE Self-Help Community, Abbvie Germany, Hiller Foundation.

Disclosure: J. G. Richter, None; T. Muth, None; R. Brinks, None; T. Koch, None; P. Angerer, None; M. Schneider, None.

1058

Levels of Fatigue Are Dependent on Country of Residence in Rheumatoid Arthritis: An Analysis Among 3920 Patients from 17 Countries.

Monika Hifving1, Polina Putritk2, Sofia Ramiro3, Maxime Douегод4, Laure Gossec5, Andreas Kese6, Ihsane Hmamouchi7 and Annelies Boonen8.

1University of Maastricht, Maastricht, Netherlands, 2Maastricht University Medical Center, Maastricht, Netherlands, 3Amsterdam Rheumatology Center/ University of Amsterdam, Amsterdam, Netherlands, 4Paris Descartes University, Paris, France, 5Pierre et Marie Curie University, Paris, France, 6Uniklinik RWTH Aachen University, Aachen, Germany, 7Mohammed V Souissi University, Rabat, Morocco.

Background/Purpose: For patients with rheumatoid arthritis (RA), fatigue is an important aspect of disease which impacts quality of life. However the complex relationship between fatigue and other disease-related or external factors remains unclear. Country of residence as a surrogate for a variety of cultural, economic and linguistic aspects might play a role, but this has never been formally explored. The aim of the study was to investigate how country of residence influences level of fatigue in addition to socio-demographic and objective disease- characteristics.

Methods: Data from a multi-national study were used (COMORA). Fatigue was measured using 0–10 VAS scale. A multivariable linear regression model (outcome fatigue) was computed using manual forward selection. Contribution of socio-demographic factors (age, gender, education, marital status), comorbidities (Wolfe-Michaud index), smoking status, clinical disease characteristics (tender and swollen joints (TJC), SJC), erosions in hands or feet (yes/no), erythrocyte sedimentation rate) and medication (all type of DMARDs, steroids and NSAIDS) was tested. Country of residence was added using the country with the highest level of fatigue (Netherlands) as reference. In a second step, sensitivity analyses were
developed replacing country of residence by country specific variables including gross domestic product (GDP), human development index (HDI), a climate indicator (latitude) and income inequality (gini index).

**Results:** 3920 patients from 17 countries (range 30 to 411, mean age 56 years (SD 13), 82% female) were included. Mean fatigue across countries was 4.13 (SD 2.8). 32.8% of all patients had fatigue scores $\geq$ 5. In multi-variable regression, female gender ($p = 0.08$) and HDI ($p = 0.04$) were associated with higher fatigue scores and SJC had limited influence on fatigue with higher contribution of TJC ($p = 0.02$). The overall model fit ($\Delta R^2 = 0.08$). Country differences in fatigue varied between -3.9 for Venezuela vs Netherlands (NL) and -0.6 (Italy vs NL) after adjustment for individual factors. When country was replaced by GDP, HDI, latitude or gini index the model fit did not significantly change. The index contributed only to GDP and HDI. The overall model improvement was lower compared to country ($R^2$ GDP = 0.14, NL country = 0.20). Interactions were not significant.

**Conclusion:** While individual demographics and objective clinical measures of disease have only a small influence on the experience of fatigue, the country of residence adds substantially. Economic and development status of the country only explain small parts of the variation among countries. More research is needed to identify these unknown aspects of RA related fatigue, e.g. cultural (attitudes, believes), linguistic or work related factors might play a role.

Disclosure: M. Hifinger, None; S. Ramiro, None; A. Kezeli, None; I. Hmamouchi, None; M. Dougados, None; L. Gossec, None; A. Kezeli, None; I. Hmamouchi, None; A. Boonen, None.

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**1059**

**Patients with RA from Wealthier Countries Perform Better on Clinical Disease Activity Measures, but Tend to Show Worse Person Reported Outcomes.** Polina Putinik, Sofia Ramiro, Andras Keszthelyi, Ihsane Hmamouchi, Maarten Dougados, Monika Hifinger, Laure Gossec and Annelies Boonen. 1Maastricht University Medical Center, Maastricht, Netherlands, 2Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garica de Orta, Almada, Portugal, Amsterdam, Netherlands, 3Uniklinik RWTH Aachen University, Aachen, Germany, 4Mohamed V Souissi University, Casablanca, Morocco, 5Paris Descartes University, Paris, France, 6Universite Hospital Maastricht, Maastricht, Netherlands, 7Pierre et Marie Curie University, Paris, France.

**Background/Purpose:** Inequalities in health between low and high income countries are often reported, but it is not known whether clinical disease activity measures ("objective") and person reported outcomes ("subjective") follow the same patterns in patients with rheumatoid arthritis (RA). The objective of this study was to investigate the patterns in RA health outcomes ("objective" vs "subjective") across countries with different level of socio-economic development.

**Methods:** Data from a cross-sectional multinational (17 countries) study COMORA was used. Contribution of gross domestic product (GDP) to clinical disease activity measures (DA528, total joint count (TJC), swollen joint count (SJC), and erythrocyte sedimentation rate (ESR)) and person reported outcomes (Patient global assessment (PatGA) (0–10), fatigue (0–10), Physician global assessment (PhysGA) (0–10) and function assessed with health assessment questionnaire (HAQ) (0–3)) was explored. All models were adjusted for potentially relevant confounders, including age, gender, education and comorbidities (Wolfe-Michael index). Models were computed with and without adjustment for current RA medication (steroids, NSAIDs and DMARDs). Additionally, models with person reported outcomes were adjusted for the presence of erosive disease, TJC, SJC, and ESR, GDP was dichotomized in low and high GDP countries (with a cut-off of 20,000 international dollars per capita (adjusted to purchasing power parity), which by data inspection was the one that discriminated best both groups).

**Results:** A total of 3920 RA patients from 17 countries (range 30–411) were included in COMORA (mean age 56 y.o. (SD13), 82% females). DA528 varied between 5.3 (Egypt) and 2.6 (Netherlands), HAQ ranged between 0.7 (Taiwan) and 1.9 (Netherlands). Venezuela had the lowest average score of fatigue (1.7) and Netherlands scored on average highest on fatigue (5.0). In models adjusted for medication, low GDP countries had on average 0.94 higher DA528, 2.84 and 1.85 higher scores on TJC and SJC, respectively, and 11.50 higher ESR compared to high GDP countries. At the same time, patients from low GDP societies had a 0.41 and 0.21 lower score on patient and physician global assessment, respectively and 0.96 lower score on fatigue compared to high GDP countries. HAQ was 0.14 higher in countries with low GDP (Table 1).

**Table 1.** Association between clinical disease activity measures and person reported outcomes with GDP

<table>
<thead>
<tr>
<th>Clinical disease activity measures</th>
<th>Person reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA528 (low vs. high) (Adjusted model, excluding medication)</td>
<td>HAQ</td>
</tr>
<tr>
<td>TJC</td>
<td>PhysGA, Fatigue</td>
</tr>
<tr>
<td>0.94*</td>
<td>2.84*</td>
</tr>
<tr>
<td>SJC</td>
<td>1.85*</td>
</tr>
<tr>
<td>ESR</td>
<td>11.5*</td>
</tr>
<tr>
<td>PatGA</td>
<td>0.41*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.96*</td>
</tr>
<tr>
<td>PhysGA</td>
<td>0.21*</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.14*</td>
</tr>
</tbody>
</table>

**Conclusion:** Patients from countries with lower socio-economic welfare score worse on clinical measures of disease activity (DA528 and its components), however, tend to score better on person reported outcomes (patient global assessment and fatigue) for the same level of objective disease activity. Cultural factors that may play a role in reporting of subjective outcomes should be further explored.

Disclosure: P. Putik, None; S. Ramiro, None; A. Kezeli, None; I. Hmamouchi, None; M. Dougados, None; M. Hifinger, Hexal AG, Germany, J. L. Gossec, None; A. Boonen, None.

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**1060**

**Musculoskeletal Surgeries and Procedures in Patients with RA: Results from a UK Retrospective Study.** H Cawston1, F Bourhis1, T Le2 and E Alenmos1. 1OptumInsight, Nanterre, France, 2Bristol-Myers Squibb, Hopewell, NJ, 3Bristol-Myers Squibb, Princeton, NJ.

**Background/Purpose:** Musculoskeletal surgeries and procedures substantially improve the quality of life of patients with RA, but represent an important burden in terms of medical costs. The aim of this study was to assess whether recent advances in RA treatment had an impact on long-term surgery rates in the UK.

**Methods:** A retrospective cohort study was conducted from 1997 to 2010, using Clinical Practice Research Database General Practice Online Data (GOLD) and Hospital Episode Statistics (HES) data. RA population was defined as all patients presenting with one or more RA read code after 01/01/1988 (index code), with no RA or juvenile RA codes before the RA index code. Patients were required to have a minimum of 12 months of data before the first RA code and to have no psoriatic arthritis-related codes over the entire period. Date of onset of disease was defined as date of first RA-related code. RA patients were matched 4:1 to non-RA patients based on their year of entry in the GOLD database, cardiovascular (CV) risk category (NCEP classification), CV treatment status, and a risk score measuring the probability of having RA. The index code of non-RA patients was defined as the date of observation closest to the index code of their matched RA patient. Surgeries such as total joint arthroplasties (TJA), non-TJA, TJA-associated procedures, as well as other orthopedic procedures were identified in HES and GOLD databases using operating procedure codes and read codes. Incidence rates (IRs) were estimated over the study period and by time since diagnosis in both cohorts. Time-to-first-surgery curves in all RA patients as well as stratified by terciles of CRP measured at diagnosis were based on Kaplan-Meier (KM) estimates. Results: Overall, 14,181 patients with RA were identified and matched to 49,935 non-RA patients. IRs in RA patients, relatively constant up to 2003, sharply increased in 2004 (IR = 4.0/100 person-years; 95% CI: 3.5, 4.3) before a steady decrease was observed up to 2006 (3.1 [2.8, 3.5]). This trend was driven by TJAs, for which an IR of 2.7 (2.3, 3.0) was observed in 2010. Majority of TJAs involved the knee (43.5%) and hip (40.2%). However, IRs of all surgeries increased from 0.1 (0.0, 0.2) to 1.4 (1.3, 1.6) from 1997 to 2010 in non-RA patients. Based on the KM analysis, the probabilities of having a surgery at 3, 5 and 10 years were 5.5%, 8.6% and 17.3%, respectively. Patients in the higher tercile of CRP at diagnosis were at higher risk of first surgery than the two lower terciles (log rank test between three groups: p = 0.0007).

**Conclusion:** Decrease in the IRs of musculoskeletal surgeries in 2005/2006 could be attributed to greater availability of biologic therapies. However, these rates have not decreased in recent years, suggesting there is an unmet need for more effective therapies. CRP levels at diagnosis were associated with higher risk of surgeries, suggesting that therapies reducing CRP may be effective to further lower surgical rates.

**Background/Purpose:** It is believed that 40% to 80% of patients with rheumatoid arthritis (RA) have cervical spine lesions. In particular, atlantoaxial subluxation (AAS) and vertical subluxation (VS) are clinically important. However, little is known about how disease activity and other factors are involved in their development. The aim of this study is to identify risk factors for upper cervical lesions in RA patients.

**Methods:** IORRA is a prospective observational cohort study of Japanese patients with RA established in 2000 at the Institute of Rheumatology, Tokyo Women’s Medical University. Approximately 5,000 patients with RA are involved in each phase of the biannual survey. In our department, when RA patients schedule surgery, dynamic X-rays of the cervical spine are conventionally taken to assess instabilities in case tracheal intubation for general anesthesia is required. In this study, we evaluated these X-rays and investigated their relevance to the integrated data in the IORRA cohort study. Inclusion criteria were: (1) scheduled surgery in our department from 1 April 2010 to 31 March 2013, and (2) registration into the IORRA cohort study.

**Results:** Median ADI was 2.8mm, and R-J was 34mm. Twenty-seven patients were included. ADI > 2 mm was associated with R-J > 10 mm (OR 0.24, 95% CI 0.07, 0.85), and ADI > 5 mm was associated with R-J > 10 mm (OR 0.14, 95% CI 0.03, 0.62).

**Conclusion:** Obese patients were significantly less likely to exhibit low disease activity at 6 and 12 month follow up, or disease remission at 12 months follow up (Table 1).
Management of Hyperlipidemia Among Patients with Rheumatoid Arthritis in the Primary Care Setting. 


Background/Purpose: Rheumatoid arthritis has been associated with an increased risk of cardiovascular morbidity and mortality. It is unclear, however, whether this knowledge has translated into improved screening and management of traditional cardiovascular risk factors such as hyperlipidemia in the primary care setting. The objectives of this study included 1) To determine the prevalence of screening for hyperlipidemia in patients with rheumatoid arthritis (RA) that are followed by primary care physicians; 2) To examine whether current Adult Treatment Panel (ATP) III guidelines for the initiation of lipid-lowering therapy are being followed in patients with RA, and 3) to assess whether proposed modifications to cardiovascular risk calculations change the percentage of RA patients with an indication for therapy.

Methods: A retrospective cohort study was performed among patients with RA in an academic medical center medical record database in the United States between 2005–2010. A validation study prior to initiation of the study demonstrated a positive predictive value of 96.7% for accurate capture of patients with RA using ICD-9 codes. Descriptive statistics were used to report the prevalence of screening and use of lipid-lowering therapy (LLT) among those with an indication for LLT. Factors associated with not receiving lipid screening were examined using logistic regression models. Finally, indication for and receipt of therapy were assessed following application of the European Union League Against Rheumatism (EULAR) recommended multiplier to the Framingham risk score.

Results: Among 1418 patients with RA followed by primary care physicians, lipid screening was ordered for 780 (55%) within the 3-year follow-up period. Patients under the age of 50 were significantly less likely to be screened whereas patients with diabetes, hypertension, chronic kidney disease, and obesity were more likely to be screened (Table). Of those with lipid results (N = 419), 50 (12%) patients had an indication for LLT based on the ATP III guidelines. Among the 50 patients with an indication for LLT, 38 (76%) received therapy. Applying the EULAR multiplier only changed the indication for LLT in two patients.

Conclusion: Although patients with RA have an increased risk for cardiovascular disease, they are often not receiving optimal management of traditional cardiovascular risk factors, such as screening for hyperlipidemia. Nevertheless, once hyperlipidemia has been identified, most patients received the appropriate lipid-lowering therapy. The EULAR multiplier does not have a measurable impact on clinical care, and new methods for assessing cardiovascular risk among patients with RA are needed.

Table. Logistic regression models for non-receipt of screening

<table>
<thead>
<tr>
<th>Univariable</th>
<th>Final Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Age (&lt;50)</strong></td>
<td>1.74 (1.38–2.19)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>1.08 (0.81–1.43)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Black or African American</strong></td>
<td>0.76 (0.61–0.95)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>1.26 (0.60–2.64)</td>
</tr>
<tr>
<td><strong>Other or unknown</strong></td>
<td>1.60 (1.46–2.48)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0.30 (0.21–0.42)</td>
</tr>
<tr>
<td><strong>Hypertension Diagnosis</strong></td>
<td>0.17 (0.10–0.32)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>0.43 (0.31–0.53)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>0.37 (0.25–0.56)</td>
</tr>
<tr>
<td><strong>Peripheral Arterial Disease</strong></td>
<td>0.32 (0.12–0.84)</td>
</tr>
<tr>
<td><strong>Tobacco use (n=564)</strong></td>
<td>Current smoker vs non-smoker or past-smoker</td>
</tr>
</tbody>
</table>

Note that odds ratios (OR) refer to NOT receiving screening. For example, age <50 is associated with an increased risk of NOT receiving screening by a factor of 1.74. *ORs <0.65 for the association between predicted probabilities and observed responses for the final multivariable model.

Disclosure: K. Jafri, None; L. Taylor, None; N. N. Mehta, None; M. Nezamzadeh, None; J. Baker, None; A. Ogdie, None.

Unique Profile of Cardiovascular Risk Factors in Rheumatoid Arthritis High-Risk Populations with Insufficient Risk Control. Ulf Müller-Ladner1, Stefan Kleinert2, Klaus Krüger1, Christian Wittig4 and Rolf Heck3.

Kerendic, ABBVIE GmbH, ABBVIE Rheumatologie und Klinische Immunologie, Bad Nauheim, Germany; 2Praxisklinik Rheumatologie-Nephrologie, Rheydtklinik, Aachen, Germany; 3Praxisklinik Rheumatologie-Nephrologie, Rheumatologische Schwerpunktpрактика, Erlangen, Germany; 4Praxisklinik St. Bonifatius, München, Germany; 5ABBVIE Deutschland GmbH & Co. KG, Wiesbaden, Germany.

Background/Purpose: More than 50% of premature deaths in patients with rheumatoid arthritis (RA) are due to cardiovascular disease (CVD). Both the cumulative burden of inflammation and the increased prevalence of conventional CVD risk factors contribute to this increase in CVD. CVD risk screening and management is therefore mandatory.

Methods: A cross-sectional study was conducted to screen RA patients for CVD risk factors at rheumatology outpatient centers in Germany. Age, gender, smoking habits, blood pressure, and lipid levels were assessed, as well as medications, comorbidities, body mass index (BMI), CVD, and standard laboratory parameters. Using these parameters, a subset of patients was assigned to 3 high-risk CVD subgroups: patients with manifest CVD, patients with diabetes mellitus (DM; type 1 or 2), and, as the CVD mortality risk is a function of age, patients <70 years of age. A achievement of target values for CVD risk factors adopted from the European Society of Cardiology (ESC) and European League Against Rheumatism (EULAR) recommendations were compared within these groups.

Results: The comparator population included 866 patients with RA. High-risk subgroups included 146 RA patients with existing CVD, 111 RA patients with DM (<70 years) and 114 RA patients aged >70 years but without DM or CVD. 49% of the CVD patients had a previous myocardial infarction or stroke, 62% had coronary heart disease (CHD), and 72% had previous arterial occlusion events. Recommended target values for CVD risk factors were not achieved by a substantial number of patients even in the high-risk populations. Depending on the subgroup, 40–45% of the patients achieved low disease activity or DAS remission, 41–63% reached the respective blood pressure target, and 0–28% reached the low-density lipoprotein (LDL) cholesterol target (Table 1). Lipid target values were rarely achieved in high-risk populations. Only a minor fraction of patients received statin therapy; there was no difference in glucocorticoid use between the high-risk and comparator populations. 65% of the investigators stated that the EULAR recommendations for the management of CVD risk in RA influenced their diagnostic and therapeutic concept.

Conclusion: Target values for CVD risk factors are rarely achieved in high-risk RA patients in routine outpatient settings, reflecting the insufficient management of CVD risk.

References

Demographics, CVD Risk Factors, and Target Values

<table>
<thead>
<tr>
<th>CVD</th>
<th>DM</th>
<th>Age ≥70</th>
<th>RA comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=546)</td>
<td>(n=111)</td>
<td>(n=114)</td>
<td>(n=866)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>64.7</td>
<td>63.3</td>
<td>73.9</td>
</tr>
<tr>
<td>Gender, men vs women</td>
<td>48.6</td>
<td>63.1</td>
<td>60.3</td>
</tr>
<tr>
<td>RF and/or ACPA positive, %</td>
<td>76</td>
<td>71.2</td>
<td>78.1</td>
</tr>
<tr>
<td>Mean disease duration, years</td>
<td>10.8</td>
<td>8.9</td>
<td>12</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>28.5</td>
<td>26.1</td>
<td>26.1</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>21.2</td>
<td>9.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Mean LDL-C, mg/dl</td>
<td>3.5</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>LDL-C &lt;32% (N=111)</td>
<td>39.7</td>
<td>43.2</td>
<td>44.8</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mmHg</td>
<td>134</td>
<td>136.7</td>
<td>133.8</td>
</tr>
<tr>
<td>Blood pressure target achieved, %</td>
<td>63</td>
<td>41.4</td>
<td>47.4</td>
</tr>
<tr>
<td>Mean L DL-C, mg/dl</td>
<td>128.9</td>
<td>126.9</td>
<td>135</td>
</tr>
<tr>
<td>LDL-C target achieved, %</td>
<td>4.3</td>
<td>20.7</td>
<td>-</td>
</tr>
<tr>
<td>mSCORE &lt;5%</td>
<td>NA</td>
<td>NA</td>
<td>23.8</td>
</tr>
<tr>
<td>mSCORE &lt;5%</td>
<td>NA</td>
<td>NA</td>
<td>11.9</td>
</tr>
<tr>
<td>mSCORE &lt;20%</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Cholesterol: HDL-C ratio</td>
<td>3.64</td>
<td>3.57</td>
<td>3.38</td>
</tr>
<tr>
<td>Anti-hypertensive therapy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combination therapy, %</td>
<td>42.4</td>
<td>34.6</td>
<td>41.5</td>
</tr>
<tr>
<td>Mean statin therapy, %</td>
<td>45.3</td>
<td>58</td>
<td>46.2</td>
</tr>
<tr>
<td>Actual statin therapy, %</td>
<td>19.5</td>
<td>7.2</td>
<td>9.6</td>
</tr>
<tr>
<td>Actual corticosteroid use, %</td>
<td>63</td>
<td>60.4</td>
<td>61.4</td>
</tr>
<tr>
<td>Corticosteroid use, %</td>
<td>46.7</td>
<td>52.2</td>
<td>53.8</td>
</tr>
<tr>
<td>Corticosteroid use, median duration, months</td>
<td>46.5</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>NSAID use, %</td>
<td>31.5</td>
<td>30.6</td>
<td>27.2</td>
</tr>
<tr>
<td>*Modified SCORE [2] adapted by introducing a 1.5-multiplication factor when the patient two of three criteria: Diastolic blood pressure &gt;90 mmHg; total cholesterol ≥200 mg/dl; smoking status.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Characteristics of Rheumatoid Arthritis Patients with and without Cardiovascular Diseases - Data from the Ontario Best Practice Research Initiative (OBRI).

Methods: Descriptive analyses were performed using physician and patient-reported data collected from the Ontario Best Practice Research Initiative (OBRI), a clinical registry of RA patients followed in routine care. CVD was defined as the presence of coronary artery disease (CAD), congestive heart failure (CHF), hypertension (HTN), arrhythmia, stroke, transient ischemic attack (TIA), and/or other heart disorders upon entering the registry (baseline). Patient demographics, clinical characteristics, socioeconomic status and treatment regimens were compared between patients with and without CVD at baseline using Chi-square and t-tests. Generalized linear regression models were used to estimate means for adjusted for age, sex, smoking history, and socioeconomic factors.

Results: Among 2305 RA patients, 725 (31.5%) had CVD at baseline. Of those with CVD, 562 (77.5%) had HTN, 68 (9.4%) had CAD, 21 (2.9%) had arrhythmia, 10 (1.4%) had CHF, 9 (1.2%) had TIA, 5 (0.7%) had stroke, and 108 (14.9%) had other heart disorders. Patients with CVD were older (64.5 ± 10.1 vs. 54.2 ± 12.9 yrs, p < 0.0001), and had longer RA disease duration (9.3 ± 10.7 vs. 8 ± 9.1 yrs, p < 0.0001). Male sex, low education and income, lack of private insurance, and smoking were also associated with the presence of CVD.

Positive rheumatoid factor (71.0% vs. 75.1%, p < 0.05) was less prevalent in CVD patients. After adjusting for age, sex, income, education, insurance status, and smoking history, there were no significant differences in disease duration but CVD patients maintained higher disease activity (see table), measured by DAS28, CDAI, RADA1, tender joint count-28 (TJC), and erythrocyte sedimentation rate (ESR). Functional status measured by HAQ was worse in CVD patients. Extra-articular features (24.9% vs. 16.0%, p < 0.05) were higher among CVD patients. CVD patients were less frequently treated with biologics (19.5% vs. 24.0%, p < 0.05) and NSAIDS (34.9% vs. 48.6%, p < 0.05) but did not differ in disease-modifying agents (DMARDs) and steroids usage compared with non-CVD patients.

Conclusion: RA patients with CVD have worse disease activity, more extra-articular features, and lower utilization of biologics and NSAIDS. The latter may be due to CVD risk with NSAIDS, but the lower utilization of biologics may require further investigation. Clarification on the CVD status of HTN patients is ongoing.

Disease Activity and Functional Status comparing RA patients with and without CVD

<table>
<thead>
<tr>
<th>Disease Activity and Functional Status Measures</th>
<th>CVD (N = 725) Adjusted Mean*</th>
<th>SE**</th>
<th>Non-CVD (N = 1580) Adjusted Mean*</th>
<th>SE**</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-ESR</td>
<td>4.6</td>
<td>0.06</td>
<td>4.4</td>
<td>0.04</td>
<td>0.007</td>
</tr>
<tr>
<td>CDAI</td>
<td>23.0</td>
<td>0.56</td>
<td>21.3</td>
<td>0.38</td>
<td>0.014</td>
</tr>
<tr>
<td>SDAI</td>
<td>24.7</td>
<td>0.64</td>
<td>23.6</td>
<td>0.44</td>
<td>0.178</td>
</tr>
<tr>
<td>RADA1</td>
<td>4.3</td>
<td>0.09</td>
<td>3.9</td>
<td>0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>SJ/C</td>
<td>6.2</td>
<td>0.20</td>
<td>5.8</td>
<td>0.13</td>
<td>0.110</td>
</tr>
<tr>
<td>TJC</td>
<td>7.0</td>
<td>0.26</td>
<td>6.2</td>
<td>0.17</td>
<td>0.014</td>
</tr>
<tr>
<td>ESR</td>
<td>27.1</td>
<td>0.92</td>
<td>24.8</td>
<td>0.61</td>
<td>0.044</td>
</tr>
<tr>
<td>CRP</td>
<td>13.8</td>
<td>0.92</td>
<td>13.1</td>
<td>0.63</td>
<td>0.575</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.3</td>
<td>0.03</td>
<td>1.2</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, income, education, insurance status and smoking history
** Standard errors are reported

Disclosure: K. Cui, None; B. Jacob, None; J. E. Pope, None; J. Widfield, None; X. Li, None; B. Kuriya, None; P. Akhavan, None; C. Bombardier, None.

Factors Associated with Recording of Rheumatoid Arthritis on Death Certificates

Background/Purpose: Death certificates can be used to study mortality due to a particular disease. However, rheumatoid arthritis (RA) often remains unreported on death certificates. We sought to determine to what extent RA is underreported and what demographic and clinical characteristics could predict mention of RA in the death certificate.

Methods: Between 1996 and 2009, we recruited 1,328 patients with RA that met the American College of Rheumatology criteria. Patients were followed prospectively. A rheumatologist assessed clinical characteristics of RA at each evaluation, including number of tender, swollen and deformed joints, presence of rheumatoid nodules, as well as Steinbrocker classification and Charlon comorbidity index. Joint damage was determined by Sharp score, using hand radiographs taken from the most recent visit prior to death. Deaths were identified through family members, friends, neighbors, other physicians, obituaries and public death databases. We obtained state-issued death certificates and mapped causes of death to ICD9 codes. Standard bivariate analyses were conducted comparing patients with and without RA at the death certificate. A multivariable logistic regression model was performed to determine what variables were associated with recording RA.

Results: By December 2013, 323 deaths had occurred during 8,326 person-years of observation, for a mortality rate of 3.8 per 100 person-years (95% confidence interval [CI] 3.4, 4.3). Of the 308 death certificates we received, 61 (19.8%) mentioned RA on the death certificate. Only two of them recorded RA as the immediate cause of death. Bivariate analysis revealed that a greater number of deformities (mean ± SD = 17.6 ± 9.0 vs. 14.4 ± 9.4; P = 0.016), higher Sharp score (mean ± SD = 192 ± 132 vs. 138 ± 112; P = 0.010) and lower socio-economic status (mean ± SD = 42.4 ± 21 vs. 48.3 ± 19; P = 0.041) were each associated with recording RA on the death certificate. Place of death, presence of rheumatoid nodules, having health insurance or an autopsy were not associated with recording RA. Multivariable analyses revealed that an increased number of deformed joints [odds ratio (95% confidence interval) = 1.04 (1.00, 1.07); P = 0.04], less comorbidity [OR (95%CI) = 0.87 (0.76, 0.99); P = 0.048] and having a certified physician sign the certificate [OR (95%CI) = 3.56 (1.16, 10.8); P = 0.026] were associated with listing RA on the death certificate.

Conclusion: In this RA cohort, a diagnosis of RA was not listed in the death certificate in 80% of patients who died. Patients with fewer deformed joints and more joint deformities were more likely to have RA reported. Studies that rely on death certificates may underestimate the mortality of RA and be biased toward patients with more severe RA and less comorbidities.

Disclosure: E. Molina, None; J. F. Restrepo, None; I. Del Rincon, None; D. Battafarano, None; A. Escalante, None.
Conclusion: Despite important advances in treatment that have accompanied the availability of biologics, there has been no meaningful improvement in RA-related mortality over this time period. A possible reason why previous studies have found no narrowing of the "mortality gap" separating RA patients from patients with NIRD is that RA patients are not representative of the general population. This may explain why RA patients show a smaller risk of death than non-RA patients, which has been found in previous studies.

Disclosure: B. R. England; None; H. Sayles; None; T. R. Mikuls; None; K. Michaud; None.

1068 Smoking-Related Mortality in Rheumatoid Arthritis: A Retrospective Cohort Study Using Electronic Medical Records. Rebecca M Joseph1, Mohammad Movahedi2 and Deborah PM Symmons2. 1NIHR Manchester Biomedical Research Centre, Manchester, United Kingdom, 2Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Smoking is a known risk factor for rheumatoid arthritis (RA) and there is evidence suggesting that many patients with RA continue to smoke. The proportion of patients with RA who smoke is therefore higher than the general population. Smoking is associated with several serious adverse events and so is likely to reduce life expectancy. The aim of this study was to examine the influence of smoking status on all-cause mortality in patients with RA.

Methods: Incident cases of RA were identified from a large UK primary care database using a validated algorithm. Patients were followed from their first code for RA until death, leaving their general practice or the last data collection date within the study window of March 1991 to January 2014. Read codes, codes for smoking cessation therapy and additional clinical information were used to define smoking status at baseline and as a time-varying exposure during follow-up. Smoking status was classified as never, current or former. Date of death was available in the database. The Cox proportional hazards model was used to compare mortality rates between smoking categories, adjusting for gender and diagnosis date (pre/post 1998). To account for possible participation bias, the RA group was compared to another enrolled group (NIRD) from 1998 to 2011.

Results: 13154 adult RA patients were identified, of whom 12431 (94.5%) had a baseline smoking status recorded and were included in the analysis. 68.9% were female and the median age was 60.8 years (IQR 50.2, 71.0). At baseline, all covariates differed significantly between the smoking categories. Former smokers had the highest prevalence of cardiovascular disease, diabetes, depression, and respiratory infection whilst current smokers had the highest prevalence of depression. The total follow-up time was 75467 person-years and there were 1719 deaths, giving a crude mortality rate of 22.8 per 1000 person years. The crude mortality rate for smoking status at baseline was 19.8, 25.6 and 24.8 per 1000 person years for non-, current and former smokers respectively. In the adjusted models, using time-varying smoking status, the risk of mortality for current smokers was nearly 80% greater than that of non-smokers (hazard ratio 1.79 (95% CI 1.46, 2.20) (Table).

Conclusion: Current smoking significantly increases the risk of death at any time after RA diagnosis compared to both non- and former smokers. A adjusted risk of death is similar for former smokers and non-smokers. Stopping smoking prior to the development of associated comorbidities may therefore help to reduce the risk of smoking-related mortality.

Disclosure: R. M. Joseph; None; M. Movahedi; None; D. P. Symmons; None.
Patients with rheumatoid arthritis (RA) have greater risk of non-Hodgkin lymphoma (NHL) than the general population. A previous two-center study suggested that the rates of progression and relapse of patients with NHL and antecedent RA were lower than those of patients with NHL alone, but that the overall risk of mortality was increased. The objective of this study was to conduct a population-based study of Medicare beneficiaries to compare the survival of patients with NHL and prior RA with that of patients with NHL alone.

**Methods**: We used for this study population-based data that links patients with cancer in the State of Texas (Texas Cancer Registry) with Medicare data in beneficiaries 65 years and older. The data file has a case capture of over 10 years.

**Results**: 8,858 NHL patients were included, of whom 2.5% (n = 226) had 1-RA claim and 2.3% (n = 203) had 2-RA claims. Overall median survival for the cohort was close to 4 years. The hazard ratio (HR) for patients in the 1-RA group was 1.14 (95% CI, 0.95--1.37), and that for the 2-RA group was 1.04 (95% CI, 0.85--1.25) compared to that of patients without RA after controlling for demographics, and stage. The risk did not significantly change after including comorbidity in the models: 1-RA group HR = 1.13, 95% CI, 0.94--1.36, and 2-RA group HR = 1.04, 95% CI, 0.85--1.26. Comorbidity was an independent factor significantly associated with mortality such that having one additional comorbidity increased risk by 20% HR = 1.20 (95% CI, 1.12--1.29), and having 5 or more comorbidities increased risk by more than 2 fold, HR = 2.31 (95% CI, 2.01--2.63).

**Conclusion**: Having antecedent RA does not confer an independent mortality risk in NHL Medicare beneficiaries. However, patients with RA and NHL with other comorbidities can have decreased survival. Additional research should evaluate the risk associated with specific comorbid conditions, and whether this potential detrimental effect is from disease burden or differential use of cancer therapies.

**Disclosure**: P. Nayak, None; Z. Abu Zahr, None; R. Luo, None; L. Elting, None; M. E. Suarez-Almazor, None.

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**Table 1. Hazard ratios of all-cause death as a function of RA, cancer, and cancer stage**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Stage at cancer diagnosis</th>
<th>HR (95% CI) comparing patients with vs. without RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Stage I</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td>Y es</td>
<td>Stage I</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
</tbody>
</table>

Stratified Cox models stratified on cancer or cancer stage, and adjusted for age (as underlying mortality risk in RA. Whether this increased mortality is a cancer-associated phenomenon, an effect of the decreased lifespan in RA, or a combination of both is unknown.

**Methods**: Using Swedish register data (2001--2009), we performed a cohort study of individuals with RA (N = 34930), matched to general population comparators (N = 169740), including cancers (N = 12676) and deaths (N = 14291). We restricted to adults with no history of malignancy between 40 and 84 years old at start of study. Using multivariable adjusted stratified Cox models we first estimated the overall association between RA and death for those with and without cancer during follow-up using age as the underlying timescale, and then stratified by cancer stage. We then estimated the effect of RA versus non-RA by cancer stage restricting to individuals with an incident cancer during follow-up. We also investigated how the effect of RA varied by time since cancer diagnosis (0–2 years, 2–5 years, >5 years since diagnosis) These analyses looked at all-cause mortality for all cancers and specific sites (lung, colorectal, female breast, prostate, malignant melanoma, and lymphoma).

**Results**: In the absence of cancer, RA was associated with a doubled mortality rate (HR = 2.1, 95% CI 2.0--2.2). In the presence of cancer, the effect of RA on mortality was lower (HR = 1.2, 95% CI 1.1--1.3), but only for advanced stage cancers. For stages I and II the relative effect of RA on mortality was doubled (HR = 2.0 and HR = 2.1, respectively). These associations remained across time since cancer diagnosis, and were reasonably similar across sites.

**Conclusion**: Our results offer limited evidence that RA would potentiate the effect of cancer on the risk of death, at least not in cancers diagnosed at advanced stage. Instead, much of the increase in mortality in RA patients diagnosed with cancer seems to reside with effects of RA independently of the cancer.

**Table 2. Hazard ratios for RA vs. non-RA among individuals diagnosed with any cancer, stratified by time since cancer diagnosis and stage at cancer diagnosis**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Stage at cancer diagnosis</th>
<th>HR (95% CI) comparing patients with vs. without RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0–2 years</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Stage I</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td>Y es</td>
<td>Stage I</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
</tbody>
</table>

The stratified Cox model is stratified on cancer status or stage, and adjusted for time since diagnosis (as underlying timescale) and age at cancer diagnosis, sex, civil status, region of residence, education, history of chronic obstructive pulmonary disease, history of diabetes, history of ischemic heart disease, and history of cerebrovascular disease.
Background/Purpose: Women with SLE are at increased risk for pregnancy complications and specific autoantibodies may result in preferential loss of female offspring. Studies on the male to female (M:F) sex ratio of births in the SLE population have been contradictory. We used a large national population-based cohort of patients with SLE to determine whether the M:F ratio of births to mothers with SLE is different than the general population as well as a population of women with rheumatoid arthritis (RA) to estimate the ratio in another chronic inflammatory disease.

Methods: SLE was defined as >2 visits in inpatient or outpatient care (National Patient Register (NPR), 1969-2011) listing an SLE ICD code with ≥1 SLE-coded visit to a specialist. A sample of general population comparators was identified from the Total Population Register. Women with a delivery were identified from the Swedish Medical Birth Register (1973-2011). We used modified Poisson regression with robust sandwich estimators to calculate the risk ratio (RR) for having a male offspring associated with an SLE diagnosis adjusted for age, year and maternal country of birth. Our primary analysis was restricted to first singleton births only. In secondary analyses, we examined all births and restricted to live births only. We also examined antiphospholipid syndrome (APS) history in the SLE populationusing any ICD10 code before or at delivery, restricted to ≥1997 when the code was available. Lastly, we calculated the M:F ratio of offspring born to women with ≥2 RA-coded visits in the NPR with ≥1 visit to a specialist before delivery.

Results: We identified 604 women with SLE before their first delivery and 1289 singleton deliveries total to women with prevalent SLE. Maternal SLE at delivery had a lower proportion of male offspring compared to the general population. The RR for male offspring associated with SLE was 0.95 (95%CI 0.88, 1.04) for first births and 0.96 (95%CI 0.90, 1.01) for all singleton births (Table). RRs did not change with adjustment by age, year or country of birth. Results were similar among live births only and including multiples. Women with both APS and SLE had a lower odds of having a male child compared to the general population. We identified 1136 women with prevalent SLE at delivery and 2674 singleton deliveries total. The M:F ratio in RA was not significantly different than the general population (first birth RR = 0.96 (95%CI 0.91, 1.02), all births OR = 0.99 (95%CI 0.95, 1.03)).

Conclusion: We observed a lower proportion of male offspring born to women with prevalent SLE at delivery compared to the general population, which was not statistically significant. We observed a significantly lower odds of male offspring born to women with SLE and APS when all births were considered. In this large study using similar techniques to identify patients as that of a group in Canada, we did not confirm their findings of a male dominance in offspring.

Table 1: Maternal characteristics and M:F sex ratio among deliveries in Sweden, 1973-2011, comparing mothers with SLE at delivery to mothers from the general population restricted to singleton births

<table>
<thead>
<tr>
<th></th>
<th>Prevalent SLE</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>604</td>
<td>18,226</td>
</tr>
<tr>
<td>Male baby, N (%)</td>
<td>293 (48.5)</td>
<td>9,303 (51.0)</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>0.94</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Table 1: Risk of high-grade cervical dysplasia or cervical cancer among women with SLE who initiated immunosuppressive drugs vs. hydroxychloroquine in a propensity score-matched analysis

Disclosure: E. V. Arkema, None; J. Asking, None; J. Salmon, None; J. F. Simard, None.

1073


Rishi Desai1, Krista Aubyrechts2, Brian Bateman3, Helen Mogun4, Sonia Hernandez-diaz4 and Seoyoung C. Kim5. 1Brigham and Women's Hospital, Boston, MA, 2Brigham and Women's Hospital, Boston, MA, 3Harvard School of Public Health, Boston, MA.

Background/Purpose: Little is known about the trends of medication use in pregnant women with autoimmune disorders. The objective of the current study was to examine the prevalence and trends of oral steroids and immunomodulatory drug use in pregnant women with rheumatoid arthritis (RA), psoriasis, and systemic lupus erythematosus (SLE).

Methods: A cohort of pregnant women with RA, psoriasis, or SLE was identified using data from the Medicaid Analytical eXtract for the period of 2000-2007. The following 3 classes of medications were identified using prescription dispensing data for these patients: 1) oral steroids, 2) non-biologic disease modifying anti-rheumatic drugs (nbDMARDs), and 3) biologic DMARDs. The proportion of women with RA, psoriasis, and SLE exposed to these medications in the following time-windows were reported: 1) 3 months pre-last menstrual period (LMP), 2) first trimester, 3) second trimester, and 4) third trimester. Trends in the use were also evaluated by calendar year.

Results: A total of 1,734 pregnant women with RA, 2,932 with psoriasis and 2,392 with SLE enrolled in M edicaid from 46 states and Washington, DC, were identified. During the 3 months pre-LMP, 16.8% of women with RA used oral steroids, 11.9% used nbDMARDs, and 4.3% used biologics. During pregnancy, the use of steroids showed modest reduction in women with RA compared to 3 months pre-LMP use (Figure). However, the use of nbDMARDs showed a marked reduction in women with RA, 14.9% used nbDMARDs, and 1.4% used biologics during the 3 months pre-LMP period. During pregnancy, use decreased for all the three classes of medications. In women with SLE, 16.7% used oral steroids, 14.9% used nbDMARDs, and 0.6% used biologics during the 3 months pre-LMP period. Use of steroids was increased moderately during pregnancy compared to 3 months pre-LMP use, but a lower proportion of women used non-biologic and biologics during pregnancy in the SLE cohort. No meaningful time trends were observed in use of these three classes of medications during pregnancy between 2000 and 2007.

Conclusion: We observed reduced use of non-biologic and biologics in women with RA, psoriasis, and SLE during pregnancy compared to before pregnancy. This reduced use may be due to lowered disease activity during pregnancy or fetal safety concerns related to the use of these agents. Oral steroids were the most commonly used therapy in all three populations at all the stages of pregnancy. Given this high use, future research evaluating the safety of steroids in pregnancy is warranted.

Table 1: Risk of high-grade cervical dysplasia or cervical cancer among women with SLE who initiated immunosuppressive drugs vs. hydroxychloroquine in a propensity score-matched analysis

Disclosure: R. Desai1, Biogen Idec, 1; K. Huybrechts2, None; B. Bateman3, None; H. Mogun4, None; S. Hernandez-diaz4, Novartis, GSK, AstraZeneca, 5; S. C. Kim5, Pfizer Inc, 2.

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A Meta-Analysis of the Risk of Venous Thromboembolism in Inflammatory Rheumatic Diseases. Jason J. Lee1 and Janet E. Pope2. 1University of Western Ontario, London, ON, 2St Joseph Health Care, London, ON.

Background/Purpose: We performed a meta-analysis investigating the risk of developing deep vein thrombosis (DVT) and/or pulmonary embolisms (PE) in patients with inflammatory arthritis, vasculitis, and connective tissue diseases (CTD) [SLE, Sjogren’s syndrome, inflammatory myositis and systemic sclerosis (SSc)].
Methods: PubMed, Embase, Cochrane Databases, and Medline were searched identifying full text English publications in adults related to rheumatologic inflammatory diseases and VTE. Data regarding rates of DVTs and PEs were extracted. Using random effects models, pooled estimates for VTE in individual and pooled diseases compared with matched populations where possible. Studies were excluded if VTEs were in the setting of pregnancy, postoperative outcomes or solely antiphospholipid antibody syndrome.

Results: Most of the 3,929 studies were excluded due to lack of rate or incidence of VTE. Twenty studies remained for analysis. Eight studies of RA identified 5,273,942 patients and 891,530,181 controls with a cumulative incidence of 107.9% (95% CI: 82.4%–136.0%) and an odds ratio of 2.95 (95% CI: 2.57–3.38) compared to age and sex, matched population. Six studies included 36,582 SLE patients with a cumulative incidence of 8.24% (95% CI: 7.67–8.82%); four studies of inflammatory myositis (N = 8,245) yielded a VTE cumulative incidence of 4.03% (95% CI: 2.38–5.67%), SSc and ANCA vasculitis rates (3 studies each) was 3.82% and 85.1% respectively. The figure shows VTEs in RA as an example.

Conclusion: Inflammatory rheumatologic diseases studied were all associated with high rates of VTEs, more nearly three times higher than the general population. Identification of those at risk is important. We cannot determine from these studies what the risk is when inflammation is effectively treated.

(a) Cumulative Incidence of VTEs in patients with RA

(b) Cumulative Incidence of VTEs in RA compared to matched control population presented as Odds Ratio

Disclosure: J. J. Lee, None; J. E. Pope, None.

1075 Risk of High-Grade Cervical Dysplasia and Cervical Cancer in Women with Systemic Lupus Erythematosus on Immunosuppressive Drugs.

Candace H. Feldman, Jun Liu, Sarah Feldman, Daniel H. Solomon and Seoyoung C. Kim. Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: Human papillomavirus (HPV) is the most common sexually transmitted disease in the US and the main cause of high-grade cervical dysplasia and cervical cancer. Prior studies suggest an increased risk of cervical cancer in women with systemic lupus erythematosus (SLE), however the relationship with immunosuppressive drugs (ISDs) is not well studied. We compared the risk of high-grade cervical dysplasia and cervical cancer among women with SLE receiving hydroxychloroquine (HCQ) to those on ISDs in a nationwide database. We hypothesized that the risk of cervical dysplasia and cervical cancer would be increased among ISD users.

Methods: We utilized US commercial insurance claims data (2001–2012) to conduct a cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia or cervical cancer in women who initiated ISDs or HCQ for SLE. The index date was defined as the dispensing date of the first ISD or HCQ after ≥2 diagnoses of SLE (ICD-9 code 710.0). We required patients to have ≥365 days of continuous enrollment prior to the index date without use of ISDs or HCQ. We assessed baseline covariates during this period. We defined the outcome, high-grade cervical dysplasia or cervical cancer, using a validated claims-based algorithm with a positive predictive value of ≥81%.

We also determined the number of gynecologic visits and procedures during follow-up. To control for potential confounders including age, comorbidities, HPV vaccination, corticosteroid use, additional medications, and healthcare utilization, initiators of ISDs were matched to HCQ initiators using propensity scores with a 1:1 ratio.

Results: Among 2,451 propensity score-matched pairs of women with SLE, the median age was 46 years, the mean follow-up was 1.15 (SD 1.38) years, and the overall follow-up was 5,622 person-years. The IR of high-grade cervical dysplasia or cervical cancer per 1,000 person-years was 2.47 in ISD initiators and 2.09 in HCQ initiators (Table). There were 114 cases of high-grade cervical dysplasia or cervical cancer in the ISD group and 5 cases in the HCQ group for a hazard ratio of 2.47 (95% CI: 0.89–6.85). The number of outpatient gynecologic visits (Rate ratio [RR] 0.93, 95% CI: 0.81–1.07) and gynecologic procedures (RR 1.13, 95% CI: 0.98–1.44) was not significantly different between the two groups.

Conclusion: Among women with SLE, initiation of ISDs may be associated with a greater, albeit not statistically significant risk of high-grade cervical dysplasia or cervical cancer compared to HCQ alone. Given the rare nature of cervical cancer and the prolonged latency period, further studies with extended follow-up are needed to confirm this finding.

Table 1. Risk of high-grade cervical dysplasia or cervical cancer among women with SLE who initiated immunosuppressive drugs* versus hydroxychloroquine in a propensity score-matched analysis**

*Immunosuppressive drugs include: methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus, abatacept, rituximab and belimumab.

**The propensity score model includes age, sex, calendar year, comorbidities, HPV vaccination, being sexually active, sexually transmitted diseases, other comorbidities, medication use including oral contraceptives and corticosteroids, Pap test, HPV DNA test, and other health care variables such as outpatient gynecologic visits (Rate ratio [RR] 0.93, 95% CI: 0.81–1.07) and gynecologic procedures (RR 1.13, 95% CI: 0.98–1.44) was not significantly different between the two groups.

Disclosure: C. H. Feldman, None; J. Liu, None; S. Feldman, None; D. H. Solomon, Pfizer Inc; 2, Agenus, 2, Lilly, 2, Corona; 2, UpToDate, 7; S. C. Kim, Pfizer Inc; 2.

1076 U.S. Geographic Trends in the Distribution and Treatment Practices of Juvenile Systemic Lupus Erythematosus: An Analysis of the Childhood Arthritis and Rheumatology Research Alliance Registry. Jennifer M. P. Woo1, Ornella J. Rullo1, Deborah K. McCurdy2 and The CARRA Registry Investigators3. 1University of California, Los Angeles, Los Angeles, CA, 2UCLA Division of Pediatric Rheumatology, Los Angeles, CA, 3Childhood Arthritis and Rheumatology Research Alliance, Durham, NC.

Background/Purpose: Human papillomavirus (HPV) is the most common sexually transmitted disease in the US and the main cause of high-grade cervical dysplasia and cervical cancer. Prior studies suggest an increased risk of cervical cancer in women with systemic lupus erythematosus (SLE), however the relationship with immunosuppressive drugs (ISDs) is not well studied. We compared the risk of high-grade cervical dysplasia and cervical cancer among women with SLE receiving hydroxychloroquine (HCQ) to those on ISDs in a nationwide database. We hypothesized that the risk of cervical dysplasia and cervical cancer would be increased among ISD users.

Methods: We utilized US commercial insurance claims data (2001–2012) to conduct a cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia or cervical cancer in women who initiated ISDs or HCQ for SLE. The index date was defined as the dispensing date of the first ISD or HCQ after ≥2 diagnoses of SLE (ICD-9 code 710.0). We required patients to have ≥365 days of continuous enrollment prior to the index date without use of ISDs or HCQ. We assessed baseline covariates during this period. We defined the outcome, high-grade cervical dysplasia or cervical cancer, using a validated claims-based algorithm with a positive predictive value of ≥81%.

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*Immunosuppressive drugs include: methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus, abatacept, rituximab and belimumab.

**The propensity score model includes age, sex, calendar year, comorbidities, HPV vaccination, being sexually active, sexually transmitted diseases, other comorbidities, medication use including oral contraceptives and corticosteroids, Pap test, HPV DNA test, and other health care variables such as outpatient gynecologic visits (Rate ratio [RR] 0.93, 95% CI: 0.81–1.07) and gynecologic procedures (RR 1.13, 95% CI: 0.98–1.44) was not significantly different between the two groups.

Disclosure: C. H. Feldman, None; J. Liu, None; S. Feldman, None; D. H. Solomon, Pfizer Inc; 2, Agenus, 2, Lilly, 2, Corona; 2, UpToDate, 7; S. C. Kim, Pfizer Inc; 2.
medications (Fig 1). Furthermore, C2 jSLE required significantly fewer medications compared to C1 (4.4 vs 5.7, respectively; p<0.01).

**Conclusion:** The heterogeneous nature of jSLE and regional variation in medication usage may have impacted the development of standardized treatment practices. Importantly, however, the overall number of required medications, glucocorticoids and NSAIDs in particular, has decreased across the U.S. Subsequently, regional and temporal variations may reflect the recent trend towards the standardization of medication practices in jSLE.

### Table 1. Demographics and characteristics of spatial analysis cohort and temporal cohorts

<table>
<thead>
<tr>
<th>Spacial Analysis Cohort</th>
<th>Cohort 1 (Diagnosis &amp; treatment prior to 2007)</th>
<th>Cohort 2 (Diagnosis &amp; treatment 2007-2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% of enrolled CARRA</td>
<td>SLE, n = 925</td>
<td>C1 (n = 355)</td>
</tr>
<tr>
<td>Female-to-Male ratio</td>
<td>64.43 (3.91)</td>
<td>185.61 (3.10)</td>
</tr>
<tr>
<td>Age of disease onset</td>
<td>12.4</td>
<td>10.7*</td>
</tr>
<tr>
<td>Disease duration prior to diagnosis (years)</td>
<td>0.56</td>
<td>0.53</td>
</tr>
<tr>
<td>ACR criteria count mean</td>
<td>4.1</td>
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<tr>
<td>ACR functional class at diagnosis</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Medication count</td>
<td>5.0*</td>
<td>5.7*</td>
</tr>
<tr>
<td>Medication count excluding glucocorticoids</td>
<td>4.0*</td>
<td>4.6*</td>
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<tr>
<td>Health insurance (%)</td>
<td>94.7</td>
<td>95.5</td>
</tr>
<tr>
<td>Male 53 (15)</td>
<td>52 (15)</td>
<td></td>
</tr>
<tr>
<td>Female 312 (88)</td>
<td>132 (95)</td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed 6 (2)</td>
<td>8 (2)</td>
<td></td>
</tr>
<tr>
<td>Part-time 24 (8)</td>
<td>33 (9)</td>
<td></td>
</tr>
<tr>
<td>Full-time 172 (57)</td>
<td>172 (57)</td>
<td></td>
</tr>
</tbody>
</table>
| Health-related Quality of Life
| EQ-5D, mean (SD)        | 0.87 (0.14)                                  | 0.88 (0.14)                                 |
| EQ-5D VAS, mean (SD)    | 78.83 (17.48)                                | 78.83 (17.48)                               |
| Mean % impairment (SD)  | 13.51 (18.76)                                | 13.51 (18.76)                               |

**Table:** Characteristics of patients with “Mild” and “Moderate-to-severe” jSLE disease severity

### Background/Purpose

Systemic lupus erythematosus (SLE) is a chronic, inflammatory disease which can impact on patients' Health-Related Quality of Life (HRQoL). This analysis was designed to characterize US SLE patients classified by physicians as having “mild” to “severe” disease, and to assess their burden of disease compared with those with “mild” disease severity.

### Methods

Data were extracted from the multi-sponsor Adelphi Lupus Disease-Specific Program, a multinational survey of clinical practice. US physicians completed Patient Record Forms (PRFs); disease severity was based on physician assessments. Patients self-reported data including EQ-5D and Work Productivity and Activity Impairment Index for SLE (WPAI-Lupus), which were included in Patient Self-Completion Records (PSRs).

### Results

PRFs and PSRs were collected from 97 rheumatologists. Of 498 patients, disease severity was classified as “mild” in 355 (71%), and “moderate-to-severe” in 139 (28%) (severity was not specified in 4 patients [1%]). Physician assessment of disease severity was predominantly based on affected organs/symptoms (considered most important by 37% and 40% of rheumatologists, respectively). Only 11% reported test results/clinical assessments as a determinant of SLE severity, with no single disease activity index widely used in clinical practice: 68% rheumatologists reported using their own systematic assessment. Physician assessment of disease severity and control of disease activity were imperfectly correlated: disease activity was controlled in 54% of patients with “moderate-to-severe” disease severity, and partially controlled or uncontrolled in 29% of patients with “mild” disease severity. “Mild-to-severe” patients initially presented with greater disease severity and organ involvement (13% had skin-only SLE at diagnosis), and more flares per 12 month period (Table), than “mild” patients. Compared to “mild” severity, “moderate-to-severe” SLE severity was associated with a greater impact on HRQoL, which was comparable to rheumatic conditions including rheumatoid arthritis and psoriatic arthritis (Table). Fewer “moderate-to-severe” patients were employed, and a higher proportion required care providers (Table). For both “mild” and “moderate-to-severe” patients, obesity was one of the most common associated comorbidities; the proportion of “moderate-to-severe” patients affected was over double that of “mild” patients (Table).

### Conclusion

“Mild-to-severe” SLE severity was associated with a greater burden of disease than patients with “mild” severity. Data show that disease severity is not consistently assessed in US clinical practice and is a multifaceted concept, imperfectly correlated with control of disease activity. Thus, there is a need for a simple, universal tool to accurately assess SLE disease activity, as well as severity, to inform physician and patient decisions regarding treatment.

### Disclosure

J. M. P. Woo, None; O. J. Rullo, None; D. K. McCurdy, None; T. CARRA Registry Investigators, None.
clinical and health in patients (pts) with systemic lupus erythematosus (SLE).

**Methods:** Self-reported (outcome) questionnaires including clinical data were applied to SLE pts and controls (c) not suffering from rheumatic diseases, both groups were capable for work. The ‘AVÉM’ questionnaire assesses eleven health relevant dimensions via 66 items and thus determines the personal attitudes towards work, see Table 1. The dimensions (d) are attributable to three areas: work engagement (d 1–5), resistance to stress (again d 5; 6–8) and the emotions accompanying occupation (d 9–11). Ethics committee approval had been obtained.

**Results:** 252 pts (95.6% female (f)) and 177 c (90.3% f) contributed data. Patients’ mean age was 40.1 ± 9.4 (c 42.8 ± 9.8) years, mean duration disease 10.5 ± 7.3 years, mean H AQ 0.8 ± 0.4 (c 0.4 ± 0.1), 86.0% reported at least one comorbidity (range 1–10, c 45.2%, range 0–4). 77.4% received at least one immunosuppressive medication (range 0–3). 40.5% were on steroids <7.5mg, 16.3% on steroids >7.5mg. 32.1% took NSAIDs.

**AVÉM** scales are depicted in Table 1. SLE pts scored significantly different to c in eight dimensions. Pts showed higher scores for 4 of 5 work engagement scales, less capability for emotional distancing, higher resignations tendencies, lower satisfaction with life and lower experiences of social support. OR indicate whether points of the T-group (see table 1) have an increased risk for lower self-rated health status compared to T+.

**Conclusion:** This is the first study applying AVÉM to SLE pts. Results detected domains that are potentially modifiable and should be considered in clinical management. Pts work engagement, resistance to stress and emotional issues should be predominantly targeted. Further study analyses will address correlations to other study parameters and confounding factors. Thus, appropriate strategies that promote healthy personal attitudes and equip pts with adequate supporting coping skills that prepare them for the challenges at their daily work might and should be developed.

**Disclosures:** J. G. Richter None; R. Brinks None; T. Muth None; T. Koch None; P. Angerer None; M. Schneider None.

**1079**

**Prevalence of Cardiac Arrhythmias in Systemic Lupus Erythematosus.** Gihyun Myung, Lindsey J. Forbess, Mariko L. Ishimori, Sumeet Chugh, Daniel Wallace and Michael H. Weisman. Cedars-Sinai Medical Center, Los Angeles, CA.

**Background/Purpose:** Cardiovascular disease is a major cause of death among systemic lupus erythematosus (SLE) patients. Although the prevalence of atrial fibrillation (0.5–1%) and QT prolongation (7%) is well studied in the general population, little is known regarding arrhythmias in SLE. The aim of this project is to determine the prevalence of arrhythmias in a SLE population.

**Methods:** We retrospectively reviewed electrocardiograms (ECGs) of SLE patients seen in inpatient, outpatient and emergency department settings over a 10-year time frame at a single academic center. A nonnormal ECG findings were confirmed by an electrophysiologist. ECGs were categorized as abnormal (arrhythmias or QT prolongation (QT > 450 ms for women; >480 ms for men) were present. Sinus bradycardia, 1st degree AV block, and sinus tachycardia were not considered arrhythmias but were recorded. Arrhythmias were also ascertained through review of ICD9 codes for the subset of SLE patients with available ECGs.

**Results:** Of 1,139 SLE patients, 235 had available ECGs. 160 were white (68%), 33 black (14%), 27 Asian (12%), and 15 Hispanic (6%). 217 were female (92%), 18 (8%) male, and the average age was 52 ± 15 (average ± SD). Through ECG review, 6% had tachyarrhythmias (3% with atrial fibrillation) and 17% had QT prolongation (Table 1). None had bradyarrhythmias. Through ICD9 code examination, more had tachyarrhythmias (15%), including atrial fibrillation (9%), compared with direct ECG review. 35 of 53 abnormal ECGs (66%) were obtained in the inpatient setting. 11 (21%) in the outpatient setting, and 7 (13%) in the emergency department. The most common ECG indication was chest pain (12% of abnormal and 16% of normal ECGs).

**Conclusion:** Sinus tachycardia was the most common ECG finding among our SLE patients. Compared to the general population, our SLE patients had a higher prevalence of atrial fibrillation and QT prolongation. This is likely an underestimation of the true arrhythmia prevalence, given that review of ICD9 codes revealed an even higher rate of tachyarrhythmias compared to direct ECG review. As QT prolongation was common in our SLE patients, it is important to be vigilant about drug interactions and the electrophysiologic effects of various medications, such as antibiotics, in these patients. Further prospective study of arrhythmias, their outcomes, and underlying causative factors (such as medication use and disease severity) in SLE patients is warranted.

**Table 1. Prevalence of Arrhythmias in SLE patients after Review of ECGs and ICD9 codes**

<table>
<thead>
<tr>
<th>Type of Review, N (%)</th>
<th>ECG, N = 235</th>
<th>ICD9 Code, N = 235</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Tachyarrhythm</td>
<td>13 (6)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>7 (3)</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Atrial tachycardia</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Supraventricular tachycardia</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal ventricular tachycardia</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>QT Prolongation</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Sinus Tachycardia</td>
<td>42 (18)</td>
<td>Not Available</td>
</tr>
<tr>
<td>Sinus Bradycardia</td>
<td>34 (14)</td>
<td>Not Available</td>
</tr>
<tr>
<td>1st Degree AV Block</td>
<td>6 (3)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

**Disclosures:** G. Myung None; L. J. Forbess None; M. L. Ishimori None; S. Chugh None; D. Wallace None; M. H. Weisman None.

**1080**

**Stroke Risks Among U.S. Medicaid Recipients with Systemic Lupus Erythematosus, 2000–2006: Racial and Ethnic Variation.** Medha Barbhaya,4 Jose A. Gomez-Puerta2, Hongshu Guan3, Daniel H. Solomon1, Joanne M. Foody1, Graciela S. Alarcon4 and Karen H. Costenbader.3 Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, University of Alabama at Birmingham, Birmingham, AL.

**Background/Purpose:** SLE patients are at increased stroke risk, but racial/ethnic variation in risk has not been examined in a population-based study. We examined risks by race/ethnicity among SLE patients in the Medicaid, the US medical insurance program for the poor. We investigated whether differential loss to follow-up and variation in mortality between racial/ethnic groups influenced Cox regression model estimates.

**Methods:** From the Medicaid Analytic eXtract (MAX) 2000–2006, containing all billing claims for patients from 47 U.S. states and Washington D.C., we identified patients 18–65 with prevalent SLE (i.e., SLE ICD-9 codes of 710.0, ~30 days apart) and/or lupus nephritis (additional >2 codes for nephritis, renal insufficiency or failure). The index date was the date when SLE or lupus nephritis definition was met. We extracted age, sex, US region, calendar year, zip code area-based socioeconomic status (SES). Baseline comorbidities and SLE-specific risk index (Ward M, J Rheum, 2000) were from ICD-9 and CPT codes until index date. Within inpatient claims, ICD-9 codes identified fatal and non-fatal, ischemic and hemorrhagic strokes (PPV 83%, Aroldare S, Pharmacoep Drug Saf, 2012). Stroke incidence rates (IR) per 1,000 person-years with 95% CIs were calculated for each racial/ethnic group. Multivariable-adjusted Cox regression models calculated cause-specific hazard ratios (HRs) for stroke from index date through end of follow-up, censoring for death or loss to Medicaid follow-up, adjusting for covariates (Table). We also used Fine and Gray proportional hazards models.
to calculate subdistribution HRs (HRsd), accounting for competing risks of death and loss to follow-up, adjusting for the same covariates.

Results: Of 42,221 SLE patients, 39,320 (93%) were female and 6,467 (15%) had lupus nephritis. Mean age at baseline was 38.13 (SD 12.29); 38% lived in the South, 23% in the West, 20% in the Northeast and 20% in the Midwest. Blacks represented 40%, Whites 38%, Hispanics 15%, Asians 5%, and Native Americans 2%. IRs were 10.02 (95% CI 9.44–10.64) per 1,000 person-years for all SLE patients, and 17.03 (95% CI 15.11–19.20) per 1,000 person-years for all lupus nephritis patients. A multivariable adjustment for additional factors, Blacks had higher stroke risks (HRcs 1.31) than Whites. (Table) This risk remained similarly elevated in competing risks models (multivariable HRsd 1.36). Among lupus nephritis patients, stroke risks among Blacks vs. Whites were also high (multivariable HRsd 1.57). Stroke risks among other racial/ethnic groups did not significantly differ from those in White patients.

Conclusion: Among US SLE and lupus nephritis patients, stroke IRs were high. After adjusting for sociodemographic and clinical factors, Blacks compared to Whites with SLE had 36% increased risks and those with lupus nephritis had 57% increased risks. A counting for competing risks did not substantially affect these estimates.

Table: Incidence Rates and Adjusted Subdistribution Hazard Ratios for Stroke Hospitalization among Medicaid SLE with the US, from 2000-2006, by Race and Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Total Number of Events Person-years</th>
<th>IR* (95% CI)</th>
<th>Multivariable-Adjusted Proportional Hazards HR (95% CI)^</th>
<th>CCI</th>
<th>Model</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>16219</td>
<td>40,204</td>
<td>8.76 (7.89–9.72)</td>
<td>1.0 (Ref)</td>
<td>1.0 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16956</td>
<td>42,091</td>
<td>12.78 (11.74–13.81)</td>
<td>1.32 (1.28–1.38)</td>
<td>1.26 (1.21–1.31)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3480</td>
<td>41,555</td>
<td>7.52 (6.46–8.58)</td>
<td>1.24 (1.12–1.35)</td>
<td>1.26 (1.09–1.43)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>6489</td>
<td>11,649</td>
<td>6.91 (5.75–8.30)</td>
<td>1.05 (0.85–1.20)</td>
<td>0.95 (0.75–1.20)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>677</td>
<td>1,653</td>
<td>10.29 (6.64–16.55)</td>
<td>1.22 (0.86–1.63)</td>
<td>1.30 (0.82–2.33)</td>
<td></td>
</tr>
</tbody>
</table>

IRR = Incidence rate, events per 1,000 person-years.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR with 95% CI</th>
<th>Model</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.017 (1.015–1.018)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Female Gender</td>
<td>1.065 (1.046–1.084)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Race/African American vs Caucasian</td>
<td>1.122 (1.088–1.157)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>CCI</td>
<td>1.213 (1.205–1.223)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>0.809 (0.810–1.603)</td>
<td></td>
<td>0.288</td>
</tr>
<tr>
<td>Antihypertensive Drug Use</td>
<td>0.772 (0.750–0.797)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.762 (0.720–0.806)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.718 (0.665–0.776)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>0.762 (0.720–0.806)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>0.718 (0.665–0.776)</td>
<td></td>
<td>-0.0001</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>1.284 (0.999–1.650)</td>
<td></td>
<td>0.0508</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.580 (0.566–0.594)</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Teaching Hospital Status</td>
<td>1.175 (1.116–1.237)</td>
<td></td>
<td>-0.0001</td>
</tr>
</tbody>
</table>

*CCI = Charlson Co-morbidity Index.

Conclusion: Though SLE and aPL Syndrome overlap significantly, we found in our analysis that after controlling the significant confounders, SLE alone is not an independent risk factor for increasing mortality risk among the CVA population. Whereas, aPL Syndrome is an independent predictor of increased risk of mortality in patients with CVA.

Disclosure: K. Mehta, None; T. M. Mehta, None; S. Puri, None; R. Soni, None; K. H. Mehta, None.

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Background/Purpose: Central nervous system involvement is common in Systemic Lupus Erythematosus (SLE) and was first described in 1873. Though ischemic involvement is more common than Intra-Cerebral Hemorrhage (ICH) in SLE, hemorrhagic involvement is more life threatening and disabling. Several studies have shown that SLE patients with ICH present with higher frequency of aPL-Phospho-Lipid Antibody (aPL) syndrome. Our study was tried to investigate if SLE or aPL syndrome independently predicts risk of ICH in CVA.

Methods: We queried the Healthcare Cost and Utilization Project’s (HCUP) Nationwide Inpatient Sample (NIS) between 2004 and 2010 and separated the hospitalizations due to or with stroke using ICD 9 diagnostic codes previously established by HCUP. A mong this population, we examined the patients with SLE and patients with aPL syndrome and compared their risk of ICH to the all stroke population using the logistic regression model.

The model was controlled for confounders which included age, sex, atrial fibrillation, chronic kidney disease, diabetes mellitus, rheumatoid arthritis, chronic rheumatic heart disease and diseases of endocardium. Using SAS 9.2, survey procedures were used to identify multivariate predictors of stroke.

Results: A total of 1,799,560 (weighted N = 8,874,475) who were hospitalized with stroke were available for analysis out of which 6,890 (weighted N = 33,662) had SLE and 13,769 (weighted N = 68,069) had aPL syndrome. On univariate analysis, patients with SLE had 4.4% mortality as compared to 4.35% in patients without SLE (p = 0.47); and patients with aPL syndrome had 11.37% mortality as compared to 4.3% in patients without aPL syndrome (p<0.0001). After controlling for confounders mentioned above, comorbid SLE was associated with decreased risk of having ICH (Odds Ratio (OR)= 0.68, Confidence Interval (CI)= 0.53–0.89, p< 0.0009) in patients with stroke. Whereas, co-morbid aPL was associated with increased risk of having ICH (OR = 1.93, CI = 1.72–2.17, p<0.0001), in patients with stroke.

Table 1: Multivariable predictors of ICH in the study population for stroke (N = 1,799,560)

<table>
<thead>
<tr>
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<th>P value</th>
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<td>Teaching Hospital Status</td>
<td>1.175 (1.116–1.237)</td>
<td></td>
<td>-0.0001</td>
</tr>
</tbody>
</table>
**Conclusion:** In addition to the understanding of increased risk of CVA in SLE and aPL Syndrome patients, further understanding of the nature of the cerebrovascular disease can influence treatment strategies. Our study showed that SLE patients are at decreased risk of hemorrhagic stroke in comparison to general stroke population. However, aPL Syndrome patients are at increased risk of hemorrhagic stroke in comparison to general stroke population. This suggests that aPL component of the disease spectrum predisposes the patients to ICH.

**Disclosure:** T. Mehta, None; K. Sheth, None; R. Soni, None; S. Puri, None; K. Mehta, None.

**ACR/ARHP Poster Session B**
**Epidemiology and Public Health (ARHP)**
**Monday, November 17, 2014, 9:30 am–4:00 pm**

### 1083

1Boston University, Boston, MA, 2Boston University School of Medicine, Boston, MA, 3Klinikum Augsburg, Augsburg, Germany, 4University of Alabama at Birmingham, Birmingham City, AL, 5University of Iowa, Iowa City, IA, 6UCSF, San Francisco, CA.

**Background/Purpose:** Patellofemoral joint (PFJ) osteoarthritis (OA) is a common source of pain and there is little evidence for rehabilitation treatment. Gait retraining treatments are effective in reducing pain in younger individuals with patellofemoral pain. Compared to self-selected step length, increased step length is related to increased PFJ stress. If step length affects PFJ stress, then individuals with a longer step length may be at increased risk of PFJ disease. The purpose of this study was to investigate the relation of step length to prevalent/worsening structural damage in the PFJ.

**Methods:** The Multicenter Osteoarthritis (MOST) Study is a NIH-funded cohort study of 3,026 individuals with or at risk for knee OA. Participants had MRI of their knee and two musculoskeletal radiologists assessed cartilage thickness, full-thickness cartilage loss and BMLs from 60 to 84-month study visits. Spatial-temporal gait parameters were collected using the Gaitrite system at the 60-month visit. Step length was measured as the distance from heel center of footprint to heel center of previous footprint from the other foot. Step length was divided into quintiles and we determined the relation of step length to prevalent full-thickness cartilage loss and BMLs in PFJ subregions using logistic regression with generalized estimating equations, adjusting for age, sex, BMI and leg length (measured from long limb films from center of femoral head to center of talus). Because knee pain from structural damage could cause a person to shorten their step length and reduce PFJ stress, in order to examine causal effects of step length, we determined the relation of step length to incident cartilage loss and BMLs from 60 to 84-months in PFJ subregions without any cartilage loss or BMLs at 60-months. In secondary analyses we normalized step length by leg length and also removed knees with frequent knee pain at 60 months.

**Results:** 4212 patellar and anterior femur subregions from 1132 knees were included. The mean age and BMI at the 60-month visit were 66.9 ± 7.5 years and 29.6 ± 4.7 kg/m², respectively, and 62% were female. While subregions in knees with the longest step length had the lowest prevalence of full-thickness cartilage loss, there was no association when adjusting for potential confounding variables. There was no association between step length and incident PFJ cartilage loss. Compared to subregions in knees with short step length, those with the longest step length were associated with 0.72 (0.52, 0.98) times the odds of prevalent BMLs in the PFJ (Table). There was no association between step length and incident BMLs. Similar results were seen in the secondary analysis.

**Conclusion:** Cartilage loss and BMLs were most common in knees with short step length but there was no relation of step length to worsening of cartilage or BML severity longitudinally. Individuals may shorten their step length to reduce PFJ stress.

Relation of step length quintiles to prevalent full-thickness cartilage loss and BMLs in subregions of the PFJ.

**Table:**

<table>
<thead>
<tr>
<th>Step Length</th>
<th>Prevalence</th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
<th>Prevalence</th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1 (Short Step)</td>
<td>26/44 (5.9%)</td>
<td>1.0 (reference)</td>
<td>p trend = 0.003</td>
<td>27/51 (5.3%)</td>
<td>1.0 (reference)</td>
<td>p trend = 0.03</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>116/219 (54.1%)</td>
<td>2.7 (2.3, 3.1)</td>
<td>0.0001</td>
<td>125/231 (54.0%)</td>
<td>2.7 (2.4, 3.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>185/306 (60.5%)</td>
<td>3.6 (3.1, 4.1)</td>
<td>0.0001</td>
<td>197/331 (59.5%)</td>
<td>3.6 (3.2, 4.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>203/362 (56.1%)</td>
<td>3.6 (3.1, 4.2)</td>
<td>0.0001</td>
<td>218/377 (58.0%)</td>
<td>3.6 (3.2, 4.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Quintile 5 (Long Step)</td>
<td>258/456 (56.4%)</td>
<td>3.7 (3.3, 4.1)</td>
<td>0.0001</td>
<td>275/479 (57.3%)</td>
<td>3.7 (3.3, 4.2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, leg length

**Disclosure:** J. Stefanik, None; K. D. Gross, None; T. D. Felson, None; J. Niu, None; N. K. White, None; A. Guermazi, Boston Imaging Core Lab, 1, Merck Serono, Genzyme, TissueGene, 5; F. Roemer, None; C. E. Lewis, None; N. A. Segal, None; M. Nevitt, None; C. Lewis, None.

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1University of California, San Francisco, CA, 2University of California, San Francisco, San Francisco, CA.

**Background/Purpose:** General population studies have found significant relationships between obesity and depression, including identifying obesity as a risk factor for onset of depression. In SLE, rates of depression are high, and depression can be a neuropsychiatric manifestation of SLE. The role of obesity as an independent risk factor for depression in SLE has not been studied. In this analysis, we examine the risk of depression onset for obese and non-obese women with SLE.

**Methods:** Analyses use data from the Lupus Outcomes Study (2004–2014) obtained through annual structured telephone interviews. All participants have physician-confirmed SLE. Depression symptoms were measured with the Center for Epidemiologic Studies Depression scale (CESD). Possible and probable depression were estimated using validated SLE-specific cut-points (20 and 24, respectively). Body mass index (BMI) was calculated from self-reported height and weight, and obesity was defined using a validated SLE-specific BMI cut-point of ≥25.8. Obesity was defined using the standard BMI obesity cut-point of 30. Cox proportional hazard models were used to estimate the risk of becoming depressed associated with obesity at baseline. Models were adjusted for age, race (white non-Hispanic vs. other), baseline disease activity (Systemic Lupus Activity Questionnaire, SLAQ), current smoking, prednisone use, and baseline functioning (SF-36 Physical Component Score). Only women were included in the analysis because the number of men was relatively small. Women who had BMI ≥18.5 or who met the depression criterion at baseline were excluded from analysis.

**Results:** Data from 718 women were available for analysis, of whom 32 had BMI ≥18.5. At baseline, 211 met the criterion for possible depression (CESD ≥ 20) and 171 for probable depression (CESD ≥ 24), leaving 471 and 515 in the analyses for possible and probable depression, respectively. BMI ranged from 18.6 — 54.9. Mean follow-up time was 9 years (range 2–11 years). In the analysis for possible depression, 31.6% of those who were not obese became depressed, compared to 48.1% of those who were obese (table). The adjusted HR (95% CI) for possible depression associated with obesity was 1.56 (1.15, 2.11). In the analysis of probable depression, 25.9% of those who were not obese became depressed compared to 42.6% of those who were obese.
obese. The adjusted HR (95% CI) for probable depression was 1.69 (1.23, 2.30). Using the standard BMI cut-point for obesity yielded similar results.

Conclusion: Obesity appears to be a risk factor for development of depression among women with SLE, even after controlling for disease activity and other relevant factors. This is a clinically important finding, as obesity is modifiable, and reducing obesity is likely to lead to additional health benefits such as reduced cardiovascular disease.

Risk of depression onset associated with obesity* among women with SLE

<table>
<thead>
<tr>
<th>Possible depression (CES-D ≥20)</th>
<th>Probable depression (CES-D ≥24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n for analysis</td>
<td>471</td>
</tr>
<tr>
<td>Obese at baseline</td>
<td>38.9%</td>
</tr>
<tr>
<td>Became depressed</td>
<td>Obese</td>
</tr>
<tr>
<td>Not obese</td>
<td>31.6%</td>
</tr>
<tr>
<td>Obese</td>
<td>25.9%</td>
</tr>
</tbody>
</table>

* Obesity defined as BMI ≥ 26.8.

Table 1. Baseline predictors of being in the Stable High (n = 272), Decreasing (n = 564) and Stable Low (n = 1916) physical activity groups. Odds ratios (OR) with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Baseline predictors</th>
<th>Stable High vs Stable Low OR (95% CI)</th>
<th>Stable High vs Decreasing OR (95% CI)</th>
<th>Decreasing vs Stable Low OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender; Women vs men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>1.0 (0.37–6.67)</td>
<td>1.0 (0.51–0.98)</td>
<td>0.71 (0.57–0.89)</td>
</tr>
<tr>
<td>35–54 vs 18–34</td>
<td></td>
<td>2.18 (1.10–4.31)</td>
<td></td>
</tr>
<tr>
<td>Rosary: Yes vs no</td>
<td>0.8 (0.53–2.9)</td>
<td></td>
<td>0.72 (0.48–1.1)</td>
</tr>
<tr>
<td>Self-efficacy for exercise, ESES</td>
<td>0.58 (0.35–0.96)</td>
<td>0.41 (0.28–0.60)</td>
<td></td>
</tr>
<tr>
<td>Exercise from friends, SSEB</td>
<td>1.53 (1.03–2.26)</td>
<td>1.60 (1.45–2.58)</td>
<td></td>
</tr>
<tr>
<td>Exercise self-efficacy, SSEB</td>
<td>1.77 (1.22–2.56)</td>
<td>1.54 (1.19–2.00)</td>
<td></td>
</tr>
<tr>
<td>Physical activity levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most vigorous intense activity</td>
<td>0.60 (0.37–0.99)</td>
<td>0.61 (0.37–0.99)</td>
<td></td>
</tr>
<tr>
<td>Moderate intense activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity lowest quartile versus highest quartile</td>
<td>2.27 (0.51)</td>
<td>2.27 (0.51)</td>
<td>2.27 (0.51)</td>
</tr>
</tbody>
</table>

Conclusions: This longitudinal study used data from the Swedish Quality Registry and a questionnaire covering sociodemographic, disease-related, psychosocial and physical activity variables. Physical activity was assessed by the International Physical Activity Questionnaire as total weekly hours of vigorous or intense activity, moderately intense activity and walking. A total of 2752 participants responding to at least two out of three questionnaires at baseline, 12 months and 24 months were aged 18–75 years, diagnosed with RA according to the ACR criteria and independent in daily living (Stanford Health Assessment Questionnaire ≥ 2.0). K-means cluster analysis was used to identify three trajectories of hours of weekly physical activity. Multinomial logistic regression was used to identify predictors of trajectory membership. Multiple imputation was used to impute missing data in potential predictors, which included sociodemographic, disease-related, psychosocial and physical activity variables.

Results: We identified three patterns of physical activity: The “Stable High” group performed on average 25 hours of physical activity per week (n = 272), the “Decreasing” group went from 22 to eight hours per week (n = 564) and the “Stable Low” performed three hours of physical activity per week (n = 1916). Predictors of being in the “Stable High” group versus the other two groups were male gender and already established health-enhancing physical activity at baseline. Increased age predicted being in the “Decreasing” group versus the other two groups. Predictors of being in the “Stable Low” group versus the other two groups were female gender, more activity limitation, lower self-efficacy for exercise and not having established health-enhancing physical activity at baseline. For detailed results, see Table.

Conclusions: The results indicate that physical activity levels are still low in the RA population. Different trajectories of physical activity over time exist and are possible to identify, with each trajectory being associated with a unique set of predictors. Modifiable predictors to improve physical activity include activity limitation and self-efficacy for exercise.

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The Effect of Foot Pain on Mobility Disability in Older Adults: The Framingham Foot Study. Alyssa B. Dufour1, Patricia P. Katz1, Y vonne M. Golightly2, A Runima Awale3 and Marrian T. Hannan3. 1 Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA, 4 University of California, San Francisco, San Francisco, CA, 5 University of North Carolina Dept of Epidemiology, Chapel Hill, NC, 6 Hebrew SeniorLife, Boston, MA, 7 Institute for Aging Research, Hebrew SeniorLife, Dept of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: While lower extremity function is thought to affect mobility, little is known of the influence of foot structure or function upon mobility limitations. We evaluated the associations of foot structure and foot function with mobility limitations in community-dwelling older men and women.

Methods: Framingham Foot Study participants (2002–2008) with performance measures of mobility limitations were included in this cross-sectional analysis. Mobility limitations were assessed using the Short Physical Performance Battery (SPPB), a composite of 3 timed performance tests (4-meter walk (s), chair stands (s), and balance test) with each test scored on a scale of 0 to 4 (total score range 0–12, higher score = better function). Previously, SPPB scores have predicted physical limitations, disability and mortality. We dichotomized SPPB as ≤ 4 to indicate mobility limitations and 4–12 as good mobility. We also examined quartiles of chair stand and walk time. Foot function while walking (pronated, supinated, normal) and weight-bearing arches (low, high, normal arch) were defined using a Telescan matscan pressure system. Age, sex, body mass index (BMI; kg/m2), current smoker (y/n) and depression (CES-D scale) were also obtained. Sex-specific multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between foot structure and function with mobility limitations, adjusting for factors above.

Results: In 556 men and 700 women, average age was 70 yrs (±10.8) and BMI was 28 (±5.2). 16% had mobility limitations, 30% had high arched and 27% had low arched foot structure; 33% had pronated and 27% had supinated foot function. Foot function was not associated with mobility limitations. In women only, low arch foot structure was associated with increased odds of mobility limitations (SPPB; OR = 2.27, p = 0.005) after adjustment (Table). No associations were seen between foot structure or function and chair stand time (hrs = 0.8–1.1, all p > 0.4). In quartiles of walk time, men in the 3rd quartile, compared to the lowest (fastest), were less likely to have a high arch foot structure (OR = 0.53) and supinated foot function (OR = 0.51). Women with a low arched foot were less likely to be in the 4th quartile (slowest walkers) compared to the fastest walkers and women with a pronated foot function were more likely to be in the 3rd quartile of walking speed compared to the fastest walkers.

Conclusion: Specific components of foot structure and function were associated with mobility limitations in our study, albeit with inconsistent patterns between men and women. Given these results, future work might examine specific regions of foot pressures and time-integral measures in order to drill down to biomechanical mechanisms.
Table 1. Odds Ratios and 95% Confidence Intervals for the Association between SPPB and Quartiles of Measured Walking Time with Foot Structure and Foot Function in Men and Women of the Framingham Foot Study.

<table>
<thead>
<tr>
<th>SPPB (1–9 versus 10–12)</th>
<th>Foot Structure</th>
<th>High Arch</th>
<th>Low Arch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pronated</td>
<td>1.03 (0.58, 1.84)</td>
<td>0.57 (0.31, 1.07)</td>
<td>0.59 (0.31, 1.12)</td>
</tr>
<tr>
<td>Over-Pronated</td>
<td>0.77 (0.42, 1.42)</td>
<td>0.826 (0.45, 1.57)</td>
<td>0.826 (0.45, 1.57)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, CES-D score, current smoking

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**Background/Purpose:** Socioeconomic disparities in health outcomes among people with osteoarthritis are well documented, with some key limitations: existing studies limit their analyses to few outcome variables at a time; they often evaluate socioeconomic status (SES) as a dichotomous exposure. As a result, there remains substantial uncertainty regarding the extent and nature of those health inequities. The data from the Osteoarthritis Initiative (OAI) allow us to comprehensively assess socioeconomic disparities in health outcomes within a large group of individuals at risk for or diagnosed with knee osteoarthritis.

**Methods:** This study includes 4081 OAI participants with full data on demographics, SES and health behaviors. Health outcomes included SF-12 measures of physical (PCS) and mental (MCS) health, the SF-36v2 for health-related Quality of Life, and the amount of time needed to complete 20m and 400m walks. Our analyses focused on baseline measurements and used ordinal least squares regressions to evaluate the associations of health outcomes with categories of family income and education, included separately and then simultaneously. All analyses were adjusted for race, sex, age, and standard errors were clustered by study site. Linear trends were assessed across income and education categories using linear contrasts.

**Results:** 58% of sample respondents were women, 18% self-identified as African-Americans, and the mean age was 61 years. Participants had an average BMI of 29kg/m², and nearly half (45%) ever smoked. 30% of all sample participants held a grade degree or diploma. Further adjustments for education and income remained independently associated with knee osteoarthritis. Differences were not explained by health behaviors, and further studies should explore pathways related to the patterns described herein.

**Conclusion:** The health of OAI participants varied strongly according to their SES, in a gradient pattern of worsening health with lower levels of income and education. This may be the most comprehensive study of the health socioeconomic gradient in a population with OA or at risk for OA. Differences were not explained by health behaviors, and further studies should explore pathways related to the patterns described herein.

**Table 1:** Differences in adjusted means (from reference) for the associations of education and income with health outcome measures in the Osteoarthritis Initiative (N = 4081), in separate ordinal least squares regression models adjusted for age, race, and sex.

<table>
<thead>
<tr>
<th>Income</th>
<th>SF-12 PCS</th>
<th>MCS</th>
<th>CESD</th>
<th>Pain</th>
<th>WOMAC Disability</th>
<th>Stiffness</th>
<th>Function</th>
<th>KOOS</th>
<th>Walk time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50K</td>
<td>-1.021</td>
<td>0.22</td>
<td>0.25</td>
<td>0.005</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>1847</td>
</tr>
<tr>
<td>50K-74K</td>
<td>-2.74</td>
<td>0.14</td>
<td>0.18</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>1893</td>
</tr>
<tr>
<td>75K-100K</td>
<td>-2.78</td>
<td>0.22</td>
<td>0.25</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>1811</td>
</tr>
<tr>
<td>&gt;100K</td>
<td>-3.12</td>
<td>0.30</td>
<td>0.35</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>1773</td>
</tr>
</tbody>
</table>

1. Reference category age: ≥50,000.00 (income) and high school (education).
2. WOMAC scores are highest of both knees.
3. MCID: minimal clinically important difference.
4. MCS: mental component summary.
5. OLI: Quality of life.
6. Linear trend evaluated using linear contrasts.

The sample included patients with limited and diffuse SSc (N = 1,125) participating in the Canadian Scleroderma Research Group Registry. As part of the Registry, patients are scheduled for annual follow-up visits. Patients with and without follow-up visits were included to account for potentially informative patient drop out. Growth mixture modeling (GMM) with robust maximum likelihood estimation was completed to identify groups of patients with distinct trajectories of disability over a three-year period, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; range: 0 (no disability) – 3 (severe disability)). Multinomial logistic regression was used to identify baseline sociodemographic and clinical variables that predicted membership in the latent growth trajectory classes.

Results: Considering fit indices (AIC, sBIC, BLRT) and substantive interpretation (class proportions, entropy), the GMM analysis identified three distinct groups of patients based on their disability trajectories. Class 1 was comprised of 53.4% of the total sample, and Classes 2 and 3 were comprised of 35.3%, and 11.2% of the total sample, respectively. Based on trajectories of HAQ-DI scores the groups were named: Minimal Disability-Increasing (Class 1; baseline HAQ-DI: 2.7), Moderate Disability-Stable (Class 2; baseline HAQ-DI: 1.20), and Severe Disability-Stable (Class 3; baseline HAQ-DI: 2.04). In Class 1, HAQ-DI scores increased by 1.2 over three years. Patients in Class 3 had more finger ulcers, more breathing problems, and more gastrointestinal problems than patients in Class 2 or Class 1. In addition, patients in Class 3 were of older age, had shorter disease duration, and were more likely to be female and have diffuse disease than patients in Class 1. Patients in Class 2, when compared to Class 1, had more finger ulcers, breathing problems, and severe Raynaud’s phenomenon, and were more likely to be older, female, and have diffuse disease.

Conclusion: Disability trajectories are not uniform across patients with SSc. Overall, patients with low baseline disability scores and disability progression had fewer finger ulcers, breathing problems, and gastrointestinal problems, less severe Raynaud’s phenomenon, were of younger age, male, had longer disease duration, and limited disease in comparison to the moderate and severe disability groups. The moderate and severe disability groups did not report significant disability progression, suggesting that for at least some patients with SSc, disability may reach a peak and then remain stable overtime.

Disclosure: S. D. Mills, Rheumatology Research Foundation, 2; R. S. Fox, None, S. Gholizadeh, None, S. C. Roesch, None, M. Baron, American College of Rheumatology Research and Education Foundation, 2; Fonds de la Recherche en Santé du Québec, 2, Canadian Institutes of Health Research, 2, Scleroderma Society of Canada, 2, INOVA Diagnostics Inc, 2; Dr. Fooke Laboratorium GmbH, 2, Euroimmun, 2, Mikrogen GmbH, 2; Fonds de la recherche en du Québec - Santé, 2, Lady Davis Institute of Medical Research of the Jewish General Hospital, 2, Pfizer Inc, 2, Actelion Pharmaceuticals US, 2; V. L. Malcarne, None.

Association of Objectively Measured Physical Activity and Metabolic Syndrome Among Adults with Osteoarthritis in the United States. Shao-Hsien Liu, Charles Eaton and Kate Lapane. 2, 3Clinical and Population Health Research Program, Graduate School of Biomedical Science, University of Massachusetts Medical School, Worcester, MA, 2, Department of Family Medicine and Epidemiology, Warren Alpert Medical School, School of Public Health, Brown University, Providence, RI, 3Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Metabolic syndrome increases the risk of osteoarthritis (OA). The accumulation of components of the metabolic syndrome is associated with a gradual increase in the risk of development and progression of knee OA. Physical activity may be a viable strategy to decrease the prevalence of metabolic syndrome. Studies examining physical activity among persons with OA are limited by self-reported data and the definitions are varied. The purpose of this study is to investigate the association between objectively-measured physical activity and metabolic syndrome among a nationally representative sample of adults with OA.

Methods: Using cross-sectional data from the 2003–2006 National Health and Nutrition Examination Survey, we identified 385 adults with OA who had physical activity measured with the Actigraph AM-7164 accelerometer worn on the right hip on an elasticized belt. Accelerometers provide a reliable and sensitive measure for the duration and intensity of bodily movement. As such, the activity counts derived from accelerometers were used to differentiate overall physical activity levels: 1) sedentary (>100 counts/min); 2) light physical activity (100 to 759 counts/min); 3) lifestyle (760 to 2019 counts/min); and 4) moderate to vigorous activity (>2020 counts/min). Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III standards. Logistic regression models estimated the relationship of quartile of daily minutes for each activity type to odds of metabolic syndrome adjusted for confounders and weighted for the complex survey design.

Results: Metabolic syndrome was present in 48.0% and of those, 11.2% met the physical activity guidelines of 150 minutes per week of moderate/vigorous activity. The proportion of sedentary time of total wear time, daily duration in light, lifestyle, or moderate to vigorous physical activity was associated with cluster components of metabolic syndrome. Relative to the least quartile of light activity, those in the highest quartile had reduced odds of metabolic syndrome (adjusted odds ratio (aOR) >296.3 versus ≤212.3 minutes/day: 0.43; 95% Confidence Interval (CI): 0.23 to 0.83; aOR 256.1–296.3 versus ≤212.3 minutes/day: 0.77; 95% CI: 0.30 to 1.97; aOR 212.4–256.0 versus ≤212.3 minutes/day: 1.43; 95% CI: 0.88 to 2.31; p-value for linear trend = 0.01).

Conclusion: Increased light physical activity was inversely associated with prevalence of metabolic syndrome among adults with OA. Effective interventions to encourage individuals with OA to increase light activity during daily living are warranted.

Disclosure: S. H. Liu, None; C. Eaton, None; K. Lapane, None.

Skeletal Muscle Fat and Its Association with Physical Function and Physical Activity in Adults with Rheumatoid Arthritis. Samannaaz S. Khoo, Brett Goodpaster and Sara R. Piva. 1University of Pittsburgh, Pittsburgh, PA, 2Sanford Burnham Medical Research Institute, Lake Nona in Orlando, FL.

Background/Purpose: Systemic inflammation in RA not only affects joints, but also body composition. People with RA tend to have lower lean body mass and higher body fat compared to healthy persons. Fat is also present inside the muscle, but little is known about how these fat depots are affected in RA, and their role in physical function. Skeletal muscle fat can potentially interfere with muscle fiber function and metabolic activity, and thus can be hypothesized to affect physical function. The aim of this study was to explore the association of skeletal muscle fat with outcomes of physical function and physical activity in persons with RA.

Methods: This was a cross-sectional, secondary analysis of baseline data from a study in adults diagnosed with RA as per the ACR criteria. Skeletal

Conclusion: Increased light physical activity was inversely associated with prevalence of metabolic syndrome among adults with OA. Effective interventions to encourage individuals with OA to increase light activity during daily living are warranted.

Disclosure: S. H. Liu, None; C. Eaton, None; K. Lapane, None.

Skeletal Muscle Fat and Its Association with Physical Function and Physical Activity in Adults with Rheumatoid Arthritis. Samannaaz S. Khoo, Brett Goodpaster and Sara R. Piva. 1University of Pittsburgh, Pittsburgh, PA, 2Sanford Burnham Medical Research Institute, Lake Nona in Orlando, FL.

Background/Purpose: Systemic inflammation in RA not only affects joints, but also body composition. People with RA tend to have lower lean body mass and higher body fat compared to healthy persons. Fat is also present inside the muscle, but little is known about how these fat depots are affected in RA, and their role in physical function. Skeletal muscle fat can potentially interfere with muscle fiber function and metabolic activity, and thus can be hypothesized to affect physical function. The aim of this study was to explore the association of skeletal muscle fat with outcomes of physical function and physical activity in persons with RA.

Methods: This was a cross-sectional, secondary analysis of baseline data from a study in adults diagnosed with RA as per the ACR criteria. Skeletal

Disclosure: S. H. Liu, None; C. Eaton, None; K. Lapane, None.

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A 5% body weight reduction is estimated to reduce the energy cost of moving by about 3 METs, so weight loss would be expected to improve physical function. The mechanisms by which skeletal muscle fat affects physical function is not clear, and perhaps muscle properties beyond its size and physical activity levels were moderate (mean DAS-28 score $\pm 1.3$). MA was inversely correlated with time to ascend one flight of stairs, and walk four meters, and directly correlated with time spent in physical activity in control participants ($r = 0.5$, $p < 0.001$). A multivariable model adjusted for age, sex, race/ethnicity, education, chronic health condition, and BMI identified MA as a significant independent contributor to the variability in stair climb time, single leg balance time and physical activity time ($r = 0.5$, $p < 0.001$).

**Conclusion:** Higher skeletal muscle fat predicts lower physical function and physical activity. The contribution is above and beyond that of body size, and muscle strength and area. The mechanism by which skeletal muscle fat affects physical function is not clear, and perhaps muscle properties beyond its size and torque production need to be considered and investigated in future studies.

**Disclosure:** S. S. Khoja, None; B. Goodpaster, None; S. R. Piva, None.

**1092**

**Does Arthritis Status Predict Starting or Stopping Work over a 2-Year Period?**

**Kristina A. Theis**, Miriam Cisternas and Louise Murphy.1

1Centers for Disease Control and Prevention, Atlanta, GA, 2MGC Data Services, San Diego, CA.

**Background/Purpose:** Employment is linked to prosperity, identity, and the ability to contribute to society. Lower employment is well documented among adults with arthritis, but less is known about trajectories of stopping or starting work and subgroups particularly at risk for not working. Our purpose was to describe longitudinal patterns in work starting and stopping among three groups of U.S. adults ($\geq$18 years): 1) those with no arthritis (arthritis-), 2) those with arthritis but no arthritis-attributable work limitation (AAWL-), and 3) those with arthritis and AAWL. For starting work, adjustment attenuated arthritis effects only among AAWL-, whereas AAWL consistently identifies a unique group of individuals at risk for increased work loss and reduced work entry over time. Identification of AAWL may be a useful indicator for offering clinical, public health, job accommodation, and other interventions to retain and gain employment.

**Disclosure:** K. A. Theis, None; M. Cisternas, None; L. Murphy, None.

**ACR/ARHP Poster Session B**

**Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes: Clinical Focus**

Monday, November 17, 2014, 8:30 AM - 4:00 PM

**1093**

**Female Sexual Function in Fibromyalgia.**

M aria Julia Gamba1, Claudia Uñ a1, Alicia Ig el1, Fernando Eraña1, Martha Vilda1, Gimena Gómez1, Griselda Redondo1, M aria Celina de la Vega1, Estella Chiuzzi1, Augusto M artin R oipedor Sr.1, Maria I nes de la Barra2, Norma Vill a3, Dario M a t4, Alba R usso2 and Osvaldo Daniel M essina1.1HOSPITAL ARGERICH, BUENOS AIRES, Argentina. 2Hospital Argirich, Buenos Aires, Argentina.

**Background/Purpose:** Fibromyalgia (FM) is a common condition in young and middle-aged women, which is mainly characterized by diffuse chronic pain and is associated with other manifestations such as fatigue, unrefreshing sleep, stiffness, anxiety and depression. Recent studies have evaluated that chronic pain syndrome and related manifestations could have a negative impact on sexual function of these patients, as well as psycho-physical abuse history could act as potential triggers of FM. **OBJECTIVE:** Assess sexual function in women with FM and correlate with tender points count, clinical severity, anxiety, depression, chronic fatigue and history of physical and psychological violence.

**Methods:** A case-control study. Between 03/01/12 and 06/30/12 were included consecutively: women $\geq$18 years diagnosed with FM according to ACR criteria 90, and healthy controls $\geq$18 years, without history of violence. We excluded patients with other causes of chronic pain disorders and psychotic disorders. We recorded: sociodemographic data, education, employment and menopausal status and sexual function by **Female Sexual Function Index** (FSFI: self-administered questionnaire that assesses six domains). In the FM group tender points count, duration of disease, medical, psychological care, presence of chronic fatigue (by Fukuda Criteria), clinical severity (FIQ-Spanish version), depression (HADS), and history of physical or psychological violence (Screening Questionnaire of Violence) were assessed. We used Chi-test, Student t test and Mann-Whitney test and Spearman correlation coefficient (significant $p < 0.05$).

**Results:** We included 52 patients in the FM group and 52 in the control group. Median age: 50 $\pm$ 9.2 and 47 $\pm$ 7.9, respectively. FM Group: Median evolution time: 60 months, mean pain points: 15 $\pm$ 3, FIQ median: 67.8 (28-86). 73.1% received medication for FM and 44.2% demanded psychological care. Patients with FM showed $<\text{level education (p < 0.001) and <work activity level (p < 0.001)$. 56% had chronic fatigue, 35% depression and 75% had a history of personal violence. The most common link with the aggressor was the current partner in cases of psychological violence (28.1%) and former partners for physical violence (31.2%). We found significant impaired sexual function vs controls (median FSFI total: 17.2 (1.2-33.3) vs. 29.4 (1.2-36), $p < 0.001$) and the difference persists analyzing each domain of the FSFI. Having violence history generated a tendency to
lower values of FSFI (no statistical significance). No correlation was found between values of FSFI and the other analyzed variables.

Conclusion: Our patients with FM had impaired sexual function compared to control group. Physical and psychological violence were frequent but weren’t related with sexuality function.

Disclosure: M. J. Gamba, None; C. Uña, None; A. Igel, None; F. Eraina, None; M. Vidal, None; G. Gómez, None; G. Redondo, None; M. C. de la Vega, None; E. Chiluzi, None; A. M. Ropedre Sr., None; M. I. de la Barrera, None; N. Villa, None; D. Mata, None; A. Russo, None; O. D. Messina, None.

1094

Work Productivity and Healthcare Utilization in Patients with Fibromyalgia and Comorbid Depression Taking Antidepressant Medication.

Jaren Landen1, Claire Burbridge2, Elizabeth Masters3, Pritha Bhadra Brown3,

Joseph Scavone1, Birolim Ersin3, Richard Visking3, Andrew Clair4 and Lynne Pauer1, Pfizer Inc, Groton, CT, Pfizer Ltd, Walton Oaks, United Kingdom, Pfizer Inc, New York, NY, Pfizer Inc, Louisville, KY.

Background/Purpose: Patients with fibromyalgia (FM) experience pain, sleep disruption, fatigue, and other symptoms that limit activity, impacting work productivity and increasing healthcare utilization. Here, we describe the burden of FM on work productivity and healthcare utilization in patients with FM taking antidepressant medication for their comorbid depression.

Methods: Patients from 38 centers in the United States, Europe (Italy, Spain), and Canada were enrolled in a phase 3 study of pregabalin efficacy over a 12 week period. Due to an additional, unintended 60 Hz stimulation signal that was originally present in the system, 8 of 15 patients randomized to 0 treatments (Sham) received a form of stimulation. The final disposition was:

<table>
<thead>
<tr>
<th>Group/ # Treatments</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>24</td>
</tr>
<tr>
<td>B</td>
<td>16</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
</tbody>
</table>

Outcome measures included a 24-hour and 7-day recall pain VAS, Fibromyalgia Impact Questionnaire (FIQ-R), Patient Global Impression of Change (PGIC), and assessment of sleep, mood and neurocognitive changes.

Results: Completion rates were excellent with 45 of 46 patients completing all 12 weeks of scheduled treatments. At the 3 month landmark endpoint, patients treated with 24 RINCE stimulations were statistically improved on VAS pain relative to the sham group (MMRM LS Mean change from baseline –3.18 vs –8.33 mm, p = 0.009). Pain responder analyses, defining a responder as ≥50% improvement from baseline, also favored RINCE but did not reach statistical significance due to small numbers (5 of 15 vs 1 of 7, p = NS). Likewise, PGIC responder analyses where a responder is defined as “Much Improved” and “Very Much Improved”, also favored RINCE (8 of 15 vs 1 of 7, NS). Additional outcome measures generally favored RINCE as well: 7 day pain recall (VAS MMRM LS Mean contrast –22.9, p = 0.013); FIQ-R total score (–24.5 vs –13.6, p = 0.11); Neurocognitive functioning – MAOS improvement: –8.64 vs +2.43 (p = 0.083); MCS cognition: –8.37 vs +0.09 (p = 0.10); MCS mental clutter: –12.90 vs +0.44 (p = 0.005). In addition, the Beck Depression Inventory and a modified Jenkins sleep questionnaire both numerically favored RINCE, but did not achieve statistical significance. Consistent with classification as a “non-significant risk” device, the adverse event profile of RINCE was very encouraging. The most common adverse event reported was potentially related to therapy was headache, reported by 3 patients out of 39 who received some form of stimulation therapy (8%). All other event reports were at rates of no more than 2 patients (5%), and were consistent with the underlying fibromyalgia.

Conclusion: Despite the very small control group of 7 patients, the benefit risk ratio of RINCE therapy with NeuroPoint appears highly favorable. This pilot study encouraged the sponsor to initiate a large, well powered pivotal trial in fibromyalgia.

Disclosure: R. M. Gendreau, Cereplex Corporation, 3; D. Deering, Cereplex Corporation, 5; J. Gendreau, Cereplex Corporation, 5; J. Hargrove, Cereplex Corporation, 3.

1096

Fibromyalgia Patients Who Have More Symptoms at Their Initial Office Visit Tend to Have a Worse Clinical Course.

Robert S. Katz, Ben J. Small, Andrea Small1, and Jung-Chul Bae, Northwestern University, Chicago, IL, “Rheumatology Associates, Chicago, IL, “Rheumatology Associates, Chicago, IL.

Background/Purpose: Patients with the fibromyalgia syndrome (FMS) experience pain, insomnia, fatigue, and memory/concentration problems. But
some fibromyalgia patients also have many additional somatic symptoms. We surveyed our patients with fibromyalgia to determine if those patients with many physical symptoms, in addition to the core FMS complaints, tended to have more challenging clinical courses, a poor response to treatment and more disabling limitations.

**Methods:** Patients from a rheumatology office practice were studied. We reviewed the charts of fibromyalgia patients and counted the number of symptoms from a list of 92 medical complaints as part of a form provided by the American College of Rheumatology. The total number of symptoms was recorded from the patient’s initial visit. We then compared the number of symptoms to the patient’s most recent office visit, a patient update form which includes patient recorded visual analog scales for health status in general, pain, fatigue, concentration, sleep, and also a HAQ activity questionnaire.

**Results:** 66 patients in this study met the 2010 ACR criteria for FMS, the number of symptoms varied from 6 to 55, with a mean number of symptoms 21.5. We found a relationship between the number of somatic symptoms and the patient’s status with regard to pain, fatigue and overall health and HAQ scores. Those patients with 19 or more symptoms tended to have worse ability to perform activities and higher levels of pain and fatigue. (See table.)

<table>
<thead>
<tr>
<th>Number of Symptoms</th>
<th>Mean HAQ</th>
<th>Mean Pain VAS</th>
<th>Mean Fatigue VAS</th>
<th>General Health Status VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 19 symptoms</td>
<td>2.18</td>
<td>5.11</td>
<td>5.04</td>
<td>4.79</td>
</tr>
<tr>
<td>19 or more symptoms</td>
<td>4.42</td>
<td>7.11</td>
<td>7.13</td>
<td>6.66</td>
</tr>
</tbody>
</table>

**Conclusion:** FMS patients with many somatic symptoms tend to have a worse course with higher levels of pain, fatigue, insomnia, and fibrofog as well as higher HAQ scores, indicating diminished physical functioning. FMS patients with a somatoform clinical picture tend to have a more challenging clinical course.

**Disclosure:** R. S. Katz, None; B. J. Small, None; A. Small, None; H. Bond, None.

**1097**

**Can We Help Identify Learning Disabilities in Fibromyalgia Patients?**

Robert S. Katz1, Lauren Kwan2 and Jessica L. Polyak2.

1Rush Medical College, Chicago, IL, 2Rheumatology Associates, Chicago, IL.

**Background/Purpose:** A previous study (ArthritisRheum:510:956) has shown that Fibromyalgia syndrome (FMS) patients may have learning disabilities. Experts in the field have identified seven types of learning disabilities. We queried FMS patients about the types of learning disabilities they might have.

**Methods:** 111 patients meeting the 2010 ACR criteria for Fibromyalgia, followed in a rheumatology office practice, were asked to fill out a questionnaire listing multiple questions and problems relating to learning disabilities. Based on responses, tentative classifications of specific learning disabilities were made from the following classifications: dyslexia, dysgraphia, dyscalculia, central auditory processing disorder, non-verbal learning disorder, visual processing disorder, and aphasia/ dysphasia/global aphasia.

**Results:** A scoring FM patients responses to a questionnaire, possible categories of learning disabilities were: 48.6% central auditory processing disorder; 36.9% dysphasia/global aphasia disorder; 34.2% visual processing disorder; 35.1% dyscalculia; 29.7% dysgraphia; 26.1% dyslexia; and 25.2% non verbal learning disorder.

**Conclusion:** Although tentative diagnosis of a learning disability needs to be confirmed by a learning disability expert, these findings suggest that fibromyalgia patients may have multiple types of learning disabilities. The most common learning disability was central auditory processing disorder, an auditory disability causing difficulty processing verbal information and interpreting speech. It is possible that learning disability specialists could help FMS patients improve their performance at school and work.

**Disclosure:** R. S. Katz, None; L. Kwan, None; J. L. Polyak, None.

**1098**

**Clinical Efficacy of the High-Concentration Capsaicin Patch for the Treatment of Carpal Tunnel Syndrome.**

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1Institute of Rheumatology, Prague, Prague, Czech Republic, 2Pain Department Faculty Hospital Saint Anna, Brno, Brno, Czech Republic.

**Background/Purpose:** Carpal tunnel syndrome (CTS) is a clinical syndrome manifested by signs and symptoms of irritation of the median nerve at the level of the carpal tunnel in the wrist. CTS is the most frequent pressure neuropathy. The conservative treatments for chronic neuropathic pain that currently exist are only moderately effective. Oral pharmaceuticals for neuropathic pain have significant side effects, and treatment efficacy tends to be modest. The use of topical analgesics allows direct application of medications to the area of pain. Capsaicin causes a brief initial sensitization followed by a prolonged desensitization of the local pain nerves. This occurs through stimulation of the transient receptor potential vanilloid-1 (TRPV1) expressing pain nerve fibers. Capsaicin dermal is an adhesive patch containing a high concentration (8%) of synthetic capsaicin. It has not been studied yet in patients with CTS.

**Methods:** The patients with clinically and electrophysiologically confirmed CTS, indicated for the treatment of highly concentrated capsaicin 8% patch due to neuropathic pain, were included in the study. The aim of the study was to determine the proportion of patients who achieve at least a 30% reduction in pain intensity on the Numeric Pain Rating Scale (NPRS) compared with baseline. There were also observed absolute and percentage decline in the scale of NPRS and prior and concomitant medications. Patients were monitored in four visits - before treatment of capsaicin patch and after 3, 6 and 12 months of application. On all visits were evaluated clinical status, monitored the intensity of pain and quality of life. The intensity of pain was evaluated using a range of intensity of pain - NPRS. Quality of life was assessed using the EQ-5D questionnaire.

**Results:** Altogether, 30 patients (four male) with symptomatic CTS were included in this study between April 2012 and April 2014. Capsaicin dermal patch reduced NPRS scores from baseline 6.3 points to 4.3 points after 3 months treatment (p < 0.001). 71% of patients experienced at least a 30% reduction in pain intensity measured with NPRS score. 64% of patients had at least a 50% reduction of pain intensity. The quality of life assessed by EQ-5D questionnaire improved significantly from 0.51 to 0.69 (three months after patch administration, p < 0.001). The consumption of concomitant medication decreased from 81% of patients at baseline to 52% after 3 months. Pain intensity decreased and EQ-5D questionnaire improved significantly gradually during the visits after 6 and 12 months. NPRS scores decreased after 12 months to 3.4 points. Capsaicin dermal patch was well tolerated. The most common adverse events were transient, mostly mild, application reaction in 8% of patients.

**Conclusion:** Capsaicin in the form of 8% dermal patch is a new treatment for peripheral neuropathic pain in patients with CTS. This study showed a high therapeutic efficacy, excellent tolerability and a significant improvement in quality of life, persisting for 12 months after administration.

**Acknowledgement:** This work was supported by the project OH for consensual development of research organization 023728.

**Disclosure:** O. Sleglova, None; M. Haki, None.

**1099**

**Which Stresses Bother Fibromyalgia Patients Most?**

Robert S. Katz1, Alexandre Small2 and Jessica L. Polyak3.

1Rush Medical College, Chicago, IL, 2University of Illinois College of Medicine, Chicago, IL, 3Rheumatology Associates, Chicago, IL.

**Background/Purpose:** Fibromyalgia patients identify stress as a factor in aggravating their pain and other symptoms. We administered a questionnaire to fibromyalgia patients to try to identify a difference between various kinds of stress and the effect on fibromyalgia symptoms.

**Methods:** Patients in a fibromyalgia office practice completed a questionnaire including various types of stresses: family, financial, job, health issues, marital, other. All patients met the 2010 ACR criteria for the diagnosis of fibromyalgia.

**Results:** 91 patients responded regarding which stresses affect their fibromyalgia the greatest.

As expected, concern regarding health issues was the greatest stress, (6.64), followed by family stress (5.81), job stress (5.55), money stress (4.69), and marital stress (4.01).

**Conclusion:** Stress is reported by many fibromyalgia patients as aggravating their symptoms. A side from health related concerns, family and job stress had the highest visual analog scale ratings as to the impact on fibromyalgia pain and related symptoms. Sometimes the rheumatologist or nurse needs to act as a psychotherapist, allowing the patient to ventilate and to discuss symptoms, but also areas of stress. Understanding the impact of
various stresses on fibromyalgia symptoms may assist clinicians in dealing with patients who have fibromyalgia.

Disclosure: R. S. Katz, None; A. Small, None; J. L. Polyak, None.

1100

System Review: The Most Common Symptoms of Fibromyalgia Patients Other Than Pain, Fatigue, Insomnia, and Cognitive Dysfunction. Robert S. Katz1 and Jessica L. Polyak2, 1Rush Medical College, Chicago, IL, 2Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia patients are somatically sensitive. The frequently complain of symptoms other than the core ones used for the diagnosis—pain, fatigue, poor sleep and cognitive problems. We queried fibromyalgia patients as to which symptoms they commonly experienced.

Methods: We administered a questionnaire to fibromyalgia patients meeting the 2010 ACR criteria. Included was a checklist of symptoms called System Review, from the American College of Rheumatology, copyright 1999.

Results: 82 fibromyalgia patients completed the questionnaire. The most frequent symptoms reported other than pain, fatigue, poor sleep and cognitive changes were headaches 39 patients (47.6%), dry eyes 37 patients (45.1%), dry mouth 37 patients (45.1%), easy bruising 27 patients (32.9%), anxiety 25 patients (30.5%), ringing in the ears 21 patients (25.6%), dizziness 21 patients (25.6%), night sweats 21 patients (25.6%), weight gain 20 patients (24.4%), and constipation 20 patients (24.4%). Aside from these top 10 symptoms, also commonly reported were double or blurred vision 19 patients (23.2%), rash 19 patients (23.2%), color changes in hands/feet 19 patients (23.2%), runny nose 18 patients (22.0%), nausea 18 patients (22.0%), mouth sores 17 patients (20.7%), shortness of breath 17 patients (20.7%), and depression 17 patients (20.7%).

Conclusion: Fibromyalgia patients commonly have symptoms other than pain and fatigue. Non-rheumatologists, who see patients with fibromyalgia with some of the symptoms listed above, such as tinnitus, dizziness, blurred vision, mouth sores, shortness of breath, etc., may not think to link them to fibromyalgia, but they are common in this illness.

Disclosure: R. S. Katz, None; J. L. Polyak, None.

1101


Background/Purpose: Fibromyalgia patients may present with localized or diffuse paresthesias. Some patients have had concerns about the possible diagnosis of multiple sclerosis and other neurological disorders. Neurologists are hesitant to use the term fibromyalgia in patients with paresthesias.

Methods: We administered a questionnaire to office patients who met the 2010 ACR criteria for the diagnosis of fibromyalgia. Included were questions on presence and location of paresthesias. Location: right arm, left arm, right leg, left leg, right side of body, left side of body, right side of face, left side of face, whole body. If numbness and tingling were present, were the symptoms constant, intermittent, frequent?

Results: 95 patients with fibromyalgia completed the questionnaire. 53 of the 95 patients (55.7%) answered positively to the question “Do you have numbness and tingling?” The mean age of the patients was 51.9 years; 83F and 12M. The paresthesia’s were considered to be diffuse (more than 2 areas of the body) in 21 patients (22.1%) and limited in 32 patients (33.6%). Patients responded that the paresthesia’s were constant in 21 patients (22.1%), intermittent in 42 patients (44.2%). 28 patients responded that numbness and tingling was frequent (29.4%).

Conclusion: 22.1% of this sample of fibromyalgia patients, taken from a rheumatology office practice, complained of diffuse paresthesias. Neurologists and Primary Care Physicians need to be aware that paresthesia’s are common in fibromyalgia.

Disclosure: R. S. Katz, None.

1102

Anxiety in Fibromyalgia Patients. Robert S. Katz1 and Frank Leavitt2. 1Rush Medical College, Chicago, IL, 2Rush University Medical Center, Chicago, IL.

Background/Purpose: In fibromyalgia (FM), it is normal to expect people burdened with the uncertainty of unresolvable medical issues to face a certain amount of anxiety. A high number of medical and anxiety symptoms are seen in FM; however, the normal reaction hypothesis may not fully explain the linkage. A further possibility is that anxiety levels differ in FM relative to other medical conditions and may even promote the progression of medical symptoms. The purpose of this study is to determine if anxiety in FM differs from other rheumatoid disorders after adjusting for illness intensity.

Methods: The study was comprised of 191 patients seen in a rheumatology practice. Of these, 79 had FMS and 112 had Non-FMS rheumatic disease. Diagnosis was based on ACR criteria. The two samples were closely matched on age (FMS: 51.2 ± 12.0 vs. 51.9 ± 15.9); the FMS sample had slightly less education (FMS: 14.8 ± 2.1 vs. 15.5 ± 2.0). The 0.7 year difference between means was significant (p < 0.05).

Patients were administered the 9-item Anxiety scale of the Profile of Mood States, and the Symptom Review section of the 1999 American College of Rheumatology Patient Forms. On the Anxiety scale, participants rated the anxiety variables listed in Table 1 on a 5 point scale, with 0 = not at all and 4 = extremely. The anxiety score is the sum of the ratings. The Symptom review is a symptom checklist covering 13 organ systems. Illness intensity is the number of symptoms endorsed as significantly affecting the individual.

Results: The mean anxiety levels of patients on the 9 items are shown in Table 1. FMS patients scored higher on 8 of the 9 anxiety items. As a whole, anxiety was significantly higher in FMS patients (12.7 ± 9.4 vs. 7.7 ± 6.3; p < 0.001). The score of 7.7 in the non-FMS group is in the normal range of healthy individuals (normative mean: 8.2 ± 6.0). Illness intensity was also significantly higher in FMS participants (16.7 ± 11.8 vs. 8.7 ± 5.3; p < 0.001). An analysis of covariance was used to subtract by statistics the effects of a higher number of medical symptoms on anxiety. Difference in anxiety remained significant after the effects of the number of medical symptoms endorsed was removed (p = 0.01).

Conclusion: Results of the analysis of covariance essentially eliminates the greater number of medical problems in FMS as an explanation for the higher level of anxiety in FMS. With symptom intensity eliminated, these results could be read as supporting that patients with FMS are more anxiety prone than other rheumatic disease patients.

However, more needs to be learned about the source of higher anxiety in FMS, since competing explanations are present. For example, the argument could be made that unexplained malfunctions of the body could in itself be catalysts for excessive worry and higher levels of anxiety. Undoubtedly patients with FMS have a greater number of medically unexplained problems.

Disclosure: R. S. Katz, None; F. Leavitt, None.

1103

Analgesic and Anti-Hyperalgesic Effects of Deep Dry Needling Therapy in Fibromyalgia Patients. B. Casanueva1, P. Rivas2, R. López-Mejías3, F. Genre4, J. Llorca4 and M. A. González-Gay5. 1Rheumatologist, Rheumatology Service at the Specialist Clinic of Cantabria, Santander, Spain, 2Physical Therapist, Specialist Clinic of Cantabria, Santander, Spain, 3Department of Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, 4Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain.

Background/Purpose: Patients with fibromyalgia (FM) complain of widespread chronic pain from deep tissues including muscles. Previous research highlights the relevance of impulse input from deep tissues for clinical FM pain. Deep dry needle stimulation is an invasive treatment modality used in the management of musculoskeletal pain. Its efficacy has been confirmed in the management of myofascial trigger points, acute and chronic low back pain, and chronic whiplash. To determine if blocking abnormal impulse input with deep dry needling stimulation of tender point may decrease hyperalgesia and clinical pain in FM patients.

Methods: 120 patients that fulfilled the ACR 1990 criteria for FM were enrolled into a prospective controlled study of 12 week. Patients were randomly split into two groups: The control group (CG), 56 women and 4 men, who continued their treatment, and the deep dry needling group (DNG), 54 women and 6 men, who, apart from continuing their medical treatment, also underwent weekly one-hour session of deep dry needling over 18 FM tender points for a 6-week-period. Study variables included pressure hyperalgesia as well as clinical pain. Patients were assessed at the start (at week 0), at the end of the 6-week intervention period (end of intervention), and were
Results: 60 patients were randomly assigned to the CG and 60 to the DNG. A total of 100 (83.3%) patients completed the study: 50 (83.3%) in the CG and 50 (83.3%) in the DNG. The mean ± SD age of participants was 53 ± 11.1 years, and the average reported in Fibromyalgia Impact Questionnaire (FIQ) was 73.1. At the beginning of the program (week 0), there were only significant differences between groups in age (56.2 in DNG versus 50.8 in the CG, p < 0.01) and McGill Pain Questionnaire (MPQ) (39.1 in DNG versus 42.4 in the CG, p = 0.03). At the end of the intervention (week 8), DNG showed reduction in the FIQ (p = 0.02), VAS of pain (p = 0.02), pain of SF-36 (p = 0.0007), MPQ (p = 0.02), Pain Catastrophizing Scale (PCS) (p = 0.02), activity engagement of Chronic Pain Assessment Questionnaire (CPAQ) (p = 0.008), pain intensity of Brief Pain Inventory (BPI) (p = 0.03), pain interference of BPI (p = 0.01), myalgic score (p = 0.0005), number of tender points (p = 0.0004), and pressure pain threshold (p = 0.002). Six weeks after the end of the treatment, DNG still showed significant differences (M) in the FIQ (p = 0.03), VAS of pain (p = 0.01), pain of SF-36 (p = 0.01), MPQ (p = 0.02), PCS (p = 0.03), engagement of CPAQ (p = 0.01), pain intensity of BPI (p = 0.04), pain interference of BPI (p = 0.01), number of tender points (p = 0.0008), myalgic score (p = 0.00001) and pressure pain threshold (p = 0.0004).

Conclusion: These results suggest that deep dry needling of tender points can reliably reduce clinical FM pain, and that peripheral input is required for the maintenance of mechanical hyperalgesia of these patients.

Disclosure: B. Casanueva. None; P. Rivas. None; R. López-Mejas. None; F. Genre. None; J. Llorca. None; M. González-Gay. None.

1104 Utility of the 2010 ACR Diagnostic Criteria for Fibromyalgia for Pediatric Patients with Juvenile Fibromyalgia. Tracy Ting1, Kimberly Barnett2, Anne Lynch-Jordan1 and Susmita Kashkar-Zuck2. 1Cincinnati Children’s Hosp, Cincinnati, OH, 2Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Juvenile Fibromyalgia (JFM) is a chronic condition characterized by widespread musculoskeletal pain, fatigue, poor sleep and significant morbidity. Currently, a classification of FM is based upon one of two published criteria – the 1990 American College of Rheumatology (ACR) criteria for adult fibromyalgia (FM) or the 1995 Yunus and Masi pediatric criteria. Both require a manual tender point examination that is controversial, not routinely or consistently applied by clinicians, and may be influenced by patient anxiety about the procedure. The newer 2010 ACR criteria allows for the use of a validated tool that excludes the use of the tender point examination and includes a clear scoring algorithm for consistency in screening and diagnosing of JFM. Both require a manual tender point examination that is controversial, not routinely or consistently applied by clinicians, and may be influenced by patient anxiety about the procedure. The newer 2010 ACR criteria allows for the use of a validated tool that excludes the use of the tender point examination and includes a clear scoring algorithm for consistency in screening and diagnosing of JFM.

Methods: Participants were patients (ages 11-17) with primary JFM diagnosis by a rheumatologist or pain physician (N = 44, M = 15.02) and gender matched controls (MC) with localized pain conditions, e.g., abdominal pain, headaches, limb pain (N = 44, M = 15.05). Physicians completed a form indicating which set of criteria they used to make a FM diagnosis (ACR 1990 or Yunus and Masi). The ACR 2010 Widespread Pain Index (WPI), regarding which body locations were painful and Symptom Severity (SS) checklist of associated somatic symptoms were administered by a trained assessor. Total scores for the WPI and SS tools were computed and the ACR 2010 algorithm was used to determine diagnosis of JFM. Also, participants were conducted to compare the two groups on number of pain locations and number of symptoms endorsed.

Results: The Yunus and Masi criteria were used the most often (93.2% of the time) by physicians to classify JFM and the ACR 1990 criteria were used far less (6.8%). When the 2010 criteria were applied, 83.7% of patients diagnosed with active FM by their primary rheumatologist met the ACR 2010 criteria. However, approximately 11.4% of patients with localized pain were also classified as having FM. JFM participants reported significantly more pain locations and associated symptoms than MC (p < 0.01).

Conclusion: Preliminary results indicate that the 2010 adult FM ACR criteria may be a useful tool to screen for JFM in an adolescent population.

Disclosure: D. Casanueva. None; P. Rivas. None; R. López-Mejas. None; F. Genre. None; J. Llorca. None; M. González-Gay. None.
Background/Purpose: Although criteria exist for fibromyalgia (FM) diagnosis, little is known about how FM diagnosis is applied and understood by physicians and patients in the US population. The 2012 National Health Interview Survey (NHIS) is the largest US population-based health survey. We examined the relation between self-reported physician FM diagnosis, polysymptomatic distress (PSD), demographics and selected symptoms captured in the NHIS.

Methods: The NHIS asked participants about receiving a FM diagnosis from a physician along with questions about joint pain and somatic symptoms. We developed NHIS FM/PSD definitions by administering germane NHIS questions and the modified 2010 ACR criteria to 415 consecutive rheumatology patients in 2 clinics. After applying these definitions to the NHIS, we estimated a PSD score (ePSD) and set a surrogate FM diagnosis (sFM) at ePSD ≥ 13. Because of differences in questions and administration between the ACR CR criteria and the NHIS, the current data should be considered approximate.

Results: The ePSD distribution in the NHIS is shown in Figure 1. Using population derived survey weights in a sample of 2,680 participants, 4.8% reported being told they had FM (FM (+)). 5.6% met the criteria for sFM (sFM (+)). Table 1 shows the subjects stratified by told FM and sFM status. Of FM (+) subjects, 83.0% were sFM (+). Subjects that were FM (+) but sFM (-) were similar to the non-FM population but with modest increases in ePSD, not working, and lifetime depression (Table 1). In addition, they were generally white (82.1%) and female (91.0%). FM (-) but sFM (+) subjects were less often white (69.1%) or female (66.8%). Women were more likely to report being told they had FM (odds ratio 8.6) but not as likely to meet sFM criteria (odds ratio 2.1).

Conclusion: More than 80% of subjects in NHIS who report being told by physicians they have FM do not satisfy sFM criteria. Among these subjects, more are female and non-minorities than in those satisfying sFM criteria. In addition, FM (+) individuals are generally indistinguishable from the non-FM population (FM (-)), but are less likely to be employed and more likely to report functional limitations and a lifetime history of depression. The cause for over-diagnosis is likely multi-factorial, but may include physician misdiagnosis, access to health care, personal beliefs, and socio-cultural ideas about FM engendered by academic and industry messaging. Regardless, our current medical approach to FM/PSD results in 3.9% of minimally symptomatic Americans reporting themselves labeled as “sick”. These results have important public health implications.

Disclosure: B. Walitt, None; R. Nahin, None; R. S. Katz, None; M. J. Bergman, None; F. Wolfe, None.

1107

A Strong Association Between Memory Loss and Word Finding Difficulties in Fibromyalgia. Robert S. Katz1 and Frank Leavitt2. 1Rush Medical College, Chicago, IL, 2Rush University Medical Center, Chicago, IL.

Background/Purpose: A core feature of fibromyalgia (FM) is cognitive dysfunction. The predominant clinical manifestations is memory loss; however impaired word retrieval frequently referred to as word finding difficulty sometimes unfolds in the clinical situation as the central patient focus. The purpose of this study is to build a more precise picture of cognitive dysfunction in FMS by examining the linkage between memory loss and word finding deficits and its relation to the severity of cognitive dysfunction.

Methods: Participants were 191 patients seen in a rheumatologic practice. Of these, 79 had FMS and 112 had Non-FMS rheumatic disease. Diagnosis was based on ACR criteria. The two samples were closely matched on age (FMS: 51.2 ± 12.0 vs. 51.9 ± 15.9; the FMS sample had slightly less education (FMS: 14.8 ± 2.1 vs. 15.5 ± 2.0). The 0.7 year mean difference was significant (p < 0.05). Data on memory loss and word finding difficulty were collected by questionnaire. Data on 8 cognitive skills and 8 aspects of mental clarity were derived from the Mental Clutter Scale that was filled out by each participant.

Results: Compared to Non-FMS patients, patients with FMS were more likely to report memory loss (69.6%) [55 of 79] to (25.0%) [28 of 112] p<0.001 and word finding difficulties (69.6%) [55 of 79] to (23.2%) [26 of 112] p<0.001. Within the FMS sample, 89.1% [49 of 55] of those with memory loss reported word finding difficulty, whereas 67.9% [19 of 28] of those in the Non-FMS with memory loss reported word finding difficulty (p<0.001). In respect to total samples, memory loss and word finding difficulty were coupled in 62.0% [49 of 79] of the FMS sample and in 17.0% [19 of 112] of the Non-FMS sample (p<0.001).

Results: of cognitive functioning as assessed by the 16 item Mental Clutter Scale show that cognitive difficulties are substantially skewed toward patients with FMS (Table 1). Compared to Non-FMS, those with FMS endorse a higher level of disturbance on the 8 of the 8 cognitive skills, and on 7 of the 8 aspects of mental clarity.

Conclusion: Cognitive difficulty varies widely depending upon the type of rheumatic disease. Patient with FMS appear to carry a considerably higher risk for memory loss and word finding difficulties than individuals with other rheumatic disease. The memory loss-FM relationship is well established and has played a central role in cognitive studies to date; whereas the role of word finding difficulty has been largely unappreciated.

Memory loss and word finding difficulties co-occur in FMS to an unusual degree. Cases in which these cognitive difficulties are coupled to the experience of multiple concurrent cognitive difficulties and greater mental fog as reflected by a high level of disturbance in 7 aspects of mental clarity.

At this stage, it is unclear why the cognitive picture is worse when memory loss and word finding difficulties co-occur in FMS or what mechanisms bind them together.

Table 1. Comparison of Rheumatic Patients With (FMS) and Without (Non-FMS) Fibromyalgia Who Endorse Both Memory Loss and Word Finding Difficulties on the Cognitive and Mental Clarity Subscales of the Mental Clutter Scale.

<table>
<thead>
<tr>
<th>Cognitive Items</th>
<th>FMS (n=49)</th>
<th>Non-FMS (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>6.4±2.6</td>
<td>4.5±2.0***</td>
</tr>
<tr>
<td>Memory</td>
<td>6.5±2.2</td>
<td>4.6±2.2**</td>
</tr>
<tr>
<td>Slowing Focused</td>
<td>6.3±2.3</td>
<td>4.7±2.5**</td>
</tr>
<tr>
<td>Multitasking</td>
<td>6.1±2.5</td>
<td>4.5±3.1**</td>
</tr>
<tr>
<td>Expressing Yourself</td>
<td>5.6±3.0</td>
<td>4.0±2.1*</td>
</tr>
<tr>
<td>Thinking Clearly</td>
<td>5.7±2.2</td>
<td>4.2±2.4*</td>
</tr>
<tr>
<td>Perceptual Clarity</td>
<td>5.3±2.3</td>
<td>4.0±2.5*</td>
</tr>
<tr>
<td>Mental Speed</td>
<td>6.2±2.3</td>
<td>4.6±2.4*</td>
</tr>
<tr>
<td>Spaciness</td>
<td>5.4±2.9</td>
<td>3.4±2.2*</td>
</tr>
<tr>
<td>Looking at life through a haze</td>
<td>4.7±3.0</td>
<td>2.9±2.4*</td>
</tr>
<tr>
<td>Cluttered thinking</td>
<td>5.5±3.7</td>
<td>3.9±3.1*</td>
</tr>
<tr>
<td>Fogginess</td>
<td>5.7±2.7</td>
<td>2.9±2.3*</td>
</tr>
<tr>
<td>Rushing thoughts</td>
<td>5.2±3.1</td>
<td>3.5±2.9*</td>
</tr>
<tr>
<td>Fuzzy headedness</td>
<td>4.9±2.7</td>
<td>2.8±2.3*</td>
</tr>
<tr>
<td>Information overload</td>
<td>5.9±2.9</td>
<td>4.1±3.1*</td>
</tr>
</tbody>
</table>

* Start of 8 Cognitive items
** Start of 8 Mental Clarity
*** p<0.05, **** p<0.001

Disclosure: R. S. Katz, None; F. Leavitt, None.

1108

Understanding Baseline Clinical Characteristics May be of Use in Considering the Response to Pregabalin in FM Patients with Comorbid Depression. Lynne Pauer1, Jaren Landen1, Pritha Bhadra Brown1, Joseph Scavone2, Richard Vissing3 and Andrew Clair4. 1Pfizer Inc, Groton, CT, 2Pfizer Inc, New York, NY, 3Pfizer Inc, Louisville, KY.
Background/Purpose: In a prior study in fibromyalgia (FM) patients taking an antidepressant for their comorbid depression, pregabalin (PGB) significantly reduced pain severity (treatment difference compared with placebo [95% CI], -0.61 [-0.91 to -0.31]). However, the effect of patients' baseline clinical characteristics on the treatment response to pregabalan has not previously been examined.

Methods: In the randomized, placebo (PBO)-controlled, 2-way crossover study, patients with FM aged ≥18 years taking a single antidepressant for their comorbid depression were randomized 1:1 to PGB (300 or 450 mg/d)/PBO or PBO/PGB. Treatment was for two 6-week periods, separated by a 2-week taper/washout. A antidepressant medication (SSRI or SNRI) was continued throughout the study. Endpoint mean pain scores (by 11-point numeric rating scale) were pooled from the two treatment periods. In this analysis, the effect of the following baseline clinical characteristics on endpoint mean pain scores was examined: pain severity (moderate, pain score of 4 to ≤7; severe, >7 to 10); depression diagnosis (major depressive disorder [MDD] or depression not otherwise specified [NOS]); prior or no prior opioid use; and Hospital Anxiety and Depression Scale-Angiety (HADS-A) or -Depression (HADS-D) score (0–21 scale). Variables were analysed as fixed factors in a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within subject error as random factors.

Results: A total of 193 patients were included in the analysis; 181 received ≥1 dose of PGB and 177 PBO. Mean age was 51.1 years and 93.3% of patients were female. Mean (median) pain, HADS-A, and HADS-D scores at baseline were 6.7 (6.9) 8.3 (8.0), and 8.0 (8.0), respectively. Endpoint mean pain scores were significantly lower (P < 0.05) with PGB compared with PBO (treatment difference, 95% CI) irrespective of patients having: moderate (-0.62, -1.06 to -0.17; n = 104) or severe pain (-0.70, -1.35 to -0.05; n = 89) pain; diagnosis of MDD (-0.73, -1.22 to -0.24; n = 84) or depression NOS (-0.54, -0.94 to -0.13; n = 101); prior (-0.70, -1.35 to -0.05; n = 44) or no prior opioid use (-0.53, -0.88 to -0.19; n = 149); HADS-A score <8 (-0.55, -1.08 to -0.02; n = 86) or ≥8 (-0.67, -1.04 to -0.31; n = 107); or HADS-D score <8 (-0.93, -1.44 to -0.42; n = 85). However, while there was a trend towards improvement with pregabalin in patients with HADS-D score ≥8, this was not significant (-0.31, -0.67 to 0.06; P = 0.098; n = 108).

Conclusion: In patients with FM taking an antidepressant for comorbid depression, pregabalin significantly improved mean pain scores irrespective of baseline pain severity, depression diagnosis, prior opioid use, or HADS-D score. This study has important clinical implications in that pregabalin improved pain in FM patients with a wide range of baseline clinical characteristics.


1109
Impact of Age on Symptom Severity and Disease Management at Fibromyalgia Diagnosis: A Multicenter, Longitudinal, Observational Study
Emmanouil Rampakakis1, Hamit Goksu2, Pinar Borman2 and Figen Tuncay3. 1Ankara Training and Research Hospital, Ankara, Turkey, 2University of Hacettepe Faculty of Medicine, Ankara, Turkey, 3Ahi Evran University, Kirsehir, Turkey.

Background/Purpose: The aim of this study was to compare the therapeutic effects of kinesio taping (KT) and local subacromial injection in patients with subacromial impingement syndrome (SIS) with regard to pain, range of motion (ROM) and disability.

Methods: Sixty-one patients with subacromial impingement syndrome were enrolled into the study. Demographic and clinical characteristics including age, sex, duration of disease were recorded. The patients were randomized into two treatment groups receiving either a single corticosteroid and local anesthetic (LA) injection, or kinesio taping performed three times by intervals of 3 day. Visual analog scale (VAS) was used to assess pain intensity, shoulder abduction, flexion and rotation range of motion (ROM) degrees were recorded and Shoulder Pain and Disability Index (SPADI) was performed to evaluate functional disability, before treatment, at the first and fourth weeks after therapies. Both groups were educated for home exercise programme.

Results: Forty-eight female and 13 male patients (mean age, 42.4 ± 6.48 years; mean disease duration, 2.35 ± 0.79 months) were included in the study. There were no differences between the groups regarding demographic variables on entry to the study. Pain, functional outcome measures were determined to have improved significantly in both groups at the end of therapies at first and fourth weeks, but these improvements were more significant in the injection group than in kinesio taping group. The improvements in pain at rest, shoulder abduction degrees, and SPADI scores at first and fourth weeks were statistically higher in injection group than in kinesio taping group.

Conclusion: We imply that single dose subacromial injection and three times of kinesio taping by 3 day intervals have favorable effects on pain and functional status in the early period (up to one month) of subacromial impingement syndrome. Although the improvement in pain intensity at rest, and ROM measurements were more significant in local injection, KT may be an alternative non-invasive method for patients suffering from subacromial impingement syndrome in the early period.

Disclosure(s): H. Goksu, None; P. Borman, None; F. Tuncay, None.
The Effect of High Intensity Laser Therapy in the Management of Myofascial Pain Syndrome of the Trapezius: A Double Blind, Placebo-Controlled Study. Umit Dundar, Utku Turkmen, Hasan Toktas, Ozlem Solak and Alper Ularsli. Akyon Kocatepe University, Faculty of Medicine, Akyonkarahisar, Turkey.

Background/Purpose: Myofascial pain syndrome (MPS) of the trapezius muscle is one of the main causes of neck pain. In this randomized, double blinded study, we planned to evaluate the effects of high-intensity laser therapy (HILT) in female patients with chronic MPS of the trapezius muscle.

Methods: The female patients with the diagnosis of MPS of the trapezius muscle, were enrolled in the study and assigned to two groups. HILT group (group1) was treated with HILT and exercise. Sham therapy group (group2) received placebo HILT and exercise. The patients were assessed for pain, cervical active range of motion, disability and quality of life. Evaluations were performed before treatment (week 0) and after treatment (week 4 and week 12).

Results: Both groups showed significant improvement for all parameters at week 4 and week 12. However, comparison of the percentage changes of parameters both at week 4 and week 12 relative to pretreatment values showed that improvement in pain scores, neck disability index and physical functioning, role limitations due to physical functioning, bodily pain, general health perceptions, social functioning and role limitations due to emotional problems compared to group 2 was better in HILT group.

Conclusion: As a result, it is concluded that HILT is an effective therapeutic method in the treatment of patients with chronic MPS of the trapezius muscle.

Key words: Myofascial pain syndrome, high-intensity laser therapy, exercise, pain, disability, quality of life.

Disclosure: U. Dundar, None; U. Turkmen, None; H. Toktas, None; O. Solak, None; A. Ularsli, None.

Cognitive Symptoms in Fibromyalgia Patients Compared with Rheumatoid Arthritis Patients. Robert S. Katz1, Ben J Small2, Alexandra Small1 and Susan Shott3. 1Rush Medical College, Chicago, IL, 2McNeal Hospital, Berwyn, IL, 3University of Illinois College of Medicine, Chicago, IL, 4Rush University Medical Center, Chicago, IL.

Background/Purpose: Many fibromyalgia syndrome (FMS) patients report impaired mental function (fibrofog.) We compared FMS and RA patients with respect to symptoms of impaired cognition.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51 ± 12) and RA (61; 45 women and 16 men; mean age 55 ± 15) completed a questionnaire about symptoms of impaired mental function, rated as 1 = never, 2 = occasionally, 3 = sometimes, 4 = mostly, and 5 = always. The two-sided Mann-Whitney test was done to compare FMS and RA patients with respect to these ratings, using a 0.05 significance level.

Results: Compared to RA patients, FMS patients had significantly worse ratings for inability to recall known words (1.9 ± 1.0 vs. 1.4 ± 0.6, p = 0.001), inability to write an idea down (1.5 ± 1.0 vs. 1.2 ± 0.4, p = 0.017), mistaking numbers that look similar (1.5 ± 0.8 vs. 1.2 ± 0.4, p = 0.034), inability to retain patterns when adding, subtracting, multiplying, or dividing (1.6 ± 1.0 vs. 1.2 ± 0.6, p = 0.02), distraction by background noises (2.3 ± 1.3 vs. 1.7 ± 1.0, p = 0.002), difficulty following directions (1.9 ± 1.1 vs. 1.4 ± 0.6, p = 0.005), trouble following conversations (1.7 ± 0.9 vs. 1.3 ± 0.6, p = 0.006), becoming disruptive in conversations (1.4 ± 0.8 vs. 1.2 ± 0.5, p = 0.027), misremembering spelling of familiar words (1.7 ± 0.9 vs. 1.4 ± 0.7, p = 0.009), losing place while reading (2.0 ± 1.1 vs. 1.6 ± 0.8, p = 0.03), difficulty expressing thoughts verbally (2.0 ± 1.1 vs. 1.5 ± 0.8, p = 0.001), poor reading comprehension (1.9 ± 1.1 vs 1.4 ± 0.8, p = 0.003), frustration when speaking (1.8 ± 1.1 vs. 1.3 ± 0.6, p = 0.003), and difficulty concentrating (2.5 ± 1.2 vs. 1.8 ± 1.0, p < 0.001).

Conclusion: FMS patients had median ratings for cognitive function that were significantly worse than patients with RA. FMS patients report significantly more symptoms of impaired concentration and mental fog. Fibrofog is a troubling problem for many fibromyalgia patients.

Disclosure: R. S. Katz, None; B. J. Small, None; A. Small, None; S. Shott, None.
Mindfulness Is Associated with Sleep Quality Among Patients with Fibromyalgia. Yuan Zhang1, Lori Lyn Price1, Nani Morgan2, Lucas Morgan3, and Chenchen Wang4

The Effects of Mulligan’s Mobilization with Movement Techniques in Patients with Lateral Epicondylitis. Ayca Cakmak1, Elcin Dereli1 and Dilsad Sindel2

Disclosure: E. Roddy, None; D. van der Windt, None; R. Ogollah, None; K. Stevenson, None; D. van der Windt, None; J. Shufflebotham, None; N. Morgan, None; L. Morgan, None; I. Zwierska, None; J. Young, None; N. Foster, None.

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The Effects of Mulligan’s Mobilization with Movement Techniques in Patients with Lateral Epicondylitis. Ayca Cakmak1, Elcin Dereli1 and Dilsad Sindel2, 1Istanbul Bilgi University, School of Health Sciences, Istanbul, Turkey, 2Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: The aim of this study was to investigate the effects of Mulligan’s Mobilization with Movement (MWM) technique in the management of pain and improvement of functional status in patients with lateral epicondylitis (LE).

Methods: A total of 40 patients with LE were randomly assigned to two groups. The MWM group (n=20) was treated with MWM technique, exercise and cold therapy. The patients in control group (n=20) received only exercise and cold therapy. The physical therapy sessions were applied in our clinics five times a week for two weeks (total number: 10). All physical therapy sessions were supervised by the same investigator. We used the Visual Analogue Scale (VAS) to assess the intensity of pain. Moreover, the intensity of pain and functional disability were evaluated by the Patient-rated Tennis Elbow Evaluation (PRTEE) Questionnaire. Both dynamometer and pinchmeter were used to assess muscle strength of the hand. Muscle strength of elbow and wrist were evaluated by the manual muscle testing method. All outcome measures were conducted at baseline and repeated immediately after treatment (post-treatment), and at 1- and 3-month follow-up assessments. To compare the difference between two groups, we used the Mann-Whitney U test (α=0.05).

Results: There was a significant decrease in VAS scores during activity scores in MWM group at post-treatment (p<0.001), 1-month (p<0.001) and 3-month (p=0.040) assessments compared with the control group. Moreover, there was a significant decrease in VAS scores at night in MWM group (p=0.024) and significant increase in pain-free grip strength (p=0.002) at post-treatment assessment compared with the control group. The PRTEE-Pain Subscales scores decreased significantly in MWM group at post-treatment (p<0.001), 1-month (p<0.001) and 3-month (p=0.001) assessments compared with the control group. For all other outcome measures, there was no statistically significant difference between the two groups at all assessment intervals (p>0.05).

Conclusion: Mulligan’s MWM techniques may be effective in reducing pain and improving in grip strength in patients with LE.

Disclosure: A. Cakmak, None; E. Dereli, None; D. Sindel, None.

1116
Mindfulness Is Associated with Sleep Quality Among Patients with Fibromyalgia. Yuan Zhang1, Lori Lyn Price1, Nani Morgan2, Lucas Morgan3, and Chenchen Wang4

Background/Purpose: Mindfulness is the ability to observe, describe, or be aware of present moment experiences without judgment or reactivity. Previous literature suggests that mindfulness-based interventions may be effective in reducing chronic pain and depression especially in fibromyalgia patients. A deliberate, situational, fibromyalgia patients commonly experience sleep disturbance, which at least partially attributes to chronic pain and depression. Therefore, we hypothesize that mindfulness could be associated with fibromyalgia patients’ sleep quality, and the effect may be explained through reducing symptoms of chronic pain and depression.

Methods: We conducted a secondary analysis of baseline data from a randomized controlled trial comparing Tai Chi and aerobic exercise among patients with fibromyalgia. Patients completed the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item, self-report questionnaire; scores ranging 39–195, with higher scores representing higher levels of mindfulness. Participants also completed the Beck Depression Inventory Second Edition (BDI-II), PROMIS Pain Interference, PROMIS Sleep Disturbance, and Pittsburgh Sleep Quality Index (PSQI). Pearson correlations were run to examine the associations of mindfulness with sleep quality and disturbance, chronic pain, and depression. Multivariate linear regressions were run to examine the predicting effect of mindfulness on sleep quality and disturbance. Chronic pain and depression were then separately introduced into the regressions to test their potential mediating effects.

Results: This study included 160 fibromyalgia patients with an average age of 51.9 years, primarily female (92%). Patients reporting higher levels of mindfulness tended to report less chronic pain (r=−0.25, p<0.01) and less sleep disturbance (r=−0.27, p<0.01), as well as lower chronic pain (r=−0.36, p<0.01), and less depression (r=−0.57, p<0.01). Patients reporting higher levels of chronic pain or depression tended to report worse sleep quality (r=0.42, p<0.01) and more sleep disturbance (r=0.42, p=0.32, p<0.01). The linear regression modeling reported that mindfulness significantly predicted sleep quality and disturbance (Table 1). The association between mindfulness and sleep quality and disturbance was partially mediated through chronic pain and depression (Table 1).

Conclusion: Mindfulness may be associated with fibromyalgia patients’ sleep quality, and the effect could possibly be explained through affecting the symptoms of chronic pain and depression. Longitudinal studies are needed to further evaluate whether improvement in mindfulness is associated with improvement in sleep quality of fibromyalgia patients.

Table 1. Linear Regression Models for the Predicting Effect of Mindfulness on Sleep Quality/Disturbance and the Mediating Effect of Chronic Pain and Depression

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFMQ</td>
<td>0.243**</td>
<td>0.239**</td>
<td>0.238**</td>
<td>0.047</td>
<td>0.046</td>
<td>0.045</td>
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<td>PRMs Pain</td>
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<td>0.168</td>
<td>-</td>
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<tr>
<td>DDI-II</td>
<td>-</td>
<td>0.118</td>
<td>0.118</td>
<td>0.008</td>
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<td>-0.244</td>
<td>0.151</td>
<td>0.151</td>
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</tr>
<tr>
<td>Male</td>
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<td>White</td>
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<td>-0.106</td>
<td>-0.106</td>
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<tr>
<td>Black</td>
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<td>-0.160</td>
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<tr>
<td>Sleep Quality (PSQI)</td>
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<tr>
<td>Model 1</td>
<td>0.458**</td>
<td>0.458**</td>
<td>0.458**</td>
<td>0.200**</td>
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<tr>
<td>Model 2</td>
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<td>0.458**</td>
<td>0.458**</td>
<td>0.200**</td>
<td>0.200**</td>
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<tr>
<td>Model 3</td>
<td>0.458**</td>
<td>0.458**</td>
<td>0.458**</td>
<td>0.200**</td>
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<td>Sleep Disturbance (PROMIS)</td>
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<tr>
<td>Model 1</td>
<td>0.458**</td>
<td>0.458**</td>
<td>0.458**</td>
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<td>0.458**</td>
<td>0.200**</td>
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</table>

Note: *p<0.05; **p<0.01; Model 1 explains the predicting effect of mindfulness on sleep quality/disturbance, with adjustment of age, gender, race, and education. Model 2 explains the partial mediating effect of chronic pain on the association between mindfulness and sleep quality/disturbance. Model 3 explains the partial mediating effect of depression on the association between mindfulness and sleep quality/disturbance.

Disclosure: Y. Zhang, None; L. L. Price, None; N. Morgan, None; L. Morgan, None; C. Wang, None.
Fibromyalgia Patients Taking Opioids Have Low Self-Efficacy and High Pain Catastrophizing but No Reduction in Pain or Improvement in Activity.

Joseph Adu1, Cecilia P. Chung2, Li Aleno Munters3, Leon Darghasian3, Rebecca Spitz4, Dana Dailey5, Barbara Rakel6, Kateleen Sluka7 and Leslie J. Crofford8. Vanderbilt University, Nashville, TN, 2University of Iowa, Iowa City, IA.

Background/Purpose: Fibromyalgia (FM) is a chronic disease of unknown etiology characterized by diffuse pain leading to fatigue, unrefreshing sleep and mood disturbances. The Fibromyalgia Activity Study with Tens (FAST) is a randomized controlled multicenter trial designed to evaluate the efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for FM. We have found that at baseline, approximately 40% of patients enrolled in FAST have been prescribed chronic opioids. Data supporting opioid efficacy for FM is lacking and they are not recommended by professional societies. The purpose of this study is to compare the baseline characteristics of FAST participants who are taking opioids to those who are not.

Methods: Patients screened for FAST (n = 44) wore ActiGraph wGT3X-BT accelerometers for 7 days prior to each visit and were evaluated by pre-randomization baseline data. These included the Demographic Health History questionnaire, the Fibromyalgia Impact Questionnaire-Revised (FIQI), the Short-form-36 Health Survey (SF-36), the Brief Pain Inventory (BPI), the Pain Self-Efficacy Questionnaire (PSEQ), the Pain Catastrophizing Scale (PCS), and others. These results were compared between patients separated into a non-opioid vs. opioid classifications (n = 25 vs. n = 19). These data were analyzed using non-parametric rank-sum (Mann-Whitney) test and Fisher’s exact test with significance set at P < 0.05.

Results: There were no significant differences between the two groups in terms of age, sex, race, education, income level, marital status, years diagnosed with FM, smoking history, and activity level as measured by actigraphy. FIQI scores, the main disease activity measure for FAST, between non-opioid and opioid users (median: 35.6; IQR: 49.5–63.6 vs. 53.1; 47.9–81.3; P = 0.01), and the SF-36, a quality of life measure, did not differ across domains except for General Health, which was lower in opioid patients (median: 38.9; IQR: 34.2–43.7 vs. 33.2; 26.1–38.9; P = 0.05). Patients in the opioid group had significantly lower ratings on the PSEQ (median: 25.5; IQR: 14.0–34.0 vs. 37.0; 25.5–49.5), which assesses patients’ confidence to accomplish specific tasks despite concurrent pain (P = 0.01). In addition, PCS total scores, which measure negative thoughts experienced during pain, were significantly higher in the opioid group (median: 22.0; IQR: 13.0–35.0 vs. 10.5; 6.0–23.0; P = 0.02), although pain severity was not significantly different based on BPI.

Conclusion: These data suggest an association between opioid use, pain catastrophizing and low levels of pain self-efficacy. The reasons for these associations are not clear, but it is possible that patients with these characteristics are more likely to be prescribed opioids. There is no evidence that patients on opioids have improved disease activity or better health outcomes than those not on opioids.

Disclosure: K. A. Kirou, None; N. Chaudhry, None.


Background/Purpose: Olecranon bursitis is a common presentation to an outpatient rheumatology practice. The differential diagnosis includes crystal-line bursitis (gout and pseudogout), inflammatory bursitis due to systemic arthritis such as rheumatoid arthritis, infectious, and hemorrhagic. We have observed a larger than expected percentage of hemorrhagic olecranon bursitis in our practice and wanted to report our experience with this entity and its management.

Methods: We systematically looked for the ICD9 diagnosis code 726.33 in our academic rheumatology outpatient practice from 2011-2014. We recorded demographic, geographic, economic, clinical, biochemical, and laboratory data as well as clinical examinations and findings, bursa fluid analysis, and response to glucocorticoid injections. We defined inflammatory cases when the tissues around the swelling were erythematous and hot and the synovial fluid was inflammatory (>2,000 WBC with predominance of PMN). Non-inflammatory cases were defined when none of the above were present. A bursitis was defined as infectious when a culture was positive and possibly infectious when culture was negative but there were no crystals in the fluid. Hemorrhagic bursitis was identified when the bursa fluid had the appearance of pure blood. A bursa was defined as large when its diameter was >5 cm (larger than golf ball), intermediate when its diameter was 2.5–5 cm and small when its diameter was <2.5 cm.

Results: We identified 9 patients. Of those, 6 were non inflammatory in appearance. All of them proved to be hemorrhagic and negative for infection on culture. The remaining 3 were inflammatory, but no crystals were identified in the fluid under polarizing microscopy. The fluid was yellow opaque in 2 of those cases and in one case there was only 1 drop of blood which was hemorrhagic in appearance. The 6 hemorrhagic cases were injected with depomedrol 40 mg and five had a dramatic response within few days/few weeks. We had no follow up in 1 patient. Of 3 inflammatory cases, one had a documented infection with MSSA, another one responded well to antibiotics, and another was lost to follow up. Of note, all of our patients were males with an average age of 54 (range: 32–72), relatively high BMI (average 30.5 with range: 21–45). Of the 6 hemorrhagic cases, 4 were large and 2 intermediate in size. Two of the inflammatory cases were small and one large. One out of 6 hemorrhagic bursa patients was on warfarin and another on dabigatran.

Conclusion: Hemorrhagic bursitis is not uncommon and should be suspected when there is no inflammation on examination. Middle age men, especially those with higher BMIs, and perhaps those on anticoagulation appeared to be at higher risk for this entity. Our experience suggests that an injection with glucocorticoids is an effective treatment strategy and leads to resolution or marked improvement within few days/few weeks.

Disclosure: K. A. Kirou, None; N. Chaudhry, None.

Comparison High Intensity Laser Therapy and Wrist Splint in the Treatment of Lateral Epicondylitis. Ekrem Akkurt1, Halim Yilmaz1, Ali Salil2, Selman Parliak3, Gulten Karaca4 and Sami Kucuksen5. MD, Konya, Turkey, 2MD, Konya, Turkey, 3MD, Konya, Turkey, 4MD, Konya, Turkey, 5MD, Konya, Turkey.

Background/Purpose: Lateral epicondylitis (LA), also known as tennis elbow, is a quite common disease with a prevalence of 1.7% and mostly seen between 3rd and 6th decade of life.

Methods: 67 elbows diagnosed with lateral epicondylitis were divided randomly into two groups as HILT (33,9 and as wrist splint (34). 33 wrists were randomly into two groups as HILT (33,9 and as wrist splint (34). In addition, 33 wrists were recommended to wear wrist splints for 6 subsequent weeks. The aim of this study is to compare the efficacy of HILT and wrist splint treatment. Patients were evaluated before and in 6th week of post treatment period using visual analogue scale for pain (VAS) during activity and resting, Disabilities of the Arm, Shoulder and Hand (DASH) Score, hand grip strength test (HGST), and Short Form 36 (SF-36).

Results: Out of the 60 patients, 14 male and 46 female with a mean age of 46.7±9.4. The treatment and 6th week scores of the HILT patients were as follows: VAS activity 8.3±3.1, 6.0±3±2.3 VAS resting 5.5±3.2±7.2, 2.7±2.4±1, DASH 53.4±22, 38.3±17.1, HGST 15.4±9.9, 21.5±13.8, SF 36 physical component 35.3±17.2, 66.7±15.7, and SF 36 mental component 46.4±17.3, 62.1±17.9 and of the wrist splint group as the following: VAS activity 7.7±2.3, 6.1±3±2.0, VAS resting 4.6±3±1.0, 2.7±3.0, DASH 4.68±16.0, 30.4±17.5, HGST 17.1±7.6, 20.8±8.1, SF 36 physical component 36.7±15.3, 50.4±18.9, and SF 36 mental component 38.6±15.7, 52.3±18.7.

The VAS activity, resting, DASH, HGST, SF36 physical, and SF36 mental component scores of both groups revealed significant improvements on comparing their pretreatment and 6th week score except the SF physical component scores, none of these variables were statistically significant when the HILT and wrist splint groups were compared. The statistical difference was in favor of the HILT group.

Conclusion: The findings of the present study suggest that both HILT and wrist splints are reliable, safe, and effective treatment options in LE patients. Although HILT has been determined to be more effective in increasing functional capacity, both groups revealed almost equally positive outcomes, in the short and long term considering pain, functional status and quality of life.

Disclosure: E. Akkurt, None; H. Yilmaz, None; A. Salil, None; S. Parliak, None; G. Karaca, None; S. Kucuksen, None.
The Relationship Between Tender Points and Disease Severity in Patients with Fibromyalgia. Oya Ozdemir1 and Fitnat Dincer2. 1Hacettepe University Faculty of Medicine, Ankara, Turkey, 2Hacettepe University, Faculty of Medicine, Ankara, Turkey.

Background/Purpose: The aim of this study was to investigate the relationship between tender point examination and disease severity in patients with a diagnosis of fibromyalgia according to the 1990 American College of Rheumatology criteria.

Methods: Sixty three consecutive female patients, with a mean age of 43.8 ± 10.5 years, were included to the study. Digital palpation of tender points was performed by the same physician (OO), after then total tender point count (TPC) and myalgic score (rated as 0=no pain, 1=mild pain, 2=a verbalclamation of pain, 3=withdrawal or flinching) were calculated. In order to assess the disease severity, Fibromyalgia Impact Questionnaire (FIQ) was used.

Results: The median duration of symptoms was 3.0 years (range; 0.5–20). The mean of total TPC and myalgic score were 14.7±3.5 and 43.8±15.9 respectively. The mean of FIQ total score was found to be 63.2±25.3 and 25.3±8.0 respectively. The mean of FIQ total score was to be found in the female patients with fibromyalgia.

Disclosure: O. Ozdemir, None; F. Dincer, None.

The Relationship Between Tender Points and Disease Severity in Patients with Fibromyalgia. Mercedes Fernandez Moreno1, Tamara Vázquez-Mosquera2, Estefanía Cortés-Pereira1, María Eugenia Vázquez-Mosquera2, Estefanía Cortés-Pereira1, María Tamayo2, Sara Relaño-Fernández3, Alejandro Mosquera4, Nataly Vazquez-Moreno1, Ignacio Rego-Perez2, Juan Fernández-Tajes2, Mercedes Fernandez Moreno1, Angel Soto-Hermida2, María Eugenia Vázquez-Mosquera2, Estefanía Cortés-Pereira1, María Tamayo2, Sara Relaño-Fernández3, Alejandro Mosquera4, Nataly Vazquez-Moreno1, Ignacio Rego-Perez2, Juan Fernández-Tajes2, Mercedes Fernandez Moreno1, Angel Soto-Hermida2, María Eugenia Vázquez-Mosquera2, Estefanía Cortés-Pereira1, María Tamayo2, Sara Relaño-Fernández3, Alejandro Mosquera4, Nataly Vazquez-Moreno1, Ignacio Rego-Perez2, Juan Fernández-Tajes2, Mercedes Fernandez Moreno1, Angel Soto-Hermida2, María Eugenia Vázquez-Mosquera2, Estefanía Cortés-Pereira1, María Tamayo2, Sara Relaño-Fernández3, Alejandro Mosquera4, Nataly Vazquez-Moreno1, Ignacio Rego-Perez2, Juan Fernández-Tajes2, Mercedes Fernandez 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that carry the same nuclear background and different mitochondrial variants, are optimal cellular model to study mitochondrial biology and function. This cellular model excludes variations from the nuclear genome in the cellular activity. The aim of this work is to test the real role of mtDNA haplogroups in cellular activity, using cybrids with mtDNA haplogroup H and J and analyzing several parameters implicated in the OA process.

Methods: Cybrids were developed using the 143B.TK rho-0 cell line and platelets from healthy (without OA) and OA donors with mtDNA haplogroups H and J. The metabolic status was evaluated by measuring both lactic acid production and glucose consumption. The respiration was evaluated with a high resolution respirometry (Oroboros). The ATP levels were obtained by luciferase reaction. The expression levels of genes implicated in inflammation (COX-2 and iNOS), Metalloproteinases (MMP-1, 3 and 13) and MnSOD, were evaluated by RT-PCR. The ROS production and percentage of apoptotic cells were measured by Flow Cytometry (mean fluorescence intensity).

Results: Cybrids carrying the mtDNA haplogroup J show higher lactic acid production (62.22 mg/ml and 52.71 mg/ml; p<0.05) and 20% higher of glucose consumption than H cybrids, therefore being more efficient using glucose via glycolysis. In addition, J cybrids show lower levels of ATP (0.027nmol ATP/mg protein) than H (0.033nmol ATP/mg protein), and higher values of oxygen consumption (36.92 nmol/mg for J and 9.97 nmol/mg for H cybrids). H cybrids had significantly higher. Results of total ROS (203.30 for H cybrids and 131.26 for J) and mitochondrial ROS (47.36 and 38.67 respectively). MnSOD expression in basal conditions was higher in cybrids H than J (2-fold) and IL-1β stimulation (5 ng/ml 24 hours) showed 2-fold increase of MnSOD in J cybrids compared to H. The analysis of inflammatory process showed that the basal expression levels of COX-2 and iNOS were higher in H than in J (H expressed 4-fold COX-2 than J; iNOS was 1.5-fold). Basal expression of MMP-1, 3 and 13 was higher in cybrids H than J. The percentage of cell in spontaneous apoptosis was similar between cybrids H (3.76%) and J (5.78%). The use of stauroporine (0.2μM, 2 hours) to induce apoptosis showed a 7-fold increase of apoptosis in H cybrids. Experiments performed in OA cybrids confirm the metabolic differences between H cybrids and J cybrids, as well as the higher susceptibility of H cybrids than to undergo apoptosis.

Conclusion: H and J cybrids have different metabolic behavior (J are more glycolysis dependent than H). Cybrids J have a lower ATP production, lower inflammatory response and produce less reactive species of oxygen. Cybrids J are less susceptible to undergo apoptosis. All these results offer a real rationale for why haplogroup J is associated with lower risk of OA.

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Impact of Genes Modulating Serum Low-Density Lipoprotein Cholesterol Levels on Progression of Joint Destruction in Japanese Patients with Rheumatoid Arthritis. Shinji Yoshida1, Katsunori Ikari1, Koichiro Yano1, Yoshiaki Toyama2, Atsuo Taniguchi3, Hisashi Yamanaka1 and Shinji Yoshida1. Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan; 2Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo, Japan; 3Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher prevalence of dyslipidemia than healthy individuals. Since RA is a chronic inflammatory disease, an inflammatory response may be partly involved in the pathogenesis of dyslipidemia. Recently, low-density lipoprotein (LDL) cholesterolemia has been reported to be a risk factor for radiographic progression of joint destruction. Several genetic loci for progression of joint destruction have been identified so far. However, the genetic predisposition factors have not yet been elucidated. The purpose of this study was to evaluate impact of genetic variants modulating serum LDL cholesterol (LDL-C) levels on progression of joint destruction in Japanese patients with RA.

Methods: This study included 1,005 Japanese patients with RA for whom Sharp/van der Heijde scores (SHS) of hands were available at a disease duration of 5 years. DNA samples of the subjects were obtained from the Institute of Rheumatology Rheumatoid Arthritis cohort study (IORRA) DNA collection. All of the patients who donated DNA samples consented to participate in this study as approved by the Tokyo Women’s Medical University Genome Ethics Committee, and satisfied the American College of Rheumatology 1987 revised criteria for the classification of RA. Thirteen single nucleotide polymorphisms (SNPs) in the 8 loci influencing serum LDL-C concentrations in the Japanese population were selected and genotyped in the DNA samples: rs611917, in SORT1; rs639, rs7575840, and rs515135, in APOB; rs3846662, in HMGCR; rs662799, in BUD13-APOA1-APOA5; rs639, in SORT1; rs515135, in SCARB1; rs523624, and rs73074, in SORLA, and rs1433099, in LDLR. 4, 7, 11, and 14, in APOE-C1. Multivariate linear regression analyses were performed to examine the association of each SNP with radiographic progression of joint destruction in the first 5 years after onset of RA, calculated as SHS of hands at the 5-year disease duration. Adjustments were made for gender, age of onset, anti-citrullinated peptide status, and year of disease onset. All SHS were log-transformed to obtain a normal distribution.

Results: Multivariate linear regression analyses revealed that the minor allele of rs662799 in BUD13-APOA1-APOA5 was associated with progression of joint destruction in the recessive model (P = 0.04). However, the association could not reach the level of the significance after Bonferroni correction for multiple comparisons. The other SNPs showed no association (Table 1).

Conclusion: We could not confirm the association between genes modulating serum LDL-C levels and progression of joint destruction in Japanese patients with RA. Our results indicated that rs662799 in BUD13-APOA1-APOA5 might be a risk factor for progression of joint destruction, but further studies would be required to confirm the association.

Table 1 Multivariate linear regression analyses of each SNP associated with progression of joint destruction

<table>
<thead>
<tr>
<th>Gene SNP</th>
<th>Allele</th>
<th>MAF</th>
<th>Risk allele</th>
<th>Test statistic</th>
<th>Orientation</th>
<th>P value</th>
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<tr>
<td>SORT1</td>
<td>rs611917</td>
<td>G/A</td>
<td>0.09</td>
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<td>HMGR</td>
<td>rs3846662</td>
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<td>0.01</td>
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<td>0.05</td>
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<tr>
<td>BUD13-APOA1-APOA5</td>
<td>rs662799</td>
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<td>0.32</td>
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<td>0.14</td>
<td>0.07</td>
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<td>SCARB1</td>
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<tr>
<td>CETP</td>
<td>rs1532624</td>
<td>T/G</td>
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<td>LDLR</td>
<td>rs681</td>
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<td>0.08</td>
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<td>APOE-C1</td>
<td>rs429358</td>
<td>C/T</td>
<td>0.16</td>
<td>0.03</td>
<td>0.36</td>
<td>0.02</td>
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</table>

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Genome-Wide Profiling of DNA from Cartilage Reveals Regions Differently Methylated in Osteoarthritics Patients. Guangju Zhai1, Ming Liu2, Yu Xiu Zhang3, Patricia E. Harper4, Erfan Aref-Eshghi5, Yann Lin6, Andrew Furey2, Roger Green7, Guang Sun2 and Proton Rahman.1. Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St John’s, NF, 2Memorial University, St. John’s, NF, 3Department of Surgery, Faculty of Medicine, Memorial University of Newfoundland, St John’s, NF, 4Discipline of Medicine, Faculty of Medicine, Memorial University of Newfoundland, St John’s, NF, 5Memorial University of Newfoundland, St John’s, NF.

Background/Purpose: Osteoarthritis (OA) represents the most common form of arthritis and has substantial clinical and economic impact. Evidence supports that DNA methylation plays a significant role in OA. The aim of the study was to identify differentially methylated loci for OA using an epigenome-wide association approach.

Methods: Cartilage samples were collected from 14 patients who underwent total hip joint replacement due to primary OA and 16 hip fracture patients who do not have evidence of hip OA. DNA was extracted from the cartilage samples and methylation profiling was performed using the Illumina Infinium HumanMethylation 450k chip, which measures about 480,000 different CpG sites covering 96% of RefSeq genes. It provides comprehensive gene region coverage, targeting multiple sites including the promoter, 5' UTR, 3' exon, gene body and 3' UTR. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: We found 18 individual CpG sites significantly associated with OA, with a mean difference in methylation level of >10% and a p value < 10^-4. Of them, six were hypermethylated and 12 were hypomethylated in OA patients. Nine of them are located within genes and other 9 are intergenic. Two genes - COLBA1 and CDKN2C - have been reported recently using the same approach as ours and the other 16 CpG sites are novel. ATG7 involves in autophagic pathway and CLCN7 causing osteopetrosis are novel promising candidates for OA.

Conclusion: We confirmed the recently reported association of COLBA1 and CDKN2C methylation with OA and identified 16 novel DNA methylation loci for OA, providing new insight into the pathogenesis of OA. Confirmation study with large sample size is underway.

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The Mitochondrial Genome Influences the Risk of Incident Knee OA. DATA from the Osteoarthritis Initiative. Angel Soto-Hermida1, Ignacio Rego-Perez2, Juan Fernandez-Tajes1, Mercedes Fernandez Moreno1, Maria Eugenia Vázquez-Mosquera3, Estefania Cortés-Pereira4, Sonia Pértiga-Díaz2, Nataly Oreo-Villar4, Carlos Fernandez-López2 and Francisco J. Blanco García1. 1Grupo de Proteómica-PBR2-ProteoRed/ISCIII Servicio de Reumatología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad de Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruña, Spain. 2Grupo de Proteómica-PBR2-ProteoRed/ISCIII Servicio de Reumatología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad de Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruña, Spain. 3Grupo de Genomica RIER/ISCIII: Servicio de Reumatología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad de Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruña, Spain. 4Grupo de Genomica RIER/ISCIII: Servicio de Reumatología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad de Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruña, Spain. 5INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), La Coruña, Spain. 6Grupo de Proteómica-PBR2-ProteoRed/ISCIII Servicio de Reumatología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad de Coruña (UDC). As Xubias, 15006 A Coruña, Spain, A Coruña, Spain.

Background/Purpose: In this study we have identified proteins differentially abundant in the serum of osteoarthritics (OA) patients comparing four different progressive pathological grades using mass spectrometry and iTRAQ technique for relative quantification. Our final aim is to establish a panel of biomarkers useful for its handling and the development and establishment of putative biomarkers (early OA grades). Among them, complement component 5 -C5-, that have been frequently identified in previous studies as candidate putative OA markers, and, furthermore, the area under the receiver operating characteristic (ROC) curve (AUC) of the model was also calculated.

Results: We have detected two big sets of proteins that could be used as putative biomarkers by our group and other, like histidine-rich criteria and were subsequently excluded from further analyses. Patients belonging to mtDNA cluster HV were significantly overrepresented in the incident knee OA group (OR = 1.395; CI = 1.044-1.863; p = 0.0024) meanwhile patients in cluster TJ were less represented in the incident group (OR = 0.692; CI = 0.466-1.026; p = 0.065). The logistic regression model showed that female gender (p < 0.001), higher BMI (p < 0.001) and contralateral knee OA (p = 0.001) were risk factors to develop incident OA; additionally, OA patients in cluster HV were at higher risk for incident knee OA than patients in cluster TJ (p = 0.016). The AUC of this regression model was 0.707.

Conclusion: The mitochondrial genome contributes to the development of incident knee OA. The assignment of the mtDNA haplogroups could be used as complementary genetic biomarkers to predict the risk of incident knee OA.


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Background/Purpose: In this study we have identified proteins differentially abundant in the serum of osteoarthritics (OA) patients comparing four different progressive pathological grades using mass spectrometry and iTRAQ technique for relative quantification. Our final aim is to establish a panel of biomarkers useful to predict the pathology in pre-radiological stages (early osteoarthritics biomarkers), but also for its handling and the developing of trials of treatment in radiological stages (late osteoarthritics biomarkers).

Methods: 15 individual samples for each condition (OA Grade 0, pre-radiological grade Stage I, and radiological stage grades II-III and IV) were pooled in three groups with the aim of reducing the contribution of individual extreme values. A fold enrichment in the low-abundant protein fraction, the pooled samples were subjected to in-solution digestion, followed by iTRAQ tagging following manufacturer instructions and Reverse Phase peptide separation in an LC system (Agilent 1200). Fractions were again separated in a nanoLC system (Temple, Eksigent) automatically deposited on a MALDI plate and analyzed by MSMS in a 4800 MALDI-TOF/TOF system (ABScienx). Relative quantitative analysis was done using ProteinPilot software (ABScienx) and modulated proteins were analyzed with String 9.0 software.

Results: We have detected two big sets of proteins modulated in the early pre-radiological OA process. Serum levels of apolipoproteins are altered when comparing Grade I vs. Grade 0. Specifically, apolipoprotein E and apolipoprotein B-100, that mediates the binding, internalization, and catabolism of lipoprotein particles are accumulated in Grade 1 samples. Furthermore, up to six components of the complement, a group of proteins involved in immune response and inflammation are decreased in serum in early OA grades. Among them, complement component 5 -C5-, that have been recently identified as key player of the OA process, is much less abundant in any OA grade in comparison to Grade 0. Proteins previously described as putative biomarkers by our group and others, like histidine-rich
glycoprotein, gelsolin and decorin, are also modulated in our study, but at later radiological stages - Grade I/II and Grade IV vs. Grade I and Grade 0. Conclusion: Our results indicate that early pathological grades of the OA process are linked to an imbalance in the metabolism and, specifically, in the lipid metabolism. Alteration of protein levels of apo-lipoproteins could be used in combination with other ‘dry’ biomarkers, as an indicator for early OA process and to detect the pathology in pre-radiological stages. Furthermore, the lower protein levels in the OA grades detected for the complement component C5 - C5-, strongly support recent in vivo data indicating that a decrease of this protein is linked to the development of the disease.

Table 1: Summary of the results

<table>
<thead>
<tr>
<th>Main proteins modulated in pre-radiological OA</th>
<th>Ratio</th>
<th>p-value</th>
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<tr>
<td>Apolipoprotein E</td>
<td>2.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Apolipoprotein B-100</td>
<td>2.0337</td>
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<tr>
<td>Apolipoprotein A-IV</td>
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<td>Complement C5</td>
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</tr>
<tr>
<td>Complement C1a</td>
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<td>0.0006</td>
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<tr>
<td>Complement C2</td>
<td>0.2666</td>
<td>0.0014</td>
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<th>Main proteins modulated in late OA</th>
<th>GI/G0</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Apolipoprotein E</td>
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<td>0.02</td>
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<tr>
<td>Zinc-alpha-2-glycoprotein</td>
<td>5.43</td>
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<td>Beta-2-glycoprotein</td>
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</tr>
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<td>Gelatin</td>
<td>1.24</td>
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<tr>
<td>Decorin</td>
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<td>0.0004</td>
</tr>
<tr>
<td>Protein 5200-A9</td>
<td>0.2339</td>
<td>0.0033</td>
</tr>
</tbody>
</table>

Table 1 Lipid profiles of hBMSCs undergoing chondrogenesis after MALDI-MSI analysis.

<table>
<thead>
<tr>
<th>mz peak</th>
<th>Lipid assignment</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>303.2</td>
<td>Arachidonic acid</td>
<td>Day 24</td>
</tr>
<tr>
<td>327.2</td>
<td>Docosahexaenoic acid</td>
<td>Day 24</td>
</tr>
<tr>
<td>723.5</td>
<td>SM (d18:1/16:0)</td>
<td>Day 2</td>
</tr>
<tr>
<td>721.5</td>
<td>SM (d18:1/16:0)</td>
<td>Day 2</td>
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<tr>
<td>729.5</td>
<td>SM (d18:1/16:0)</td>
<td>Day 2</td>
</tr>
<tr>
<td>730.5</td>
<td>PE (18:0/20:4)</td>
<td>Day 24</td>
</tr>
<tr>
<td>741.5</td>
<td>SM (d18:1/16:0)</td>
<td>Day 2</td>
</tr>
<tr>
<td>778.5</td>
<td>St (d16:0/16:0)</td>
<td>Day 14</td>
</tr>
<tr>
<td>801.5</td>
<td>Pc (18:0/18:0)</td>
<td>Day 2</td>
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<tr>
<td>819.5</td>
<td>PC (18:0/20:4)</td>
<td>Day 24</td>
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<td>826.5</td>
<td>PC (18:0/18:1)</td>
<td>Day 2</td>
</tr>
<tr>
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<td>PC (18:0/20:0)</td>
<td>Day 2</td>
</tr>
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<td>883.6</td>
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<td>Day 2</td>
</tr>
<tr>
<td>943.5</td>
<td>PI (18:0/18:0)</td>
<td>Day 14</td>
</tr>
</tbody>
</table>

PC: phosphatidylcholine; SM: sphingomyelin; PE: phosphatidylethanolamine; ST: sulfatide; PG: phosphatidylglycerol; PI: phosphatidylinositol.

Disclosure: J. Mateos, None; C. Ruiz-Romero, None.

1127 Mass Spectrometry Imaging Revealed Potential Lipid Chondrogenic Biomarkers for Cell-Based Therapy in Cartilage. Beatriz Rocha1, Berta Cillerio-Pastor2, Gert Eijkel2, Valentina Calamia1, Lucia Lourido1, Carolina Fernandez-Costa1, Patricia Fernandez-Puente1, Jesus Mateos3, Cristina Ruiz-Romero1, Ron MA Heeren2 and Francisco J. Blanco Garcia1. 1Grupo de Proteoma-PBR2-ProteoRed/ISCIII-Servicio de Reumatologia. Instituto de Investigacion Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidad da Coruña (UDC). A Xubias, 15006, A Coruña, Spain, 2AMOLF, Amsterdam, Netherlands.

Background/Purpose: Recent studies highlight the importance of lipid metabolism in the modulation of chondrogenesis. Specifically, the positive chondrogenic effect of acid ceramidase, which is necessary to maintain the metabolic balance of several bioactive lipids, during the chondrogenesis of mesenchymal stem cells (MSCs) has been demonstrated. Therefore, knowledge on the distribution and modulation of lipids during chondrogenesis could be highly valuable to improve MSC-based cartilage therapies by the discovery of new chondrogenic markers. In this work, mass spectrometry imaging (MSI) has been employed to characterize the spatial distribution of lipids in human bone marrow MSCs (hBMSCs) during the first steps of their chondrogenic differentiation.

Methods: hBMSCs micromasses obtained from 3 osteoarthritic donors and collected at day 2 and 14 of chondrogenesis were gelatin-embedded and cryo-sectioned into thin sections for MSI. Samples were then sprayed with matrix and analyzed by matrix-assisted laser desorption ionization (MALDI-MSI) to obtain the lipid profiles. Statistical methods such as PCA and discriminant analysis were used for data interpretation. Lipid images were generated with Biomap software. Data were confirmed by Real-Time PCR analyses.

Results: A total of 14 lipid profiles were obtained by MALDI-MSI and discriminated in different lipid classes, including fatty acids, sphingolipids and phospholipids (Table 1). Among the lipid classes identified, we found phosphatidylcholines and sphingomyelins levels decreased during chondrogenic differentiation (Figure 1). These data suggest that hBMSCs mobilize the SMs in order to produce cartilage extracellular matrix.

Conclusion: The data compiled herein are undoubtedly useful for a better understanding of the molecular processes that occur during the differentiation of these cells towards cartilage-like tissues. In addition, the differential lipid profiles described in our study might serve as useful differentiation markers for the development of cell-based therapies for cartilage repair. In fact, the loss of SM during chondrogenesis might be used as a novel chondrogenic marker.

Table 1: Lipid profiles of hBMSCs undergoing chondrogenesis after MALDI-MSI analysis.

<table>
<thead>
<tr>
<th>mz peak</th>
<th>Lipid assignment</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>739.5 PC (16:0/18:1)</td>
<td>Day 24</td>
<td></td>
</tr>
<tr>
<td>790.5 PC (18:0/18:0)</td>
<td>Day 24</td>
<td></td>
</tr>
<tr>
<td>327.2</td>
<td>Docosahexaenoic acid</td>
<td>Day 24</td>
</tr>
<tr>
<td>303.2</td>
<td>Arachidonic acid</td>
<td>Day 24</td>
</tr>
<tr>
<td>237.2</td>
<td>Docosahexaenoic acid</td>
<td>Day 24</td>
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<tr>
<td>518.5</td>
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<td>SM (d18:0/18:0)</td>
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<tr>
<td>530.5</td>
<td>PE (18:0/20:4)</td>
<td>Day 24</td>
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<td>541.5</td>
<td>SM (d18:1/16:0)</td>
<td>Day 2</td>
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<tr>
<td>568.5</td>
<td>ST (d16:0/16:0)</td>
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<td>599.5</td>
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<td>683.6</td>
<td>SM (d18:0/18:0)</td>
<td>Day 2</td>
</tr>
<tr>
<td>739.5</td>
<td>PI (18:0/18:0)</td>
<td>Day 24</td>
</tr>
<tr>
<td>753.6</td>
<td>PE (18:0/20:4)</td>
<td>Day 24</td>
</tr>
<tr>
<td>755.5</td>
<td>PE (18:0/20:4)</td>
<td>Day 24</td>
</tr>
</tbody>
</table>

PC: phosphatidylcholine; SM: sphingomyelin; PE: phosphatidylethanolamine; ST: sulfatide; PG: phosphatidylglycerol; PI: phosphatidylinositol.
After silencing PIWIL4 we assessed proliferation by cell counting. We analysed expression of PIWIL4 mRNA in PBMC isolated from patients with RA, systemic lupus erythematosus (SLE), axial spondyloarthritis (axSpA) and from healthy controls (HC, n=6–12 each).

Results: PIWIL2, 3 and 4 but not PIWIL1 could be detected in both RA and OA SF without significant changes (RA/OA mean dCt = 3.87/2.83, 9.50/12.32, 2.63/3.21). A high expression of PIWIL4 was also found in ST patients with RA and OA (mean dCt = 3.59/2.31). PIWIL4 mRNA were further enhanced by Poly(I:C) in both RASF and OA SF-2.9-fold (p = 0.003)/4.3-fold (p = 0.013), LPS 2.1-fold (p = 0.026)/2.6-fold discr (p = 0.025) and TNFα in combination with IL1β 1.9-fold (p = 0.003)/1.7-fold (p = 0.007). However, on the protein level no induction of PIWIL4 expression was detected.

Treatment of RASF with 5-AZA did not regulate PIWIL4 expression, treatment with TSA down-regulated PIWIL4 mRNA to 0.4-fold (p = 0.003); DZNep to 0.7-fold (p = 0.026) and 8-aza-deoxy treatment caused a 1.4-fold induction of PIWIL4 mRNA (p = 0.043).

PIWIL4 silencing in RASF significantly decreased mRNA expression of the histone deacetylase HDAC1 (to 0.6-fold, p = 0.003), but not HDAC2 or HDAC3. Furthermore PIWIL4 silencing decreased cell proliferation in RA SF stimulated with TNFα and IL1β by 30% (p = 0.034).

In PBMC of patients with RA the expression of PIWIL4 was higher than in HC (mean dCt = 2.18 vs 2.64, p < 0.05), but lower than in patients with SLE (mean dCt = 1.42, p < 0.001). There was no difference between RA and axSpA patients (mean dCt = 2.30).

Conclusion: We have demonstrated that PIWIL4 expression is regulated by inflammatory cytokines and epigenetic modifications with functional consequences on proliferation suggesting a role of PIWIL4 in the activation of synovial fibroblasts in RA.

Disclosure: L. Pleštilová, FP7 OSTEOIMMUNE 289150, 2; N. Gaur, None. M. Filková, MHCR project 023728, 2; B. Aardi-Vegh, EuroTEAM, 2; L. Senolt, MHCR project 023728, 2; A. Ciurea, Pfizer Inc, 2; Abbott Immunology Pharmaceuticals, 5; AbbVie Immunology Pharmaceuticals, 5; Merck Pharmaceuticals, 5; UCB, 5; B. E. Gay, None. J. Vencovsky, MHCR project 023728; M. Neidhart, None. S. Gay, None. A. Jungel, IMI-BCT-Cure, 2, IAR, 2.

1129

FCGR2A Polymorphism and Response to Anti-TNF Treatment in Rheumatoid Arthritis. G. Avila1, Jesús Tornero2, Antonio Fernandez Nebro3, Francisco Blanco4, Isidoro Gonzalez-Alvaro5, Juan D. Cañete6, Joan Mamo7, Javier Ballina8, Benjamín Fernandez Gutierrez9, Alejandro Olives5, Horacio Corominas10, Alba Erra11, Raúl Tortosa12, María Ámérica López-Lasanta13, Adrián Aterido14, Antonio Julia15 and Sara Marsal16. 1Hospital Research Institute, Barcelona, Spain, 2Hospital Sant Rafael, Barcelona, Spain.

Background/Purpose: Recently, evidence for a specific association of the non synonymous SNP in FCGR2A rs1801274 with treatment response in Adalimumab-treated patients (P = 0.01; OR = 0.95 [95% CI = 0.82–0.88]) but not in Infliximab (P = 0.3) or Etanercept-treated patients (P = 0.82). Including smoking status as a covariate of rs1801274 association with treatment response showed no evidence of confounding (P = 0.2).

Conclusion: We have found, for the first time a specific association of FCGR2A with the response to Adalimumab in RA at 3 months of therapy. The lack of validation of the previous specific association of FCGR2A with Infliximab could be due to the low effect size of the genetic association or to differences between patient cohorts. Finally, we have also found a positive association with smoking and the response to anti-TNF agents.

Table 1 Epidemiological and Clinical Features of the Study Cohort

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<tr>
<th>Feature</th>
<th>All (n=340)</th>
<th>Infliximab (n=126)</th>
<th>Adalimumab (n=95)</th>
<th>Etanercept (n=127)</th>
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<td>Age (years)</td>
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<td>43±11</td>
<td>45±12</td>
<td>42±13</td>
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<tr>
<td>Disease duration (mean DAS28)</td>
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<td>10±7</td>
<td>10±9</td>
<td>11±9</td>
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<tr>
<td>&amp;&lt;sub&gt;1&lt;/sub&gt;R (n (%)</td>
<td>270 (78)</td>
<td>96 (76)</td>
<td>72 (77)</td>
<td>102 (80)</td>
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<td>Smokers (%)</td>
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<td>52 (42)</td>
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<td>43 (44)</td>
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<td>PIWIL4 expression (Fold)</td>
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<td>12 weeks</td>
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<td>4.2±1.0</td>
<td>3.8±1.0</td>
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<td>EULAR response (%)</td>
<td>261 (75%)</td>
<td>87 (70%)</td>
<td>75 (78%)</td>
<td>65 (71%)</td>
</tr>
<tr>
<td>Non-responder (%)</td>
<td>88 (25%)</td>
<td>38 (30%)</td>
<td>19 (20%)</td>
<td>30 (24%)</td>
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1130

IRF8 Gene Contributes to Disease Susceptibility and Interacts with HLA-KB By Modulating Interferon Signatures in Patients with Systemic Sclerosis. Maria Ainsendi1, Mathieu Giraud1, Nadira Ruhehaj2, Philippe Dieule3, Eugénie Koumakis4, Barbara Ruiz3, Paolo Airo5, Daniela Cusi7, Marco Mattucci-Cerinic8, Erika Salvi9, Giovanna Cuomo10, Eric Hachulla10, Elizabeth Dietz1, Paolo Caramaschi1, Valeria Ricci1, Jerome Avoou1, Cristiane Kayser16 and Yannick Allanore17. 1University of Milano, Milano, Italy, 2AO Spedali Civili, Brescia, Italy, 3University of Milano, Milano, Italy, 4AO Spedali Civili, Brescia, Italy, 5University Sapienza, Rome, Italy, 6AO Spedali Civili, Brescia, Italy, 7University and Medical Complex, UTS Wollongong, Australia, 8Paris Descartes University, Rheumatology A department and INSERM U1016, Cochin Hospital, Paris, France, 9Paris Descartes University, INSERM U1016, Institut Cochin, Sorbonne Paris Cité, Paris, France, 10University of Milano, Milano, Italy, 11University of Milano, Milano, Italy, 12University of Napoli, Naples, Italy, 13University of Milano, Milano, Italy, 14Hospital Lariboisiere, Claude Bernard, Paris, France, 15University of Milano, Milano, Italy, 16University of Napoli, Naples, Italy, 17Paris Descartes University, Rheumatology A department and INSERM U1016, Cochin Hospital, Paris, France.

Background/Purpose: Systemic Sclerosis (SSc) is a polygenic autoimmune disease (AID) characterized by fibroblast dysregulation. It shares some genetic bases with other AIDs, as evidenced by autoimmune gene pleiotropism. Fibroblast dysregulation can also be observed in Primary Biliary Cirrhosis (PBC), another polygenic AID, which can be associated with SSc in the so called Reynold’s Syndrome. The present study was undertaken to investigate whether single nucleotide polymorphisms (SNPs) identified by a large GWAS in PBC might contribute to SSc susceptibility by a cross-disease approach.

Methods: Sixteen PBC susceptibility SNPs were genotyped in a total of 1,616 SSc patients and 3,621 healthy controls all of whom were of European Caucasian origin.

Results: We observed an association between PLCL2 rs1372074 (OR = 1.23 [95% CI 1.12–1.33]; P = 7.72×10⁻⁵), NF-kB rs7665090 (OR = 1.16 [95% CI 1.06–1.25]; P = 0.01) and IRF8 rs1117432 (OR = 0.75 [95% CI 0.67–0.86]; P = 2.50×10⁻⁴ with SSc susceptibility. We subsequently queried associations according to the main subtypes and found that
ns1372072 and ns1117432 were associated with the limited cutaneous subgroup ($P_{\text{adj}}=0.001$ and $P_{\text{adj}}=0.003$, respectively) and that rs7665090 was conversely associated with the diffuse cutaneous subset ($P_{\text{adj}}=0.007$). We then looked for genotype – phenotype correlations by measuring mRNA expression of PBMC, obtained from patients (n=39) and controls (n=24), and observed that the IRF8 protective allele was associated with decreased IFIT1 expression reflecting type 1 interferon signature. We investigated gene interactions between the 3 associated SNPs that revealed an epistatic interaction between NF-kB and IRF8 SNPs ($OR=0.56$ [95% CI 0.00–0.74], $P=4.9\times 10^{-5}$). Interestingly, we observed that the effects of IRF8 and NF-kB were only observed in patients carrying the susceptibility allele from both genes.

Conclusion. By a cross disease approach querying pleotropic genes, we identified 2 new susceptibility genes for SSc and confirmed IRF8 locus. We also identified functional effects of IRF8 variant affecting interferon signature and that an interaction between IRF8 and NF-kB genes might play a role in SSc susceptibility.

Disclosure. M. Arismendi, None; G. Giraud, None; N. Ruzevajli, None; P. Dieud, None; E. Kousakis, None; B. Ruiz, None; P. Airo, None; D. Cusi, None; M. Matucci-Cerinic, None; E. Salti, None; G. Cuomo, None; E. Hachulla, None; E. Diot, None; P. Caramaschi, None; V. Riccieri, None; J. Avouac, None; C. Kayser, None; Y. Allano, None.

1131

Identification of Genetic Variants Associated with Response to Adalimumab Plus Methotrexate in Patients with Early Rheumatoid Arthritis

Alia Skapenko1, Hendrik Schuiz-Koppo1, Viswanath Devanarayan, Kenneth Idder, Feng Hong, Joseph S. Smolen, Arthur Kavanagh, Hartmut Kupper1 and Jeffrey F. Warrington2

1University of Munich, Munich, Germany, 2Abbvie b.v. Research Center, Worcester, MA, 3Abbvie Inc., North Chicago, IL, 4Abbvie Inc., North Chicago, IL, 5Vienna and Hietzing Hospital, Vienna, Austria, 6University of California San Diego, La Jolla, CA, 7Abbvie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: For patients with rheumatoid arthritis (RA) who fail to attain remission or low disease activity after 6 months of methotrexate (MTX) treatment, TNF inhibitors should be considered for patients with a high risk of aggressive disease. The objective was to identify genetic variants associated with response to adalimumab (ADA) + MTX in patients with early RA.

Methods: OPTIMA was a 78-week, multicenter, randomized, double-blind, period, double-blind study in which patients were randomized to 1:1:1 combination therapy with ADA + MTX or MTX alone for the first study period of 26 weeks. Enrolled patients were invited to participate in a genetic sub-study and asked to provide written, informed consent. 384 variants in genes previously shown to be associated with RA or treatment response were assayed using the illumina BeadXpress press GoldenGate assay. Changes in the 28-joint disease activity score (DAS28) from baseline to 26 weeks and the total Sharp score (TSS) following 26 weeks of treatment were assessed for association for allele status using genotypic tests.

Results: A total of 413 patients randomized to ADA + MTX were included in the genetic sub-study. Three SNPs within the APoH gene were significantly associated with a response to ADA + MTX (Table). APOH (b2-GP1) has been shown to stimulate macrophages and to produce TNF-a in a TLR4-dependent manner, and some studies have suggested that RA patients display increased levels of autoantibodies against b2-GPI. Additionally, eight SNPs within the MAP2K6 gene, which has been shown to be activated in RA, were significantly associated with a response to ADA + MTX. Other SNP within genes that have been associated with RA susceptibility or treatment response to TNF-a inhibitors, such as ABCB1, IL21, and STAT4, also showed an association with ADA + MTX treatment. For some genes, such as APOH and MAP2K6, multiple SNPs were identified, suggesting that haplotype analysis could identify stronger associations. Additional SNPs within TRAF6, RAG1, APOH, and CDK6 were also associated with a change in TSS (DTSS >0).
Disclosure: R. Arya, None; D. R. Inmaculada, None; V. S. Farook, None; J. F. Restrepo, None; D. A. Winnier, None; M. J. Fourcado, None; D. Battafarano, None; S. Kumar, None; M. A. de Almeida, None; J. E. Curran, None; C. P. Jenkinson, None; J. Blango, None; R. Duggirala, None; A. Escalante, None.

1133 Genetic Variants Influencing Joint Damage in Mexican Americans and European Americans with Rheumatoid Arthritis. Rector Arya1, del Rincon Inmaculada2, Vidya S Farook3, Jose Felix Restrepo3, Deidre A Winnier4, Marcel J Fourcado5, Daniel Battafarano1, Satish Kumar2, Marcio AA de Almeida2, Joanna E Curran2, Christopher P Jenkinson6, John Blango7, Ravindranath Duggirala8 and Augustin Escalante9. 1University of Texas Health Science Center at San Antonio, San Antonio, TX, 2Texas Biomedical Research Institute, San Antonio, TX, 3San Antonio Military Medical Center, JBSA - FT San Houston, TX.

Background/Purpose: Joint damage in rheumatoid arthritis (RA) has been shown to be heritable, but knowledge on specific genetic determinants of joint damage in RA is limited. We have used the ImmunoChip array to examine whether genetic variants with relevance to susceptibility to multiple autoimmune diseases including RA, influence variation in joint damage in Mexican Americans (MA) and European Americans (EA) with RA.

Methods: We recruited 720 MA and 424 EA patients with RA from public, private, military and VA rheumatology clinics. Joint damage was quantified using a radiographic assessment of both hands and wrists, scored for erosions and joint space narrowing using Sharp's technique. The Sharp scores were transformed using inverse normalization to approximate a normal distribution for the subsequent association analyses. To identify ethnic outliers, principal components (PCs) were derived using EIGENSTRAT principal component analysis. We conducted association analyses with the transformed Sharp score as a quantitative trait and were adjusted for sex as a covariate.

Results: After excluding SNPs due to the following reasons: stringent quality control, admixture and cryptic relationship inference analyses, and SNPs with minor allele frequency below 1%, our Sharp score association analyses involved 127,563 and 128,387 autosomal SNPs in MA and EA, respectively. Both phenotypic and genotypic data were available for 666 MAs ranging from p < 10^-5 to p < 10^-6 in the M3P5K14 gene on chromosome 17. In EAs, there were 28 SNPs from chromosomes 1, 4, 6, 9, and 21 with strong p-values ranging from p < 1 x 10^-5 to p < 1 x 10^-6. In MA and EA, samples using the program PLINK. We used the linear regression additive genetic model which included covariates age, sex, and the first two principal components (PC1 and PC2) to adjust for potential population stratification influences.

Conclusion: Our genetic study of the key players in the NOD2 pathway identified novel genetic associations in TAB1 and TAB2 variants (rs111447766, rs111576955, rs76778446, and rs19995739) in EAs passing Bonferroni thresholds (P < 3.46 x 10^-5 in AA; P < 1.12 x 10^-4 in EA). TAB1 is involved in kinase activator activity while TAB2 is involved in polyubiquitin binding molecular functions. Our case-control analysis using BiOGPS of these genes confirmed their high expression in retina, CD4+ T cells, and CD8+ T cells of human tissues. Previous studies have shown that TAB1 has been found to play a role in skin homeostasis, wound repair, and oncogenesis. Further, both TAB1 and TAB2 have been found to be redundant protein of the ligand-induced TAK1 activation in macrophages, and that deletion of either TAB1 or TAB2 results in macrophage death.

Conclusion: Our genetic study of the key players in the NOD2 pathway identified novel genetic associations in TAB1 in AAs and TAB2 in EAs. These findings will give insight into the genetic etiology of RA in adult sarcoidosis cases among AAs and EAs.

Disclosure: G. Dumancas, None; I. Adrianto, None; A. M. Levin, None; M. C. Iannuzzi, None; B. A. Rybicki, None; C. Montgomery, None.

1134 Role of NOD2 Pathway in Sarcoidosis Cases with Characteristics of Blau Syndrome. Gerard Dumancas1, Indra A di Bentua2, Albert M. Levin3, Michael C. Iannuzzi4, Benjamin A. Rybicki5, and Courtney Montgomery6. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2Henry Ford Health System, Detroit, MI, 3SUNY Upstate Medical University, Syracuse, NY.

Background/ Purpose: Blau syndrome (BS) is a rare autosomal dominant, autoinflammatory syndrome characterized by the clinical triad symptoms of symmetric arthritis, dermatitis, and granulomatous recurrent uveitis, similar to that of early onset sarcoidosis. The phenotype of the disease has proven to be more complex than initially thought but most commonly involves cutaneous and arthritis manifestations. Eye disease is rarely the presenting symptom but significant visual impairment has been observed in 46% of patients. Polymorphisms in the nucleotide oligomerization domain 2 (NOD2) are known to be associated with susceptibility to BS, Cohn's disease and sarcoidosis. Studies have shown that dysregulation of NOD2 signaling is involved in the pathogenesis of a variety of inflammatory disorders and has been implicated in the development of autoimmune disease, allergy, and asthma. A such, the goal of our study was to investigate the involvement of the NOD2 pathway genes in sarcoidosis cases that presented with disease similar to BS in African Americans (AAs) and European Americans (EAs).

Methods: Our AA case-control analysis comprised 51 AA sarcoidosis cases with positive skin and bone/joint involvement (~35.3% also have eye involvement), and 253 AA sarcoidosis cases without any skin and bone/joint involvement. Our EA case-control analysis consisted of 27 EA sarcoidosis cases with positive skin and bone/joint involvement (~14.8% have eye involvement), and 135 EA sarcoidosis cases without any skin and bone/joint involvement. Genotyping was performed at the Oklahoma Medical Research Foundation (OMRF) using the Illumina HumanOmni1Quad array and imputed using IMPUTE2/tpbo. Quality control included removal of SNPs with call rate < 80% and Hardy-Weinberg proportion tests P < 0.001. We evaluated 3,582 SNPs in AAs and 2,639 SNPs in EAs from 30 genes within the NOD2 pathway. Single-marker association test was performed using EMMAX adjusted for sex as a covariate.

Results: We observed novel significant associations in a TAB1 variant in AAs (rs35506409) and TAB2 variants (rs111447766, rs111576955, rs76778446, and rs19995739) in EAs passing Bonferroni thresholds (P < 3.46 x 10^-5 in AAs; P < 1.12 x 10^-4 in EA). TAB1 is involved in kinase activator activity while TAB2 is involved in polyubiquitin binding molecular functions. Our case-control analysis using BiOGPS of these genes confirmed their high expression in retina, CD4+ T cells, and CD8+ T cells of human tissues. Previous studies have shown that TAB1 has been found to play a role in skin homeostasis, wound repair, and oncogenesis. Further, both TAB1 and TAB2 have been found to be redundant protein of the ligand-induced TAK1 activation in macrophages, and that deletion of either TAB1 or TAB2 results in macrophage death.

Conclusion: Our genetic study of the key players in the NOD2 pathway identified novel genetic associations in TAB1 in AAs and TAB2 in EAs. These findings will give insight into the genetic etiology of BS in adult sarcoidosis cases among AAs and EAs.

Disclosure: G. Dumancas, None; I. Adrianto, None; A. M. Levin, None; M. C. Iannuzzi, None; B. A. Rybicki, None; C. Montgomery, None.

1135 Genes Involved in Cartilage Synthesis and Risk to Knee Osteoarthritis. Abhishek M Ishra Sr., Rajeshwar Srivastava II, Divya Sanghi III, Arij Singh IV and Devendra Parmar V. King George's Medical University,, Lucknow, India.

Background/ Purpose: Osteoarthritis (OA), characterized by gradual loss of articular cartilage in the joint, is a leading cause of disability among the elderly people. Though the etiology and pathogenesis of OA is obscure. Several studies have suggested that OA is not only related with aging, calcium and vitamin D deficiency; OA risk is also associated with several genetic susceptibility loci. The aim of this study to elucidate the genetic background of osteoarthritis.

Methods: In a case-control study; 500 cases with knee osteoarthritis (KO A) and an equal number of age matched healthy controls were included. Cases were diagnosed using the ACR guidelines for KOA. Blood were drawn for DNA, RNA and lymphocyte isolation. PCR-RFLP method, TaqMan
null
Vasoactive Intestinal Peptide (VIP) Genetic Variants Determine VIP Serum Levels and Could be Used As a Prognosis Biomarker. 

Amalia Lamana1, Iria Valino-Seane2, Luis Rodriguez-Rodriguez1, Javier Leceta3, Yasmín Juarranz4, Ana M. Ortiz García4, Carmen Martínez-Mora5, Benjamin Fernández-Gutiérrez2, Isidoro González-Alvaro1, Sara Scaramuzzino2, Delphine Nigon3, Cedric Lukas3, Yannick Allanore4, Anne Cambon-Thomsen2, Alain G. Cantagrel9, Philippe Dieude10 and Arnaud Constant11.

Background/Purpose: VIP has shown immunoregulatory properties in assays performed with human or murine cells. VIP has demonstrated a therapeutic effect in a murine model of collagen-induced arthritis. We recently reported that low VIP serum levels (sVIP) were associated to a worse clinical course in patients with early arthritis despite receiving a more intense treatment.

Purpose: determine whether genetic variants of VIP lead to variations in sVIP.

Methods: Princesa Early Arthritis Register Longitudinal (PEARL) study includes patients with early arthritis in which demographic, clinical, laboratory, therapeutic and radiological data are collected for 5 years follow-up (baseline, 6, 12, 24 and 60 months). Biological samples are obtained at each visit. sVIP had been measured in a previous study (Martinez et al. 2014). Patients with the highest and 9 patients with the lowest sVIP were selected for sequencing of VIP gene. Primers were designed to produce overlapping amplimers covering the VIP coding region (exons 1 to 3). Sequencing kit and capillary electrophoresis on a 3500XL Genetic Analyzer (Applied Biosystems [ABI]). 16 single nucleotide polymorphisms (SNPs) were differentially expressed in patient groups with extreme sVIP. Rs3823082, rs35643203, rs71575932, rs7755568 and rs688136 were selected for validation (trend statistical significance \( p < 0.2 \) in population \( n = 20 \)).

Results: in 457 patients (80% female, median age 54 years, [interquartile range 42–66]), 60% RA, 40% undifferentiated arthritis from PEARL study through RT-PCR and specific Taqman probes (ABI). Fisher’s exact test was applied to determine the significance level in the distribution of genotypes between patients with low and high sVIP. Kruskal-Wallis test was used to assess potential differences in sVIP between SNPs genotypes. To determine the effect of SNPs on disease activity, cumulative DMARD treatment and radiological progression, we fitted 3 multivariate analysis using generalized estimating equations for repeated measures. Statistical analysis was performed using Stata 12.1 for Windows.

Results: In the whole population, the minor allele frequency was 23.2% for rs3823082, 6.5% for rs35643203, 7.5% for rs71575932, 6.8% for rs7755568 and 34% for rs688136. Patients with at least one minor allele for rs35643203, rs71575932 or rs7755568 (p = 0.015; being these SNPs in linkage disequilibrium) and those carrying the TT genotype of rs3823082 (p = 0.07) showed significantly lower sVIP, and these genotypes showed an additional trend to lower disease activity. Patients homozygous for the minor allele of rs688136 showed a slight trend to higher sVIP \( (p = 0.27) \). Patients carrying one minor allele for rs35643203 and being homozygous for the T allele of rs8323082 displayed higher DAS28 along the follow-up if they were ACPA negative \( (p = 0.07) \), required more intensive DMARD treatment \( (p = 0.028) \) and showed higher radiological progression \( (p = 0.007) \). Patients with CC genotype of rs688136 showed a trend to lower disease activity \( (p = 0.17) \).

Conclusion: in our PEARL population genetic variants of VIP associated with low serum levels of this peptide may be a biomarker of severe disease in EA patients.

Disclosure: A. Lamana, None; I. Valino-Seane, None; L. Rodriguez-Rodriguez, None; J. Leeta, None; Y. Juarranz, None; A. Martínez-Mora, None; B. Fernández-Gutiérrez, None; I. González-Alvaro, None; R. P. Gomariz, None; R. García-Vicuña, None.

TACR1 rs7371863 Single Nucleotide Polymorphism Is a Genetic Risk Factor for Sicca Syndrome in Fibromyalgia Patients. 

L. Rodríguez-Rodríguez1, José Ramon Lamas2, Juan Á. Jover1, Sara Baena4, Antonio Collado1, Javier Rivera2 and B. Fernández-Gutiérrez1.

Background/Purpose: Fibromyalgia (FM) is a condition characterized by chronic widespread pain associated to multiple symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes. In recent years, many candidate gene association studies have been designed and carried out to identify the genes associated with FM. However, the study of the genetic factors associated to disease severity or to the presence of coexisting comorbidities, and therefore, potentially useful as predictors of disease outcome, is a relatively unexplored field. The aim of the study was to analyze in FM patients the genetic risk factors involved in the presence of symptoms and symptoms associated with this disease, and/or severity.

Methods: We included Spanish Caucasian patients diagnosed with FM according to 1990 ACR criteria. First, we used a discovery cohort (DC) of 564 patients, recruited from 15 centers throughout the Spanish geography. Subsequently, we used a replication cohort (RC) of 397 patients from the DNA Bank for Genetic Research in FM and Chronic Fatigue Syndrome of the FF Foundation and from the National DNA Bank (Salamanca, Spain). In the DC we studied the association between 320 single nucleotide polymorphisms (SNPs), located in 22 loci, and the presence of symptoms and syndromes associated with FM (depression, headache, sleep disorders, myofascial syndrome, irritable bowel syndrome, chronic fatigue, vertiginous syndrome, chronic cystitis, and sicca syndrome) and disease severity, using the FIQ (Fibromyalgia Impact Questionnaire) and the HADS (Hospital Anxiety and Depression Scale). In the RC, we studied those SNPs and those variables that were associated in the discovery cohort. As the dependent variables were dichotomous or continuous, linear or logistic regressions were performed, respectively, to study the genetic association, using an additive model of effects. The odds ratio (OR), with 95% confidence intervals [95% CIs], was used to assess the strength of association between genotypes and the main dichotomous variables. Analyses were adjusted for sex and time from the onset of pain symptoms. P values were adjusted for the number of main variables and a cutoff of 0.05 was established to select those SNPs to replicate in the RC. DC and RC results were pooled using meta-analysis techniques. P value was corrected considering the number of linkage disequilibrium blocks in which the analyzed SNPs were included.

Results: in the DC, we observed 10 SNPs with an adjusted p-value lower than 0.05: rs47607050, rs4760816, rs2171363 (associated to sleep disturbances), rs174696, rs10171225, rs3717863 (associated to sicca syndrome), rs2422148, rs2216307 (associated to vertigo), and rs12654778, rs10434128 (associated to HADS depression). After replication in the RC and pooling the results from both cohorts, only the rs3717863 variant, from the TACR1 gene, showed a significant association with a lower risk of sicca syndrome (adjusted OR 0.56 [95% CI 0.42 – 0.76], p = 0.0022).

Conclusion: TACR1 gene could play a role in the development of sicca syndrome in FM patients.

Disclosure: L. Rodríguez-Rodríguez, None; J. R. Lamas, None; J. A. Jover, None; S. Baena, None; A. Collado, None; J. Rivera, None; B. Fernández-Gutiérrez, None.

Association of Polymorphisms on OPG, RANK and RANKL with ACNA Presence and Erosions: Results of a Meta-Analysis on 1570 Rheumatoid Arthritis Patients. 

G. Rodriguez-Rodriguez1, Sara Scaramuzzino2, Delphine Nigon3, Yannick Allano4, Olivier Vittecoq5, Thierry Schaeverbeke3, Jacques More4, Jean Sibilia4, Anne Cambon-Thomsen4, Alain G. Cantagrel9, Philippe Dieude10 and Arnaud Constant11.

Background/Purpose: Rheumatoid Arthritis (RA) is a multifactorial complex disease characterized by the presence of anti-citrullinated peptides antibodies (ACPA) and joints erosions. The mechanisms of bone erosions in RA are mediated by the RANK-RANKL-Osteoprotegerin (OPG) system. Some single nucleotide polymorphisms (SNPs) on RANK, RANKL and OPG genes have been previously associated with RA susceptibility. The aim of this study was to assess the association between 1 SNP on RANK (rs8086340), 3 SNPs on RANKL (rs7984870, rs7325635, rs1054016) and 1 SNP on OPG (rs2073618) and ACPA presence or joint erosions.

Methods: Patients: the study was based on 3 French cohorts: ESPOIR cohort (n=632 early RA patients, 76% of females, mean age: 50 years,
ACPA +: 49%, presence of erosions in 36.6%, RMP cohort (n=249 early RA patients, 75% of females, mean age: 50 years), ACPA +: 73%, presence of erosions in 39%) and FRA-CPRI cohort (n=689 long-standing RA patients, 76% of females, mean age: 61 years, ACPA +: 62%, presence of erosions in 68%). Genotyping: the 5 SNPs located on RANK, RANKL, and OPG were genotyped by Kbiosciences (GB). Statistical analysis: The proportion of patients with ACPA presence or presence of erosions were compared according to the allele carriage of each SNP by a Chi square test for each cohort separately. A meta-analysis on the 3 cohorts assessing the risk of ACPA presence or the risk of erosions according to the allele carriage of each SNP was performed using Mantel-Haenszel method. **Results:** were expressed as Odds ratios (OR) and 95% confidence intervals (95%CI). Correction for multiple tests was performed using Bonferroni method, so p-value set at p<0.003. Furthermore, the SNP located on RANKL had a protective effect against ACPA presence after Bonferroni correction: G allele of rs7325635: OR=0.63 [0.47–0.86], p=0.003, whereas the 2 other SNPs were not significantly associated with ACPA presence. Moreover, the SNP located on OPG was significantly associated with a protection against erosions after Bonferroni correction: G allele of rs2073618: OR=0.68 [0.52–0.88], p=0.004. **Conclusion:** This meta-analysis performed on 3 French cohorts identified 1 SNP on RANKL, 1 SNP on RANKL associated with protection against ACPA presence and 1 SNP on OPG associated with protection against erosions in RA. **Disclosure:** A. Ruysen Witrand, None; S. Scaramuzzino, None; D. Nigon, None; C. Lukas, None; Y. Allanore, None; O. Vittecoq, None; T. Schaeverbeke, None; J. Morel, None; J. Sibilla, None; A. Cambon-Thomsen, None; A. G. Cantagrel, None; P. Dieude, None; A. Constantin, None.

ACR/ARHP Poster Session B
Health Services Research

Monday, November 17, 2014, 8:30 AM – 4:00 PM

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Comparisons of Quality of Life, Resource Use and Physical Functioning in RA Patients Classified as High, Moderate or Low Risk for Rapid Radiographic Progression. E. Alemao, S. Joo, P. Allison, M. Ai, M. Rutten-van Molken, C. Banerjee, C. Iannaccone, M. Fris, N. Shadrack, K. Liao, and K. Morey, None. Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 1 Bristol-Myers Squibb, 1 BMS, 1 BMS, 3; C. Iannaccone, None; M. Ai, None; N. Shadrack, AbbVie, Amgen, Genentech, 2, BMS, UCB, Crescendo Biosciences, 9; K. Liao, BMS, Crescendo Biosciences, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Biosciences, UCB, 2; K. Liao, None.

Background/Purpose: The risk of serious infections can vary across biologics. For example, in the 2-year AMPLE trial, serious infections occurred in 3.8% of SC abatacept-treated patients and 5.8% of adalimumab-treated patients. In the 1-year ATTEST trial, serious infections occurred in 1.9% of IV abatacept-treated patients and 8.5% of infliximab-treated patients. Little is known about the healthcare costs associated with serious infections. This study quantified real-world healthcare costs associated with serious infections among biologic-naive RA patients initiating first-line biologic treatment. **Results:** used to estimate serious infection costs in a hypothetical cohort of RA patients treated with abatacept, adalimumab or infliximab based on data from AMPLE and ATTEST. **Methods:** Retrospective, observational cohort study based on US administrative claims data. Study patients initiated first-line biologic treatment (abatacept, adalimumab, etanercept, certolizumab, golimumab, or infliximab) between January 1, 2008 and September 1, 2012 (initiation index), were aged ≥18 years, had continuous insurance enrollment for 12 months before (baseline) and 12-24 months after (follow-up) the index date, had no baseline biologic treatment, and had ≥2 baseline medical claims with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code for RA (714.0x). Published algorithms and medical coders were consulted in compiling a list of ICD-9-CM diagnosis codes for serious infections. Patients were identified as having experienced a serious infection if they incurred a hospitalization with a primary diagnosis indicative of a serious infection. The cost of serious infections, measured during follow-up, included the cost of the serious infection hospitalization, follow-up outpatient medical claims with diagnoses of the same serious infection, and anti-infective medications. **Results:** The samples included 19,412 patients with 1 year of follow-up and 11,699 patients with 2 years of follow-up: in both samples, mean age was 53 years and 77% were female. Over the 1-year and 2-year follow-ups, 3.4% (n=669) and 6.2% (n=720) of patients experienced a serious infection, respectively. The most common serious infection was pneumonia. The total mean (median) cost of serious infections per patient experiencing a serious infection was $19,072 ($10,439) in the 1-year and $21,021 ($11,306) in the

Table: QoL, Resource Use and Physical Functioning at 12 Months in Patients at Low, Moderate and High Baseline Risk of RRP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Low Risk of RRP</th>
<th>Moderate Risk of RRP</th>
<th>High Risk of RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D, mean (SD)**</td>
<td>0.83 (0.14)</td>
<td>0.79 (0.15)</td>
<td>0.72 (0.19)</td>
</tr>
<tr>
<td>ER visits, % of pts*</td>
<td>23.4</td>
<td>24.6</td>
<td>28.2</td>
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<tr>
<td>Nursing home visits, % of pts*</td>
<td>2.4</td>
<td>2.7</td>
<td>14.6</td>
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<tr>
<td>Home healthcare visits, % of pts*</td>
<td>4.8</td>
<td>13.5</td>
<td>36.0</td>
</tr>
<tr>
<td>Surgeries, % of pts*</td>
<td>15.4</td>
<td>25.4</td>
<td>38.2</td>
</tr>
<tr>
<td>DME use, % of pts*</td>
<td>21.0</td>
<td>32.3</td>
<td>58.4</td>
</tr>
<tr>
<td>Hospital visits, % of pts*</td>
<td>13.3</td>
<td>20.4</td>
<td>37.1</td>
</tr>
<tr>
<td>mHAQ, mean (SD)**</td>
<td>0.39 (0.42)</td>
<td>0.65 (0.50)</td>
<td>0.72 (0.19)</td>
</tr>
</tbody>
</table>

*p<0.05 based on Chi-square test; **p<0.05 based on analysis of variance.

**Conclusion:** Patients categorized as having high risk of future RRP at baseline (compared with moderate and low risk of RRP) had worse outcomes at 12 months for QoL, resource utilization and physical functioning. These findings suggest that therapies are needed to improve QoL and resource utilization in these high-risk patients.

Disclosure: E. Alemao, BMS, 3, BMS, 1; S. Joo, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3, P. Allison, None; M. Ai, None; M. Rutten-van Molken, None; S. Joo, Bristol-Myers Squibb, 1, BMS, 3; C. Iannaccone, None; M. Al, None; N. Shadrack, AbbVie, Amgen, Genentech, 2, BMS, UCB, Crescendo Biosciences, 9; K. Liao, BMS, Crescendo Biosciences, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Biosciences, UCB, 2; K. Liao, None.

1142
Healthcare Costs Associated with Serious Infections Among Biologic-Naive Rheumatoid Arthritis Patients Initiating First-Line Biologic Treatment. S. Johnston1, S. Kelly2, A. Nadkarni3, K. Wilson2, B. Limone2 and M. Hochberg, 3Tuven Health Analytics, Bethesda, MD, 3Bristol-Myers Squibb, Plainsboro, NJ, 3University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: The cost of serious infections, measured during follow-up, included the cost of the serious infection hospitalization, follow-up outpatient medical claims with diagnoses of the same serious infection, and anti-infective medications. **Results:** The samples included 19,412 patients with 1 year of follow-up and 11,699 patients with 2 years of follow-up: in both samples, mean age was 53 years and 77% were female. Over the 1-year and 2-year follow-ups, 3.4% (n=669) and 6.2% (n=720) of patients experienced a serious infection, respectively. The most common serious infection was pneumonia. The total mean (median) cost of serious infections per patient experiencing a serious infection was $19,072 ($10,439) in the 1-year and $21,021 ($11,306) in the
2-year groups. Applying the serious infection cost estimate to the 2-year AMPL-E and 1-year ATT-TEST trial findings in a hypothetical cohort of 1000 biologic-naïve patients, the 2-year expected cost of serious infections per 1000 biologic-naïve patients would be $798,811 for SC abatacept (3.8% × $21,021 × 1000) and $1,219,237 for adalimumab; and the 1-year cost would be $362,371 for IV abatacept and $1,697,420 for infliximab.

Conclusion: In this pharmacoeconomic study of biologic-naive RA patients initiating biologic treatment, serious infections were associated with substantial healthcare costs over 1- and 2-year periods. Biologic treatments that are associated with lower infection risk may confer important cost savings related to serious infections.

Disclosure: S. Johnston, Truen Health Analytics, 3; S. Kelly, Bristol-Myers Squibb, 1; Bristol-Myers Squibb, 3; A. Nadkarni, Bristol-Myers Squibb, 1; Bristol-Myers Squibb, 3; K. Wilson, Truen Health Analytics, 3; B. Limone, None; M. Hochberg, Bristol-Myers Squibb, Eli Lilly, EMD Serono, Genentech/Roche, Novartis Pharma, Pfizer, UCB, 5, NIH, 2.

1143 Preferences of Biologic Treatment Characteristics Among Rheumatoid Arthritis Patients Who Are Current Biologic Therapy Users. David M. Kerr1, Angela E. Williams2, Ozgur Tunceli1, Bingcao Wu1, Judy Stephenson2, Laura Horne2 and Alfred Sackeyfio2. 1HealthCore, Inc., Wilmington, DE, 2Medimmune, LLC, Cambridge, United Kingdom, 3AstraZeneca, Wilmington, DE, 4AstraZeneca, Mochester, United Kingdom.

Background/Purpose: To identify the most and least important characteristics of rheumatoid arthritis (RA) treatment according to patients currently on biologic therapy.

Methods: From the HealthCore Integrated Research Environment, RA patients (ICD-9-CM: 714.0x) >18 years old with >1 claim for a biologic therapy between 5/1/2012 and 7/31/2013 were identified. All eligible patients were targeted to complete a survey measuring their quality of life, RA treatment history, treatment satisfaction, and treatment preferences, among other measures. The Maximum Difference Scaling Instrument (MaxDiff) was used to determine what characteristics of RA treatments (e.g., efficacy; side effects; costs; how, when, and where the medication is administered) were most and least important to the patients. A MaxDiff score >100 denotes characteristics that are important to the patient, while a score < -100 signifies characteristics of higher importance.

Results: There were 9,802 patients meeting all study criteria, of which 219 completed a patient survey. Survey patients were 56 years old on average, 82% were female, 89% were white, and 51% had at least a 4-year college degree. 29% of patients were currently taking etanercept, while the next most common treatments were adalimumab (22%), infliximab (17%), and abatacept (12%).

The MaxDiff results identified the 3 most important characteristics of RA treatment were related to the efficacy of the treatment: ‘Keeps my disease from getting worse’ (MaxDiff score = 209), ‘Improves my physical abilities’ (199), and ‘Reduces Pain’ (195). ‘Potential side effects’ (117) and ‘How long treatment effects last’ (102) were relatively important, while ‘How quickly (within a few weeks)’ treatment works (70) and ‘Personal costs’ (67) were less important. The least important characteristics were those that identified the ‘how’, ‘when’, and ‘where’ of treatment administration: ‘How treatment is given (oral, injection, IV, etc.)’ (15), ‘How often treatment must be taken’ (13), and ‘Where treatment is given (home, doctor’s office, hospital, etc.)’ (13). Results were consistent across groups based on their current biologic therapy.

A separate question found that 75% of patients would like to take their medication at home if it were possible; however, the MaxDiff results show that relative to efficacy this is not a priority for patients. Additionally, when asked why patients stopped taking prior biologic therapy the statement ‘I didn’t feel that the drug was working’ was cited as a major reason 66% of the time, more than any other reason. ‘I don’t like needles’ and ‘I don’t like infusions’ were cited as major reasons for stopping therapy just 1% and 3% of the time, respectively; while the cost of treatment and side effects were a major reason 13% and 21% of the time, respectively.

Conclusion: The effectiveness of RA treatment is the most important attribute according to patients currently treated with biologic therapy, while administration characteristics were seen as relatively unimportant. Reducing symptoms, improving physical abilities, and slowing disease progression should be considered as primary outcomes in studies comparing RA treatments.


1144 Economic Implications for Policies Regarding Triple Therapy Use in Patients with Rheumatoid Arthritis. Nick Bansback1, Diane V. Lacaille2, Daphne Gu3, Kamran Shojaian3 and Aslam H. Anis3. 1University of British Columbia, Vancouver, BC, 2Arthritis Research Centre of Canada/University of British Columbia, Richmond, BC, 3Centre for Health Evaluation and Outcome Sciences, Vancouver, BC.

Background/Purpose: Recent randomized controlled trials in rheumatoid arthritis (RA) patients have determined that a strategy of first adding the two Disease Modifying Anti-Rheumatic Drugs (DMARDs) sulfasalazine and hydroxychloroquine to methotrexate (a combination known as Triple Therapy) is neither inferior nor less safe than first adding anti-TNF drugs in patients with active disease despite methotrexate. The implication is that inexpensive triple therapy should be initiated prior to expensive biologic therapy. In this study we examine historical biologic and Triple Therapy use in British Columbia (BC), Canada over the past 10 years. We sought to estimate the potential savings in expenditures if Triple Therapy use had been more prevalent, and project potential future cost-savings.

Methods: We examined a population-based cohort of all BC patients with a rheumatologist diagnosis of RA identified from administrative data. We selected prevalent RA cases who used a biologic for the first time between 2001 and 2010 and examined their prior DMARD history from prescription billing data. For each year, we calculated the proportion of patients that had used Triple Therapy, the average drug prices, and the average duration patients remain on Triple Therapy. Since not all patients can use Triple Therapy, we conducted a series of scenarios which estimated the cost that would have been saved if a higher proportion of patients had used Triple Therapy.

Results: In total, we examined 2726 RA patients who started their first biologic over the time period. Triple therapy use prior to biologic therapy has increased over time, from 15.2% in 2001 to 24.4% in 2010. The average duration patients remained on triple therapy was 1.13 years. Of the $62 million spent on patients first year of biologics, a scenario where 80% of patients would have received triple therapy instead would have resulted in cost savings to BC of $47.3 million over the 10 year period (figure 1). Assuming similar patterns of triple therapy use across Canada, projections suggest future cost-savings of over $12 million per year if triple therapy is used in 80% of patients prior to biologic use. Various sensitivity analyses are performed.

Conclusion: Higher utilization of Triple Therapy will require a willingness for rheumatologists to prescribe it, and a willingness for patients to use it. With the benefit of hindsight, higher use of Triple Therapy prior to biologic initiation would have released a substantial amount of pharmaceutical spending to alternative treatments. Importantly, with less than 25% of patients currently receiving triple therapy prior to a biologic, there is still a considerable potential for future savings. Strategies such as academic detailing and patient decision aids may be good investments if they can change treatment choices.

Disclosure: N. Bansback, None; D. V. Lacaille, None; D. Gu, None; K. Shojaian, None; A. H. Anis, Pfizer Inc, 2, Antares, Pfizer, Abbvie, 5.
Evaluation of Biologic Treatment Patterns, Clinical Outcomes, and Healthcare Resource Utilization Post-Tumor Necrosis Factor Inhibitor Discontinuation in Rheumatoid Arthritis (RA) patients (pts) with inadequate response to a TNF inhibitor (TNFi), limited evidence exists from observational studies and indirect comparisons of randomized trials to support switching to a nonTNFi vs another TNFi. These exploratory analyses evaluate clinical outcomes and healthcare resource use (HCRU) after switching from a TNFi to another TNFi or nonTNFi biologic across 2 de-identified real world data sources.

Methods: Pts (≥18 years) with ≥2 outpatient or 1 inpatient visit for RA (ICD-9: 714.xx) and (1) HCRU-reported TNFi discontinuation and switch to a biologic or conventional DMARD (CDMARD) within 180 days in Humedic EHR database (7/07-7/13) or (2) switched from TNFi to another biologic (or 1 pt to tofacitinib) in Truven MarketScan® claims database (2010–2013) were included. Pts had continuous enrollment/follow-up ≥6 months (mo) before and after (12) or 18 (EHR) mo after discontinuation. EHR cohort was followed for 18 mo-all cause HCRU and change in patient-reported pain scores (0–10 on provider-determined scales; ≥30 days pre/post-switch). Claims cohort was evaluated for subsequent biologic switching and RA-related HCRU costs. Multivariable analyses evaluated the impact of switching to a TNFi vs nonTNFi on RA-related costs.

Results: Of 2799 pts who discontinued a TNFi (47% etanercept, 28% adalimumab, 21% infliximab, 4% other) in EHR cohort, reasons were lack of efficacy (14%), AE/other clinical reason (16%), cost (6%), or unknown (65%). Following discontinuation, 21% switched to another biologic (67% TNFi) and 11% to CDMARD. In the claims cohort, 68% switched to another TNFi, of whom 43% switched again vs 28% of those first switched to a nonTNFi biologic. Among EHR pts with pre/post-switch pain scores, TNFi (n=58), nonTNFi biologic (n=19), or CDMARD (n=55) switchers had mean (standard deviation (SD)) pain reductions of 0.72 (3.12), 1.11 (2.87), and 0.42 (3.88), respectively. Office visits comprised the largest HCRU category in the 18 mo after switching; mean (SD) number: 42.7 (34.5), 57.6 (47.3), and 38.4 (33.3) for TNFi, nonTNFi, or CDMARD switchers, respectively. Nearly half (n=72) the difference in office visits with TNFi vs nonTNFi was associated with biologic administration procedures. Unadjusted mean (SD) RA-related costs were $27544 ($21100) for TNFi vs $44742 ($30743) for nonTNFi switchers. Including biologic administrations without RA diagnosis (TNFi, $386; nonTNFi, $973; CDMARD, $159; P=0.0001), the mean cost was attributed to outpatient visits, followed by prescriptions (18%). Biologic administration visits accounted for 89% of outpatient cost differences. NonTNFi therapy was associated with 32% higher total RA-related costs in adjusted analyses (p<0.0001).

Conclusion: NonTNFi switchers were less likely to switch again and had greater pain reduction vs TNFi switchers (in a small subset). NonTNFi switching is not cost-effective in RA-related costs, largely due to in-office administration. NonTNFi therapies that do not require in-office administration may reduce switching and costs. Disease outcomes and financial considerations of clinical decision-making warrant future prospective structured research.

Disclosure: J. Harnett, Pfizer Inc, 1; Pfizer Inc, 3; D. Wiederkehr, Pfizer Inc, 1; Pfizer Inc, 3; R. Gerber, Pfizer Inc, 1; Pfizer Inc, 3; D. Gruben, Pfizer Inc, 1; Pfizer Inc, 3; A. Koenig, Pfizer Inc, 1; Pfizer Inc, 3; J. Bouret, Pfizer Inc, 1; Pfizer Inc, 3.

Cost-Effectiveness of Adalimumab for Rheumatoid Arthritis in Germany. Christian Gissel1, Georg Götz2, Holger Reppl3, and Uwe Lange3.

Background/Purpose: In Germany, Rheumatoid Arthritis (RA) can be treated with TNF-α inhibitors after the failure of conventional disease-modifying antirheumatic drugs like Methotrexate. The clinical use of TNF-α inhibitors grew from 2% of treated RA patients in 2000 to 20% in 2008. In 2012, Adalimumab was the most popular TNF-α inhibitor and the best selling drug in the German statutory health insurance system with net expenditure of € 581 mn. We aim to analyze the determinants of cost-effectiveness of Adalimumab and Methotrexate combination therapy for the treatment of RA in Germany.

Methods: We set up an individual patient sampling lifetime model to simulate 10,000 hypothetical patients. Health benefits are recorded in terms of quality-adjusted life years (QALYs). Quality of life is derived from patients' Health Assessment Questionnaire (HAQ) scores. Initially, patients can achieve one of three responses according to American College of Rheumatology (ACR) criteria or fail the therapy. Each ACR response is associated with an improvement in functional status. In each cycle, treatment might be discontinued due to loss of efficacy or adverse events. The patient is then switched to the next available treatment or palliative care. In the Adalimumab simulation arm, we add Adalimumab and Methotrexate combination therapy to the treatment algorithm after failure of both Methotrexate monotherapy and conventional triple therapy. Extensive sensitivity analysis investigates the effects of baseline age and functional status, cost and health effects discounting, methods for estimating quality of life and time horizon.

Results: In the base case, patients gain 7.07 QALYs with conventional synthetic therapy and 9.92 QALYs if a Adalimumab combination therapy is added to the treatment algorithm. The incremental cost-utility ratio (ICUR) is € 24,492 based on German list prices. If mandatory rebates and taxes are deducted for international comparison, the ICUR is only € 17,277. A dali-

Economic Implications of Flares Among Patients with Early Rheumatoid Arthritis (RA). James Signorovitch1, K eith Betts2, Vishvas Garg2, and Y anjun Bao1.

Methods: The OPTIMA trial2 who were re-randomized to methotrexate (MTX) monotherapy in Period II after achieving LDA.
Netherlands, D.K. 53,483 and D.K. 76,081 for Denmark, T.W.D. 301,385 and T.W.D. 428,729 for Taiwan, and 196,498 Kč and 279,525 Kč for the Czech Republic, respectively.

**Conclusion:** Flares after biologic withdrawal in early RA patients who achieved LDA are found to be costly based on the HAQ-costs mapping as published. Real world direct assessment of the consequences of biologic withdrawal is recommended to further the understanding of this practice.

### Table 1: Direct, Indirect and Total Costs for RA patients with disease flares

<table>
<thead>
<tr>
<th>Country</th>
<th>DAS Change &gt; 0.6</th>
<th>DAS Flare</th>
<th>HAQ Change &gt; 0.22 and HAQ &gt; 0.5 at baseline</th>
<th>Non-DAS Flare</th>
<th>PPVs</th>
<th>Total N</th>
<th>Total N</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>€ 2.706</td>
<td>€ 1.558</td>
<td>€ 2.999</td>
<td>€ 1.105</td>
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<tr>
<td>Netherlands</td>
<td>€ 14.826</td>
<td>€ 8.810</td>
<td>€ 15.308</td>
<td>€ 7.011</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>€ 17.531</td>
<td>€ 10.368</td>
<td>€ 18.307</td>
<td>€ 8.117</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>D.K. 130.886</td>
<td>D.K. 77.403</td>
<td>D.K. 136.671</td>
<td>D.K. 60.590</td>
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</tr>
<tr>
<td>Taiwan</td>
<td>TWD 113.840</td>
<td>TWD 65.544</td>
<td>TWD 126.166</td>
<td>TWD 46.487</td>
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</tr>
<tr>
<td>Direct cost</td>
<td>TWD 633.720</td>
<td>TWD 370.631</td>
<td>TWD 643.998</td>
<td>TWD 294.948</td>
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<td>Total cost</td>
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<td>TWD 436.175</td>
<td>TWD 770.164</td>
<td>TWD 341.435</td>
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</tr>
<tr>
<td>Czech Republic</td>
<td>D.K. 74.222</td>
<td>Kč 42.734</td>
<td>Kč 82.258</td>
<td>Kč 30.399</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct cost</td>
<td>Kč 406.656</td>
<td>Kč 241.646</td>
<td>Kč 419.877</td>
<td>Kč 192.302</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>Kč 480.878</td>
<td>Kč 284.379</td>
<td>Kč 502.135</td>
<td>Kč 222.610</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


**Disclosure:** J. Signorovitch, Analysis Group, Inc., 3; K. Betts, Analysis Group, Inc., 3; V. Garg, AbbVie, 1, AbbVie, 3; Y. Bao, AbbVie, 1, AbbVie, 3.

### 1148

**Evaluation of a Methodological Approach to Determine Timing of Rheumatoid Arthritis Disease Onset Using Administrative Claims Data**

**Background/Purpose:** The identification of patients with recent-onset rheumatoid arthritis (RA) is often desirable to create inception cohorts of patients. We evaluated an approach to identify the timing of RA onset using administrative claims data from public (Medicare) and commercial health plans.

**Methods:** The study sample consisted of RA patients participating in Corrona, a large North American RA registry, linked to administrative medical and pharmacy claims data from Medicare (2006 to 2011) or a U.S. commercial health plan (2005–2012). We estimated year of RA onset in the claims data using several algorithms that were based on the following factors: 1) different ICD-9 diagnosis code for RA (e.g. 714.0, 714.2, 714.21 vs. 714.xx from any claim), 2) absence of use of any disease modifying anti-rheumatic drugs. We compared the estimated year of RA onset using the claims-based algorithms to that recorded by rheumatologists in the Corrona registry (gold standard). We reported accuracy as a positive predictive value (PPV), calculated if the year of RA onset from the claims data agreed (1-1 year) with that documented in Corrona. We conducted a subgroup analysis limited to patients whose disease duration was 2 years or less at their first rheumatologist visit to improve the reliability of disease onset ascertainment by reducing recall bias and misclassification of the gold standard.

**Results:** In the main analysis, using ICD-9 codes 714.0, 714.2, 714.81 from a physician visit, the PPVs for accurately classifying year of RA onset ranged from 62% to 68%. When ICD-9 codes 714.x from any type of claim were used, PPVs were higher, ranging from 67% to 100%.

**Conclusion:** Claims-based algorithms can be used with high validity to identify patients with recent onset RA. Additional research will focus on reasons and opportunities to reduce misclassification of disease onset.

**Disclosure:** J. Zhang, none; F. Xie, none; L. Chen, none; J. D. Greenberg, Corrona, LLC; L. Corrona, LLC; A. Z. Kacmar, Celgene, Novartis and Pfizer; J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. Ngem, Pfizer, BMS. Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. Ngem, Pfizer, BMS, Crescendo, AbbVie, 5.

### 1149

**Novel Adherence Measures for Infusible Therapeutic Agents in Rheumatoid Arthritis**

**Background/Purpose:** Adherence is under consideration for quality reporting in a number of disease states. Published data on adherence of biologics reveal a wide range of calculation methods. Biologics administered via infusion do not lend themselves to the typical measures of adherence, such as the medication possession ratio (MPR) or proportion of days covered (PDC). The purpose of this study was to investigate a number of newly constructed proxies for medication adherence across two of the more commonly prescribed infusible biologic agents: infliximab (IFX) and abatacept (ABA).

**Methods:** Using the Optum™ Clinformatics™ database of insured individuals, IFX (n = 417) and ABA (n = 431) members who were continuously eligible for benefits one-year post-induction were selected for adherence analyses. New measures of medication adherence were designed for calculation over the maintenance phase of treatment (Table 1). For both IFX and ABA, the fourth dose constitutes the beginning of maintenance. Maintenance infusions are recommended every eight weeks for IFX and every four weeks for ABA. The total study measurement period was one year, beginning with the induction infusion, though only maintenance infusions were subjected to adherence measures. As a reference, mean maintenance intervals were also calculated for both groups.

**TABLE 1. New Measures of Medication Adherence**

<table>
<thead>
<tr>
<th>Adherence Measure</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients w/thru/fill Gap %</td>
<td>cats/g %</td>
<td>total number of patients who show at least one refill gap &gt; 20% based on labeling guidelines for maintenance treatment</td>
</tr>
<tr>
<td>Cumulative Amount of Time w/thru/fill Gap %</td>
<td>cats/t %</td>
<td>% of patients who have at least one refill gap &gt; 20% based on labeling guidelines for maintenance treatment</td>
</tr>
<tr>
<td>Cumulative Time Off Treatment</td>
<td>cats/t %</td>
<td>% of patients who have at least one refill gap &gt; 20% based on labeling guidelines for maintenance treatment</td>
</tr>
<tr>
<td>Days of Uninterrupted Use</td>
<td>days</td>
<td>length of time from index date to the first refill gap &gt; 20% based on labeling guidelines for maintenance treatment</td>
</tr>
<tr>
<td>Observed vs. Expected Refill Ratio</td>
<td>o/er %</td>
<td>actual infusions in measurement period/expected infusions in measurement period</td>
</tr>
<tr>
<td>Repeated Observations of Under-use</td>
<td>rou/uu %</td>
<td>total number of refill gaps &gt; 20% based on labeling guidelines for maintenance treatment</td>
</tr>
</tbody>
</table>
Results: Mean maintenance intervals approximated recommended guidelines. IFX patients had a mean observed infusion interval (MOII) of 53 days (recommended 56 days) while ABA patients demonstrated a MOII of 33 days (recommended 28 days). ABA patients had a significantly greater amount of CTOx than IFX patients (78.56 vs 61.08 days), and a significantly shorter number of DoUU (164 vs 286 days). ABA patients had a significantly lower OVERR than IFX patients (0.73 vs 0.97), and were over 3 times as likely as IFX patients to show a PRGR > 20% (68.4% vs 20.6%). The ROIU was more than 4 times higher for ABA than IFX patients (1.91 vs 0.42), while the CATRG=20% was also higher for ABA patients (32.23 days) compared to IFX patients (20.63 days). Finally, the VITBR for 0–7 days was lower for ABA patients than IFX patients (88.2% vs 93.2%). All measured adherence outcomes were significantly different between groups (p < 0.001).

Conclusion: This study piloted a number of measures designed to assess infusion adherence. Results indicated more favorable adherence outcomes for IFX-treated patients compared to ABA patients. Substantial differences may result from assumptions made regarding day’s supply and calculation methods for adherence when using medical claims. Quality reporting should include all details for days’ supply assumptions and calculation methods. Future studies should examine the relationship between these new measures of adherence and more clinically relevant endpoints and/or cost outcomes to determine if they possess any predictive utility.

Disclosure: R. Meyer, Janssen Scientific Affairs, LLC, 3; M. Ingham, Janssen Scientific Affairs, LLC, 3; J. Tkacz, Janssen Scientific Affairs, LLC, 5; B. Brady, Janssen Scientific Affairs, LLC, 5; C. Ruetsch, Janssen Scientific Affairs, LLC, 5; C. Rutkove, Janssen Scientific Affairs, LLC, 5; C. Rutkove, Janssen Scientific Affairs, LLC, 5.

1150
Marked Differences in Euro-Qol-5-Dimensions Preference Sets Based on Hypothetical or Experience Based Valuation. Anna Cooper, Johan A. Karisson and Anders Gürfe. Lund University, Faculty of Medicine, Lund, Sweden.

Background/Purpose: Health related quality of life (HRQoL) can be expressed as utility, a value anchored at 0 (death) and 1 (perfect health, forming the basis for health economic evaluations. Utilities are determined by means of a generic instrument such as Euro-Qol-5-Dimensions (EQ-SD), a questionnaire rating mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a 3-level scale. Each set of responses made by the individual constitutes a “health state”, which is translated into a utility score by means of a a preference set (weights) from a reference population. Many preference sets are available (rating onexs own health), and we intended to compare these to the standard, or over time. As expected, SE utilities (experience based) are higher than UK (hypothetical). This holds true both for baseline utilities and PASS cut-off values. This difference must be accounted for in health economic evaluations and when comparing studies using different EQ-SD preference sets.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>都在</th>
<th>RA</th>
<th>SpA</th>
<th>PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>360</td>
<td>230</td>
<td>80</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.3 (41.8-63.5)</td>
<td>59.9 (47.6-65.7)</td>
<td>43.7 (34.0-53.5)</td>
</tr>
<tr>
<td>Woman (%)</td>
<td>66.4</td>
<td>74.3</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2. Patient acceptable symptom state cut-off points in RA, SpA and PsA

<table>
<thead>
<tr>
<th>Measure</th>
<th>PA</th>
<th>Baseline</th>
<th>PASS</th>
<th>Sens/Spec</th>
<th>Followup</th>
<th>Sens/Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-UK</td>
<td>0.66</td>
<td>72/29</td>
<td>0.69</td>
<td>72/79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-SE</td>
<td>0.78</td>
<td>76/80</td>
<td>0.78</td>
<td>78/81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpA</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-UK</td>
<td>0.69</td>
<td>73/78</td>
<td>0.78</td>
<td>68/85</td>
<td></td>
<td></td>
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<tr>
<td>PsA</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-SE</td>
<td>0.78</td>
<td>64/80</td>
<td>0.85</td>
<td>84/85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-UK</td>
<td>0.69</td>
<td>56/61</td>
<td>0.69</td>
<td>72/79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-SE</td>
<td>0.79</td>
<td>56/61</td>
<td>0.8</td>
<td>72/79</td>
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</tbody>
</table>

Followup: 2.5–25 months. Sensitivity/Specificity stated in %. All results have a significance of p < 0.05 unless stated otherwise.

1 University of Pennsylvania, Philadelphia, PA; 2 Emory University School of Medicine, Atlanta, GA; 3 Dallas VA Medical Ctr, Dallas, TX; 4 University of North Carolina at Chapel Hill, Chapel Hill, NC; 5 John Hopkins University, Baltimore, MD; 6 University of Michigan, Ann Arbor, MI; 7 Texas Children’s Hospital, Houston, TX; 8 Massachusetts General Hospital, Boston, MA; 9 Baltimore VA and University of Maryland School of Medicine, Baltimore, MD; 10 Washington Univ School of Med, Saint Louis, MO.

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1 University of Pennsylvania, Philadelphia, PA; 2 Emory University School of Medicine, Atlanta, GA; 3 Dallas VA Medical Ctr, Dallas, TX; 4 University of North Carolina at Chapel Hill, Chapel Hill, NC; 5 John Hopkins University, Baltimore, MD; 6 University of Michigan, Ann Arbor, MI; 7 Texas Children’s Hospital, Houston, TX; 8 Massachusetts General Hospital, Boston, MA; 9 Baltimore VA and University of Maryland School of Medicine, Baltimore, MD; 10 Washington Univ School of Med, Saint Louis, MO.

Background/Purpose: Development of young rheumatology investigators is critical to the future of rheumatology. Beyond funding, the specific barriers to maintaining a career in rheumatology research remain unclear. The objective of this study was to determine the perceived barriers and facilitators to a career in rheumatology research.

Methods: A web-based survey was conducted among the domestic ACR membership from Jan-Mr 2014. Inclusion criteria were current or previous fellowship in rheumatology, ACR membership, and an available email address. Non-rheumatologist members were excluded. The instrument was developed by the Early Career Investigator subcommittee using a Delphi method to identify and distill facilitators and barriers to a career in research for inclusion in the survey. The survey also assessed demographics, research participation, and free text response for ways in which the ACR could support young investigators. After excluding incomplete surveys and duplicates, demographics were summarized. The chi-squared test was used to assess differences in rating of barriers and facilitators by category of respondents. Linear regression was used to assess factors that contribute to interest in a career in research.

Results: 349 members (164 ACR fellows, 101 non-fellows, 84 non-fellows, 101 non-fellows) completed the survey. The average age was 34 years (range 21–76) and 233 were women (67%). The majority (70%) were part of an academic department, 60% had completed a fellowship in rheumatology, 38% had ACR membership, and an available email address. The most highly ranked barrier and facilitator of a career in research among rheumatologists is the lack of protected time (73% of respondents), followed by salary and lack of institutional support. Free text comments were analyzed by content analysis using NVivo software.

Table 2. Patient acceptable symptom state cut-off points in RA, SpA and PsA

<table>
<thead>
<tr>
<th>Measure</th>
<th>PA</th>
<th>Baseline</th>
<th>PASS</th>
<th>Sens/Spec</th>
<th>Followup</th>
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<tr>
<td>RA</td>
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</tr>
<tr>
<td>EQ5D-UK</td>
<td>0.66</td>
<td>72/29</td>
<td>0.69</td>
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<tr>
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</tr>
<tr>
<td>EQ5D-UK</td>
<td>0.69</td>
<td>73/78</td>
<td>0.78</td>
<td>68/85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EQ5D-SE</td>
<td>0.78</td>
<td>64/80</td>
<td>0.85</td>
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<tr>
<td>EQ5D-UK</td>
<td>0.69</td>
<td>56/61</td>
<td>0.69</td>
<td>72/79</td>
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</tr>
<tr>
<td>EQ5D-SE</td>
<td>0.79</td>
<td>56/61</td>
<td>0.8</td>
<td>72/79</td>
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<td></td>
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</tbody>
</table>

Followup: 2.5–25 months. Sensitivity/Specificity stated in %. All results have a significance of p < 0.05 unless stated otherwise.
support, as well as personal skills or traits such as hard work, resilience, initiative, persistence and passion for the job. Personal skills were significantly more often cited by recipients of an R01 than other groups (71% vs 49%, p = 0.001). Evaluation of free text comments revealed few additional themes including gender issues and lack of flexibility to allow part-time work to care for children.

**Conclusion:** To our knowledge, this is the first study to examine barriers and facilitators to a career in rheumatology research from the perspectives of young investigators, established investigators, mentors, and fellows. Knowledge of such barriers and facilitators may assist in designing interventions to support young investigators during vulnerable points in their career.

### Table. Demographics of Survey Participants (N = 430)

<table>
<thead>
<tr>
<th>Current Position</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Bath Rheumatologist</td>
<td>309 (72%)</td>
</tr>
<tr>
<td>Pediatric Rheumatologist</td>
<td>62 (14%)</td>
</tr>
<tr>
<td>A. Bath Fellow</td>
<td>42 (10%)</td>
</tr>
<tr>
<td>Pediatric Fellow</td>
<td>17 (4%)</td>
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</table>

<table>
<thead>
<tr>
<th>Place of Employment</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic Medical Center</td>
<td>306 (71%)</td>
</tr>
<tr>
<td>Clinical Practice</td>
<td>91 (22%)</td>
</tr>
<tr>
<td>Industry</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Government</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Retired</td>
<td>4 (1%)</td>
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</table>

<table>
<thead>
<tr>
<th>Academic Appointment</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instructor (or equivalent</td>
<td>34 (8%)</td>
</tr>
<tr>
<td>Junior Faculty</td>
<td></td>
</tr>
<tr>
<td>Assistant Professor</td>
<td>102 (24%)</td>
</tr>
<tr>
<td>Associate Professor</td>
<td>58 (13%)</td>
</tr>
<tr>
<td>Professor</td>
<td>89 (21%)</td>
</tr>
<tr>
<td>Other (or no academic</td>
<td>147 (34%)</td>
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<tr>
<td>Appointment)</td>
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<table>
<thead>
<tr>
<th>Year Completed Fellowship</th>
<th>Median (IQR)</th>
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<tr>
<td>1960-1969</td>
<td>6 (1%)</td>
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<tr>
<td>1970-1979</td>
<td>27 (6%)</td>
</tr>
<tr>
<td>1980-1989</td>
<td>73 (17%)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>51 (12%)</td>
</tr>
<tr>
<td>2000-2009</td>
<td>96 (23%)</td>
</tr>
<tr>
<td>2010-2016</td>
<td>131 (30%)</td>
</tr>
</tbody>
</table>

| Missing                   | 6 (1%)      |
| Female Sex                | 241 (56%)   |
| Medical School in the US  | 338 (74%)   |
| Underrepresented Minority*| 28 (7%)     |

<table>
<thead>
<tr>
<th>Effort** median (IQR)</th>
<th></th>
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<tbody>
<tr>
<td>Clinical</td>
<td>50% (20-75%)</td>
</tr>
<tr>
<td>Research</td>
<td>15% (2-70%)</td>
</tr>
<tr>
<td>Teaching</td>
<td>5% (4-10%)</td>
</tr>
<tr>
<td>Administrative</td>
<td>5% (0-11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Successful Funding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation fellowship/post-doc award</td>
<td>92 (21%)</td>
</tr>
<tr>
<td>Foundation career development award</td>
<td>99 (23%)</td>
</tr>
<tr>
<td>NIH Loan Repayment Program</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>NIH K-series or VA career development award</td>
<td>76 (18%)</td>
</tr>
<tr>
<td>NIH R01</td>
<td>59 (14%)</td>
</tr>
<tr>
<td>Other NIH awards</td>
<td>71 (17%)</td>
</tr>
<tr>
<td>Other grants</td>
<td>141 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Researcher</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>171 (40%)</td>
</tr>
<tr>
<td>Young Investigator</td>
<td>88 (20%)</td>
</tr>
<tr>
<td>Mentor</td>
<td>76 (18%)</td>
</tr>
<tr>
<td>Research effort ≥50%</td>
<td>134 (31%)</td>
</tr>
<tr>
<td>Research effort ≥70%</td>
<td>100 (23%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Research**</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>88 (51%)</td>
</tr>
<tr>
<td>Epidemiology/Health Services</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Translational</td>
<td>99 (58%)</td>
</tr>
<tr>
<td>Basic Science</td>
<td>53 (31%)</td>
</tr>
</tbody>
</table>

All percentages are of the total N = 430. *An "under-represented minority within rheumatology" was defined as Black, Hispanic, or Native American (that is, American Indians, Alaska Natives, and Native Hawaiians) **Effort estimates exclude fellows.

**Mentor refers specifically to a mentor of a young investigator.

Among those currently engaged in research (N = 371), participants were allowed to select more than one answer so the total adds to greater than 100%. Abbreviations: NIH = National Institutes of Health.

**Disclosure A. Ogdie, None; S. Angeles-Han, None; U. Makris, None; Nelson, None; A. Shah, None; Y. Jiang, None; J. M. Kahlenberg, None; E. Muscal, None; F. V. Castelino, None; A. Golding, None; A. Kim, Pfizer Inc, S; A. Mgeni, S; Janssen; Pharmaceutica Product, L.P., S; Kyph, Inc., 2.

1152

**Euroqol-5-Dimensions Utility Gain in Rheumatoid Arthritis, Treated with Abatacept, Rituximab, Tocilizumab or Tumor Necrosis Factor Inhibitors.** Anders Gülfe1, Johan A. Karlsson1 and Lars-Erik Kristensen2.

1Lund University, Faculty of Medicine, Lund, Sweden, 2Lund University, Faculty of Medicine, Malmö, Sweden.

Background/Purpose: We have earlier demonstrated that EuroQol-5-Dimensions (EQ-5D) utility improves rapidly after commencement of tumor necrosis factor inhibition (TNFi) in rheumatoid arthritis (RA) and other arthritides, and that it is fairly stable for up to 7 years in those remaining on therapy(1). The development of utility over time in RA treated with other biologics is not well known.

Methods: Demographics, core set data, EQ-5D and data on drug treatment for patients with established RA on biologics from southern Sweden were retrieved from an observational database. Diagnosis was as the treating rheumatologist, and has been shown to comply with 1987 ACR criteria in 95% of cases. Time frame was January 2006 - March 2014. EQ-5D utilities based on the British weights were computed and means and plotted over time.

Results: There were 2418 patients treated with Abatacept (ABA), Rituximab (RTX), Tocilizumab (TOZ) or tumor necrosis factor inhibitors (TNFi) with utilities at treatment start (Table 1). Patients lacking baseline EQ-5D (n = 913) did not differ appreciably from the main cohort (data not shown). TNFi patients had shorter disease duration and fewer previous DMARDs than patients on ABA, RTX or TOC, as these drugs were seldom started in bio-naive patients. EQ-5D utility development over time is shown in Figure 1.

Conclusion: Despite starting at very low mean utilities, patients receiving ABA and TOC display rapid utility gains similar to TNFi although at a lower level, reflecting more longstanding and treatment resistant disease. As compared to the other biologics, the utility gain after commencement of RTX therapy starts at a level similar to TNFi (perhaps more bio-naive patients with recent malignancy or other contraindications to TNFi) but is more gradual. Such differences may influence the area under the curve and thus accumulation of quality-adjusted life years. The continuing improvement observed in all groups may partly reflect a selection of patients responding and thus adhering to therapy.

Reference:


### Table 1. Baseline characteristics by therapy. Values are mean(SD) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Abatacept</th>
<th>Rituximab</th>
<th>Tocilizumab</th>
<th>TNFi</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>100</td>
<td>230</td>
<td>121</td>
<td>1967</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.0 (12.1)</td>
<td>60.2 (12.3)</td>
<td>57.9 (13.5)</td>
<td>56.6 (13.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>82 (80.4)</td>
<td>166 (72.2)</td>
<td>98 (80.3)</td>
<td>1520 (77.3)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>15.9 (8.6)</td>
<td>15.5 (11.4)</td>
<td>18.6 (11.7)</td>
<td>12.2 (11.7)</td>
</tr>
<tr>
<td>Baseline HAQ</td>
<td>1.46 (0.61)</td>
<td>1.35 (0.67)</td>
<td>1.43 (0.64)</td>
<td>1.18 (0.64)</td>
</tr>
<tr>
<td>Baseline DAS28</td>
<td>5.50 (1.41)</td>
<td>5.04 (1.57)</td>
<td>5.68 (1.34)</td>
<td>5.10 (1.37)</td>
</tr>
<tr>
<td>Number of previous DMARDs*</td>
<td>5.9 (3.2)</td>
<td>5.3 (2.8)</td>
<td>5.2 (2.8)</td>
<td>3.0 (1.9)</td>
</tr>
<tr>
<td>Number of ongoing DMARDs**</td>
<td>0.7 (1.0)</td>
<td>0.8 (0.6)</td>
<td>0.7 (0.6)</td>
<td>0.8 (0.6)</td>
</tr>
<tr>
<td>Steroids, yes/no, (%)</td>
<td>66 (64.7)</td>
<td>156 (67.8)</td>
<td>82 (67.2)</td>
<td>1164 (59.2)</td>
</tr>
</tbody>
</table>

TNFi, tumor necrosis factor inhibitors; DMARD, disease modifying antirheumatic drug; HAQ, Health assessment questionnaire.

*including biologics

**excluding ongoing biologic

Figure 1. EQ-5D utility (mean, 95% CI) development for RA patients remaining on therapy.

**Disclosure A. Gülfe, None; J. A. Karlsson, None; L. E. Kristensen, Abbvie, Pfizer, UCB, BMS, Roche, MSD, 5.
Area of Residence and Socio-Economic Factors Significantly Affect Access to Biological Therapy for Rheumatoid Arthritis Patients in Romania. Catalin Codreanu1, Corna Mogosan2, Ruxandra Ionescu2, Ioan Ancuta3, Magda Parvu4 and Simona Rednic5. 1Dr. Ion Stoia Clinical Center of Rheumatic Diseases, Bucharest, Romania, 2Dr. Ion Stoia Clinical Center of Rheumatic Diseases, Bucharest, Romania, 3Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania, 4Dr. I. Cantacuzino Hospital, Bucharest, Romania, 5Colentina Clinical Hospital, Bucharest, Romania, 6University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Background/Purpose: Clinical trials have proven the efficacy of biological therapy for rheumatoid arthritis (RA) worldwide. However, high costs have set boundaries to their use, especially in developing countries. Whereas in Europe, there are countries without any biological reimbursed, other countries have a more liberal prescription, regardless of the RA duration and previous therapy. To be eligible for biologics, in Romania, patients with active RA must be non-responders to at least two synthetic DMARDs; up to date four biological products are reimbursed: infliximab, etanercept, adalimumab, rituximab. The aim of the study is to evaluate patient’s accessibility to biological therapy on a national scale (41 counties and Bucharest, i.e. the capital) and the correlation with socio-economical indicators for each region.

Methods: Observational study carried out in 41 counties and Bucharest. Data was gathered from the Romanian Registry of Rheumatic Diseases, while the socio-economic indicators were extracted from the yearbook of the National Institute for Statistics (EUROSTAT).

Results: The sample enrolled data of 4507 RA patients (4267 being treated with drugs and 240 being eligible for biologics). The mean age was 56.69 yrs (+/- 12.07), 85.24% women, 67.80% live in urban residences, with a mean RA duration of 12 yrs. 80.20% (n=3614) of patients had access to biologics in their county of residence, whereas 19.80% (n=893) of patients were treated elsewhere. The group treated outside of their county of residence come from areas with high deficit of physicians (1.67 physicians/1000 inhabitants, compared to 3.24 physicians/1000 inhabitants, for the group treated locally) and with a decreased welfare (GDP/inhabitant: 6634.83 € compared to 4891.02 €, p<0.001). The total number of rheumatologists working in a county varies from none (7 counties do not have any rheumatologist) to 75 (in Bucharest). There is a positive correlation between areas with better living conditions and the number of local working rheumatologists (r=0.54, p<0.001). Patients living in urban areas (70.20%) have significantly greater access to biologics in their county of residence compared to patients living in rural environments (29.7%), most of them being forced to travel in order to be taken into care by a rheumatologist. The patients’ age does not impact on their access to biological therapy. On a national scale, the majority of RA patients who are treated outside their county of residence chose the capital, Bucharest 53.73% (805/1498) of patients treated in Bucharest came from a different geographical area.

Conclusion: In Romania, the accessibility of RA patients to biological therapy greatly varies according to the socio-economic situation of their county of residence. Living in an area with a low socio-economic status significantly decreases the patients’ chances of getting treated with biologics compared to other national counties, even when therapeutic protocols are equal and equivalent.

Disclosure: C. Codreanu None; C. Mogosan None; R. Ionescu None; I. Ancuta None; M. Parvu None; S. Rednic None.

Increasing Discrepancies Between Physician Assessment of Disease Activity and Patient Global Health in Germany Between 2000 and 2012. Dörte Huscher1, Katinka A Ibrecht2, Katja Thiels2, Sascha Bischoff2, Andrea Krause2, Susanna Späthling-M estekemper3, Siegfried Wassenberg4 and Angela Zink1. 1German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, 2German Rheumatism Research Centre, Berlin, Germany, 3Immanuel Krankenhaus Berlin, Berlin, Germany, 4Praxis für Innere Medizin/Rheumatologie, München, Germany, 5Fachkrankenhaus, Ratingen, Germany.

Background/Purpose: We have seen remarkable achievements in disease control (DAS28) in rheumatoid arthritis in the past decade. They were, however, not accompanied to the same degree by improvements in patient reported outcomes. To evaluate whether the relationship between patient global health and physician assessment of disease activity, both measured on numerical rating scales 0–10, has changed in the last decade and if these changes differ between diagnoses or depend on sex, age, disease duration or education.

Methods: Patients recorded in the National Database of the German Collaborative Arthritis Centres between 2000 and 2012 for whom both physician and patient assessments were available were evaluated. The percentages of patients assessing their global health worse than the physician rated disease activity were analysed for rheumatoid arthritis (RA, on average n=6,554 each year), ankylosing spondylitis (AS, n=1,079), psoriatic arthritis (PsA, n=1,391), systemic lupus erythematoses (SLE, n=800) and polymyalgia rheumatica (PMR, n=489) with regard to sex, age, disease duration and education.

Results: In 2000, patient ratings were on average 0.9–1.6 scores worse than physician ratings. These differences further increased by 0.4–1.2 score units until 2012. In 2000, patient ratings at least one score worse than physician ratings were found in 62–65% of patients with RA, AS, PsA and PMR, and in 53% of patients with SLE. We saw an increase in poorer patient ratings by 12–16% for all diagnoses but AS (+7%) between 2000 and 2012. Male patients showed a stronger increase in discrepant ratings over time. Patients aged up to 40 had a higher agreement between physicians and patients than older patients. Poorer patient ratings were more frequent in patients with longer disease duration and lower education. The higher rates with both increasing age and disease duration are probably also reflecting the burden of co-morbid conditions. When analysing by logistic regression which parameters predict a poorer patient than physician rating, calendar year played a significant role in all diagnosis groups after adjusting for sex, age, disease duration and education.

Conclusion: The discrepancies between patient and physician ratings have increased over the past decade for various diagnoses. In addition to a rising importance of quality of life in public perception in recent years, in times of almost universal internet access this might also reflect the better informed patient with higher expectations. These changes should be taken into account when comparing patient reported outcomes over long periods. In general, our findings underline the need to consider carefully the patient view when assessing treatment outcomes.

Disclosure: D. Huscher None; K. Albrecht None; K. Thiels None; S. Bischoff None; A. Krause None; S. Späthling-M estekemper None; S. Wassenberg None; A. Zink None.

Economic Impact of Frequent Gout Flares in a Managed Care Setting. Robert Jackson1, Aki Shiozawa2, Erin Buysman3, Aylin Altan2, Stephanie Korre4 and Hyon K Choi5. 1Takeda Pharmaceuticals International, Inc, Deerfield, IL, 2Optum, Eden Prairie, MN, 3Boston University School of Medicine, Boston, MA.

Background/Purpose: Gout is the most common inflammatory arthritis in the US. For most patients, excruciatingly painful gout attacks (“flares”) are the major clinical burden of the disease. The goal of this study was to assess the association of flare frequency with economic outcomes including all-cause and gout-related health care costs to better understand the economic benefit of reducing flare frequency.

Methods: This cohort study used administrative claims data from a large US health plan of commercially insured and Medicare Advantage enrollees. Patients were identified based on medical and pharmacy claims for gout between January 2009 and April 2012. The 12 months prior to the index gout

Figure 1: Predictors of a poorer patient than physician rating (odds ratios with 95% confidence interval); age, disease duration and calendar year in 5-years steps.

Disclosure: D. Huscher None; K. Albrecht None; K. Thiels None; S. Bischoff None; A. Krause None; S. Späthling-M estekemper None; S. Wassenberg None; A. Zink None.
claim was used to assess baseline confounders. Gout flares were assessed in the 12 months following the index gout flare based on diagnoses for gout or joint pain followed within 7 days by claims for NSAIDs, colchicine, corticosteroids, or joint aspiration/drainage. Flare frequency, gout treatments, and all-cause and gout-related health care costs were assessed in the 12 months following the index gout flare. Patient characteristics and economic outcomes were compared between patients with infrequent flares (0–1 flares in the 12-month follow-up period) to those with 2 or ≥3 flares. Generalized linear models were used to adjust for potential confounders.

Results: Our study included 102,703 patients; 89,201 had 0–1 flares, 9,714 had 2 flares, and 3,788 had ≥3 flares. Demographic and baseline characteristics did not appear to be meaningfully different among these groups (Table). After adjusting for potential confounders, patients with 2 or ≥3 flares had significantly higher mean all-cause and gout-related total health care costs compared to those with 0–1 flares. A adjusted all-cause costs were $11,786, $12,625, and $15,328 in those with 0–1, 2, and ≥3 gout flares, respectively (p < 0.001 comparing 0–1 flares to 2 flares; p = 0.001 comparing 0–1 flares to ≥3 flares). A adjusted gout-related costs were $1,804, $3,014, and $4,363, in those with 0–1, 2, and ≥3 gout flares, respectively (p < 0.001 comparing 0–1 flares to 2 or ≥3 flares).

Conclusion: The economic implications of frequent gout flares are significant, particularly when comparing patients with infrequent flares (0–1 flares per year) to those with 2 or ≥3 flares. Gout-related costs were 67% higher in those with 2 flares and nearly 150% higher in those with ≥3 flares compared to those with infrequent flares. This suggests significant cost benefit to a disease management plan with a goal of reducing flare frequency to fewer than 2 per year. Future research should consider costs beyond those related to health care utilization and include costs from other sources such as missed work and loss of worker productivity.

### Table. Demographics and Baseline Patient Characteristics by Flare Frequency

<table>
<thead>
<tr>
<th>Flare Frequency</th>
<th>N</th>
<th>0–1 Flares</th>
<th>2 Flares</th>
<th>≥3 Flares</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (sd)</td>
<td>56.3 (13.9)</td>
<td>56.3 (13.8)</td>
<td>57.0 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>68,704 (77.0)</td>
<td>7279 (79.6)</td>
<td>3005 (79.3)</td>
<td></td>
</tr>
<tr>
<td>Insurance Type, n (%)</td>
<td>68,595 (76.9)</td>
<td>7533 (77.5)</td>
<td>2875 (75.9)</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>20,606 (23.1)</td>
<td>2181 (22.5)</td>
<td>913 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td>11,938 (13.4)</td>
<td>1592 (16.4)</td>
<td>679 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11,938 (13.4)</td>
<td>1592 (16.4)</td>
<td>679 (17.9)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64,389 (72.2)</td>
<td>6781 (69.8)</td>
<td>2576 (68.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Aian/Other</td>
<td>9185 (10.3)</td>
<td>993 (10.2)</td>
<td>380 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3689 (4.1)</td>
<td>346 (3.6)</td>
<td>153 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Net Worth, n (%)</td>
<td>37,416 (41.9)</td>
<td>4593 (46.7)</td>
<td>1815 (42.1)</td>
<td></td>
</tr>
<tr>
<td>≤$250,000</td>
<td>43,425 (48.7)</td>
<td>4299 (43.2)</td>
<td>1595 (42.1)</td>
<td></td>
</tr>
<tr>
<td>≥$250,000</td>
<td>8360 (9.4)</td>
<td>876 (9.0)</td>
<td>278 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Quan-Charlson comorbidity index, mean (sd)</td>
<td>0.60 (1.15)</td>
<td>0.59 (1.13)</td>
<td>0.71 (1.23)</td>
<td></td>
</tr>
<tr>
<td>Renal Impairment, n (%)</td>
<td>18,025 (20.2)</td>
<td>1526 (16.4)</td>
<td>679 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>26,071 (29.2)</td>
<td>2613 (26.6)</td>
<td>1005 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Conditions, n (%)</td>
<td>68,005 (76.2)</td>
<td>7042 (72.9)</td>
<td>2782 (75.8)</td>
<td></td>
</tr>
<tr>
<td>Baseline Health Care Utilization</td>
<td>18,878 (20.9)</td>
<td>1815 (20.2)</td>
<td>726 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Inpatient Visits, n (%)</td>
<td>9758 (10.9)</td>
<td>975 (10.0)</td>
<td>440 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Emergency Room Visits, n (%)</td>
<td>23,385 (26.2)</td>
<td>2693 (27.7)</td>
<td>1212 (32.0)</td>
<td></td>
</tr>
<tr>
<td>Number of Outpatient Visits per Patient, mean (sd)</td>
<td>12.8 (14.1)</td>
<td>12.7 (13.9)</td>
<td>15.9 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Baseline Serum Uric Acid Level, mean (sd)</td>
<td>7.36 (1.96)</td>
<td>7.36 (1.96)</td>
<td>7.36 (1.96)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on 12,741, 1358, and 542 patients, respectively, who had serum uric acid results available.

### Background/Purpose: To assess patient satisfaction with the rheumatology telemedicine service provided to a rural town in northern Australia.

### Methods: A prospective, questionnaire-based exploratory study of patients seen in Mount Isa rheumatology telemedicine clinics during 2012 was done. Control groups included patients travelling over 3 hours to be seen face-to-face in Townsville, and patients seen face-to-face in Mount Isa. A 5-point Likert scale was used to explore themes of communication, confidentiality, physical examination, rapport, medication safety and access.

### Results: This study evaluated 107 rheumatology outpatients (49 rheumatologists, 46 face-to-face in Townsville, 12 face-to-face in Mount Isa). Patients seen in Mount Isa travelled a median of 3km for telemedicine and 5km for face-to-face appointments. The face-to-face Townsville control group travelled a median of 354km. New patients comprised 14% of consultations. Satisfaction with themes related to quality-of-care was high with over 90% selecting ‘agree’ or ‘strongly agree’ to these questions. Comparing models of care, there were no significant differences in the rates of those selecting ‘strongly agree’ across questions, apart from a single question related to rapport which favoured the Mount Isa face-to-face model (p=0.018). When asked whether they would rather travel to Townsville than participate in a telemedicine consultation, 63% of patients selected ‘disagree’ (17%) or ‘strongly disagree’ (46%).

### Conclusion: These results suggest that patients are satisfied with a rheumatology telemedicine service, and may prefer this alternative to extensive travelling. Evaluation in other settings is recommended before generalizing this finding.

### Disclosure: K. Poulsen, None; L. Roberts, None; C. Millen, None; U. Lakshman, None; P. Buttimer, None.

Background/Purpose: Persistence with osteoporosis therapies is associated with clinical outcomes. The goal of this study is to examine patient-reported persistence with zoledronic acid, a once-yearly bisphosphonate infusion, and to identify the factors associated with non-persistence with zoledronic acid therapy.

Methods: A cross-sectional study of patients affiliated with a large US health plan was conducted via a mailed survey. The Optum Research Database was used to identify female patients receiving a zoledronic acid infusion (index date) 13–19 months prior to the November 2013 survey administration. Patients were required to be age 50 or older at index date with continuous enrollment in medical and pharmacy benefits and an osteoporosis diagnosis in the 6 months prior to the index date. Patients who received the index infusion in a long-term care institution or had a diagnosis of Paget’s disease or cancer during the 6-month pre-index period were excluded. Data collection included a pilot-tested patient survey to assess patient clinical and demographic characteristics, experiences associated with index zoledronic acid therapy (e.g., side effects and barriers to treatment), knowledge of osteoporosis and zoledronic acid therapy, attitudes toward medication, and availability of support for disease and therapy management. Mailed survey administration followed the Dillman tailored design method. Survey data were collected from November 2013 to January 2014. The chi-squared test was used to examine the differences in survey responses between patients who did and did not receive a follow-up infusion. The survey was analyzed as the whole cohort and specifically by the presence of biologic treatment.

Results: 291 patients with AS were registered at the first visit, 218 on biological drugs, mean age was 44.3 years, mean time from diagnoses was 13.6 years, 26.1% were female. With higher functional impairment, described by BASFI, there is a trend in age increase, increase in time from diagnosis, percentage of work impairment and also decrease in percentage of work-active patients. There is also deterioration in clinical impairment (ASDAS-CRP) and QoL observed with higher BASFI. See the results in table 1 & 2; values presented as mean, n.a.-not applicable.

Conclusions: Patients with worse functional impairment revealed more significant difference of their QoL, work productivity and revealed also worse clinical outcomes and higher WPAI (in -biologic treated patients). There is a trend of decreasing number of work active patients who are not on biologics. For patients not treated with biologics, BASFI is a very good cost predictor.

Acknowledgement: Supported by the Research program of the Ministry of Health of the Czech Republic IGA MZ CR: No. 000 000 23728.

Table 1: Initial visit of AS patients

<table>
<thead>
<tr>
<th>Patients on biologic drugs</th>
<th>Non-biologic</th>
<th>Whole cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS-CRP 0.016</td>
<td>0.016</td>
<td>0.016</td>
</tr>
<tr>
<td>% WPAI 19%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>% of work active 39%</td>
<td>39%</td>
<td>39%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bio patients on biologic treatment</th>
<th>w/o patients without biologic treatment</th>
<th>Whole - Whole cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS-CRP 1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>% WPAI 23%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>% of work active 40%</td>
<td>40%</td>
<td>40%</td>
</tr>
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</table>

Table 2: Follow-up observations

<table>
<thead>
<tr>
<th>Visit</th>
<th>1st visit</th>
<th>2nd visit</th>
<th>3rd visit</th>
<th>4th visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>218</td>
<td>206</td>
<td>192</td>
<td>178</td>
</tr>
<tr>
<td>No. of patients with active disease</td>
<td>162</td>
<td>150</td>
<td>136</td>
<td>122</td>
</tr>
<tr>
<td>No. of patients with CRP &gt; 3</td>
<td>25</td>
<td>23</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>No. of patients with BASFI &gt; 3</td>
<td>20</td>
<td>18</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>ASDAS-CRP 2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>% WPAI 22%</td>
<td>22%</td>
<td>22%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>% of work active 39%</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
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</tbody>
</table>

Whole patient cohort

<table>
<thead>
<tr>
<th>Bio patients on biologic treatment</th>
<th>w/o patients without biologic treatment</th>
<th>Whole - Whole cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS-CRP 1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>% WPAI 23%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>% of work active 40%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Bio – patients on biological treatment; w/o - patients without biological treatment; Whole – Whole cohort of patients
Background/Purpose: To investigate annually real-practice costs of biologic therapy for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) cohort treated by tight control and treat to target strategy permitting dose reduction. 

Methods: 200 Italian patients in treatment with biologic therapy including all five TNF inhibitors (adalimumab, ADA; certolizumab, CER; etanercept, ETA; golimumab, GOL; infliximab, IFX), abatacept (ABA), tocilizumab (TCZ) and anakinra (ANK) adhering to local health centre protocol, in northeast Italy counting population of 250,000 people, were investigated. ABA and TCZ were used as second and third biologic line. 127 were affected from RA, 64 from PsA and 11 from AS. All patients were controlled every 3 months for disease activity or remission following EULAR criteria (DAS 28-CRP < 2.6 or ASDAS < 1.3). After achieving sustained remission for at least 12 months doses of biologics were reduced and maintained when activity permitted it. Real-practice costs were supplied by payment bureau of local health centre for the year 2013. Costs for eventual concomitant DMARDs, NSAIDs, steroids and other pain killers were excluded. Periods of treatment stops because of justified or unjustified causes were included.

Results: Clinical remission by tight control and treat to target strategy was achieved in 81 RA (63.7%), 26 PsA (66.6%) and 22 AS (64.7%) patients. Dose reduction was very frequent for RA (49.6%), PsA (69%) and AS (44%); and significantly more frequent in patients treated with ETA (69.6%) than ADA (30.2%). Dose reduction was infrequent for the other biologics and beyond first biologic line. Total annual costs of biologics for the year 2013 were €1,463,470, mean costs per patient per year were €7,317. Mean annual costs per patient per year were €5,376 for ETA, €6,511 for CER, €6,876 for ANK, €8,485 for IFX, €8,953 for GOL, €9,285 for ADA and €9,404 for ABA.

Conclusion: a) Clinical remission was achieved by tight control and treat to target strategy in high proportion of patients with RA, PsA and AS; b) Dose reduction was very frequent in real-practice conditions; c) This was especially possible during ETA and first line biologic treatment; d) Permitting dose reduction importantly decreased expected annual costs for biologics in real-practice conditions.

Disclosure: B. Raffeneiner, None; C. Botsios, None; M. Ragazzi, None; E. De Menis, None.

1161

The Price of a Positive Test: Is It Worth the Cost? Lara H. Huber, Kristen Morella, Natasha M. Ruth and Murray H. Parso. Medical University of South Carolina, Charleston, SC.

Background/Purpose: The ACR Choosing Wisely Campaign top 5 lists highlight the appropriate use of autoantibody testing, thereby reducing unnecessary spending. Positive autoantibodies (ANA) are one of the most common reasons for referral to pediatric rheumatology clinics. The prevalence of positive ANAs in the pediatric population ranges from 3 – 36%. ANAs are useful when used for confirmation of a suspected diagnosis and for risk stratification of a known diagnosis, but ANAs are often inappropriately used to screen for autoimmunity resulting in positive tests with unclear clinical significance. We hypothesize that a large amount of health care dollars are spent on laboratory and radiographic tests related to a positive ANA and that general pediatricians are more likely to order an ANA than pediatric rheumatologists when confronted with the same clinical scenario.

Methods: We conducted a retrospective chart review of new patients referred for a positive ANA to the pediatric rheumatology clinic at our institution from July 1, 2010 through June 30, 2011. We recorded findings from the history and physical examination, any studies ordered prior to and at the time of the rheumatology visit, and the final diagnosis. The history, physical examination, and baseline laboratories were reviewed by 2 pediatric rheumatologists, 3 pediatric hospitalists, and 2 ambulatory pediatricians blinded to the final diagnosis, ANA titer, and other studies. The reviewers indicated whether they would have ordered an ANA. A list of gross charges for the studies was obtained from the laboratory and department of radiology at our institution.

Results: Seventy-five patients were identified. The total charges equaled $195,402 with a mean of $2,605 per patient. Only 5 patients had a primary rheumatologic disease. Two patients had lupus, 2 had JIA, and 1 had UCTD. Hyperrheumatoid was the most common diagnosis, and 24% of patients had a negative ANA on repeat testing. There was a significant difference in the total charges per patient based on the final diagnosis (primary rheumatologic disease vs. other diagnosis, p = 0.0499). The interrater reliability between all 7 reviewers was fair with an intraclass correlation coefficient of 0.303; it was moderate between rheumatologists with a kappa statistic of 0.478. There was not a significant difference between the number of ANAs ordered by the 3 groups. The responses for the patients with a rheumatologic disease were analyzed. The rheumatologists agreed on ordering an ANA for all these patients, but there was disagreement among the general pediatricians.

Conclusion: ANAs are useful when used appropriately, but they generate large amounts of unnecessary spending if used inappropriately. Most patients with a positive ANA did not have an autoimmune disease bringing into question the necessity of the initial ANA test. When comparing the utilization of ANAs between pediatric rheumatologists and general pediatricians, there was not a significant difference in the number of tests ordered; however, the rheumatologists more accurately identified patients with a rheumatologic disease.

Disclosure: L. H. Huber, None; K. Morella, None; N. M. Ruth, None; M. H. Parso, None.

1162

Patterns of Use of Long-Term (> 5 Years) Oral Bisphosphonate Prescription Among Primary Care Providers and Rheumatologists for the Treatment of Osteopenia and Osteoporosis in a Veteran Population. M. H. Huber1, Stephanie Ogorzaly2 and Maya A. Mattar2. Cleveland Veterans Affairs Medical Center, Cleveland, OH, 2Cleveland Veterans Affairs Medical Center, Cleveland, OH, 3University Hospitals Case Medical Center, Cleveland, OH.

Background/Purpose: Osteoporosis is a widely prevalent but underrecognized condition. Oral bisphosphonates are considered first-line treatment of osteoporosis in men and women however long-term use is associated with potential adverse effects. In patients taking bisphosphonates for at least 5 years, it is generally recommended that the need for continued bisphosphonate therapy be reevaluated and a drug holiday be considered.

Methods: We conducted a computerized retrospective cohort study of all veterans, male and female > 50 years of age at the Cleveland VA Medical Center receiving a prescription for an oral bisphosphonate for greater than 5 years. Medication compliance was determined by a medication possession ratio (MPR) greater than 0.8 over 5 years (MPR = total number of days supplied/total number of days since first fill). We excluded patients receiving bisphosphonates for Paget’s disease or an indication other than osteoporosis/osteopenia (ICD9 codes 733.00, 733.90,733.01, 733.02). We identified whether prescribers were rheumatologists or primary care providers. We reviewed laboratory testing for serum 25 (OH) D3 at any time during bisphosphonate therapy, and VA pharmacy prescriptions for Calcium and Vitamin D supplementation. Chart review of clinical notes and radiology reports was performed to determine if baseline and follow-up bone mineral densitometry (BMD) were obtained and documented.

Results: 100 patients met inclusion criteria, 78 male and 22 female, mean age 76 years (range 50-96). The diagnosis was osteoporosis in 54%, osteopenia in 21%, and not documented in 23%. The most commonly prescribed bisphosphonate was alendronate (71%). The duration of bisphosphonate therapy ranged from 5 to 14 years (mean 8 years).

Conclusion: The large majority (95%) of patients on long-term bisphosphonate therapy in this veteran population were managed by PCPs rather than

<table>
<thead>
<tr>
<th>Description of oral bisphosphonate by primary care provider</th>
<th>Description of oral bisphosphonate by rheumatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (total N=100)</td>
<td>n=100 %</td>
</tr>
<tr>
<td>Documentation of BMD at initiation of bisphosphonate</td>
<td>90 44 46.3</td>
</tr>
<tr>
<td>Documentation of follow-up BMD</td>
<td>5 100 37</td>
</tr>
<tr>
<td>Glomerular filtration rate &lt; 30 ml/min</td>
<td>0 0 3 3.2</td>
</tr>
<tr>
<td>Serum level of 25(OH)D3</td>
<td>5 100 60 63.1</td>
</tr>
<tr>
<td>Active order for Calcium</td>
<td>5 100 71</td>
</tr>
<tr>
<td>Active order for Vitamin D</td>
<td>5 100 72</td>
</tr>
</tbody>
</table>

Conclusion: The large majority (95%) of patients on long-term bisphosphonate therapy in this veteran population were managed by PCPs rather than
Predictors of Cholesterol and Lifestyle Discussions in Rheumatoid Arthritis Visits: Impact of Perceived RA Control and Comparison with Other Prevention Topics. Christie M. Bartels1, Joanna Wong2, Heather Johnson1, Katy Voelker3 and Maureen Smith1. 1University of Wisconsin School of Medicine and Public Health, Madison, WI, 2Tufts University School of Medicine, Boston, MA, 3Univ of Wisconsin School of Medicine and Public Health, Madison, AA.

Background/Purpose: Experts recommend discussing modifiable cardiovascular disease (CVD) risk factors in RA visits. We examined the predictors of discussions about cholesterol and or lifestyle (weight, diet, exercise) in RA visits among patients eligible for improved cholesterol control, and compared them to other prevention topics: vaccination, bone health. We hypothesized that cholesterol/lifestyle discussions would depend on perceived RA control at a given visit.

Methods: Electronic health records were used to identify RA patients with uncontrolled cholesterol who received primary and rheumatology care in a health system with 3 rheumatology clinics (2004–2011). Those with diabetes, CVD, chronic kidney disease with low density lipoprotein (LDL) cholesterol >100 mg/dL and without such conditions whose LDL exceeded 130 mg/dL had visit notes reviewed by trained abstractors until LDL control or censoring for loss of continuity, death, or end of data. “RA control” was defined as stated by a rheumatologist in the visit note. We used logistic regression to calculate the odds ratios (OR) and 95% confidence intervals reflecting RA control as a predictor of cholesterol/lifestyle or other prevention discussions after controlling for sociodemographics, comorbidity (ACG score), and clinic.

Results: 1785 abstracted RA visits showed a mean age 60 years, 84% female, 93% white, 10% smokers, and mean BMI was 30.2 (SD 7.3). Prevalent CVD was noted in 18%, diabetes 15%. Overall 37% of visits reported controlled RA, and 31% discussed either cholesterol or lifestyle (13% cholesterol). As hypothesized, perceived RA control at a visit increased the odds of cholesterol/lifestyle discussion at that visit (OR 1.54, 0.97; 1.98; Table 1). Other predictors of cholesterol/lifestyle discussions included single marital status, Medicaid, higher ACG score and hyperlipidemia codes or medications. In contrast, black race, non-English language, tobacco use, obesity and chronic kidney disease (CKD) predicted lower odds of such discussions. RA control was not predictive of vaccine or bone health discussions which showed less variation. Obese patients had lower odds of any prevention discussions. Clinic effects were significant for cholesterol and vaccine discussions but not bone health (data not shown). Limitations of our study include a visit note level analysis, which may not reflect care over several visits or without documentation, and use of subjective “RA control” definitions, although this may reflect usual care.

Conclusion: Perceived RA control predicted higher odds of cholesterol/lifestyle discussions, but not vaccine or bone health discussions. Concerning low discussion rates in at-risk patients with tobacco use, obesity, chronic kidney disease, and black race and clinic variation call for improved quality guidelines and systematic practices to address modifiable CVD risk factors in RA visits.

TABLE 1. Predictors of cholesterol & lifestyle discussions vs. other prevention topics in RA visits

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR [95% CI]</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Control</td>
<td>1.54*</td>
<td>1.15</td>
<td>1.93</td>
</tr>
<tr>
<td>Age Categories</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>1.01</td>
<td>0.71</td>
<td>3.43*</td>
</tr>
<tr>
<td>Race Black (vs A/Non)</td>
<td>0.38*</td>
<td>0.25</td>
<td>0.57</td>
</tr>
<tr>
<td>Other race/ethnicity</td>
<td>2.95*</td>
<td>0.83</td>
<td>0.55</td>
</tr>
<tr>
<td>Non-English</td>
<td>0.12*</td>
<td>-</td>
<td>5.96*</td>
</tr>
<tr>
<td>Single (Married ref)</td>
<td>1.71*</td>
<td>0.87</td>
<td>0.46*</td>
</tr>
</tbody>
</table>

* Indicates significant OR and 95% CI; ** Indicates omitted for colinearity.
Conclusion: Well-educated and younger patients apparently have potentially decisive advantages with regard to access to expensive treatments, even a country with highly developed welfare like Norway. A stronger effect of education in later years might be explained by changes in prescription practice and social trends towards longer education, pointing at increasing health gaps between education groups. Findings are relevant as the impact of age and education on access might result in avoidable adverse impact on health.

Disclosure: P. Putrik, None; S. Ramiro, None; E. Lie, None; A. Kessei, None; D. van der Hejde, None; R. Landewe, None; T. K. Kien, None; T. Uhlig, None; A. Boonen, None.

5 Year Budget Impact Analysis of Biosimilar Infliximab for the Treatment of Rheumatoid Arthritis in UK, Italy, France and Germany. Ji Seon Kim1, Jung An Hong1 and Alex Kudrin2. 1CELLTRION HEALTHCARE, INCHEON, South Korea, 2CELLTRION, Inc., Inchon, South Korea.

Background/Purpose: Biosimilar infliximab has been approved by EMA based on comparable quality, safety and efficacy profile to infliximab for the management of inflammatory autoimmune disorders including rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn’s disease, ulcerative colitis (UC), psoriatic arthritis (PsA), and psoriasis. Recent studies have shown considerable potential savings through the use of biosimilars for the treatment of inflammatory diseases, including the biologic Class drugs.

Methods: We aimed to evaluate the budget impact of the introduction of biosimilar infliximab in treatment of Rheumatoid arthritis from the payer and patient perspectives by using an Excel based budget-impact model over a five-year time horizon. The model calculated patients eligible for infliximab treatment based on the total population, annual population growth rate, and prevalence of RA in 4 major EU countries: UK, Italy, France, and Germany. The acquisition cost of comparator infliximab was assumed to be fixed after the introduction of infliximab. The price of the biosimilar infliximab is currently unknown; therefore, three different discount scenarios (10%, 20%, and 30%) were applied to evaluate the budget impact. The market uptake was assumed to be 25% in the first year.

Results: The total budget saving for the 10% price discount scenario for all four countries for 2015, 2016, 2017, 2018, and 2019 was €12,880,000, €15,450,000, €18,560,000, €22,260,000, and €26,710,000, respectively. The total budget saving for the 20% price discount scenario for 2015, 2016, 2017, 2018, and 2019 was €25,750,000, €33,490,000, €43,550,000, €56,610,000, and €73,600,000, respectively. The total budget saving for the 30% price discount scenario for 2015, 2016, 2017, 2018, and 2019 was €38,630,000, €51,740,000, €68,700,000, €88,750,000, and €106,630,000, respectively.

Conclusion: The introduction of the biosimilar infliximab as a treatment option for patients with Rheumatoid arthritis could achieve substantial cost savings. In the scenarios tested, the total 5 year saving across UK, Italy, France and Germany ranged from €96 million to €433 million.

Disclosure: J. Kim, None; J. Hong, None; A. Kudrin, None.

A Description and Comparison of Treatments for Low Back Pain in the United States. Elizabeth G. Salt, Yegeynia Gokun, Anna K. Herr and Jeffrey Talbrett. University of Kentucky, Lexington, KY.

Background/Purpose: Low back pain (LBP) affects 67% to 84% of persons residing in industrialized countries, and is a significant source of lost productivity, disability, and increased health care costs (treatment costs estimated at $90 billion). Both pharmacologic (i.e., opioids “fair” evidence to support use) and non-pharmacologic (i.e., exercise therapy-“good” evidence) treatments are recommended for LBP management. Because the prevalence of LBP and opioids use (p = .0014) differs between the U.S. Census Regions, we compared the treatments used for LBP and their related costs between regions.

Methods: De-identified patient health claims data from persons with LBP (ICD-9 codes-724.2 [lumbar]) along with treatments received (CPT codes-97001 [physical therapy (PT)]) and medication records was extracted from a large commercially insured dataset (January 1, 2007-December 31, 2009) (N=1,630,438). After using descriptive statistics to describe the sample and the frequency of received LBP treatments, we used Pearson’s Chi-Squared Test of Independence to compare therapy and medication usages among the different regions.

Results: An opioid was used by 49.8% (n=812,479) of this sample while nonpharmacologic therapies were rarely used (8%-psychological therapies; 19%-exercise therapies; 12%-PT). Opioids had the lowest standardized cost ($161,000 vs. $295,000 for physical therapy).


5.13* [3.52; 7.46] 3.04* [2.17; 4.26]
anti-convulsants (n=49,073) had the highest standardized cost ($452). The median costs for non-pharmacologic treatments are variable ($5,526-$40-hot/cold packs). We found significant differences in the medications and therapies used in the U.S. Census Regions (p < .0001; Figure 1).

**Conclusion:** There is a lack of adherence to treatment recommendations for LBP and significant differences in the receipt of various LBP treatments per U.S. Census Region. Further research is needed to explore this discrepancy.

**Methods:** Patients were referred by local primary care physicians to a solo community rheumatology practice. The rheumatologist triaged the paper referrals, and those with suspected inflammatory arthritis were selected to be initially seen by the ACPAC physiotherapist (ACPAC triage model). Patients in whom the physiotherapist suspected inflammatory arthritis were given a workup with laboratory and x-ray testing as per advanced directives. These patients were then booked as priority to see the rheumatologist. The average number of days from referral to the initiation of DMARDS was determined for those patients confirmed to have a diagnosis of IA. A retrospective chart review using the rheumatologists EMR was conducted on new referrals that were seen solely by the rheumatologist (Traditional triage model) and suspected to have IA. The time from referral to the initiation of DMARDS was also determined for this group.

**Results:** One hundred and twenty-one patients were triaged by the ACPAC physiotherapist prior to the assessment by the rheumatologist. Forty-eight patients (48%) were diagnosed with IA and 31 patients were started on a DMARD. Twenty-nine patients (93.5%) were started on a DMARD at the second Rheumatology visit. The average number of days from referral to Rheumatology visit for patients with IA was 73 days. The average number of days from referral to initiation of DMARDS was 75 days. We compared these findings to patients from a retrospective chart review using the Traditional Triage Model. One hundred and ten charts were retrospectively reviewed on patients with suspected IA. There were 53 patients (48%) diagnosed with IA and forty-three patients were started on a DMARD. Fifteen patients (35%) started on a DMARD at the first Rheumatology visit, and 28 patients (65%) started on a DMARD at the second Rheumatology visit. In this group, the average number of days from referral to Rheumatology visit was 84 days. The average number of days from the referral to the initiation of DMARDS was 125 days.

**Conclusion:** The utilization of an ACPAC trained physiotherapist with advanced directives to triage suspected inflammatory arthritis referrals prior to a Rheumatology assessment resulted in an earlier initiation of DMARDS with the majority of patients starting a DMARD at the first Rheumatology visit. This approach may serve as a model for other settings in which there is a need for health human resources in musculoskeletal care.

**Disclosure:** V. Ahluwalia, None; T. Larsen, None.

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**Background/Purpose:** An experienced Advanced Clinician Practitioner in Arthritis Care (ACPAC) trained physiotherapist with advanced directives using a standardized Electronic Medical Record (EMR) triage tool conducted a 15 minute assessment on patients with suspected inflammatory arthritis. We evaluated the time from referral to the initiation of Disease Modifying Antirheumatic Drug (DMARD) therapy in those patients who had been triaged and confirmed to have inflammatory arthritis (IA).

**Methods:** Patients were referred by local primary care physicians to a solo community rheumatology practice. The rheumatologist triaged the paper referrals, and those with suspected inflammatory arthritis were selected to be initially seen by the ACPAC physiotherapist (ACPAC triage model). Patients in whom the physiotherapist suspected inflammatory arthritis were given a workup with laboratory and x-ray testing as per advanced directives. These patients were then booked as priority to see the rheumatologist. The average number of days from referral to the initiation of DMARDS was determined for those patients confirmed to have a diagnosis of IA. A retrospective chart review using the rheumatologists EMR was conducted on new referrals that were seen solely by the rheumatologist (Traditional triage model) and suspected to have IA. The time from referral to the initiation of DMARDS was also determined for this group.

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**Disclosure:** V. Ahluwalia, None; T. Larsen, None.

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**1169**  
**Hippocampal Atrophy Is Associated with Anti-NR2 Antibodies in Patients with Systemic Lupus Erythematosus and Primary Sjögren’s Syndrome.**  
Maria B Layvnsnes1, Mona K Beyer2, Jan T Kvaløy1, Ole J Greve1, Simone Appenzeller3, Ema Harboe4, Anne B Tjensvoll1, Lasse G Guransson1 and Vibeke Olsson1,2,3,4.  
1Departments of Rheumatology, Stavanger University Hospital, Stavanger, Norway; 2Department of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.  
**Background/Purpose:** Antibodies against the NR2 subtype of the NMDA-receptor (anti-NR2 antibodies) are detected in patients with systemic lupus erythematosus (SLE) and primary Sjögren’s syndrome (SS). It is known from murine lupus models that these antibodies can cause hippocampal atrophy and cognitive impairment when they gain access to the brain. Reduced hippocampal volumes have been described in both SLE and primary SS patients; but a link between anti-NR2 antibodies and hippocampal atrophy has never been described in humans until now.

**Methods:** A population-based cohort of 50 SLE (all fulfilling the ACR criteria) and 50 primary SS patients (all fulfilling the AECG criteria) were clinically examined and cerebral MRI scanning performed. Anti-NR2 antibodies were measured in cerebrospinal fluid (CSF). We applied the SPN software and compared hippocampal volumes between patients with and without anti-NR2 antibodies.
Results: 16 % of the SLE patients and 12 % of the primary SS patients had anti-NR2 antibodies in CSF. Patients with anti-NR2 antibodies had less grey matter in their hippocampi compared to patients without these antibodies. There were no differences in grey matter volumes in other areas of the brain. Hippocampal grey matter volumes did not differ between the two total groups of SLE and primary SS patients, and there were no statistical significant interactions between groups and anti-NR2 antibodies. No effect on hippocampal volumes were found for presence of anti- phospholipid antibodies, disease duration, or present use of corticosteroids.

Conclusion: Less hippocampal grey matter is observed in SLE and primary SS patients with anti-NR2 antibodies compared to those without these antibodies. This indicates that anti-NR2 antibodies may cause neuronal death in humans, as previously demonstrated in mice with autoimmune disease.

Figure 1: Clusters of voxels with GM loss in patients with anti-NR2 antibodies (p < 0.05, FWE corrected). The cluster color represents the statistical significance of GM decrease according to the gradation of the color bar.

Disclosure: M. B. Lauvens, None; M. K. Beyer, None; J. T. Kvaløy, None; O. J. Greve, None; S. Appenzeller, None; E. Harboe, None; A. B. Tjensvoll, None; L. G. Garansson, None; R. Omdal, None.

1170 Neurological Complications during Anti-TNF Therapy: A Prospective Imaging and Electrophysiological Study. Evripidis Kaltsonoudis1, Anastasia Zikou2, Paraskevi V. Voulgari3, Spyridon Konitsiotis4, Maria Argyropoulou2 and Alexandros A. Drosos5. 1Rheumatologist, Ioannina, Greece, 2Lecturer of Radiology, Ioannina, Greece, 3Associate Professor of Rheumatology, Ioannina, Greece, 4Associate Professor of Neurology, Ioannina, Greece, 5Professor of Medicine/Rheumatology, Ioannina, Greece.

Background/Purpose: The aim of this study was to investigate the performance of diffusion-weighted imaging (DWI) in detecting high signal intensity areas (HSIA), as potential signs of bone inflammation, in wrist and metacarpophalangeal (MCP) joints of rheumatoid arthritis (RA) patients, in comparison with short tau inversion recovery (STIR) MRI images.

Methods: 26 patients with RA in clinical remission underwent MRI including DWI (with apparent diffusion coefficient (ADC) maps), T1-weighted (T1w) and STIR images. 13 were rescanned after 4 months. ADC scans were scored for bone marrow edema (BME) according to Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging scoring system (RAMRIS) and DWI scans were scored for absence (0) or presence (1) of HSIA in bone marrow. STIR and DWI images were reviewed separately by one reader and ADC values were calculated in each of 21 bone regions of the wrist and MCP joints. For calculation of ADC, regions of interest (ROIs) were drawn, which covered the maximal possible subcortical bone areas, including both areas with high and with normal signal, avoiding erosions (method A). Furthermore, in DWI positive areas, ROIs were also placed within the HSIA (method B). ADC values were divided into 4 groups based on STIR and DWI scores as seen in the table below and nonparametric tests were used to compare groups. The reproducibility of the scores was analyzed by kappa (k) values, intra-class correlation coefficient (ICC), and smallest detectable difference (SDD) and change (SDC).

Results: STIR showed more positive lesions (332 HSIA (=bone marrow edema)) than DWI (50 HSIA) (p<0.001; Fisher’s exact test). Mean ADC of “STIR-only” (STIR+/DWI-) positive lesions (318±172×10-3 mm2/s) was significantly lower than lesions, where both STIR and DWI were positive (STIR+/DWI+; 894±486×10-3 mm2/s) (p<0.001; Mann-Whitney U test). ADC values increased with increasing STIR scores (see table). The median ADC in DWI positive areas, with method A (759±10×10-3 mm2/s) was slightly lower than the median ADC with method B (846×10-3 mm2/s; p-value 0.048; Wilcoxon signed rank test). There was no statistically significant difference between baseline and 4 months follow-up scans in any parameters (p=0.9, 0.8 and 0.2 for STIR, DWI and ADC respectively; Wilcoxon signed rank test). The intraobserver agreement was good to excellent using STIR (k=0.80) and DWI (k=0.76), respectively (baseline). The intraobserver ICC of ADC measurements was 0.85. Intraobserver SDD of ADC at baseline was 60×10-3 mm2/s, whereas intraobserver SDD between baseline and 4 months follow up was 108×10-3 mm2/s.

Conclusion: DWI, including ADC measurements, in bones of patients with RA were highly reproducible and may partially reflect BME on STIR MRI. Further studies are needed to investigate if the method is useful for monitoring treatment response and/or predicting disease progression.
Assessing the Validity and Reliability of a Novel MRI Semi-Automated Algorithm for Quantifying Bone Loss in the Hand.

**Background/Purpose:** Magnetic resonance imaging (MRI) is a sensitive method to detect local inflammation in rheumatoid arthritis (RA), visualizing synovitis, bone marrow edema and tenosynovitis. The prevalence of MRI-detected tenosynovitis and the diagnostic value in early arthritis are unclear. This study aimed to identify the frequency of MRI-detected tenosynovitis at MCP joints in patients with rheumatoid arthritis (RA).

**Methods:** A randomised, double-blind, placebo-controlled, crossover study was designed. Inclusion criteria included patients with early arthritis (DAS28 3.7 – 5.1) and a visible or palpable joint swelling at the MCP orPIP joint. 71 patients (49 female, mean age 56.2 ± 13.6 years, disease duration 4.9 years, range: 6 months – 14 years) with 89 (range: 0–3) synovitis (MCP) joints were included. Each patient's MCP 2 and 3 were dichotomized into the joint with more severe synovitis and the joint with less severe synovitis. The association of inflammation severity and cartilage damage and in order to eliminate inter-patient confounders, each patient's MCP 2 and 3 were dichotomized into the joint with more severe synovitis versus the joint with less severe synovitis for a paired Wilcoxon test of dGEMRIC value. The study was approved by the local ethics committee and written informed consent was obtained from all patients prior to the MR examination.

**Results:** 69 patients fulfilled the 2010 RA classification criteria during the first year and were compared with the other patients. Within RA-patients compared with healthy controls (n = 32), patients with early RA showed a significantly higher dGEMRIC value (median of difference: 47.12, CI [16.6; 62.76]) between the joint with more severe synovitis and the joint with less severe synovitis. To test the association of inflammation severity and cartilage damage and in order to eliminate inter-patient confounders, each patient's MCP 2 and 3 were dichotomized into the joint with more severe synovitis versus the joint with less severe synovitis for a paired Wilcoxon test of dGEMRIC value. The study was approved by the local ethics committee and written informed consent was obtained from all patients prior to the MR examination.

**Conclusion:** Our data concur with the concept that synovitis severity is associated with cartilage damage. The local inflammatory status on a joint level correlated significantly with the extent of cartilage degradation.

**Disclosure:** D. P. Sewerin, None; D. C. Schleich, None; A. Mueller-Lutz, None; P. D. B. Ostendorf, None; C. Rubbert, None; D. C. Buchbender, None; P. D. M. Schneider, None; P. D. G. Antoch, None; D. F. Miese, None.

1174 Evaluating MRI-Detected Tenosynovitis of the Hand and Wrist in Early Arthritis.

**Background/ Purpose:** Magnetic resonance imaging (MRI) is a sensitive method to detect local inflammation in rheumatoid arthritis (RA), visualizing synovitis, bone marrow edema and tenosynovitis. The prevalence of MRI-detected tenosynovitis and the diagnostic value in early arthritis are unclear. This study aimed to identify the frequency of MRI-detected tenosynovitis at the metacarpophalangeal (MCP) and wrist joints in early arthritis and the association with RA and CRP and ESR within RA.

**Methods:** 178 early arthritis patients underwent unilateral 1ST extremity-MRI at baseline. The MCP and wrist-joints were scored using the RA MRI Scoring (RAMRIS) system extended with Haavardsholm's tenosynovitis score. 89 patients fulfilled the 2010 RA classification criteria during the first year and were compared with the other patients. Within RA-patients com-
parisons were made for anti-citrullinated-peptide-antibody (ACPA) positivity and for radiographic progression during year-1.

**Results:** 65% of all patients had MRI-detected tenosynovitis. RA-patients had tenosynovitis more often than non-RA patients (75% versus 59%, p=0.023). The flexor tendons at MCP-5, the extensor tendons at MP-2 and MP-4 and extensor compartment I of the wrist were more frequently affected in RA than in other diagnoses (odds ratio’s 2.28 (95% confidence interval CI) 1.2-7.0), 9.1 (95% CI 1.9-42.8), 14.2 (95% CI 1.7-115.9), 4.0 (95% CI 1.4-11.1) respectively. These associations were independent of local MRI-detected synovitis. Specificities were all >82%. Within RA, tenosynovitis-scores were not associated with ACPA positivity or radiographic progression.

**Conclusion:** MRI-detected tenosynovitis is common in early arthritis. The flexor tendons at MCP-5, the extensor tendons at MP-2 and MP-4 and the first extensor compartment of the wrist are more often affected in RA, independent of local synovitis.

**References:**
2. Li et al, JMRI 2012.

**Table 1:** Mean wrist cartilage T2* values and corresponding MRI RA RMIS scores in 5 subjects with RA.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Lunate</th>
<th>Scaphoid</th>
<th>Radius</th>
<th>Global</th>
<th>BMEL</th>
<th>MRI Scoring</th>
<th>Bone Erosion</th>
<th>JSN</th>
<th>DASCPRP28</th>
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<td>8</td>
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<td>1</td>
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**Feasibility and Clinical Implication of Radiocarpal Cartilage T2* MRI Imaging in Rheumatoid Arthritis.** Valentina Pedoia, Fabian Su; Andrew J. Burghardt, Jonathan Graft, John B. Imboden, Mary Nakamura, Ursula Heilmeyer, Thomas M. Link and Xiaojuan Li. *Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA; Division of Rheumatology, UCSF, San Francisco, CA, SFVAM/C/UCSF, San Francisco, CA.*

**Background/Purpose:** Rheumatoid arthritis (RA) disease progression and anti-rheumatic treatment efficacy have traditionally been monitored by evaluation of radiographs. However, MRI has emerged as a more sensitive tool to depict synovial and articular inflammatory changes in early and low disease activity that are not radiographically evident. In particular, T2* MRI allows the detection of early-stage cartilage damage. There are no prior reports of using T2* MRI to evaluate cartilage composition changes in the wrist of RA patients. In this study we assessed the feasibility of using cartilage T2* MRI mapping in RA patients and the association of T2* values with RA MRI scoring (RAMRIS).

**Methods:** Three wrist MRI scans for RA patients (52±13.3 yrs, 4 f, DASCRP28: 3.72±2.26, RA) and two healthy subjects (27±4 yrs, 1 f) were scanned on a 3T MR scanner (GE, Healthcare) using the standard imaging protocol recommended by the OMERACT group and a coronal T1w (time of spin-lock = 0/10/20/50 ms; spin-lock frequency = 500Hz, resolution 0.21×0.21×3 mm3). For both volunteers, scan/re-scan data were acquired after repositioning. Radiocarpal joint cartilage was segmented semi-automatically in the lunate, scaphoid and radius. Lunate, scaphoid and radius bone were automatically segmented using active contours initialized by the cartilage segmentations. The individual bone masks were used to perform piecewise rigid registration between the 4 echo images. Reliability measurements were computed as coefficients of variation (CV). MRI wrist images were scored using the OMERACT RA MRI Scoring (RAMRIS) system. Joint space narrowing (JSN), bone erosion and bone narrow edema-like lesion (BMEL) scores were correlated with T2*.

**Results:** The mean scan/re-scan T2* CVs were 1.48%, 3.60% and 5.62% for the lunate, scaphoid and radial cartilage. The overall CV was 3.59%. In Table 2, the mean cartilage T2* values and MRI scores are reported. Strong linear correlations were found between the overall T2* value and both BMEL (R=0.87, p<0.01) and erosion scores (R2=0.95; p=0.01). Fig. 1 shows FSE T2 IDEAL sequence and the corresponding T2 map of representative RA cases with high T2* (432.2 ms) and low T2* (36.9 ms).

**Conclusion:** We demonstrated excellent in vivo reproducibility of MRI T2* quantification in wrist cartilage. Despite the small sample size, the results obtained demonstrate the feasibility of using T2* MRI to study the progression of cartilage damage and response to therapy in the wrist of RA patients.

**References:**
2. Li et al, JMRI 2012.
Evaluation of a Simplified Version of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) Comprising 5 Joints (RAMRIS5)  

Background/Purpose: Semi-quantitative measurement of inflammatory pathologies of the hand in magnetic resonance images (MRI) is a mandatory, but time-consuming task for RA controlled studies in Rheumatoid Arthritis (RA). The objective of this study was to evaluate a simplified version of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) reduced to five joints of the hand (RAMRIS5).  

Methods: 94 patients with rheumatoid arthritis (62 female; age 59±12 years, range 25–83 years; disease duration 60±90 months (median: 22 months, first quartile: 7 months, third quartile: 66 months) from the REMISION PLUS study cohort who had complete files on C-reactive protein (CRP) levels and Disease Activity Score of 28 joints (DAS28) and complete MRI of the clinical dominant hand at baseline and after one year under anti-rheumatic therapy (follow-up time 12.5±11 months) in a dedicated extremity MRI scanner at 0.2T were included in this retrospective study. MRI images were scored according to the RAMRIS criteria by two readers in consensus. Spearman correlations of the RAMRIS sum-score, subscores for RAMRIS of the metacarpophalangeal joints (RAMRIS MCP), wrist (RAMRISWrist) and a reduced score comprising the MCP 2 and 3, capitate bone, triquetral bone, distal ulna were assessed. Additionally, Spearman correlations of MRI scores, CRP levels and DAS28 were calculated.  

Results: There was a strong correlation between RAMRIS5 and the RAMRIS sum-score for all patients (r = 0.87, p < 0.001) at baseline and follow up (r = 0.87, p < 0.001). Among the subscores there was a significant correlation between RAMRIS5 and RAMRIS MCP (baseline: r = 0.66, p < 0.001; follow-up: r = 0.74, p < 0.001) as well as between RAMRIS5 and RAMRISWrist (baseline: r = 0.72, p < 0.001; follow-up: r = 0.69, p < 0.001) at baseline and follow up. The correlation between RAMRIS5 and CRP (baseline: r = 0.21, p < 0.05; follow-up: r = 0.03, p = 0.76) or DAS28 (baseline: r = 0.17, p = 0.11; follow-up: r = 0.31, p < 0.01) were weak, similarly as observed for conventional RAMRIS for CRP baseline: r = 0.29, p < 0.01; follow-up: r = 0.10, p = 0.34; for DAS28 baseline: r = 0.20, p = 0.05; follow-up: r = 0.32, p < 0.01).  

Conclusion: RAMRIS5, a modified shorter RAMRIS score based on five joints of the hand is a viable tool for semi-quantitative assessment and is now practical, and showed change for synovitis and oedema where RAMRIS did not. 3D SW is a novel measure that needs careful interpretation as it includes more than one type of change. Quantitative analysis depends upon accurate and automatic identification of all hand bones; these results show excellent accuracy of around 1/3 pixel.

Quantitative RA MRI  

Table 1: Change in quantitative and RAMRIS measures  

Bone | Mean point-to-surface distance (mm) | 90% point-to-surface distance (mm)  
--- | --- | ---  
Capitate | 0.15 | 0.33  
Hamate | 0.14 | 0.31  
Lunate | 0.19 | 0.42  
M2_dist | 0.22 | 0.48  
M2_prox | 0.21 | 0.50  
M3_dist | 0.21 | 0.48  
M3_prox | 0.18 | 0.42  
M4_dist | 0.19 | 0.41  
M4_prox | 0.14 | 0.31  
M5_dist | 0.17 | 0.36  
M5_prox | 0.19 | 0.46  
P2_dist | 0.27 | 0.61  
P2_prox | 0.24 | 0.54  
P3_dist | 0.24 | 0.54  
P3_prox | 0.19 | 0.42  
P5_dist | 0.20 | 0.46  
P5_prox | 0.24 | 0.54  
Radius | 0.24 | 0.54  
Scaphoid | 0.21 | 0.47  
Trapezium | 0.18 | 0.39  
Trapezoid | 0.18 | 0.39  
Triquetrum | 0.26 | 0.56  
Ulna | 0.20 | 0.44

Voxel size was 0.47 × 0.47 × 0.45 mm. Note mean accuracy is typically around 1/3 of a voxel, and 90th percentile is still typically sub-voxel.

Background/Purpose: Magnetic Resonance Imaging (MRI) has been established as a useful modality to evaluate synovitis, bone edema, and bone erosion in patients with rheumatoid arthritis (RA). Most of previous MRI studies in RA, however, have focused their evaluation only on finger, wrist, or knee joints. In daily clinical practice for RA, we use whole-body MRI technique to validate effect of anti-arthritic drugs. The purpose of this study was to clarify the efficacy of tocilizumab (TCZ) in patients with RA using this technique.

Methods: A total of 21 consecutive RA patients on TCZ in our department between 2008 and 2014 were included in this retrospective study. Contrast whole-body MRI (1.5T) was performed before and one year after the initiation of TCZ. MRI images were assessed by one experienced radiologist without any clinical information. Hand joints were evaluated according to RA-modified RAMRIS scoring system (RAMRIS) and the other joints (atlantoaxial, shoulder, hip, and knee joints) were scored in the modified RAMRIS for this study.

Results: Mean age was 54.7 years old and mean duration of the disease 2.7 years. Of the subjects, 67% were on methotrexate and 24% had a history of other biologic agents. Mean DAS28-ESR at baseline was 5.04. After one year, clinical remission was obtained in 76%, 57% and 57% by DAS28-ESR, CDAI and SDAI, respectively. TCZ treatment led to improvement (Figure) in whole-body synovitis score (p 0.01, Wilcoxon signed-rank test) from baseline (median 0.96, range [0.00–7.31]) to one year (22.2, range [0.00–137.8]). Whole-body MRI-bone-erosion-score (r = 0.57). Changes in RAMRIS synovitis score of hands did not correlate with those of other joints in whole-body MRI.

Conclusion: TCZ exhibited significant efficacy and improvement in synovitis and bone edema. Changes in synovitis, bone edema, or erosion detected by hand MRI did not correlate with those of other joints in whole-body MRI. Whole-body MRI may be a potent tool to evaluate the inflammation and structural damage of the joints in RA independent of traditional hand MRI.

Table 2: Baseline characteristics, MRI endpoints (OMERACT RAMRIS), and safety overview

<table>
<thead>
<tr>
<th>Age (mean (SD))</th>
<th>47.8 (12.3)</th>
<th>50.8 (12.8)</th>
<th>47.8 (11.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>21 (58.3)</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0)</td>
<td>2 (5.4)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (5.7)</td>
<td>2 (5.4)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Mean duration of disease, years (SD)</td>
<td>0.8 (0.1–2.2)</td>
<td>0.8 (0.1–8.5)</td>
<td>0.6 (0.1–1.9)</td>
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<tr>
<td>Mean DAS28 (ESR), mean (SD)</td>
<td>6.25 (0.94)</td>
<td>6.50 (0.75)</td>
<td>6.44 (0.78)</td>
</tr>
<tr>
<td>Mean mSopes score, mean (SD)</td>
<td>5.81 (3.82)</td>
<td>5.69 (3.53)</td>
<td>5.30 (3.93)</td>
</tr>
<tr>
<td>Baseline bone marrow edema score, mean (SD)</td>
<td>2.89 (1.74)</td>
<td>2.58 (1.74)</td>
<td>2.22 (1.52)</td>
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<tr>
<td>Baseline erosion score, mean (SD)</td>
<td>9.42 (10.62)</td>
<td>7.47 (7.55)</td>
<td>12.19 (14.85)</td>
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Change from baseline in OMERACT RAMRIS erosion score L5 (mean (SD), evaluable set)

<table>
<thead>
<tr>
<th>Month 3* (Primary)</th>
<th>0.77 (0.43)</th>
<th>0.86 (0.43)</th>
<th>0.74 (0.43)</th>
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<tbody>
<tr>
<td>Month 6*</td>
<td>1.26 (0.42)*</td>
<td>1.45 (0.42)**</td>
<td>1.29 (0.42)**</td>
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<tr>
<td>Month 12*</td>
<td>1.52 (0.42)**</td>
<td>1.70 (0.42)**</td>
<td>0.95 (0.46)</td>
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</table>

Change from baseline in OMERACT RAMRIS bone marrow edema score L5 (mean (SD), evaluable set)

<table>
<thead>
<tr>
<th>Month 3* (Primary)</th>
<th>0.80 (0.42)</th>
<th>0.69 (0.40)</th>
<th>0.70 (0.42)</th>
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<tbody>
<tr>
<td>Month 6*</td>
<td>1.22 (0.40)</td>
<td>1.29 (0.40)**</td>
<td>1.28 (0.42)**</td>
</tr>
<tr>
<td>Month 12*</td>
<td>2.26 (0.42)**</td>
<td>1.16 (0.43)</td>
<td>1.66 (0.44)</td>
</tr>
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</table>

Change from baseline in OMERACT RAMRIS synovitis score L5 (mean (SD), evaluable set)

<table>
<thead>
<tr>
<th>Month 3* (Primary)</th>
<th>0.36 (0.24)</th>
<th>0.44 (0.25)</th>
<th>0.44 (0.25)</th>
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<tbody>
<tr>
<td>Month 6*</td>
<td>0.40 (0.25)</td>
<td>0.40 (0.25)</td>
<td>0.36 (0.24)</td>
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<tr>
<td>Month 12*</td>
<td>0.11 (0.25)**</td>
<td>0.08 (0.25)**</td>
<td>0.18 (0.26)</td>
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Change from baseline in OMERACT RAMRIS synovitis score L5 (mean (SD), evaluable set)
Do Patients with Active RA Also Have Inflamed Atherosclerotic Plaques on PET-MRI? Sarah Skeoch,1 Heather Williams,2 Penny Cristanacce3, Jacqueline James4, Paul Hocking5, Yonne Alexander1, John Walton1 and Ian N. Bruce1.

1University of Manchester, Manchester, United Kingdom; 2Central Manchester University Hospitals Trust, Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; 3Chalmers University of Technology, Göteborg, Sweden; 4Swedish Medical Center, Seattle, WA, USA; 5Macherey-Nagel, Düren, Germany; 6Bioclinica Inc, Boca Raton, FL, USA; 7UCB, Brussels, Belgium; 8Abbott Laboratories, Abbott Park, IL, USA.

Background/Purpose: Inflammation plays a key role in the progression and destabilisation of atherosclerotic plaque in the general population. In RA, inflammation is thought to accelerate atherosclerosis and may lead to a more unstable plaque phenotype.1,2 Fludeoxyglucose PET-CT (FDG-PET-CT) is a nuclear imaging technique which can be used to quantify carotid plaque inflammation. Histology studies have shown that FDG-uptake correlates with macrophage content of plaque and it has been used to identify vulnerable lesions and evaluate the effects of statins. We hypothesised that patients with active arthritis would have carotid plaque inflammation on FDG-PET and that plaque inflammation would correlate with the degree of disease activity using the DAS-28 score.

Methods: Patients with active arthritis (DAS-28=3.2), who had evidence of carotid plaque on ultrasound, were invited to have MRI and FDG-PET-CT scan of the carotid arteries. Those on statins, or those with a history of cancer, or recent infection, were excluded.

Following MRI scans performed on a 3 Tesla scanner, patients subsequently attended for a PET-CT within 2 weeks. FDG tracer was injected after a 6 hour fast. The scan was performed 2 hours after injection. Patients were positioned in a specialist head support to mimic MRI position. Mandible to sternal notch distance was also measured to ensure similar positioning during the 2 scans.

T1-weighted sequences from the MRI and PET-CT images were co-registered, then a region of interest (ROI) was drawn round the plaque. Fluorodeoxyglucose uptake in the ROI was measured by a physicist, blinded to clinical information. The tissue activity was divided by the injected activity per kilo to give a maximum standardised uptake value (SUVmax). Descriptive and parametric statistical analyses were performed.

Results: Forty PsA patients randomized to either placebo or abatacept in a multicenter, double-blind, controlled trial (RCT) were included in the study. SUVmax of the 8 features was assessed using Wilcoxon signed-rank test. Smallest detectable change was assessed using ICC (0.80) for all or some readers in hand and (0.60) for some readers in foot. Significant difference was detected between placebo and abatacept (p=0.05 for some readers in hand).

Conclusion: Plaque inflammation was demonstrated in all subjects, despite the cohort having no history of cardiovascular disease and relatively small lesion. Larger longitudinal studies are required to further investigate the relationship between disease activity and plaque inflammation and to study the effects of inflammation on plaque progression.
foot. Baseline interreader ICC was good (ICC 0.72–0.96) for all features, except periarticular inflammation and bone proliferation in the hand and tenosynovitis in the foot (ICC 0.25–0.44). Intra- and interreader ICC for change scores varied. ICC was overall low (table 2). Guyatt’s responsiveness index (GRI) was high for inflammatory features in the hand and metatarsophalangeal joints of the foot (GRI 0.67–3.13) (bone oedema not calculable). Minimal change and low prevalence may explain low ICC and GRI for bone damage.

Conclusion: PsAMRIS showed overall good intrareader agreement in the hand and foot and the inflammatory features were responsive to change, suggesting that PsAMRIS is a valid tool for MRI assessment of hands and feet in PsA clinical trials.

Table 1

<table>
<thead>
<tr>
<th>HAND</th>
<th>PsAMRIS features (Range of total score)</th>
<th>Baseline</th>
<th>Change</th>
<th>Baseline</th>
<th>Change</th>
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<tbody>
<tr>
<td>PsAMRIS</td>
<td>Plaque</td>
<td>A)</td>
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<td></td>
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<tr>
<td>Synovitis (0–42)</td>
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<tr>
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Table 2

<table>
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<th>HAND</th>
<th>PsAMRIS features (Range of total score)</th>
<th>Baseline</th>
<th>Change</th>
<th>Baseline</th>
<th>Change</th>
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<td>PsAMRIS</td>
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<tr>
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Background/Purpose: Six to 39% of patients with cutaneous psoriasis (PSO) can develop psoriatic arthritis (PsA). The transition from skin disease to joint involvement is only partially characterized. Advanced imaging can depict signs of subclinical joint involvement. The present study analyses the prevalence of hand-MRI signs of inflammation in PSO patients without clinical history of synovitis, dactylitis and enthesis and no positive CASPAR criteria at any time, but evidence of bone proliferative changes on high resolution peripheral computed tomography (HR-pQCT) of the dominant hand.

Methods: PSO patients underwent HR-pQCT (Scanco Medical, Switzerland) and L3 MRI (Siemens, Germany) of the dominant hand. HR-pQCT focused on the metacarpophalangeal (MCP) joints 2 and 3. Imaging analysis searched for erosions and new bone formation (bony spurs) with a periartricular location. MRI of the whole hand was conducted to detect osteitis, synovitis, tenosynovitis of the flexor tendon, periarticular inflammation at the MCP,PIP and DIP regions of the 2nd to 5th finger, according to the definitions of key pathologies provided for the PsAMRIS scoring system. Patients participated after signing informed consent. The study was conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BfS).

Results: Images were acquired from 55 PSO patients (36.4% female) of mean age 49.5 ± 11.2 years, mean disease duration 15.2 ± 15.4 years and mean PASI score of 6.2 ± 0.8. The most prevalent subtype was psoriasis vulgaris (73%), while nail psoriasis was present in 51% and scalp involvement in 29%. On HR-pQCT erosions were found in 29% of patients, while MRI showed new bone formation in 17%. Sixty-two patients (47%) showed at list one of the mentioned signs of MRI (or MIP)/SRI detectable inflammation. In detail, osteitis was found in 6 patients (11%), while synovitis in 21 (38%); synovitis and periarticular inflammation were detected in 2 patients (4%). In the total sample, partial correlations (controlling for the influence of age and disease duration) between periarticular bone changes observed on HR-pQCT and osteitis as well as synovitis on MRI did not show any significant correlations.

Conclusion: MRI signs of inflammation can be found in patients with cutaneous psoriasis without a history of arthritis. No evident relation seems to link these signs to bony changes observed on HR-pQCT. Longitudinal assessment of inflammation might provide deeper insight into the relationship between inflammation and changes in bone microstructure before the onset of clinical signs of arthritis.

Disclosure: D. Simon, None; F. Faustini, None; M. Engbrecht, None; A. Kleyer, None; R. Kocjan, None; J. Haschka, None; S. Kraus, None; A. J. Hube, None; M. Sticherling, None; G. Schett, None; J. Rich, None.

Background/Purpose: Fatigue deposition in sacroiliac joints in ankylosing spondylitis patients seen by MRI. Zaying Hu1, Qing Lv1, Xiaohong Wang2, Zetao Liao3, Zhiming Lin4 and Jieuo Gu5. 2Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, 3University of Erlangen-Nuremberg, Erlangen, Germany, 4St. Vincent Hospital, Vienna, Austria.

Background/Purpose: Fatigue deposition (FD) is often seen in ankylosing spondylitis (AS) patients in the sacroiliac joints (SJs). Magnetic Resonance Imaging (MRI) is a useful equipment to detect FD. The feature of FD of AS patients is seldom reported. We planned to investigate the feature of FD in SJs in AS patients seen by MRI that may help in diagnosing.
Method: This was a retrospective study. MRI images of SIJs of 353 AS patients and 224 non-spondyloarthritids (SpA) patients were read by a radiologist and a rheumatologist without knowing the history of patients. FD were recorded and compared between two groups.

Results: Totally 1154 SIJs were studied and FD were recorded in 611 (52.95%) of them. FD was significantly more often to be seen in AS group than in non-AS group (71.95% vs. 22.99%, p < 0.001). There was no difference of positive FD rate between the left SIJ and the right SIJ either in AS group (left vs. right = 70.82% vs. 73.99%, p = 0.05) or non-AS group (24.13% vs. 21.88%, p = 0.05). FD was more frequently seen in the upper than the lower half SIJs in AS group (79.89% vs. 64.02%, p < 0.001). The ilium bones were with more FD than the sacrum bones in AS group (83.85% vs. 60.06%, p < 0.001). The rate of FD was of no difference between the upper and the lower half SIJs or between the ilium and sacrum bones in non-AS group (both p > 0.05).

Conclusion: Our study found that fatty deposition was much more often to be seen in AS patients than non-AS subjects. FD appeared more in the upper and ilium bones and did not depend much on age in AS patients.

Disclosure: Z. Hu, None; Q. Lv, None; X. Wang, None; Z. Liao, None; Z. Li, None; J. Gu, None.

1186
Prevalence of MRI Spinal Lesions Typical for Axial Spondyloarthritids in Patients with Inflammatory Back Pain. Manouk de Hooge1, Jean-Baptiste Pialat2, Antoine Feydy2, M. Monique Reijnierse3, Pascal Claudepierre4, Alain Saraux5, Maxime Dougados2 and Desiree van der Heijde1. 1Leiden University Medical Center, Leiden, Netherlands, 2Hopital Edouard Herriot, Lyon, France, 3Henri Mondor Teaching Hospital, Creteil, France, 4CHU de la Cavale Blanche, Brest, Cedex, France.

Background/Purpose: A cut-off value of ≥3 inflammatory lesions was suggested by the ASAS/OMERACT group, as positive MRI of the spine (MRI spine) group. Moreover, fatty lesions on MRI spine are associated with axial spondyloarthritids (axSpA). In this study, the aim was to determine the prevalence of inflammatory (BME) and fatty lesions on MRI spine in patients (pts) with and without axSpA.

Methods: Pts aged 18-50 with inflammatory back pain (≥3 months, ≥3 years) from 25 participating centers in France were included in the DESIR-cohort (n = 708). All available baseline MRI were independently scored by 2 well-calibrated readers, blinded to any other data. In case of disagreement, an experienced radiologist served as adjudicator. Agreement between local and centralized readers disagreed, an experienced radiologist served as adjudicator. Agreement between local and centralized readers disagreed, an experienced radiologist served as adjudicator.

Conclusion: In a low percentage of pts without axSpA BME and fatty lesions are found indicating that spinal BME and fatty lesions are specific for patients with axSpA. These lesions are especially prevalent in pts with sacroiliitis on imaging. In this cohort, a cut-off ≥2 or ≥3 BME lesions and similarly ≥2 or ≥3 fatty lesions discriminate best between pts with and without axSpA.
Reproducibility of Magnetic Resonance Imaging Diffusion Weighted Imaging in Axial Spondyloarthritis Patients and Healthy Subjects. [akob M. Mallér1, Inge Juhl Sørensen2, Mikkel Østergaard3, Henrik Thomsen4, Ole Rentek Madsen5 and Susanne Juhl Pedersen6. 1Department of Radiology, Copenhagen University Hospital Herlev, Copenhagen, Denmark, 2Copenhagen University Hospital at Glostrup, Glostrup, Denmark, 3Copenhagen University Hospital at Herlev, Copenhagen, Denmark, 4Copenhagen University Hospital at Glostrup, Glostrup, Denmark, 5Copenhagen University Hospital at Herlev, Copenhagen, Denmark].

Background/Purpose: Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique where the image contrast is dependent on the diffusion of the extracellular free water molecules. DWI is widely used in oncology imaging, but only few papers address DWI in spondyloarthritis (SpA). From DWI the apparent diffusion coefficient (ADC) can be calculated and hence the diffusion in a region of interest (ROI) can be quantified. The water diffusion reflects the cellularity and thus it may be used as a quantification of inflammatory cells. The aim of the study was to measure the reproducibility of DWI in SpA patients and healthy subjects.

Methods: 25 SpA patients (13 females, mean age 36.1 years (SD 9.6); 12 males, mean age 42.3 (SD 10.8) and 24 healthy subjects (13 females, mean age 42.7 (SD 13.2); 11 males, mean age 45.3 (SD 7.5)) were MRI examined at 1.5T two times with a mean interval of 6.8 days (SD 0.9). A 5mm (gap 1.2mm) sagittal single-shot echo-planar imaging DW sequence with four b values (0;50;500;800) and a resolution of 2x2x2mm was performed on to T5. ADC maps were calculated based on all b values. The M RIs were anonymized and read in random order without information on time point and clinical data. On ADC maps 50mm circular ROIs were placed in each vertebral body corner just inside cortex. ADC was measured on the sagittal slice in the middle of the spine and on the adjacent slice to the right and left to the middle. ADCs from the four ROIs were pooled. Another ROI was placed in the middle of the spine and on the adjacent slice to the right and left to the middle. ADC maps were calculated based on all b values. The M RIs were anonymized and read in random order without information on time point and clinical data. On ADC maps 50mm circular ROIs were placed in each vertebral body corner just inside cortex. ADC was measured on the sagittal slice in the middle of the spine and on the adjacent slice to the right and left to the middle. ADCs from the four ROIs were pooled. Another ROI was placed in the right and left pedicle and in the spinous process from L1 to L5. The inter-reader variability was measured by intra-class correlation coefficient (ICC). Intra-reader variability was measured by a second reading of the examinations at time point (TP) 2.

Results: Overall ICC of the vertebral bodies between TP1 and TP2 was 0.80 (95% CI: 0.77–0.83). At TP1, ICC between the right and middle slice was 0.89 (95% CI: 0.87–0.90) and between left and middle slice 0.89 (95% CI: 0.87–0.90). Intra-reader reliability was 0.94 (95% CI: 0.93–0.95). For the right pedicle ICC was 0.44 (95% CI: 0.33–0.54), for the left pedicle 0.49 (95% CI: 0.39–0.58), for the spinous processes 0.20 (95% CI: 0.07–0.32).

Table 1: ICC (95% CI) measurements per vertebral body.

<table>
<thead>
<tr>
<th>Vertebral Body</th>
<th>Inter-reader Reliability</th>
<th>Intra-reader Reliability</th>
</tr>
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<tbody>
<tr>
<td>T6</td>
<td>0.64 (0.39–0.80)</td>
<td>0.83 (0.70–0.90)</td>
</tr>
<tr>
<td>T7</td>
<td>0.58 (0.33–0.75)</td>
<td>0.62 (0.50–0.68)</td>
</tr>
<tr>
<td>T8</td>
<td>0.39 (0.11–0.622)</td>
<td>0.75 (0.59–0.85)</td>
</tr>
<tr>
<td>T9</td>
<td>0.57 (0.32–0.75)</td>
<td>0.85 (0.71–0.95)</td>
</tr>
<tr>
<td>T10</td>
<td>0.49 (0.29–0.69)</td>
<td>0.75 (0.65–0.85)</td>
</tr>
<tr>
<td>L1</td>
<td>0.77 (0.55–0.89)</td>
<td>0.90 (0.84–0.99)</td>
</tr>
</tbody>
</table>

Table 1: ICC (95% CI) measurements per vertebral body.

Conclusion: MR DWI is overall a reproducible imaging sequence performed in the sagittal plane. The reproducibility is better in the lumbar spine compared to lower thoracic spine. Pedicles and spinous processes are not reliably imaged by DWI.

References:

Disclosure: J. M. Møller, None; I. J. Sørensen, None; M. Østergaard, None; H. Thomsen, None; O. R. Madsen, None; S. J. Pedersen, AbBVie, 2.

1189

Conventional Magnetic Resonance Imaging (MR) and Hybrid 18F-Fluoride Positron Emission Tomography (MRI) and 18F-Fluoride PET/MRI of the Spine and the Sacroiliac Joints - a Detailed Description of Pathologic Signals in Patients with Active Ankylosing Spondylitis. Xenophon Baraliakos1, Dr. Christian Buchbinder2, Prof. Dr. Benedikt Ostendorf2, Verena Ruhlmann3, P. Heusch4, F. Miese5, K. Beiderwellen6, Matthias Schneider4, G. Antoch7 and Jürgen Braun8. 1Rheumazentrum Ruhrgebiet, Herne, Germany, 2University Duisburg-Düsseldorf, Düsseldorf, Germany, 3University Duisburg-Essen, Medical Faculty, Duisburg, Germany, 4University Duisburg-Essen, Medical Faculty, Essen, Germany, 5University Duisburg, Medical Faculty, Düsseldorf, Germany, 6MNR-Klinik, Düsseldorf, Germany, 7University Duisburg, Medical Faculty, Düsseldorf, Germany.

Background/Purpose: PET is a nuclear imaging technique that depicts functional processes within the body based on gamma rays. The biologically active molecule used for PET is the bone-seeking agent18F labeled Fluoride (18F-F). The concentrations of tracer reflect tissue metabolic activity of regional bone perfusion and bone remodeling. We tested the performance of integrated 18F-Fluoride positron emission tomography and magnetic resonance imaging (PET/MRI) of the whole spine and the sacroiliac joints and compared bone marrow edema (BME) and structural (fat deposition, FD) and metabolic findings (18F-F) in patients with active ankylosing spondylitis (AS).

Methods: 13 AS patients (6 male, 7 female, mean age 37.8±11.4 years, all BASDAI>4, no anti-TNF treatment) underwent a 3-Tesla MRI and integrated PET/MRI 40 minutes after injection of a mean dose 157 MBq of 18F-Fluoride of their whole spine and the SIJ's. Two readers scored all images independently and the lesions where both readers showed agreement were considered for analysis. Inflammatory activity (bone marrow edema, BME), structural lesions (fat deposition) and focal 18F-Fluoride uptake were recorded on the level of a vertebral quadrant (VQ) or SIJ-quadrant (SQ), where one VQ and SQ consisted of 4 VQs (superior anterior and posterior and inferior anterior and posterior).

Results: A acquisition of whole-spine 18F PET/MRI including the SIJ was successful in all patients. There was excellent agreement in the reading of the two readers. For the SIJ, a total of 104 SQs could be analyzed by M R I and PET/MRI and 44.2% showed BME, while FD 42.3% and 18F-F in 46.2% SQs. BMD without FD was found in 60.9%, the majority with concomitant 18F-F. In comparison, FD alone without BME was found in 59.1% SQs and in those, parallel 18F-F was seen in only 7.7% SQs. The combination of BME and FD was found in 17.3% SQs and in those, parallel 18F-F was seen in 72.2% SQs. For the spine, a total of 1,196 VQs could be analyzed and 9.9% showed BME, while FD was found in 18.2% and 18F-F 5.4% VQs. BME without FD was found in 41.5% and in those, parallel 18F-F was seen in 14.3% VQs. In comparison, FD without BME was found in 68.3% VQs and in those, 18F-F was 8.7% VQs. Finally, the combination BME/FD was found in 5.8% VQs and in those, 18F-F uptake 40.6%. The highest mean SUVmax per lesion was found in both the SIJ (28.1±13.5) and the spine (25.7±21.1) in SIJ or VQs or SQs with a combination of BME and FD.

Conclusion: In this first study on hybrid 18F-F/PET/MRI of active AS patients we show that rather BME than chronic changes is associated with osteoblastic activity. The combination of BME and FD showed the highest 18F-F uptake, confirming our previous finding that this is the strongest predictor of future syndesmophyte formation.

Disclosure: X. Baraliakos, None; D. C. Buchbender, None; P. D. B. Ostendorf, None; V. Ruhlmann, None; P. Heusch, None; F. Miese, None; K. Beiderwellen, None; M. Schneider, None; G. Antoch, None; J. Braun, None.

1190

Osteoarthritis-like Changes Are Present in the Tibia and Femur 1 Year Following ACL Reconstruction. Valentina Pediola1, Drew A. Lansdown2, Nita C. Zar2, Charles Mcdonald3, C. Benjamin Ma2 and Xiaojian Li4. 1Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, 2Department of Orthopedic Surgery, UCSF, San Francisco, CA, 3Department of Epidemiology and Biostatistics, San Francisco, CA.

Background/Purpose: Statistical Shape Modeling (SSM) is a promising tool that has the ability to characterize complex shapes in a brief feature vector. The application of SSM in 2D imaging is widely used, though 3D MRI application is still a challenge. Injury of the anterior cruciate ligament (ACL) is a high risk factor for developing post-traumatic osteoarthritis (OA). The aim of this study is to analyze the longitudinal shape changes of the tibia and femur in patients with ACL injuries using a novel 3R-based SSM algorithm. We hypothesized that distinct shape changes are present one year following ACL injury.

Methods: Bilateral knees were scanned using a 3T MRI scanner (GE Healthcare) for 15 patients (29.3±4.2 yrs, 5 female) with ACL injuries prior to surgical reconstruction, and at 6 and 12 months after reconstruction.
controls (30.5 ± 2.3 years; 3 female) with no history of knee injuries underwent MR imaging at baseline and 12 months later. The imaging protocol included sagittal T2 fast spin-echo (FSE) images with TR/TE = 4000/49.3 ms, resolution 0.39 × 0.39 × 1.5 mm, slice spacing of 1.5 mm. The SSIM is extracted individually from the segmentation of tibia and femur. Each principal component analysis (PCA)’s mode of the model describes a different aspect of the bone shape. Starting from the mean model’s vector we can return to the space domain after the perturbation of a single mode. This method allows for the identification of the specific shape feature that is described in each mode. The first 20 modes were analyzed. The difference in mode values between baseline, 6-month, and 12-month follow-up were compared to the changes in the control knees from baseline to 12 months. Unpaired t-tests were used to compare longitudinal changes in ACL-injured and control knees, with significance set at alpha less than 0.05.

Results: The variation in M mode 10 for the tibia from baseline to 12 months is significantly different between injured (19.46 ± 28.83) patients and controls (11.68 ± 22.18). The change in M mode 11 in the injured group occurs primarily in the second 6 months, as the variation between 6 and 12 month is 18.17 ± 33.31, which is significantly different as well. The variation of the same mode in the first 6 months is not significantly different (1.29 ± 22.18). A decrease of this mode is related with an expansion and elevation of the lateral tibial plateau.

The variation in M mode 12 for the femur from baseline to 6 months and 12 months is significantly different between injured patients (6 months: 15.28 ± 28.67, 12 month 21.67 ± 21.86) and controls (4.85 ± 17.79). The change in M mode 12 in the injured group occurs primarily in the first 6 months. A decrease of the mode value is related to a flattening of the lateral femoral condyle, and to an increase of the height in the intercondylar notch.

Conclusion: In this study the longitudinal shape changes in the femur and tibia in ACL patient was analyzed. The observed expansion and elevation of the lateral tibial plateau is similar to previously observed radiographic changes in patients with OA. Significant differences are also observed in the shape of the lateral femoral condyle following ACL injury. This novel methodology may lead to the development of imaging biomarkers for post-traumatic OA.

Disclosure V. Peda, None; D. A. Lansdown, None; M. Zaid, None; C. McCullough, None; C. B. Ma, None; X. Li, None.

1192

Erosions Detected By Magnet Resonance Imaging in Patients with Juvenile Idiopathic Arthritis (JIA) Are True Erosions As Visualized By Computed Tomography. Stephanie Finzel1, Georg A. Schett2 and Nikolay Tzaribachev3. 1University of Erlangen-Nuremberg, Erlangen, Germany; 2Pediatric Rheumatology, Bad Bramstedt, Germany.

Background/Purpose: Chronic arthritides occurs relatively frequent in childhood. Patients with polyarticular disease might have a destructive disease course and thus a worse outcome. In adult rheumatology MRI is known to detect erosions in early stages. In children little is known about changes in bone structure during the course of JIA and thus erosions detected by MRI are discussed controversially. (1–3)

To test, whether MRI erosions in patients with chronic arthritides are true erosions as detected by conventional computed tomography (CT).

Methods: Six children (all female) with a median age of 14 years, 4 with polyarthritides, 1 – psoriatric arthritis and 1 with systemic scierosis were identified as having both MRI and CT of the same wrist during retrospective chart review. The median disease duration was 4 years. All patients were treated with surg methotrexate and NSAAR.

A descriptive statistical approach was chosen due to the relatively low number of patients.

Results: Overall 55 surfaces were evaluated both in MRI and CT; in MRI 9 erosions were detected by MRI and 19 by CT. In MRI erosions were localized in the Os capitatum and hamatum, whereas in CT erosions were found in all carpal bones despite the scaphoid as well as in the 2nd through 4th proximal metacarpal bone. Of the 9 erosions detected in MRI, 5 were confirmed as being true bone erosions. In CT 4 MRI erosions were detected as vessel channels in CT. Widths in MRI varied from 1.50–3.50mm, and depths from 2.00–4.00mm. In CT widths ranged from 0.57–3.07mm, and depths from 0.95–3.24mm. Due to contrast agent artifacts, no physiological vessel channels could be detected, whereas in CT 254 vessel channels were found. Visualization of os pisiforme was difficult in MRI because of soft tissue and signal of immature bone.

Conclusion: Erosions in the bone of patients with chronic arthritides visualised by MRI relate to pathological cortical defects as detected by conventional CT. Our findings suggest that these pathologic CT-alterations represent either premature or manifest bone erosions identical to those in adult bone. Given the irradiation dose of conventional CT, future imaging studies are needed in order to evaluate the significance of novel CT-techniques with lower irradiation load such as HR-pQCT for use in juvenile chronic arthritides.

Disclosure S. Finzel, None; G. A. Schett, Abbott, Celgene Corporation, Roche, and UCB, 2, Abbott, Celgene Corporation, Roche, and UCB, 5; N. Tzaribachev, None.

1193

Diagnostic value of Contrast-Enhanced MR-Angiography in diagnosing large Vessel Vasculitis. Sabine Adler, Marco Spricher, Harold Bone, Thorsten Klink and Peter M. Villing, University Hospital Bern, Bern, Switzerland.

Background/Purpose: Diagnosis of large-vessel vasculitis (LVV) remains difficult despite clinical and serological signs and symptoms. Detection by histology might be unavailable in exclusive thoracic or abdominal involvement. PET-scans rarely are ready to be used in everyday practice and CT-scans might miss vascular deformities. The value of easily accessible, contrast-enhanced MR-angiographies has only rarely been described.

Methods: Between 2005 and 2012 we investigated 76 patients (44 females, 32 males, aged 18–82 years, mean age 64.5 years) with clinical and serological suspicion of LVV by contrast-enhanced M R-angiography (MRA). Gadolinium was used as contrast-medium. Twenty-nine patients underwent both thoracic and abdominal MRA, 32 patients had thoracic and 15 patients abdominal MRA only. Additional histologies of the temporal arteries were performed in 22 patients. MRAs were independently reviewed by two radiologists. Correlations were measured for clinical, serological, histological and radiological parameters.

Results: LVV was diagnosed by MRA in 20/76 patients with 13/20 being abdominal and 7/20 thoracical vasculitides. Out of those, nine patients showed both thoracic and abdominal LVV. Interobserver agreement regarding LVV correlated in all but one patient. Compared to LVV there was fibrosis in 36/76 patients, vascular stenosis in 2/76 and arterial dissection in another 1/26 patients. The remaining 10/76 patients showed no vascular abnormalities. In 7/22 biopased patients, histology was positive for temporal arteritis; 2 out of those 7 patients had additional LVV. Neither erythrocyte
Cofilin-1 is a ROS Sensor in Regulating the NLRP3 Inflammasome
Yong Hwan Park, Daniel L. Kastner and Jae Jin Chae. National Human Genome Research Institute, Bethesda, MD.

Background/Purpose: NLRP3 (NOD-like receptor family, pyrin domain containing 3) has a pivotal role in nucleating inflammasome, cytoplasmic multiprotein complexes that mediate the maturation of the proinflammatory cytokines interleukin-1β (IL-1β) by activating caspase-1. Mutations in the gene encoding NLRP3 cause a series of autoinflammatory disease, cryopyrin-associated periodic syndromes (CAPS). It has been reported that generation of reactive oxygen species (ROS) is one of the major NLRP3 inflammasome activating factor. However, the molecular mechanism of relationship between change of cellular redox state and NLRP3 inflammasome activation has not been elucidated. Here we show that cofilin-1, a redox sensitive actin binding protein, is involved in NLRP3 inflammasome activation.

Methods: Mouse bone marrow derived macrophages (BMDM s) were obtained by differentiating bone marrow progenitors from tibial and femoral bone with M-CSF for 7 days. Inflammasome activation experiments were performed in two stages, initial LPS priming for 3 h and then inflammasome activation for 30 to 50 min by replacing the medium with RPMI 1640 medium supplemented with activators (ATP or nigericin). Inflammasome activation was analyzed by Western blotting of secreted interleukin-1β (IL-1β). The lysates from BMDM s or PT67 cells transiently with expression constructs for the wild-type (WT) or various deleted forms of NLRP3 were immunoprecipitated with anti-cofilin-1 antibody.

Results: When the NLRP3 inflammasome is activated, not only activated IL-1β but also inflammasome components, such as ASC and caspase-1 are secreted. We found that cofilin-1 is also secreted along with IL-1β from the LPS-primed BMDMs when the cells are treated with ATP, a NLRP3 inflammasome activator. In addition, knockdown of cofilin-1 reduces inflammasome activation in response to ATP, which suggests that cofilin-1 has an important role for the activation of the NLRP3 inflammasome. Cofilin-1 directly interacts to the nucleotide-binding domain (NBD) of NLRP3 protein. However, when the cells are stimulated with the NLRP3 inflammasome activators, ATP or nigericin, cofilin-1 is oxidized and dissociated from NLRP3. Indeed, the interaction of cofilin-1 with NLRP3 is increased significantly when the oxidation sites of cofilin-1 are substituted from cysteine to alanine. Finally, we found that NLRP3 inflammasome activation is attenuated when WT cofilin-1 is replaced with the oxidation-resistant mutant cofilin-1.

Conclusion: Taken together, these results suggest that cofilin-1 is a key component in regulating the activation of the NLRP3 inflammasome in response to ROS. Furthermore, since cofilin-1 is an actin binding protein that depolymerizes and severs actin filaments, and is able to translocate into mitochondria during oxidative stress condition, our finding about the interaction of cofilin-1 with NLRP3 provides an important molecular mechanism for the mitochondrial localization of the NLRP3 inflammasome.

Disclosure Y. H. Park; None; D. L. Kastner; None; J. J. Chae; None.
Results: We clearly show for the first time that TLR9 is not crucial in inflammatory arthritis. Indeed, TLR9 is not required for arthritis development in CIA as TLR9-KO mice strongly developed clinical arthritis. Accordingly, WT and KO mice produced similar levels of anti-collagen antibodies. As a control, we verified that WT and KO mice responded to complete Freund’s adjuvant. Moreover, inflammation and joint destruction were observed in both WT and TLR9-KO mice and at a similar level. In agreement with those observations, no statistically significant difference was noted within WT and KO mice regarding the percentage of the activity of lymphocytes and neutrophils in the blood, spleen and lymph nodes. Osteoclastogenesis and complement activation (C3a) after being estimated in arthritic mice were similar in WT and TLR9-KO mice. Importantly, TLR7 does not compensate TLR9 deficiency in vivo as there is no TLR7 over-expression in TLR9-deficient mice. The impact of TLR9 on cytokine secretion in vivo is currently being analyzed. In human samples, we have shown that leukocytes from healthy donors and RA patients express endosomal and cell surface TLR9 at the same extent and accordingly TLR9 expression is not correlated with disease activity in patients.

Conclusion: This is the first demonstration that TLR9-KO mice clearly develop arthritis. Immune cells from RA patients do not over-express TLR9 in comparison to healthy donors. Our results thus suggest that TLR9 does not play a crucial role in inflammatory arthritis development in the CIA model and that there is no intrinsic abnormal TLR9 expression in RA patients. This also suggests that TLR9 is not strongly involved in the recognition of DAMP in RA.

Disclosure: J. Mussard, None; M. Ribon, None; G. Clavel, None; M. C. Boissier, None; P. Decker, None.

Background/Purpose: In gout, monosodium urate (MSU) crystals trigger acute inflammation. MSU has been reported to activate NLRP3 inflammasome via ROS-dependent pathways, which results in IL-1beta secretion and cell death. To date, we have shown that febuxostat, a potent inhibitor of XOR inhibition not only decreases uric acid level in the blood but also suppresses crystal-induced inflammation. MSU has been reported to activate NLRP3 inflammasome and mitochondrial ROS as well as IL-1beta secretion, and led to decreased mitochondrial membrane potential and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages. In this study, we examined its effect on IL-1beta secretion and cell death in activated macrophages.

Methods: Bone marrow-derived macrophages were primed, incubated with febuxostat and stimulated with MSU. IL-1beta in the supernatant, intracellular ATP, mitochondrial ROS and membrane potential were analyzed. Results: MSU treatment resulted in the production of mitochondrial ROS as well as IL-1beta secretion, and led to decreased intracellular ATP (iATP) levels and depolarization of mitochondrial membrane potential. All these intracellular mechanisms were inhibited by febuxostat. Accordingly, M1b-TEMPO, a mitochondria-targeted antioxidant, inhibited IL-1beta secretion by decreasing mitochondrial ROS production in addition, artificially decreased iATP induced IL-1beta secretion and depolarization of mitochondrial membrane potential in activated macrophages. Conclusion: These results suggested that MSU induces IL-1beta and cell death via two pathways: 1) mitochondrial ROS formation, 2) iATP reduction and mitochondrial dysfunction. Both pathways can be inhibited by febuxostat, suggesting that XOX inhibition not only decreases uric acid level in the blood but also suppresses crystal-induced inflammation.

Disclosure: J. Nomura, Teijin Pharma Limited, 3; N. Busso, None; M. Tamura, Teijin Pharma Limited, 3; T. Kobayashi, Teijin Pharma Limited, 3; A. So, None.

Background/Purpose: The sex hormone prolactin (PRL) has immunomodulatory properties, can be produced by immune cells, and elevated PRL serum levels have been reported in rheumatoid arthritis (RA) patients. Here we examined synovial expression of PRL and PRL receptor (PRLR) in patients with inflammatory arthritis, their expression in polarized macrophages from patients and healthy donors, and the effects of PRL on macrophage activation.

Methods: PRL levels in paired synovial fluid (SF) and peripheral blood of RA (n = 19), psoriatic arthritis (PsA, n = 13) and gout (n = 11) patients were measured using an immunofluorescent metric assay. PRL mRNA expression was measured in synovial tissue (ST) of RA (n = 25), PsA (n = 11) and gout (n = 12) patients, and in macrophages differentiated in RA, PsA, spondyloarthritis (SpA) and gout SF by qPCR. PRLR protein expression was determined in ST of RA (n = 19), PsA (n = 15) and osteoarthritis (OA, n = 9) patients by immunohistochemistry and detected in specific cell types by immunofluorescence. IL-6 production by IFN-y and IL-10 -differentiated macrophages following stimulation with CD40L or TNFα in the absence or presence of PRL was measured by ELISA.

Results: PRL protein levels were similar in serum and SF of RA, PsA and gout patients, as was mRNA expression in RA, PsA and gout ST. Of interest, PRL mRNA expression significantly correlated with clinical disease parameters in PsA (DA28, R = 0.729, P = 0.017) and RA (ESR, R = 0.424, P = 0.049). PRL expression was also detected in monocyte-derived macrophages from RA patients, and significantly higher (P < 0.01) in healthy donor macrophages differentiated in pooled SF of RA and PsA compared to SpA and gout SF. In RA SF-differentiated macrophages PRL production was increased by CD40L or IgG stimulation but not LPS or TNFα.

Conclusion: Our results provide the first evidence that PRL is produced locally in the synovium of patients with inflammatory arthritis, and contributes to the activation of macrophages in the presence of other inflammatory stimuli.

Disclosure: M. W. Tang, None; S. Garcia, None; D. M. Gerlag, GlaxoSmithKline, 3; K. A. Reedquist, None; P. P. Tak, GlaxoSmithKline, 3.

Background/Purpose: The main pathological feature of osteoarthritis (OA) is degradation of the articular cartilage. Other important hallmarks include subclinical inflammation of the synovium and ectopic formation of new bone and cartilage at the ligaments or joint margins, termed osteophytes. Alarmins S100A8 and S100A9 are major products of activated macrophages regulating cartilage damage and synovial activation during murine and human osteoarthritis (1). OA. In the current study we investigated whether S100A8 and S100A9 are involved in osteophyte formation during experimental OA and if S100A8/A9 predicts osteophyte progression in early human OA.

Methods: OA was elicited in S100A8-/- and wild-type C57BI/6 mice in two experimental models that differ in degree of synovial activation. Osteophyte size, S100A8, S100A9 and VDIPEN expression was measured on osteophytes. Chondrogenesis was induced in murine mesenchymal stem cells (MSCs) in the presence of S100A8. Levels of S100A8/A9 were determined in plasma of early symptomatic OA patients of the CHECK cohort study and serum of early symptomatic OA patients of the CHECK cohort study. In vitro, PRLR expression was determined in human monocyte-derived macrophages following stimulation with CD40L or TNFα in response to PRL.

Conclusion: This is the first demonstration that TLR9-KO mice clearly develop arthritis. Immune cells from RA patients do not over-express TLR9 in comparison to healthy donors. Our results thus suggest that TLR9 does not play a crucial role in inflammatory arthritis development in the CIA model and that there is no intrinsic abnormal TLR9 expression in RA patients. This also suggests that TLR9 is not strongly involved in the recognition of DAMP in RA.

Methods: Plasma was obtained from a cross-sectional cohort of 58 SLE patients. We collected prospectively demographic and clinical data including ACR classification criteria and SLE disease activity index score (SLEDAI). For comparison, blood samples were collected from 65 age and gender matched healthy donors. Plasma levels of MBL, CL-L1, M-ficolin (Ficolin-1) and H-ficolin (Ficolin-3) were measured using Time Resolved Immuno-Flurometric Analysis (TRIFMA). The association with a key element of the clinical picture, lymphopenia, may indicate a pathogenic role of Ficolin-3 in SLE.

Results: The plasma concentrations of several of the pattern recognition molecules of the Lectin Pathway were significantly altered in a cross-sectional co-hort of SLE patients showing low levels of CL-L1 and M-ficolin and high levels of H-ficolin. In the subgroup of patients with lymphopenia, this manifestation was associated with a high level of H-ficolin. The association with a key element of the clinical picture, lymphopenia, may indicate a pathogenic role of Ficolin-3 in SLE.

Conclusion: The plasma concentrations of several of the pattern recognition molecules of the Lectin Pathway were significantly altered in a cross-sectional co-hort of SLE patients showing low levels of CL-L1 and M-ficolin and high levels of H-ficolin. In the subgroup of patients with lymphopenia, this manifestation was associated with a high level of H-ficolin. The association with a key element of the clinical picture, lymphopenia, may indicate a pathogenic role of Ficolin-3 in SLE. A limitation of the study is small SLE subgroups.

Disclosure: A. Troldeborg, None; S. Thiel, None; M. J. Laska, None; B. Deleuran, None; J. C. Jensenius, None; K. Stengaard-Pedersen, None.


Methods: Human umbilical cord endothelial cells (HUVEC) were grown in hypoxia (1% oxygen, equivalent to 7.6 mmHg) to mimic conditions found in the RA joint or normoxia (21% oxygen, 159.6 mmHg) in the presence or absence of TNF-α or lipopolysaccharide (LPS). Expression of PAD-4 and citrullinated histone H3, a PAD-4 target, were measured by western blot, and levels of surface adhesion molecules, intercellular adhesion molecule (ICAM)-1, ICAM-2, vascular cell adhesion molecule (VCAM)-1 and E-selectin, were measured by FACS. Neutrophils were isolated from whole blood donated by healthy volunteers. Cell adhesion assays were performed in which binding of 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein, acetoxyethyl ester (BCECF-AM) labelled neutrophils to HUVEC monolayers was measured using a fluorescent plate reader. A capture ELISA was established and validated to compare NET release between experimental conditions.

Results: Culture of HUVEC under hypoxia increased PAD-4 expression by 13.5% (1.2 fold) with levels of citrullinated histone H3 elevated by 1415.3% (15 fold). Hypoxia modulated both basal expression of ICAM-1, ICAM-2, VCAM-1 and E-selectin as well as on stimulation with TNF-α or LPS. Hypoxia also increased neutrophil adhesion to HUVEC monolayers from 3+/−3.1% to 47+/−12.0% of total cells added (p<0.0002). NET formation of phorbol 12-myristate 13-acetate (PMA)-stimulated neutrophils was elevated under hypoxia compared to unstimulated controls (49.6% vs. 58.4%, p<0.01). Co-culture experiments demonstrated enhanced NETosis of PMA-stimulated neutrophils cultured with HUVEC compared to neutrophils cultured alone under normoxia (p<0.05).

Conclusion: We have shown that hypoxia modulates; PAD-4 expression; citrullination of histone H3; adhesion molecule expression in HUVEC; neutrophil adherence to HUVEC monolayers; and NET release. Furthermore, co-culture of neutrophils with HUVEC under normoxia elevates NET production on stimulation. Given that these processes are all relevant to the pathogenesis of citrullinated antigens in RA, further experiments are currently underway to dissect the modulatory effects of hypoxia on NETosis and investigate the effects of ACPA positive RA- IgG on these cellular conditions.

Disclosure: A. A. Khawaja, None; C. Pericleous, None; L. W. Thomas, None; M. Ashcroft, None; J. C. Porter, None; I. Giles, None.
Type I Interferon Promotes Inflammatory Cytokine Production By Inhibiting Mir-146a Maturation in SLE.

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the uncontrolled inflammation along with overproduced inflammatory cytokines, among which type I interferon (IFN) is recognized as a crucial pathogenic factor. The expression of mir-146a, which plays a key role in negatively controlling both the innate and adaptive immune responses, is reduced in the peripheral blood cells of SLE patients and accounts for the overactivated inflammatory responses in SLE. However, the mechanism of the reduction of mir-146a is still not fully understood. Not only are miRNAs regulated at the transcriptional level, their biogenesis consists of complex posttranscriptional processing that is affected by many factors, some of which are indicated to be associated with autoimmune diseases and can even be regulated by IFN. In this study, we tested whether the key pathogenic cytokine of SLE, type I IFN, is responsible for the dysregulation of mir-146a through regulating its posttranscriptional processing.

Methods: Gene expression was measured with RT-qPCR, northern blotting, or western blotting. MCPIP1 expression was knocked down in THP1 cells with a lentivirus encoding a short hairpin RNA targeting MCPIP1. Gene expression data for IFN-inducible genes, MCPIP1, and mir-146a in the peripheral blood cells of SLE patients was used in the correlation analysis.

Results: The pretreatment of THP1 cells with type I IFN attenuated the induction of mir-146a by LPS. Further investigation revealed that this phenomenon happened on the posttranscriptional level, along with downregulated pre-mir-146a, but not pri-mir-146a or its original unspliced transcript. We then demonstrated that the expression of MCPIP1, which is reported to limit mir-146a maturation by antagonizing the function of DICER1, was enhanced by type I IFN. Knocking down the expression of MCPIP1 abolished the inhibition of mir-146a and alleviated the enhancement of the expression of inflammatory cytokines by type I IFN. Finally, we demonstrated that MCPIP1 expression was elevated in the peripheral blood cells of SLE patients and its expression correlated positively with the IFN score and negatively with the level of mir-146a.

Conclusion: Our data suggest that elevated type I IFN inhibits the maturation of mir-146a and contributes to the reduction of mir-146a via MCPIP1 in SLE patients, providing new insights into the mechanisms by which the overproduction of type I IFN in SLE patients amplifies inflammation and even destroys immune tolerance. This knowledge may lead to more-specific therapeutic approaches, targeting downstream effectors of type I IFN. Our findings also indicate that the posttranscriptional regulation of miRNA maturation may be involved in the pathogenic process of SLE and may account for the dysregulated inflammatory gene expression in this disease.

Disclosure: B. Qu, None; J. Cao, None; F. Zhang, None; N. Shen, None.
Oral Administration of Nano-Emulsion Curcumin in Mice Suppresses Inflammatory-Induced NFkB Signaling and Macrophage Migration.

Nicholas A. Young1, Michael Bruss2, Mark Gardner2, William Willis2, Xiaokui Mo1, Giancarlo Valiente1, Yu Cao1, Zhongfa Liu2, Lai-Chu Wu1 and Wael N. Jarjour1.

1The Ohio State University Wexner Medical Center, Columbus, OH, 2The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: The major obstacles to successful use of curcumin as an anti-inflammatory agent are its low solubility in water and rapid metabolism, which both translate to poor systemic bioavailability. To protect against metabolism and to enhance accessibility systemically, we have previously reported a novel formulation of nano-emulsified curcumin (NEC) that increases relative bioavailability by over 10-fold. In this study, we validated the bioactivity of NEC in vivo and characterized the associated mechanisms of immunosuppression.

Methods: Since curcumin has been shown to inhibit NFkB activation, we used BALB/C-Tg(NFkB-RE-luc)-Xen mice, which contain a firefly luciferase reporter gene under the control of kB responsive elements. Mice were treated with identical concentrations of curcumin in aqueous suspension (SC) or NEC by oral gavage and subsequently challenged with LPS. Acute systemic inflammation was measured and quantitated on the Xenogen imaging system (IVIS 200). Whole blood was collected for flow cytometry and serum was analyzed by ELISA. Acute peritonitis was induced in BALB/C mice by thioglycollate injection with and without NEC administration or oral gavage and subsequently challenged with LPS. Acute peritonitis, levels of T-cells and B-cells were not affected. Scratch assays to measure cell migration were performed on a human cells.

Results: Treatment with NEC significantly reduced LPS-induced inflammation relative to SC, as measured by IVIS detection of NFkB activity. Flow cytometry of peripheral blood indicated that circulating monocytes were reduced with administration of NEC and levels of LPS receptors TLR4 and RAGE were down-regulated on the surface of cells. Induction of monocytic chemoattractant protein (MCP)-1 secretion by LPS stimulation was significantly reduced with NEC administration. While macrophage recruitment was significantly reduced with NEC administration in thioglycollate-induced peritonitis, levels of T-cells and B-cells were not affected. Scratch assays to measure in vitro cell migration showed that curcumin significantly inhibited responses in both THP-1 cells and primary human macrophages.

Conclusion: In this study, we establish a novel system to screen and validate curcumin-derived drugs for longitudinal analysis in vivo. Furthermore, our results validate NEC as a candidate for future therapeutic studies and demonstrate that curcumin can suppress inflammation by selectively inhibiting macrophage migration via NFkB and MCP-1 inhibition.

Dental Fillings in Juvenile Idiopathic Arthritis: A Retrospective Study of 10 Years.

Artur H.规矩1, Rashmi Perumal2, Lara L. Beretta1, None; W. N. Jarjour1, None; L. van Bon, None; S. Nierkens, None; A. Santaniello, None; L. Beretta, None; T. Radoštak, None.

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Oral Administration of Nano-Emulsion Curcumin in Mice Suppresses Inflammatory-Induced NFkB Signaling and Macrophage Migration.

Nicholas A. Young1, Michael Bruss2, Mark Gardner2, William Willis2, Xiaokui Mo1, Giancarlo Valiente1, Yu Cao1, Zhongfa Liu2, Lai-Chu Wu1 and Wael N. Jarjour1.

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Background/Purpose: The major obstacles to successful use of curcumin as an anti-inflammatory agent are its low solubility in water and rapid metabolism, which both translate to poor systemic bioavailability. To protect against metabolism and to enhance accessibility systemically, we have previously reported a novel formulation of nano-emulsified curcumin (NEC) that increases relative bioavailability by over 10-fold. In this study, we validated the bioactivity of NEC in vivo and characterized the associated mechanisms of immunosuppression.

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Conclusion: In this study, we establish a novel system to screen and validate curcumin-derived drugs for longitudinal analysis in vivo. Furthermore, our results validate NEC as a candidate for future therapeutic studies and demonstrate that curcumin can suppress inflammation by selectively inhibiting macrophage migration via NFkB and MCP-1 inhibition.

Dental Fillings in Juvenile Idiopathic Arthritis: A Retrospective Study of 10 Years.

Artur H.规矩1, Rashmi Perumal2, Lara L. Beretta1, None; W. N. Jarjour1, None; L. van Bon, None; S. Nierkens, None; A. Santaniello, None; L. Beretta, None; T. Radoštak, None.

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Expression of Lectin-like Transcript 1, the Ligand for CD161, in Rheumatoid Arthritis.

Paulina Chai1, Johan Bijzet2, Minke G. Hultema3, Bart-Jan Kroezen4, Elisabeth Brouw5 and A Anehmier M.H. Boots5. 1University of Groningen, University Medical Center Groningen, Groningen, Netherlands, 2University Medical Center Groningen, Groningen, Netherlands.

Background/Preparation: Precursor Th17 lineage cells expressing CD161 are implicated in rheumatoid arthritis (RA) pathogenesis. CD4+CD161+ T cells were found to accumulate in RA synovial fluid (SF) and tissue (ST) where they may acquire a non-classical T-helper 1 phenotype. The endogenous ligand for CD161 is lectin-like transcript 1 (LLT1). Previously, the LLT1-CD161 interaction was reported to co-stimulate T cell effector functions and to enhance IFN-γ production. This prompted us to investigate whether LLT1 is upregulated in arthritic joints. To that end we investigated the presence and identity of LLT1-expressing cells in RA synovial fluid and synovial tissue.

Methods: Paired samples of peripheral blood (PB) and SF mononuclear cells (n=14) and digested ST cells (n=4) from late-stage rheumatoid arthritis patients were analyzed for LLT1 expression by flow cytometry. Cell suspensions were stained with fluorochrome labeled anti-human LLT1, T cell marker CD3 and B cell marker CD20. Whole blood was collected for flow cytometry and serum was analyzed by ELISA. Acute peritonitis was induced in BALB/C mice by thioglycollate injection with and without NEC administration or oral gavage and subsequently challenged with LPS. Acute peritonitis was induced in BALB/C mice by thioglycollate injection with and without NEC administration or oral gavage and subsequently challenged with LPS.

Results: Levels of LLT1 in peripheral blood and synovial fluid were found to be increased in patients with RA compared to healthy controls. In RA ST, LLT1-expressing cells were detected in the lining layer, sublining layer and in areas with lymphoid infiltrates. The LLT1 staining pattern overlapped with the CD68 (macrophages) staining pattern. Flow cytometric analysis of digested ST confirmed that LLT1 is expressed on CD68+ cells.

Conclusion: This is the first study showing that surface-expressed LLT1 is present in arthritic joints in RA. The finding of LLT1 expression by macrophages in synovial tissue suggests potential crosstalk with CD161+ T-cells. Ligand of CD161-LLT1 on CD4 T cells and macrophages respectively, may contribute to modulation of their function at the level of the joint.

Disclosure: P. Chai, None; J. Bijzet, None; M. G. Hultema, None; B. J. Kroezen, None; E. Brouw, None; A. M. H. Boots, None.

1206

Low Dose Colchicine Anti-inflammatory Effects Are Transduced By AMP-Activated Protein Kinase (AMPK).

Ru Bryn1, Robert Terkeltaub2 and Yun Wang2. 1VA Medical Center/University of California San Diego, San Diego, CA, 2VA Medical Ctr/University of California San Diego, San Diego, CA.

Background/Preparation: AMPK is a master metabolic energy regulator, whose tissue activity drops in response to nutritional excesses, alcohol consumption, and in obesity, metabolic syndrome and diabetes, and high levels of soluble urate. In addition to its anti-inflammatory effects, AMPK activity promotes microtubule stabilization. Therefore, we tested the effects of AMPK activation on urate crystal-induced inflammatory responses, and the hypothesis that AMPK activation transduces the capacity of the microtubule stabilizing agent colchicine to limit gout-like inflammation.

Methods: We studied bone marrow derived macrophages (BMDMs) from AMPKα1 knockout (KO) and wild type (WT) mice, and human monocytic THP-1 cells, and assessed a low concentration (10 nM) of colchicine achieved by "low dose regimens" for both prophyaxis and treatment of gout in humans. We examined expression and phosphorylation (activation) of AMPK α and of LKB1, the major upstream activating kinase for AMPK. We also assessed negative regulators of AMPK phosphorylation (phosphatases 2A and 2C), and parameters of NLRP3 inflammasome activation (inOS, arginase, respectively). We studied acute MSU crystal-induced inflammation in vivo in subcutaneous air pouches.

Results: Colchicine (10 nM) increased AMPK α and LKB1 phosphorylation in cultured macrophage lineage cells, but phosphatases 2A and 2C were unchanged. Colchicine (10 nM) enhanced protein expression of total AMPK α translationally in BMDMs. Furthermore, colchicine (10 nM) promoted
macrophage polarization toward anti-inflammatory M2 phenotype by increasing ratio of arginase (M2-like) to INOS (M1-like) mRNA expression. Colchicine partially but significantly inhibited capase-1 cleavage and IL-1β maturation, as well as release of IL-1β and CXCL1 in response to MSU crystals in WT but not AMPKα1 KO BMDMs. Hence, manifold anti-inflammatory effects of colchicine were AMPK-dependent. Last, acute gout-like inflammation (neutrophil infiltration) were attenuated by pharmacologic AMPK activation in WT (p < 0.01 compared to non-treated mice, 95% CI of difference: 1.6 to 5.6) in vivo.

Conclusion: AMPK transduced multiple low dose colchicine anti-inflammatory effects in vitro, including promotion of M2 macrophage polarization, inhibition of NLRP3 inflammasome activation and reduction of IL-1β and CXCL1 release. Moreover, AMPKα1 knockout significantly enhanced model acute gout-like inflammation. Our results reveal a novel molecular mechanism of action for colchicine, and suggest that decreased AMPK activation triggered by certain nutritional excesses and co-morbidities may heighten the inflammatory potential of deposits of urate crystals. Hence, colchicine, and other pharmacologic AMPK activators currently in the clinic for other conditions (methotrexate, salicylates, high dose aspirin, metformin), may have the potential to enhance efficacy of anti-inflammatory prophylaxis and treatment of gouty inflammation.

Disclosure: R. Bryan, None; R. Terkeltaub, A Star Zenea, Takeda, Rebumb, Abovibe, BioM arin, Quest, S. Y. Wang, None.

1207

Novel Role of Liver X Receptor Alpha (LXRα) in the Attenuation of TLR Signalling: Implications in Congenital Heart Block. Susmita Bagchi1, Mark Halushka 2, Robert M. Clancy 3 and Jill P. Buyon 4. 1New York University School of Medicine, New York, NY, 2John Hopkins Pathology, Baltimore, MD.

Background/Purpose: Anti-SSA/Ro associated congenital heart block provides a unique opportunity to examine the effector arm of immunity and define the molecular mechanisms that link maternal antibodies and the inflammatory cellular response. Based on an agnostic survey of transcripts from macrophages stimulated by immune complexes (IC) containing anti-Ro, 60KD Ro, and ssRNA-hY3, risk and protective genes were recently compiled. Two highly significant candidates in the injury spectrum, one enhancing - interleukin 6 (IL6), and one attenuating - liver X receptor alpha (NR1H3 or LXRα), which has been shown to decrease NFkB-induced expression, were identified. Accordingly, this study was initiated to determine the potential functional significance of these candidates, specifically, whether LXRα activation influences TLR7/8 ligand and downstream NF-kB-dependent cytokine release underlying both overt inflammation and the transition to established fibrosis.

Methods: The approach included both in vitro and in vivo studies. The former employed TLR7/8 stimulated human macrophage cell lines (THP1) and peripheral blood macrophages in the presence and absence of a LXRα ligand, and the latter used a lipopolysaccharide/phosphatidyl serine tissue from the heart of a fetus dying with CHB and an age matched control. Immunohistochemistry and a mouse model of CHB with hY3 and GW3965 compared to hY3 alone (N=3) in a heart from a fetus dying with CHB and an age matched control. As expected, hY3 treatment increased IL-6 mRNA (10±6 RFUs with 12.5 μg/ml CHB/MCD, and 9297±223 RFUs with 25 μg/ml CHB/MCD, mean±SEM, P<0.001 by ANOVA). In LXRα KO mice, detected with a fluorescence microplate reader. Both findings were confirmed by analysis of the TLR7/8 ligand with fluorescent microscopy. Importantly, pretreatment of neutrophils with low or lower dose (10 or 25 μM), but not high dose (75 μM), atorvastatin, significantly attenuated cholesterol-induced NETosis in vitro.

Conclusion: Our studies indicated that cholesterol loading can induce neutrophil extracellular trap formation in vitro. Low-dose atorvastatin can attenuate cholesterol-induced NETosis. Our preliminary results indicate a potential role of hypercholesterolemia in NET formation and a potential beneficial role for statins.

Disclosure: M. L. Liu, None; M. Bashir, None; K. Williams, None; V. Werth, A, A, 9.

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Cholesterol Loading Induces Neutrophil Extracellular Traps, and Atorvastatin Attenuates This Effect. Ming-Lin Liu1, Muhammad Bashir2, Kevin Williams3 and Victoria Werth4. 1University of Pennsylvania, Philadelphia, PA, 2Philadelphia VA, Hospital, Philadelphia, PA, 3Temple University School of Medicine, Philadelphia, PA.

Background/Purpose: Neutrophils are the most common white blood cell, but their role in autoimmune and cardiovascular diseases has been underestimated. As part of host defense, neutrophils release granule proteins and chromatin DNA into the extracellular space to form neutrophil extracellular traps (NETs). Recent studies reported the presence of NETs in atherosclerotic lesions, and NETs promote thrombosis. Moreover, pharmacological inhibition of NET formation through peptidyl-arginine deiminase blockade can reduce atherosclerosis and arterial thrombosis in mice. Hypercholesterolemia is the underlying cause of atherosclerotic cardiovascular disease. Nevertheless, the effects of cholesterol loading on NET formation and the relevant cellular mechanisms have not been investigated.

Methods: Primary neutrophils were isolated from healthy donors by sequential centrifugation with Histopaque 1077 and 1119. Cultured human HL-60 cells were differentiated into neutrophil-like cells with 1% DMSO. Cholesterol was delivered to primary and HL-60 neutrophils as a water-soluble complex with methyl-β-cyclodextrin (MCD, Col/MCD), which is widely used to modify the cholesterol content of cultured cells without potentially confounding effects from receptor engagement. Cells were fixed and stained with Sytox Green, which indicates exposed nucleic acids. Formation of NETs was assessed with a fluorescence microplate reader and by fluorescence microscopy. To study the effects of atorvastatin on NET formation, selected plates were pretreated with this agent before exposure to Col/MCD.

Results: We found that Col/MCD loading could induce NET formation in a time- and dose-dependent manner in primary neutrophils (4491±60 RFUs (relative fluorescent units) for control) without Col/MCD, 6553±206 RFUs with 12.5 μg/ml Col/MCD, and 9297±223 RFUs with 25 μg/ml Col/MCD, mean±SEM, P<0.001 by ANOVA). In HL-60 neutrophils, detected with a fluorescence microplate reader. Both findings were confirmed by examination of the NET structure with fluorescent microscopy. Importantly, pretreatment of neutrophils with low or lower dose (10 or 25 μM), but not high dose (75 μM), atorvastatin, significantly attenuated cholesterol-induced NETosis in vitro.

Conclusion: These data support the novel identification of a link between TLR7 activation and expression of a potential anti-inflammatory checkpoint, LXRα. In vitro and in vivo approaches suggest that LXRα may represent a thwarted attempt to forestall a smoldering NY 3-driven inflammatory milieu.

Disclosure: S. Bagchi, None; M. Halushka, None; R. M. Clancy, None; J. P. Buyon, None.

1209

Anti-Scavenger Receptor Autoantibodies Disrupted Marginal Zone Macrophage Integrity Via Bruton’s Tyrosine Kinase. Hao Li1, Qi Wu1, PingAr Yang2, Zheng Wang1, Jun Li1, Bao Luo1, Jeffrey C. Edberg2, Hui-Chen Hsu3, John D. M. Bunz4 and Robert P. Kimberly on behalf of PROFILE investigators. 1University of Alabama at Birmingham, Birmingham, AL, 2Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Ibrutinib, a Btk kinase activity inhibitor, is a novel inhibitor under development for autoimmune disease therapy. We have demonstrated that Btk was significantly upregulated in spleen MØs of lupus prone BXD2 mice that spontaneously develop lupus (auto Abs). As loss of control on Btk expression in myeloid cells has been implicated previously to cause mislocation and loss of marginal zone macrophages (M ZMs), a critical apoptotic bleb clearance barrier, in the spleen, the purpose of the present study is to determine a possible pathogenic
role of autoAb to disrupt MZM integrity through upregulating Btk activity in MZMs. The implication of these results in human systemic lupus erythematosus (SLE) was further studied.

Methods: Purified polyreactive monoclonal antibodies isolated from the spleen of BXD2 mice were screened for their reactivity to MZM specific scavenger-receptors including MR, CO, and -SR-A. AutoAb that are either reactive or non-reactive to anti-MARCO/-SR-A were individually administrated to recipient B6 mice to evaluate the pathogenic effects on MZMs. Confocal microscope analysis and FACS analysis were carried out to quantify the percentage of MZMs in the spleen and evaluate the expression of phospho-Btk (pBtk). ELISA was carried out to determine the autoAb titers.

Results: In BXD2 mice, elevated anti-MARCO/-SR-A autoAbs in the sera correlated with the loss of MZMs in the spleens. Different purified monoclonal autoAbs were administrated into normal B6 mice. Disruption of MZMs was observed in normal B6 mice when recipient mice were administrated with polyreactive autoAbs that exhibit high reactivity to both MR, CO, and -SR-A. In these mice, there was gradual induction of pBtk in the MZMs. Increased pBtk was also observed in MZMs of BXD2 mice, and this induction can be efficiently blocked via early global inhibition of endogenous apoptosis using a pan-caspase inhibitor, z-VAD. Delivery of Ibrutinib either systemically or via an Ibrutinib-liposome strategy to target MZMs specifically, prevented MZM loss and attenuated autoantibodies mediated glomerulonephritis in autoAb administrated B6 or BXD2 mice. Surprisingly, anti-MARCO/-SR-A autoantibody administration also induced the reduction of MZMs in the spleen of FcγRII−/− or C3−/− mice, suggesting that autoAb-mediated MZM loss is not related to either antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). In SLE patients, higher serologic levels of anti-MARCO/anti-SR-A autoAb titers exhibited significant positive correlation with the development of end-stage-renal disease (ESRD). Loss of MZMs was also identified in SLE patient spleens.

Conclusion: The present study suggests a novel autoAb-mediated systemic autoimmune disease mechanism based on the induction of pBtk in MZMs to break a critical barrier that is crucial to keep apoptotic debris in the spleen. The present study further suggests the potential to develop anti-MARCO/-SR-A into a novel biopharm for apoptosis clearance defects and development of ESRD in human SLE.

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1210
The Role of the Transcription Factor C/EBP Responsive Element Binding Protein 1 in Polyarthritis-MDA Induced Tolerance.

Kerrin Klein1, Renate E. Gay2, Christoph Kolling3, Li-Hing Lin4, Steffen Gay4 and Caroline Ospelt5

1 Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland; 2 Zurich University Hospital, Zurich, Switzerland; 3 Schuth Clinic, Zurich, Switzerland; 4 Inflammation and Remodeling Research Unit, Pfizer, Cambridge, MA.

Background/Purpose: In macrophages, repeated stimulation of Toll-like receptor (TLR) 4 leads to adaptation of signaling pathways and epigenetic modifications resulting in a tolerant state of the cell that protects infected tissues from damage. We have recently shown that in contrast to macrophages, rheumatoid arthritis synovial fibroblasts (RAFS) lack these protective mechanisms and keep on secreting inflammatory cytokines and matrix degrading metalloproteinases also after repeated stimulation with LPS. The objective was to investigate mechanisms behind tolerizable and non-tolerizable effects in RAFS.

Methods: RAFS were treated with LPS (100 ng/ml), 24h after the initial stimulation, cells were re-stimulated with LPS (10 ng/ml) for another 24h. The expression levels of IL6, IL8, CCL10, matrix metalloproteinases (MMP) 1 and 3, as well as RIG1 and OAS1, were analyzed by quantitative Real-time PCR or ELISA. Nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) promoter activities in RAFS (n=4) were evaluated by Dual-Luciferase reporter assays after repeated stimulation with LPS. RAFS (n=8) were transfected with siRNAs targeting C/EBP responsive element binding protein 1 (C/EBP1) and scramble siRNAs as control prior to stimulation with LPS (100 ng/ml, 24h). Activation of C/EBP1 after repeated LPS stimulation was analyzed in nuclear extracts (n=2) using p-C/EBP1 antibodies.

Results: RAFS (n=10) maintained their production of IL6 after repeated TLR4 stimulation (single stimulation: 13.2 ± 5.8 pg/ml, double stimulation: 12.4 ± 7.1 pg/ml). A lack of tolerizable effects of RAFS was also found for MMP1 and MMP3, whereas the interferon-responsive genes OAS1, RIG1, MDA5 and CCL10 were tolerizable. RAFS (n=5) secreted 531.3 ± 385 pg/ml CCL10 after a single LPS stimulation and 111.7 ± 97 pg/ml CCL10 after double stimulation (p<0.05). Reporter gene activities for NF-κB and AP-1 were similar in single and double stimulated RAFS, excluding potential differences in the activation of these transcription factors as underlying mechanisms for tolerizable/non-tolerizable effects in RAFS. Silencing of C/EBP1 reduced the LPS-induced expression levels of the tolerizable genes CCL10 (x-fold: ctrl 148 ± 121; silenced 101.8 ± 6.6, p<0.05), whereas LPS-induced expression levels of the non-tolerizable genes IL6, IL8, MMP1 and MMP3 were not affected. Similar effects of C/EBP1 silencing were obtained when secreted protein levels of LPS-induced CCL10, IL6, IL8, MMP1 and MMP3 were measured. The phosphorylation of C/EBP1 was not changed by LPS double compared to single stimulation indicating that C/EBP1 activation was not altered by double stimulation.

Conclusion: The expression of tolerizable genes in RAFS is dependent on the transcription factor C/EBP1. Based on the fact that C/EBP1 activation is not altered by repeated LPS stimulation, epigenetic modifications on target gene promoters that effect the recruitment of C/EBP1 to promoters are likely to provide further understanding of molecular mechanisms that might contribute to tolerization effects seen in RAFS.

Disclosure: K. Klein, IMI-BT Cure, IAR Epielings; R. E. Gay, IMI-BT Cure, IAR Epielings, euroTEAM, 2; C. Kolling, None; L. L. Lin, Pfizer Inc; S. S. Gay, IMI-BT Cure, IAR Epielings, euroTEAM, 2; C. Ospelt, IMI-BT Cure, IAR Epielings, euroTEAM, 2.

1211
Gene Expression Profile in Muscle Tissue before and after Immunosuppressive Treatment in Patients with Myositis.

Joan Rauf1, Inge Ma Loel2, Yi-Wen Chen3, Rongye Shih4, Inger Nennesmo4, Helene Alexander-Nor8, M. Arjan Dastmalchian6, Maria Karolokova7, Karinnebyonina Nagaraju9 and Ingrid E. Lundberg10, 1Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, 2Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, 3 Research Center for Genetic Medicine, Children’s National Medical Center, Washington DC, USA., Washington DC, DC, 4Children’s National Medical Center, Research Center for Genetic Medicine, Washington DC, USA, Washington DC, WA, 5Institution for Laboratory Medicine (LABMED), Karolinska Universitetssjukhuset, Huddinge, Stockholm, Sweden, Stockholm, Sweden, 6 Karolinska Institutet, Department of medicine, Rheumatology Unit, Karolinska Universitetssjukhuset Solna, Stockholm, Sweden, Stockholm, Sweden, Stockholm, Sweden, 7Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, 8Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, 9Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, 10Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Autoimmune muscle diseases such as polymyositis (PM) and dermatomyositis (DM) are characterized by infiltration of inflammatory cells, production of cytokines and chemokines, as well as the expression of major histocompatibility complex (MHC) class I on skeletal muscle fibers. Patients are conventionally treated with high doses of glucocorticoids in combination with additional immunosuppressive drugs. Nevertheless, many patients have persisting muscle weakness even after prolonged treatment.

Objectives: To investigate the effect of conventional immunosuppressive treatment on gene expression profiling in skeletal muscle biopsies from patients with PM and DM, taken before and after treatment in order to develop further understanding of molecular mechanisms that might contribute to the persisting compromised function.

Methods: Biopsies (vastus lateralis muscle) from six newly diagnosed untreated patients with PM (n=2) or DM (n=4) before and after a median of 8.5 months of immunosuppressive treatment were examined by gene expression microarray analysis. Functional associations were analyzed by using Ingenuity Pathway Analysis. Tissue sections from corresponding biopsies were evaluated for MHC class I molecule expression, inflammatory infiltrates, and signs of fiber regeneration/degeneration. Selected genes that displayed changes in expression were validated by western blot (WB).

Results: Evaluation of the biopsies taken after a median of 8.5 months of treatment showed MHC class I staining in muscle fibers, presence of CD3 positive cells (low in general with few positive cells scattered throughout the tissue) and CD68 positive cells (frequent but also ranging from scattered to frequent).
mononuclear cells to infiltrate). By microarray analyses alterations were observed in the overall gene expression in muscle tissue. As expected most of the genes related to immune response such as interferon (IFN) pathway and inflammasome (e.g. AIM-2 and Caspase-1) were down-regulated. In addition alterations were seen in the expression of genes involved in muscle tissue remodeling suggesting protein breakdown as well as muscle regeneration (e.g. by up-regulation of the FKBP5 gene which encodes the protein important in basic cellular processes involving protein folding/transferring). Validation of changes in gene expression by WB confirmed changes in protein expression; AIM-2 (p = 0.044) and Caspase 1 (p = 0.035) were significantly down-regulated, while FKBP5 (p = 0.020) was up-regulated after chronic glucocorticoid treatment.

Conclusion: Together, these data indicate that during conventional immunosuppressive treatment of myositis patients transcriptional modifications in genes involved in muscle tissue inflammation and remodelling are taking place and their changes could be validated by changes in protein expression. The alteration indicate that besides the beneficial down-regulation of inflammatory pathways there are signs of protein breakdown which may have a negative consequence in muscle repair and may contribute to a defect recovery of muscle strength that may be seen in patients with PM/DM despite immunosuppressive treatment.

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1212
Behcets Disease in Females Due to Mutation in NEMO, the NF-Kb Essential Modulator.

A lex Wessel1, Spiros Vonortas2, Evgenia Zilberman-Rudenko2, Richard Siegel2 and Eric Hanson2. 1NIH, Bethesda, MD, 2NIAMS, Bethesda, MD, 3National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, 4NIAMS, Bethesda, MD, 5National Institute of Health, Bethesda, MD.

Background/Purpose: Behcets disease (BD) is a chronic multi-system inflammatory disorder associated clinically with oral and genital ulceration, uveitis, erythema nodosum, and other inflammatory disease. The cause of BD is unknown. A current hypothesis is that an autoinflammatory reaction in individuals with a permissive genotype may arise due to altered cellular signal transduction events and hence altered immune cell function. This reaction may be triggered in these individuals due to infectious agents or microbes not generally considered pathogenic. The family of NF-kb transcription factors are activated in various signaling pathways involved in microbial sensing, immunity, and inflammatory disease. Previously, a case of familial Behcets was described in two females harboring a mutation in the C-terminal Zinc finger domain of NEMO, the NF-kb essential modulator, a key regulator of NF-kb activation.

Methods: We evaluated female patients diagnosed with Behcets disease who harbor mutation in the NEMO C-terminus, in addition to those with mutation affecting another ubiquitin binding domain. Patient mononuclear cells in addition to patient-mutation-reconstituted NF-kb reporter T cell lines were stimulated with TNF, Toll-like Receptor (TLR) ligands Flagellin and LPS, in addition to anti-CD3/CD28, and PMA/ionomycin. Gene expression, cytokine production and biochemical analyses including co-immunoprecipitation of endogenous proteins implicated in the regulation of NF-kb activation were performed to characterize signaling and cellular responses.

Results: Mutation leading to premature truncation of the C-terminal Zinc finger in females is associated with a BD phenotype. NF-kb activation by reporter assay in cells harboring the patient mutation reveals enhanced NF-kb activation in response to TNF and TLR5 stimulation compared to the response seen in cells harboring other NEMO mutation not associated with BD. Cytokine production by capture assay indicates LPS induced IL-1b, TNF and GMCSF were approximately 2-fold increased compared to unrelated controls. No cytokine responses were normal or reduced. Co-immunoprecipitation studies following cell stimulation with TNF reveal impaired stabilization of the NF-kb negative regulator A20 at the receptor in cells harboring the patient mutation.

Conclusion: These results illustrate that single gene defects may lead to phenotypes observed in complex genetic disease. Molecular characterization of the altered signaling resulting from NEMO mutation may yield important insights into more common rheumatic disease such as BD.

Disclosure: A. Wessel, None; S. Vonortas, None; J. Zilberman-Rudenko, None; R. Siegel, None; E. Hanson, None.

1213
Absence of Hormone Responsive Estrogen Receptor Alpha Reduces the Activation of Plasmacytoid Dendritic Cells in Lupus Prone Mice. Jennifer L. Scott1, Melissa A. Cunningham2, Osama S. Naga3, Jack E G. Eudy4, Jenna R. Wirth5 and Gary S. Gilkeson6. 1Medical University of South Carolina, Charleston, SC, 2MUSC, Charleston, SC.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects women at a 9 to 1 ratio compared to men. To further understand mechanisms underlying the female predominance our laboratory is investigating the role of estrogen receptor alpha (ERα) in SLE disease development. In lupus-prone mice, absence of hormone responsive ERα increased survival and decreased glomerulonephritis despite no effect on autoantibody production or renal immune complex deposition. To explain this protective effect, we hypothesized ERα deficiency impacts innate immune responses and in particular plasmacytoid dendritic cell (pDC) function. Our previous work showed ERα deficiency reduced the bone marrow derived dendritic cell (DC) toll-like receptor (TLR) mediated type I interferon response. To determine the significance of the reduced dendritic cell interferon response in disease development we investigated the impact of ERα deficiency on splenic pDC activation state ex vivo in pre-disease lupus-prone mice.

Methods: We measured the number, maturation state, and activation state of pDCs ex vivo from the spleens of pre-disease (12 to 14 week old) WT and hormone responsive ERα deficient female lupus-prone mice (NZM2410) using flow cytometry. pDCs were identified as singlets live, CD11b+/B220-/SiglecH-/.

Results: ERα deficiency reduced the activation state of spleen pDCs from pre-disease lupus-prone mice. The frequency of spleen pDCs expressing the activation markers MHC class II and pDC-TREM was reduced by ERα deficiency (n = 20, p = 0.002, p = 0.06). This finding was specific to lupus-prone prone mice. We did not detect any alteration in the frequency of activated pDCs between WT and ERα deficient age and sex matched C57BL/6 mice. To determine if the reduced frequency of activated pDCs was the result of ERα deficiency mediated alterations in pDC maturation or Toll-like receptor (TLR) responsiveness, we measured pDC maturation state ex vivo and TLR responsiveness in vitro in pDCs from WT and ERα deficient lupus-prone mice. ERα deficiency did not affect the maturation state of spleen pDCs, as measured by Ly49Q expression. However, ERα deficiency reduced TLR 9 mediated activation of bone marrow derived pDCs. After stimulation with TLR 9 ligand, a greater frequency of pDCs from WT mice expressed TLR 9 mediated activation of bone marrow derived pDCs, sorted as live, CD11b+/B220+, and CD11c+, after TLR 9 stimulation in vitro.

Conclusion: Our findings suggest the absence of hormone responsive ERα reduces in vivo pDC activation state by impairing pDC responsiveness to TLR ligands in lupus-prone mice. These findings may explain the protective role of hormone responsive ERα deficiency in SLE.

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ACR/ARHP Poster Session B
Metabolic and Crystal Arthropathies: Mechanisms of Disease
Monday, November 17, 2014, 8:30 AM - 4:00 PM

1214
Oxidative Stress from Use of Allopurinol - Is There a Reason for Patients with Gout to Take Vitamin C? Lisa K. Stamp1, Peter T. Chapman1, John L. Scott1, Mark J. Ida1, Irida Khaled1, An character Kotecki1,2 and Anthony L. Scott1. 1University of Otago, Christchurch, Christchurch, New Zealand, 2Christchurch Hospital, Christchurch, New Zealand, 3Canterbury Health Laboratories, Christchurch, New Zealand.

Background/Purpose: During acute gout attacks neutrophils are activated and release a number of pro-inflammatory cytokines and enzymes. One of these enzymes is myeloperoxidase (MPO), which we have previously shown to be elevated in the circulation of patients with acute gout. Furthermore, MPO was associated with increased oxidation of urate as demonstrated by the increased concentration of allantoin in the plasma of these patients. Thus, oxidative stress is a feature of acute attacks of gout. Allopurinol is the most commonly used urate
lowering therapy. It is rapidly metabolised by aldehyde oxidase to oxyipurinol as well as superoxide and hydrogen peroxide. Oxyipurinol exerts most of its inhibitory effects on xanthine oxidoreductase. In our previous work, allopurinol use was also associated with an increase in allantoin, indicating that it increases oxidative stress. The aim of this study was to determine the effects of allopurinol on plasma ascorbate (vitamin C), because its levels are sensitive to oxidative stress.

Methods: Patients with gout and a serum urate >0.36 mmol/L were recruited. Twenty patients already receiving allopurinol were randomised to either increase the dose of allopurinol or commence vitamin C 500 mg/d. Twenty patients not receiving urate lowering therapy were randomised to either start allopurinol or vitamin C 500 mg/d. Plasma ascorbate, allantoin, myeloperoxidase, oxyipurinol and serum urate were measured at day 0 and week 8.

Results: As expected at day 0, the 20 patients receiving allopurinol had significantly lower serum urate compared to those not on allopurinol (0.44 vs 0.54 mmol/L, p < 0.001). Use of allopurinol was also associated with significantly lower plasma ascorbate levels (38.8 vs 56.7 μM, p = 0.03) and higher MPO levels (29.4 vs 18.0 μM, p < 0.001) at day 0. There was a non-significant increase in serum allantoin.

In the 10 patients who commenced allopurinol there was a significant reduction between day 0 and week 8 in serum urate (0.57 vs 0.41 mmol/L, p = 0.0003) and plasma ascorbate (54.2 vs 28.1 μM, p = 0.003) and an increase in plasma allantoin (2.6 vs 3.0 μM, p = 0.04). Plasma MPO was not affected by allopurinol. There was a significant negative correlation between plasma oxyipurinol and plasma ascorbate concentrations (r = -0.54, p = 0.0004). For the 10 patients who stayed on their original dose of allopurinol, supplementation with vitamin C increased plasma vitamin C (48.4 vs 68.1 μM, p = 0.01) but had no effect on either urate or allantoin levels.

Conclusion: These results suggest that allopurinol promotes oxidative stress thereby depleting plasma ascorbate. Supplementation with vitamin C can increase plasma ascorbate in patients on allopurinol. The clinical significance of oxidative stress and low plasma ascorbate remains to be determined but our results indicate there may be a reason other than urate lowering therapy. It is rapidly metabolised by aldehyde oxidase to oxyipurinol as well as superoxide and hydrogen peroxide. Oxyipurinol exerts most of its inhibitory effects on xanthine oxidoreductase. In our previous work, allopurinol use was also associated with an increase in allantoin, indicating that it increases oxidative stress.

Disclosure: L. K. Stamp, Astra Zeneca; S. Abbvie, 5; P. T. Chapman, None; J. L. O'Donnell, None; I. Khalilova, None; R. Turner, None; A. Kettle, None.

1215 Circulating Mediators of Bone Remodeling in Patients with Tophaceous Gout. Ashika Chhana, Opea Aa1, Gregory Gamble, Karen E. Callon1, Anthony Doyle1, Mark Rogers1, Fiona McQueen, Anne Horne, Ian R. Reid, J. L. O’Donnell, None; I. Khalilova, None; R. Turner, None; A. Kettle, None.

Background/Purpose: Disordered bone remodeling has been implicated in the development of bone erosion in tophaceous gout. The function of bone cells in the skeleton is regulated by a number of factors, including soluble mediators that influence osteoclast and osteoblast function. The aim of this study was to determine the relationship between bone erosion and circulating mediators of bone remodeling in people with tophaceous gout.

Methods: One hundred patients with tophaceous gout were prospectively recruited from rheumatology outpatient clinics. Bone erosion at articular sites was assessed by two readers in conventional computed tomography (CT) scans of the feet using a validated semi-quantitative erosion score, and in plain radiographs (XR) of the hands and feet using a modification of the Sharp-van der Heijde score. Readers were blinded to all clinical details, including laboratory results. Hip, spine and total body bone mineral density (BMD) was also measured. The following soluble mediators of bone remodeling were measured in serum by ELISA: osteoprotegerin (OPG, a soluble decoy receptor for RANKL), sclerostin (an osteocyte-derived Wnt inhibitor), dickkopf-1 (DKK-1, a Wnt inhibitor), and fibroblast growth factor-23 (FGF-23, an osteocyte-derived regulator of phosphorous and vitamin D).

Results: CT bone erosion scores positively correlated with circulating OPG concentrations (r = 0.22, p = 0.03), and negatively correlated with sclerostin concentrations (r = -0.29, p = 0.003). Similar correlations were observed for XR erosion scores for OPG (r = 0.30, p = 0.002), and sclerostin (r = -0.21, p = 0.04). Necrotic femur MPO positively correlated with OPG concentrations (r = 0.34, p = 0.001), and positively correlated with sclerostin concentrations (r = 0.24, p = 0.02). Similar relationships were observed for total body BMD. No relationship was observed between bone erosion scores or BMD, and DKK-1 or FGF-23 concentrations. In linear regression analysis, OPG and sclerostin were independently associated with CT erosion score (p = 0.005 for OPG and p = 0.003 for sclerostin, R² for model 0.16, p = 0.0001). Similarly, OPG and sclerostin were independently associated with neck of femur BMD (p = 0.002 for OPG and p = 0.04 for sclerostin, R² for model 0.13, p = 0.001). These relationships persisted after adjusting for eGFR.

Conclusion: In people with tophaceous gout, circulating OPG and sclerostin levels are independently associated with both central and peripheral bone loss. The direction of the associations does not support a direct role for bone-remodelling factors in pathogenesis of bone erosion, but may reflect compensatory or repair mechanisms to maintain bone homeostasis at both central and peripheral sites.

Disclosure: A. Chhana, None; O. A. A., None; G. Gamble, None; K. E. Callon, None; A. Doyle, None; M. Rogers, None; F. M. McQueen, None; A. Horne, None; I. R. Reid, None; J. Cornish, None; N. Dalbeth, None.

1216 The Relationship Between Serum Homocysteine, Uric Acid and Renal Function in Chronic Gouty Patients: 2 Year Follow-up Results. Eun-Hye Park, Sang Tae Choi and Jung-Soo Srong. Chung-Ang University College of Medicine, Seoul, South Korea.

Background/Purpose: Hyperhomocysteinemia is one of the important factors for the endothelial cell damage and also a risk factor for cardiovascular events. Gout is known to be associated with cardiovascular disease (CVD) as well. Although both hyperhomocysteinemia and gout are related to CVD, the only few cases about serum homocysteine (Hcy) in gouty patients have been reported. In this study, we investigated the associations between serum Hcy level and the other parameters including serum uric acid level, renal function, and cholesterol profiles in chronic gouty patients with longitudinal follow-up data.

Methods: Ninety-one male patients with chronic gout and 97 age-matched healthy male controls were included in this study, and the average age of each was 51.19 ± 15.08 and 51.57 ± 17.01 years old, respectively. Among them, 33 patients with gout and 39 healthy controls underwent follow-up tests for Hcy levels with 24.00 ± 9.12 months on average. Serum Hcy levels were measured by a competitive immunoassay using direct chemiluminescent. The estimated glomerular filtration rate (eGFR) was calculated using modification of diet in renal disease equation, and then chronic kidney disease (CKD) was defined as an eGFR below 60 ml/min/1.73m².

Results: In the serum uric acid level, there was no significant difference between chronic gouty patients and controls (6.15 ± 2.23 mg/dL vs 5.82 ± 1.22 mg/dL, p = 0.214). In contrast, gouty patients showed significantly higher levels in serum Hcy than those in controls (13.96 ± 4.05 μmol/L vs 12.67 ± 3.51 μmol/L, p = 0.022). In patients with chronic gout, serum Hcy level was negatively correlated with eGFR (γ = -0.413, p < 0.001), while it was uncorrelated with serum uric acid levels or cholesterol profiles. Serum Hcy levels were not different between the groups treated with allopurinol and with benzbromarone. When we observed the follow-up results in chronic gouty group, the change of serum Hcy level was positively correlated with the change of serum creatinine level (γ = 0.560, p < 0.001), and negatively correlated with the change of eGFR (γ = 0.556, p < 0.001). However the change of serum Hcy level was uncorrelated with the changes of uric acid level or lipid profiles. The chronic gouty patients with CKD showed significantly higher serum Hcy level than those without CKD (17.45 ± 6.68 μmol/L vs 13.15 ± 3.46 μmol/L, p < 0.001), and the follow-up result also showed similar tendency (19.12 ± 4.29 μmol/L vs 15.69 ± 5.73 μmol/L, p = 0.059). In multiple linear analyses, serum Hcy level was affected by eGFR (β = -0.385, p < 0.001), however, was not affected by the serum uric acid level.

Conclusion: Serum Hcy level was elevated in chronic gouty patients than in controls. The change of serum Hcy level was negatively correlated with the change of eGFR. Hyperhomocysteinemia in chronic gouty patients was related with decreased renal function, and was not with serum uric acid or lipid profiles.

Disclosure: E. H. Park, None; S. T. Choi, None; J. S. Song, None.

1217 The Random Urine Uric Acid to Creatinine Ratio As a Predictor of 24-Hour Urine Uric Acid Excretion in Gout Patients. Sang Tae Choi, Jung-Soo Song and Eun-Hye Prark. Chung-Ang University College of Medicine, Seoul, South Korea.

Background/Purpose: Gout is an inflammatory disease resulted from an increased body pool of uric acid. The measurement of 24-hour uric acid excretion is important to evaluate the disease status as well as to select the
kind of uric acid lowering agents. However, 24-hour urine collection is inconvenient, and frequently unreliable due to errors in collection. The average person excretes approximately 1 g/day creatinine, and thus a lot of studies showed that the random urine protein to creatinine ratio was well correlated with 24-hour urine protein excretion rate. In this study, we investigated the utility of the random urine uric acid to creatinine ratio for predicting 24-hour urine uric acid excretion in gouty patients.

Methods: The cross-sectional study included 37 gouty patients without any use of uric acid lowering agents. The average age was 47.7 ± 17.7 years old and 34 out of 37 were male patients. 24-hour urine collections of the patients were conducted to the evaluate uric acid excretion and renal function. Random urine uric acid and creatinine specimens were obtained from all participants at the day when 24-hour urine collection was conducted. The creatinine clearance (Ccr) was measured from the 24-hour urine collected sample, and chronic kidney disease was defined as the Ccr levels below 60 ml/min/1.73m2.

Results: The mean of 24-hour uric acid excretion was 602.4 ± 236.0 mg, and those of serum uric acid levels and Ccr values were 7.31 ± 1.31 mg/dl and 100.9 ± 33.2 ml/min/1.73m2, respectively. Random urine uric acid to creatinine ratio was closely correlated with the absolute and log transformed 24-hour uric acid excretions (γ = 0.450, p = 0.005; γ = 0.474, p = 0.003, respectively). In the linear regression analysis, the amount of absolute 24-hour uric acid excretion was estimated by 0.812 × (random urine uric acid to creatinine ratio) + 290.466 (R² = 0.450, p = 0.005). The correlation between random urine uric acid to creatinine ratio and 24-hour urine uric acid excretion was also found in the patients with chronic kidney disease (γ = 0.900, p = 0.037).

Conclusion: Random urine uric acid to creatinine ratio showed positive correlation with the absolute and log transformed 24-hour urine uric acid excretions. The random urine uric acid to creatinine ratio would be a good predictor of 24-hour urine uric acid excretion in gouty patients.

Disclosure: S. T. Choi, None; J. S. Song, None; E. H. Park, None.

1218

The Reduction of Serum Uric Acid Level Might Prevent Atherosclerosis in Mice. Y. Oshikata Kimura1, Tamiko Y. Yanagida2, Akiko Onda2, Hajime Kono1, Makiko Takayama1, Kurumi Asako1, Akiko Okamoto1, Hirotsubo Kikuchi2 and Toshihiro Nak1.1 The University of Tokyo, Tokyo, Japan, 2Teikyo University School of Medicine, Tokyo, Japan.

Background/Purpose: Excess amount of uric acid in human body causes acute inflammation, gout. In addition, uric acid is identified as a danger signal and is implicated in playing roles in chronic inflammatory processes. Recently several retrospective studies have reported that serum uric acid level might be one of the independent risk factors of atherosclerosis. However there has been no prospective study showing the association of serum uric acid level and atherosclerosis. It’s not still clear whether uric acid progresses atherosclerosis. Using the transgenic mice expressed uricase, an uric acid hydrolytic enzyme, we investigated the reduction of serum uric acid level could mitigate atherosclerosis in mice.

Methods: We prepared uricase transgenic mice based in C57BL/6 mice. They expressed the uricase secreted to extracellular space and their serum uric acid level were decreased. We bred Uricase-transgenic mice with LDL receptor deficient or apolipoprotein E deficient mice to develop LDLR-/-Uricase1/2 mice or ApoE-/-Uricase1/2 mice, respectively. LDLR-/-Uricase1/2 mice and ApoE-/-Uricase1/2 mice received high-fat diet for 16 weeks. Then their hearts and aortas were removed at 22 weeks of age. Aortic sinuses of these mice were stained with oil red O and measured area of atherosclerosis lesions.

Results: The volumes of atherosclerosis lesions in aortic sinuses of LDLR-/-Uricase1/2 mice (0.231 ± 0.032 mm3) and those of serum uric acid levels and Ccr values were 7.31 ± 1.31 mg/dl and 100.9 ± 33.2 ml/min/1.73m2, respectively). In the linear regression analysis, the amount of absolute 24-hour uric acid excretion was estimated by 0.812 × (random urine uric acid to creatinine ratio) + 290.466 (R² = 0.450, p = 0.005). The correlation between random urine uric acid to creatinine ratio and 24-hour urine uric acid excretion was also found in the patients with chronic kidney disease (γ = 0.900, p = 0.037).

Conclusion: Random urine uric acid to creatinine ratio showed positive correlation with the absolute and log transformed 24-hour urine uric acid excretions. The random urine uric acid to creatinine ratio would be a good predictor of 24-hour urine uric acid excretion in gouty patients.

Disclosure: S. T. Choi, None; J. S. Song, None; E. H. Park, None.

1219

Lack of Gene-Diuretic Interactions on Risk of Incident Gout: The Nurses’ Health Study and Health Professionals Follow-up Study. Ying Bai1, Tony R. M. Mentiplay1, Gary Curhan2, Eilu A. Stahl3, David B. Mount4, Robert M. Plenge5, Peter Kraft6 and Hyon K Choi6.1 Brigham and Women’s Hospital, Boston, MA, 2Harvard Medical School, Boston, MA, 3University of Otago, Dunedin, New Zealand, 4Harvard Medical School, Boston, MA, 5Mt. Sinai School of Medicine, New York City, NY, 6Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, 7Boston University School of Medicine, Boston, MA.

Background/Purpose: Diuretics, particularly thiazide and loop diuretics, increase the risk of gout, likely through urate transporters (e.g., OAT4) and volume depletion promoting urate reabsorption. As the prevalence of hypertension is remarkably high in gout patients (74% in the US general population), diuretic use is commonly encountered in gout care as a first line anti-hypertensive agent. A recent analysis based on 106 self-reported incident cases of gout in the Atherosclerosis Risk in Communities (ARIC) Study has reported that diuretic-induced gout occurs only among those with a genetic predisposition to hyperuricemia (Ann Rheum Dis 2013). If confirmed, these genes could potentially be used to predict gout from diuretic use, a first line agent for hypertension and congestive heart failure.

Methods: We examined the potential interaction between urate genes and diuretic use in relation to the risk of incident gout in 6788 women from the Nurses’ Health Study (NHS) and 4012 men from the Health Professionals Follow-up Study (HPFS). Two genetic risk scores (GRS) were created from common urate SNPs for eight previously known genes (GRS8, used by the ARIC study above) as well as for 29 known genes (GRS29, a new score incorporating additional novel genes). We ascertainment incident gout cases using the American College of Rheumatology survey criteria. We used Cox proportional hazards models for associations and interactions of interest.

Results: Our study included 310 and 674 confirmed cases of incident gout in the NHS and HPFS cohorts, respectively. In the NHS, compared with no thiazide or loop diuretic use, their use was associated with a multiplicative RR of 1.97 (95% CI 1.32 to 2.93) among those with a GRS8 below the median and 2.33 (95% CI 1.73 to 3.13) for those with a GRS8 above the median (p for interaction = 0.21) (Table 1). The corresponding RRs according to GRS29 categories were 1.89 (95% CI 1.28 to 2.79) for below the median and 2.39 (95% CI 1.77 to 3.24) for above the median (p for interaction = 0.33). Similarly, two previously purported genes, SLC2A9 (GLUT9) and SLC22A11 (OAT4), showed no significant interactions (p for interactions > 0.05). Further, the lack of interaction persisted in our analyses when limited to those with hypertension in both cohorts, except for SLC22A11 acid level by expressing secretable uricase may inhibit the progression of atherosclerosis.
among women, which showed a significant interaction but in the opposite direction to that in the recent ARIC study.  

Conclusion: These prospective studies based on a large number of incident cases of confirmed gout indicate that individuals with a genetic predisposition for hyperuricemia are not at an increased risk of developing diuretic-induced gout as compared with those without such a predisposition. These findings do not support the potential utility of these genes to assess gout risk in relation to diuretic use.

### Table 1  Relative Risk for Incident Gout According to Diuretic Use and Genetic Urate Score Based on 8 Urate SNPs (GRS8) and 29 Urate SNPs (GRS29)

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<th>GRS8</th>
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<tr>
<td></td>
<td>Below median</td>
<td>Above median</td>
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<tr>
<td>Thrombosis Risk</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>No. of Cases</td>
<td>73</td>
<td>53</td>
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<tr>
<td>Person-Years</td>
<td>78216</td>
<td>13386</td>
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<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>1.97 (1.32, 2.93)</td>
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<tr>
<td>MIV adjusted</td>
<td>0.28</td>
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**Adjusted for age, BMI, non-smokers, use of hormone therapy (NHS), history of hypertension, systolic and diastolic blood pressure, alcohol, total energy intake, and intake of sugar-sweetened soft drinks, meat, seafood, and dairy products.**

**Disclosure:** Y. Bao, None; T. R. Merriman, None; G. Curhan, None; E. A. Stahl, None; D. B. Mount, None; R. M. Plenge, None; P. Kraft, None; H. K. Choi, Takeda Pharmaceuticals International, Inc; 5, AstraZeneca, 5.

### 1220

**Higher Inflammatory Response in Elderly Patients During Gout Attack.**

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**Background/Purpose:** Clinical experiences suggest that gout attacks in elderly patients are accompanied by stronger systemic inflammatory response including fever, higher C-reactive protein (CRP) and erythrocyte sedimentation ratio (ESR) as compared those in younger patients. As such, it is often difficult to differentiate them from septic arthritis, leading to frequent use of empiric antibiotics and unnecessary diagnostic and therapeutic joint surgery. To define whether gout attacks are accompanied by stronger systemic inflammatory response with age.

**Methods:** In this retrospective study, medical records of patients who were evaluated for a possible gout attack between January 2000 and April 2014 were examined. The presence of fever (>37.8°C), levels of C-reactive protein (CRP) and erythrocyte sedimentation ratio (ESR) on attack were compared between young (<50 years), middle aged (50-65 years) and elderly patients (>65 years).

**Results:** Gout attacks were observed in 188 patients with 34 young, 54 middle aged and 100 elderly patients. Baseline characteristics of three groups differed; elderly patients had more comorbidities including diabetes mellitus (p<0.001), hypertension (p<0.001), coronary artery disease (p=0.015), cerebrovascular accident (p<0.001), and cancer (p=0.031) as compared other groups. The elderly patients had a low body mass index (BMI ) (24.60±4.65, 24.55±3.30, 23.27±3.12, p=0.041 by ANOVA) and longer disease duration (2.76±5.16, 4.20±6.13, 6.58±9.23 years, p=0.028 by ANOVA).

Fever was more often present in the elderly patients (17.6% in young vs. 29.6% in middle aged vs. 50.0% in elderly, p=0.001 by chi-square test). Although numbers of involved joints during attacks did not differ between groups (p=0.636), CRP and ESR levels during gout attack increased significantly with age (Figure 1).

**Conclusion:** Since gout attacks in elderly patients are accompanied by stronger systemic inflammatory response, often resembling sepsis or septic arthritis, it is crucial to correctly diagnose them as gout so that unnecessary invasive diagnostics including joint lavage and prolonged antibiotic treatment can be avoided.

**Key words:** gout, age, elderly, fever.

**Disclosure:** J. A. Yang, None; J. H. Lee, None; E. Y. Lee, None; E. B. Lee, None; Y. W. Song, None; J. K. Park, None.
Serum Uric Acid As an Independent Risk Factor for Progression of Chronic Kidney Disease in Gout Patients with Urice Acid Lowering Agent. Young Hyup Lim, Eun-Jung Park, Seulkie Lee, Hemin Jeong, Hyungjin Kim, Jinseok Kim, Jaejoon Lee, Hoon-Suk Cha and Eun-Mi Koh. 1Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Jeju, South Korea, 2Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Seoul, South Korea, 3Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 4Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Seoul, South Korea, 5University of Colorado, Denver, CO.

Background/Purpose: Hyperuricemia is particularly common in patients with chronic kidney disease (CKD). Its role, however, as a risk factor for renal outcomes of CKD is debated. This aim of study was to evaluate long-term effect of serum uric acid (SUA) level on progression of CKD in gout patients with uric acid lowering treatment.

Methods: All patients who had a first visit for gout with CKD at Samsung Medical Center between 1995 and 2003, and follow-up until December 2012 or expired during follow up period were included and retrospective analyzed. CKD was defined as an estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73m² via MDRD Study equation more than 3 months. All serum creatinine and matched SUA taken during follow up period were analyzed by using Mixed effect model to determine the effect of SUA level on renal outcome.

Results: 1221 patients were analyzed, mean age of the patients 51.3 and mean follow up duration was 13 years. Baseline eGFR and serum creatinine were 47.7 mL/min/1.73m² and 1.62 mg/dL, respectively. Maintaining the SUA below 6 mg/dL showed protective effect on serum creatinine and eGFR compared with SUA more than 6 mg/dL (p < 0.0001 and p = 0.02, respectively). Mixed effect model demonstrated that the protective effect on renal outcome with maintaining the SUA below 6 mg/dL, was statistically significant after adjusting baseline age, follow-up time, hypertension, diabetes mellitus, history of cardiovascular disease, obesity, and intrinsic renal disease (p < 0.0001). Hypertension, diabetes mellitus and follow-up time were independently associated with progression of chronic kidney disease (p < 0.001, p < 0.001 and p < 0.001, respectively). In particular, for every 1 mg/dL increase of the SUA, serum creatinine revealed to be increased 0.02 mg/dL when the SUA is more than 6 mg/dL (p < 0.0001).

Conclusion: Our long term follow up data demonstrated the SUA level was associated with progression of CKD in gout patients. Maintaining of SUA level below 6 mg/dL would be essential to protect renal function in gout patients with CKD.

Disclosure: Y. H. Lim, None; E. J. Park, None; S. Lee, None; H. Jeong, None; H. Kim, None; J. Kim, None; J. Lee, None; H. S. Cha, None; E. M. Koh, None.

1222
Suppressive Effect of Butyrate on Monosodium Urate (MSU) Crystal-induced IL-1 beta Production Is Mediated Via Inhibition of Class I Histone Deacetylases. Maartje Cleophas, Tania Crisan, Heidi Lemmers, Helga Toenhake-Dijkstra, Gianluca Fossati, Tim Jansen, Charles Dinarello, Mihai Netea, Helga Toenhake-Dijkstra, Maartje Cleophas, Heidi Lemmers, Helga Toenhake-Dijkstra, Mihai Netea, Tim Jansen and Lee Joosten. 1Radboud University Medical Center, Nijmegen, Netherlands, 2Radboud University Medical Center, Nijmegen, Netherlands, 3Radboud University Medical Center, Nijmegen, Netherlands, 4Vall d’Hebron University Hospital, Barcelona, Spain, 5University of Colorado, Denver, CO.

Background/Purpose: Gout is an autoimmune disease characterized by the deposition of monosodium urate (MSU) crystals in the joints of hyperuricemic patients and subsequent attacks of severe gouty arthritis. Major lines of research investigating the proinflammatory effects of uric acid have been mainly focused on MSU crystal-induced processes that come into role once uric acid reaches supersaturation. However, some indications exist that uric acid can directly have pro-inflammatory effects. In this study we investigate the effects of high uric acid exposure on the cytokine production of primary human immune cells in coinoculation with MSU crystals and synergizing agents.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested from gout patients and healthy volunteers. Cells were pre-treated with uric acid, allantoin or left untreated for 24h and then subjected to 24h stimulation with TLR2 or TLR4 ligands in the presence or absence of MSU. Cytokine production was assessed using specific sandwich ELISA kits. mRNA levels were measured using quantitative real-time PCR.

Results: MSU crystals stimulation alone did not induce detectable levels of IL-1β and IL-6 neither in patients nor in controls, however, synergy was present between MSU and Pam3CSy or LPS. Of high importance, higher levels of IL-1β and IL-6 were seen in patients compared to controls. An enhanced pro-inflammatory cytokine production was also observed when cells were specifically pretreated with uric acid, together with a significant downregulation of IL-1Ra but not IL-10. This observation correlated with mRNA levels for these cytokines observed in uric acid pre-treated cells.

Conclusion: In this study we propose a mechanism in which high uric acid concentrations might influence inflammatory responses by facilitating IL-1β production in immune cells. We show that a mechanism for the amplification of IL-1β consists in downregulation of IL-1Ra production that has the role of counterbalancing IL-1β auto-induction loop. As a consequence, patients having hyperuricemia could be at risk of exhibiting increased vulnerability upon encounter of acute inflammatory stimuli and this might induce enhanced states of inflammation.

Disclosure: T. Crisan, None; M. Cleophas, None; H. Lemmers, None; H. Toenhake-Dijkstra, None; M. Netea, None; T. Jansen, Abbvie, UCB, Abbvie, 5, AstraZeneca, 5, UMS, S. Jansen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8; C. Dinarello, None; M. Netea, None; L. Joosten, None.
Pegloticase for Tophus Debulking: Comparison of Dual Energy Computerized Tomography (DECT), Musculoskeletal Ultrasound (MSK-US) and Topographic Caliper Measurement for Assessing Debulking Rate. Dojdi Modjnin, Elaine Karis, Soteros Gytoopoulos, Jonathan Samuelu, Robert T. Keenan, Daisy Bang, Kristen Lee, Svetlana Kasronutksy-Samuels, Daria B. Crittenden and Michael H. Pillinger. NYU School of Medicine, New York, NY, 2, Duke University, Durham, NC, 3, NYU School of Medicine, New York, NY, 4, NYU Langone Medical Center, New York, NY, 5, NYU Langone Medical Center, New York, NY, 6, 7, 8, 9, School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Pegloticase is approved for lowering serum urate (sUA) in chronic refractory tophaceous gout (CRTG), but the rate of tophus resolution is not well defined, in part owing to limitations of measurement techniques. DECT permits 3-dimensional, non-congruent, perpendicular planes, whereas MSK-US and caliper measurement assess the rate of tophus debulking during pegloticase treatment.

Methods: A 32-year old male with a 10 year history of CRTG underwent a 13-infusion, twice-monthly course of pegloticase 8 mg, with sUA assessment of tophi, physical exam, and MSK-US imaging (gray scale, 18 MHz probe) every 3 months, as well as DECT and X-Rays (pre/post-treatment) of the hands and feet prior to each infusion. Monthly caliper measurements of 3 index tophi, a 13-infusion, twice-monthly course of pegloticase 8 mg, with sUA assessment of tophi, but comparisons between DECT and other imaging modalities are limited. We conducted an n-of-1 pilot study comparing DECT, MSK-US and surface caliper measurement to assess the rate of tophus debulking during pegloticase treatment.

Results: 8 tophi were noted on physical exam of the hands and feet, with 3 selected as index tophi. Whereas physical exam identified 4 tophi on the right hand, DECT revealed 15; whereas X-ray identified a single erosive lesion in the right hand, DECT identified 4 more in the feet. Pegloticase persistently lowered the patient’s sUA to <0.5 mg/dl. Caliper measurements at the start and end of treatment revealed 73, 60, 63% reductions of the index tophi, whereas MSK-US showed 29, 80, and 41% reductions of the same tophi, respectively. In contrast, DECT revealed 100% resolution of all 3 index tophi, and resolution/improvement of all other tophi identified. Initial DECT images revealed a composite tophus volume of 2,177 mm3 on the right hand and 900mm3 on the left, each decreased to 130 mm3 by study completion. On calibration curves, the tophus volume was estimated to be decreased over time despite overall reduction. On MSK-US, some individual tophi appeared to “soften” and expand initially, followed by overall size reduction.

Conclusion: Pegloticase rapidly reduced all tophi assessed. While all assessment modalities were informative, correlation between them was poor, probably relating to the fact that calipers and MSK-US measure tophus area in non-congruent, perpendicular planes, whereas DECT measures volume. As previously reported, DECT identified occult urate deposition not visible on physical exam. Interestingly, tophi may fluctuate in size, even transiently increasing, during the process of resolution, revealed on ultrasound as tophus “softening” and loss of structure. Moreover, DECT imaging indicated that some urate deposits fully resolved even as their visible/palpable lesions persisted, possibly because of persistence of soft tissue swelling and/or fibrosis. We conclude that urate resorption begins early in the course of pegloticase therapy, but may be hard to recognize because of fluctuating volumes. While all imaging modalities have value, DECT is superior for identifying total (including occult) urate deposition, assessing absolute volume of deposits, and confirming urate resolution, even when soft tissue swelling persists. DECT may therefore be particularly valuable when soft tissue swelling persists. DECT may therefore be particularly valuable for identifying total (including occult) urate deposition, and confirming urate resolution, even as their visible/palpable lesions persist, possibly because of fluctuating volumes. While all imaging modalities have value, DECT is superior for identifying total (including occult) urate deposition, assessing absolute volume of deposits, and confirming urate resolution, even as their visible/palpable lesions persisted, possibly because of fluctuating volumes.

Disclosure: D. Modjnin, None; E. Karis, None; S. Gytoopoulos, None; J. Samuelu, None; R. T. Keenan, AstraZeneca, 2; S. Takeda, 2, 3, 4, Crealta, 5; D. Bang, None; K. Lee, None; S. Kasronutksy-Samuels, None; D. B. Crittenden, Amgen, 3; M. H. Pillinger, Takeda, Savient, Crealta, 2, Crealta, 5.

ACR/ARHP Poster Session B
Micoscopic Rheumatic and Inflammatory Diseases
Monday, November 17, 2014, 8:30 AM - 4:00 PM

1225
Clinical Presentation and Cytokine Production Abnormalities in a Cohort of Patients Carrying NLRP12 GENE VARIANTS. Antonella Insalaco1, Luigi Raganelli2, Manuela Pardeo2, Virginia Messi2, Denise Pires Marafon Jr.3, Francesca Romana Leprì3, Elisa Pisanscilli4, Claudia Bracaglia5, Valeria Gerloni6, Rebecca Nicola7, Elisabetta Cortis8, Fabrizio De Benedetti Sr.9, and Giusi Principe. Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 2 Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 3 Istituto Ortopedico Gaetano Pini, Milan, Italy, 4 Santa Maria della Stella Hospital, Orvieto, Italy.

Background/Purpose: The NLRP12 related autoinflammatory disorder (NLRP12-RD) is a rare autosomal dominant disease, caused by mutations in the NLRP12 gene. Clinical manifestations are extremely heterogeneous. We describe clinical features and inflammatory response of a cohort of patients carrying different NLRP12 variants, some of which not yet described as being associated with NLRP12-RD.

Methods: Twelve Italian patients (6 males) carrying NLRP12 variants were identified. Blood samples obtained from 9/12 NLRP12 patients and family members were analyzed for the presence of the variants. A total of 9/12 patients (81%) received ex vivo with 1 mg/ml of Zymosan for 22h. Whole blood RNA analysis was also performed, using a human immune array (TaqMan® Human Immune Array from Applied Biosystems), containing 92 genes typically involved in the immune response.

Results: The median age at symptoms onset was 11.4 months (IQR 4.6–35.2) and the median of disease duration was 6.8 years (IQR 4.1–11).

Sequencing of NLRP12 gene in the 12 patients revealed 5 heterozygous mutations: p.F402L(n=6), G448A(n=1), H304Y(n=1), R1030G(n=1) and G39V(n=2). Two patients were homozygous for NLRP12 variants F402L and G39V. In 6/12 variants of NLRP3 were also found: Q703K(n=4) and V198M(n=2). All patients had symptoms consistent with a recurrent inflammatory syndrome: 11/12 presented recurrent episodes of skin lesions, 11/12 arthralgia, 10/12 recurrent fever episodes, 8/12 arthritis, 10/12 headache, 11/12 fatigue, 3/12 conjunctivitis, 5/12 recurrent abdominal pain and lymphadenopathy. 4/12 had oral aphthosis, 4/12 sensorineural deafness. In the attacks 5/12 patients showed increased acute phase reactants. In 5/12 patients anakinra was administered because of the severity of phenotype and the persistence of elevated acute phase reactants. In 2 of these 5 patients lack of efficacy led withdrawal of anakinra and introduction of tocilizumab with good response. In vitro cytokine release studies, performed in 9 patients, showed that the production of IL-6 and TNF-α was significantly higher in patients carrying the NLRP12 variants compared to patients with JIA (IL-6: 2841 ± 1662 ng/ml and 1496 ± 982.4 ng/ml, p=0.002 and p=0.007) and even higher in homozygous patients; no significant difference in IL-1β production was found (2134 ± 1026 ng/ml versus 1527 ± 930.3 ng/ml, p=0.29). Whole blood RNA samples collected from 5 NLRP12 patients were compared to 6 whole blood RNA samples collected from healthy controls comparable for age. At basal level, we did not find significant differences in the expression of 92 genes evaluated.

Conclusion: Our data in vitro and in vivo suggest that these NLRP12 variants are pathogenic. The role played by the concomitant presence of the NLRP3 variants remains to be clarified, though an effect in modifying the disease phenotype cannot be excluded. Our data also confirm the clinical and functional heterogeneity of NLRP12 related disorder, a condition often misunderstood. Furthermore, although the small number of patients treated, our data suggest that inhibition of IL-6 may be effective in NLRP12-related disorder.

Disclosure: A. Insalaco, None; L. Raganelli, None; M. Pardoe, None; V. Mesia, None; D. Pires Marafon Jr., None; F. R. Lepri, None; E. Pisanscilli, None; C. Bracaglia, None; V. Gerloni, Abbvie, Novartis, 2, R. Nicolai, None; E. Cortis, None; F. De Benedetti Sr., Novartis, Novimmune, Hoffmann-La Roche, SOBI, 5; G. Principe, None.

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Studying Patients with Autoinflammatory Diseases: The Past, Present, and a Perspective for the Future. Jonathan S. Hausmann1, Catherine Biggs2, Donald P. Goldsmith3, and Fatima Dedegolu4. 1Beth Israel Deaconess Medical Center, Boston, MA, 2Boston Children’s Hospital, Boston, MA, 3St Christopher’s Hospital for Children/Drexel College of Medicine, Philadelphia, PA, on behalf of CARRA investigators, Palo Alto, CA.

Background/Purpose: Autoinflammatory diseases (AIDs) are uncommon disorders characterized by recurrent episodes of systemic and organ-specific inflammation. Because of their rarity, finding large numbers of patients to study has been challenging. This project will compare the results of a retrospective chart review of patients with AIDs at a single academic medical center, with those of participants within the Childhood AThritis and
Conclusion: Using the traditional methodology of a single-center retrospective chart review, we described the patients with AIDs seen at BCh, and estimated the frequency of various AIDs within this population. This research required little cost and relatively little time. Limitations included incomplete documentation in some cases, and the variety of AIDs identified was limited.

The CARRA registry, on the other hand, was a modern, multicenter effort that allowed enrollment of patients from multiple sites at a faster rate, and with a greater variety of diagnoses. However, this registry required significant financial investments in technology and operational costs. The fact that PFAPA, the most common pediatric AID, represented a minority of subjects within the CARRA registry suggests that physicians enrolled a select number of patients, possibly due to the time required for the consent, enrollment, and data-uploading processes.

Integration of registries into the patient’s electronic health records will potentially minimize the current barriers to research. In addition, we believe that online patient communities can also contribute valuable information. In future studies, we plan to empower and engage patients with AIDs through social media to collaborate in the design and implementation of research studies. Our efforts could exponentially expand the number of patients available to participate in research, and help our understanding of these complex disorders.

Disclosure: J. S. Hausmann, None; C. Biggs, None; D. P. Goldsmith, None; F. Dedegolu, None.

1227
Cryopyrinopathy with a Myeloid-Specific NLRP3 Mutation. Patrycia Hoffmann1, Qing Zhou2, Amanda Ombrello2, Anne Jones2, Beverly Barham2, Ivona Aksentijevich3 and Daniel L. Kastner.1 1Division of Rheumatology, Ospedale Pediatrico Bambino Gesu, IRCCS, Rome, Italy, 2Ospedale Pediatrico Bambino Gesu, IRCCS, Rome, Italy, 3Novimmune S.A., Plan-Les-Ouates, Geneva, Switzerland.

Background/Purpose: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a newly described autoinflammatory disease. We describe clinical phenotype and cytokine profile of our patient.

Methods: A 10 years-old young girl presented at 10 months of age with recurrent fever, hepatosplenomegaly and nodular erythematous skin lesions; she progressively developed lypodystrophy, arthralgia, arthritis and edema of eyelids. Skin biopsy showed features of lobular panniculitis. Laboratory tests showed persistent elevated acute phase reactants with anemia, recurrent leucopenia, thrombocytopenia and hypoparaglobulinemia. Immunological and cytokine studies performed on bone marrow were normal. Subsequently, the patient developed nephrotic syndrome. Renal biopsy revealed a minimal change glomerulopathy responsive to high-dose glucocorticoid. Response to hydroxychloroquine, colchicine, cyclosporine-A, and anakinra was unsatisfactory. Complete sequencing of TNFRSF1A and MVK genes showed no mutations. A nalysis of the PSM B8 (proteasome subunit b type 8) gene revealed the presence of c.220A>T (p.(T745) variant in heterozygotic status that has never been reported before. In order to assess the dysregulated inflammatory response, we evaluated the cytokine profile in patient’s sera using the Luminex multiplexing assay. Whole blood RNA analysis was also performed using a human immune array (TaqMan® Human Immune Array from Applied Biosystems), containing 92 genes typically involved in the immune response.

Results: Serum samples (n=4) were collected during the last two years. We found high levels of IFN-γ (mean ± S.D.: 113.3 pg/ml ± 64.21), of IFN-γ inducible protein 10 (IP-10, also called CXCL10) (1641 ± 892.5 pg/ml) and of IFN-γ inducible protein 9 (IP-9, also called CXCL11) (582.9 ± 335.6 pg/ml) and especially of CXCL9, also known as monokine induced by γ-interferon (MIG) (18161 ± 6485 pg/ml) compared to healthy controls or pediatric patients with sjIA during active disease. Two whole blood RNA samples collected from our Candle patient were compared to 6 whole blood RNA samples collected from healthy controls comparable for age. We obtained results consistent with those obtained by serum cytokine measurement: IFN-γ, CXCL10 and CXCL11 mRNA expression were significantly increased compared to healthy controls (1.88, 32.7 and 4.1 fold higher

Disclosure: P. Hoffmann, None; Q. Zhou, None; A. Ombrello, None; A. Jones, None; B. Barham, None; I. Aksentijevich, None; D. L. Kastner, None.

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Involvement of the IFN-Ω Pathway in a Patient with Candle Syndrome Carrying a Novel Variant of PSMB8 Gene. Antonella Insalaco1, Giusi Principe1, Manuela Pardeo2, Virginia MESSIA2, Andrea M assoti1, Cristina de M in3, Claudia Bra caglia1, Rebecca Nicolei1, Ivan Caillo2 and Fabrizio De Benedetto Sr.3. 1Division of Rheumatology, Ospedale Pediatrico Bambino Gesu, IRCCS, Roma, Italy, 2Ospedale Pediatrico Bambino Gesu, IRCCS, Roma, Italy, 3Novimmune S.A., Plan-Les-Ouates, Geneva, Switzerland.

Background/Purpose: The CARRA registry suggests that physicians enrolled a select number of patients, possibly due to the time required for the consent, enrollment, and data-uploading processes. Involvement of the IFN-Ω pathway in a patient with CANDLE syndrome is a newly described autoinflammatory disease. We describe clinical phenotype and cytokine profile of our patient.

Methods: A 52 year-old perimenopausal pediatrician presented to the rheumatology service with a 6 month history of constitutional symptoms, arthralgia and myalgia. She was negative for inflammatory markers. WBC also normalized at 5.060 K/uL. Whole-exome sequencing, targeted deep resequencing of NLRP3 in blood and buccal cells demonstrated similar levels of mosaicism, but only in the peripheral blood. We then analyzed 192 colonies each from subcloned amplicons derived from monocytes, granulocytes, T lymphocytes, B lymphocytes, fibroblasts, and buccal cells. This confirmed the presence of the mosaic mutation at a ratio similar to the exome data in monocytes and granulocytes but not in lymphocytes, cultured fibroblasts, or buccal cells.

Conclusion: To our knowledge this abstract represents the first report documenting lineage-specific NLRP3 mosaicism, established by subcloning amplicons from six different cell types. The patient’s initial presentation of urticarial rash before puberty and reoccurrence during menopause along with constitutional symptoms, arthralgia and myalgia was not classic for Muckle-Wells syndrome, however the clinical presentation was suggestive of a cryopyrinopathy. The molecular demonstration of lineage-specific NLRP3 mosaicism, taken together with the clinical response to anakinra, confirm the diagnosis of cryopyrinopathy, and underscore the emerging role of massively-parallel sequencing in clinical diagnosis.

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IFN-γ absence of biallelic mutations of PSMB8 gene. The presence of high levels of IFN-γ and of IFN-γ related chemokines points to a major pathogenic role of the IFN-γ pathway, which appears to be similar to what has been recently reported in CANDLE (Liu et al.). The pathogenic role of the variant T74S remains to be elucidated: a potential role is suggested by its presence in a patient with a classical phenotype and with a dysregulation of the IFN-γ pathway, taking into account that this variant is close to the known pathogenic mutation T75M.

Disclosure: A. Insalaco, None; G. Prencipe, None; M. Pardeo, None; V. Mousa, None; A. Masotti, None; C. de Min, Novimmune; C. Bracaglia, None; R. Nicolai, None; I. Caiello, None; F. De Benedetti Sr., Novartis; Novimmune; Hoffmann-La Roche, SOBI; AbbVie; 2, AbbVie Novartis, Novimmune, Hoffmann-La Roche, SOBI, 5.

1229

Is NOD2-Associated Autoinflammatory Disease Remotely Related to Familial Mediterranean Fever or Continuum of It?

M. Shen, Bo Shen and Qingping Yao Cleveland Clinic, Cleveland, OH.

Background/Purpose: NOD2-associated autoinflammatory disease (NAID) is a newly described autoinflammatory disease characterized by periodic fever, dermatitis, polyarthritides, gastrointestinal and sicca symptoms. It is genotypically associated with NOD2. Its clinical phenotype may superficially resemble familial Mediterranean fever (FMF). We report a case series to illustrate the similarities and differences between these two autoinflammatory diseases.

Methods: Three patients with NAID or FMF were cared for by the authors between 2012 and 2014, and their phenotypes and genotypes were retrospectively studied. Genetic testing for MEFV and NOD2 mutations was performed.

Results: The clinical phenotypes and genotypes of these patients are summarized (Table). Patient 1 presented with recurrent fever, abdominal pain/diarrhea, chest pain, and arthralgia since the age of 5 years. Her symptoms responded well to colchicine, and FMF was diagnosed in the presence of heterozygous K69R. Patient 2 is the niece of patient 1 and presented with symptoms since the age of 17 years and shared the similar phenotypes with her aunt except the presence of recurrent erythematous patches of the skin and longer lasting gastrointestinal symptoms. FMF was suspected, but she had a transiently mild response to colchicine. Genetic testing identified the NOD2 mutations IVS8 +15B and R702W and negative MEFV. NAID was diagnosed with a complete response to oral sulfasalazine. Patient 3 is a man and presented with recurrent fever and abdominal pain/diarrhea since the age of 17 years, with mild response to colchicine. Genetic testing identified heterozygous M694V in the MEFV and NOD2 mutation IVS8 +15B.

Conclusion: Both NAID and FMF appear similar phenotypically, but they are distinct. The symptoms can last longer than 3 days, and sporadic dermatitis is common in NAID, whereas erysipelas-like erythema with sparse infiltrate on the lower extremities is a feature of FMF. NAID does not respond to colchicine. Both MEFV and NOD2 genes are located on chromosome 16 and share similar gene structures. This case study suggests that these two diseases could be remotely related.

Disclosure: M. Shen, None; B. Shen, None; Q. Yao, None.

1230

Efficacy of Interleukin-1 Targeting Drugs in Familial Mediterranean Fever Patients: Pinar Cetin1, Ismail Sarı2, Betul Sozeri2, Ozlem Cam3, Merih Birlik, Fatos Önen, Nurullah Akkoc and Servet Akar1. 1Dokuz Eylül University School of Medicine, Izmir, Turkey; 2Ege University School of Medicine, Izmir, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent episodes of fever accompanied by sterile peritonitis. The most devastating complication of FMF is the development of secondary amyloidosis which has a potential risk for developing end stage renal disease. However cholehicine is the most effective treatment regimen in FMF patients, 5-10% of patients are refractory. However, there are several drugs being tested in this group of patients. The most promising group of drugs appears to be the anti-IL-1 therapies. The objective of this study is to demonstrate the efficacy of anakinra and canakinumab in FMF patients who followed up in our outpatient clinics.

Methods: In this study we included 20 cholehicine resistant FMF patients (16 adults and 4 children) diagnosed according to the Tel–Hashomer or Sheba Medical Center criteria, who are receiving anti-IL-1 treatments (anakinra n= 14; canakinumab n= 6). A retrospective review of medical records of anti-IL-1 recipients was performed. The main clinical characteristics of these patients and their genotypes for MEFV gene and the evolution after anti-IL-1 were recorded. Laboratory response was evaluated with erythrocyte sedimentation rate(ESR) and C-reactive protein (CRP).

Results: The median age of patients was 23 (14-50), the median disease duration was 16 years (4-46) and the median follow up time in clinic was 12 years (1-26). 16 were homoyzogous for the M694V mutation. Attacks per month and year were significantly decreased after anti-IL-1 therapy p < 0.05 (Table 1). The median follow-up of the anakinra and canakinumab patients were 14 (4-36) and 18 (4-25) months respectively (p = 0.51). All patients were also receiving background colchicine with a median dose of 1.5 mg. There is a trend towards a decreasing dose of colchicine after anti-IL-1. A cute phase response was also significantly decreased after IL-1 treatments (p < 0.05, Table 1). Besides the effectiveness on acute attacks we also noted significant decreases in proteinuria in patients with amyloidosis (9 gr to 3.7 gr/day in the adult and 25.6 mg/m²/hour to 12 mg/m²/hour in the pediatric patient). In a median 16 months of follow-up there were only one serious adverse event (pneumonia) in a patient receiving anakinra therapy however, after anti-biotic treatment we resumed treatment in this patient.

Conclusion: In this study we revealed that 95% of our colchicine-resistant patients responded to the anti-IL-1 targeting agents. These drugs tolerated well and only one patient had serious adverse events during the 16 months of follow-up. We also noted significant amelioration of proteinuria in amyloidosis patients. IL-1 receptor antagonists anakinra and canakinumab seem to be safe and effective treatment options in colchicine-refractory FMF patients.

Table 3: Number of attacks and acute phase protein levels before and after anti-IL-1 treatment. 

<table>
<thead>
<tr>
<th></th>
<th>Attack/week before treatment</th>
<th>Attack/week after treatment</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Anakinra (n=10)</td>
<td>1 (0-3)</td>
<td>0.5 (0-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Canakinumab (n=6)</td>
<td>1 (0-3)</td>
<td>0.5 (0-3)</td>
<td>0.003</td>
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</table>

CRP mg/l

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<th></th>
<th>CRP mg/l before treatment</th>
<th>CRP mg/l after treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra (n=10)</td>
<td>52.5 (5-15)</td>
<td>12.5 (1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Canakinumab (n=6)</td>
<td>43.3 (5-15)</td>
<td>12.5 (1-3)</td>
<td>0.004</td>
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</tbody>
</table>

ESR mm/h

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<thead>
<tr>
<th></th>
<th>ESR mm/h before treatment</th>
<th>ESR mm/h after treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra (n=10)</td>
<td>43 (8-110)</td>
<td>14 (5-100)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Canakinumab (n=6)</td>
<td>52.5 (5-140)</td>
<td>11 (6-53)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Disclosure: P. Cetin, None; I. Sari, None; B. Sozeri, None; O. Cam, None; M. Birlik, None; F. Onen, None; N. Akkok, None; S. Akar, None.

1231

Evidence Based Recommendations for Genetic Diagnosis of Familial Mediterranean Fever: Gabriella Giancane, Nienke te Haar2, Nico Wulfraat3, Bas van ‘t As4, Karyl Barron5, Vernon E. Hentgen6, Tilman Kallinich4, Hui Ozcakal4, Jürgen A. Anton6, Paul Briggman7, Luca Cantarini1,3, Jost Frengen1, Caroline Galatelli2, Marco Gattorno6, Gilles Graeber6, Michael Hoffer6, Isabelle Kountcheva8, J. K. buhermeier-Deschner4, Hein Lachmann9, Anna Simon10, Brian Feldman10, Yosef Uziel11 and Seza Ozen12. 1UMC, Utrecht, Netherlands, 2Utrecht, Netherlands, 3University Medical Center Utrecht, Utrecht, Netherlands, 4Wilhelmina Children’s Hospital/UMC Utrecht, Utrecht, Netherlands, 5NHS, Bethesda, MD, 6versailles Hospital, Le Chesnay Cedex, France, 7Charité, University Medicine Berlin, Berlin, Germany, 8Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, 9Pediatric Rheumatology Unit, Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain. 10Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, 11University of Siena, Siena, Italy, 12Bicêtre Hospital, University of Paris SUD, Paris, France. 13Istituto Giannina Gaslini, Genova, Italy, 14Hospital Tenon, Paris, France. 15Centre Multisite Romand de Rhumatologie Pediatrique, Lausanne, Switzerland, 16Technische Universität Hamburg, Hamburg, Germany. 17University College London Medical School, London, United Kingdom, 18Randboudumc, Nijmegen, Netherlands. 19The Hospital for Sick Children, Toronto, ON, 20Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, 21Department of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey.
Background/Purpose: Familial Mediterranean Fever (FMF) is a disease that starts in childhood and can lead to significant morbidity. In 2013, an initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) has been launched for children and young adults with rheumatic diseases. For FMF, attention was focused on genetics. The aim of the SHARE recommendations in FMF is to provide a diagnostic tool for inexperienced pediatric rheumatologists to cope with FMF in their clinical practice. This is possible through a correct interpretation of the diagnostic value of MEFV mutations in predicting FMF phenotype.

Methods: An expert committee was instituted, consisting of pediatric rheumatologists, and search terms for the systematic literature review were defined. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement during the online survey were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 3386 articles, of which 25 considered relevant and therefore scored for validity and level of evidence. 17 articles were scored valid and used in the formulation of the recommendations. 8 recommendations were finally accepted with 100% agreement after the consensus meeting (Table 1). Topics covered for diagnosis were: clinical versus genetic diagnosis of FMF; genotype-phenotype correlation; genotype-phenotype correlation; congenital vs acquired disease; silent carriers and risk for amyloidosis; role of the specialist in FMF diagnosis.

Conclusion: The SHARE initiative provides recommendations for the diagnosis of FMF and thereby facilitates improvement and uniformity of care.

FMF Recommendations

1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing.
2. Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype.
3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutation in the position 680 to 694 on exon 10, must be considered at risk of having a more severe disease than those carrying only one mutated allele (heterozygotes).
4. The E148Q variant is common, of unknown pathogenic significance and as the only MEFV variant does not support the diagnosis of FMF.
5. Patients homozygous for M694V mutation are at risk for an early onset disease.
6. Individuals, homozygous for M694V, who are not reporting symptoms, should be evaluated and followed closely in order to consider therapy.
7. For individuals with two pathogenic mutations for FMF who don’t report symptoms, if there are risk factors for AA amyloidosis (such as country of origin, family history and persistently elevated inflammatory markers) treatment and close follow-up should be considered.
8. Consultation with an autoinflammatory disease specialist may be helpful, in order to aid in the indication and interpretation of the genetic testing and diagnosis.

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Canakinumab Therapy in Patients with Familial Mediterranean Fever. Serdal Ugurlu, Emir Seyahi, Gulen Hatemi, Aysa Hacioglu, Fatma Nihan Akkoc and Huri Ozdogan. Cerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: According to a recent pilot study Canakinumab reduced the frequency of attacks in 9 patients with Familial Mediterranean Fever (FMF) resistant to colchicine with no apparent side effects(1). We present our experience with Canakinumab in FMF patients resistant or intolerant to colchicine.

Methods: The charts of the patients with FMF who were on Canakinumab were evaluated retrospectively with regard to response and safety.

Results: There were 30 patients with FMF (16 F/14 M) receiving canakinumab for various indications. Here we report 28 (15 F/13 M) who had at least 3 injections. Six patients had concomitant diseases such as psoriasis (1), ankylosing spondylitis (3), polyarteritis nodosa (1), ankylosing spondylitis and polyarteritis nodosa (1). The indications for canakinumab (150mg/mo) were insufficient response to colchicine in 15 (>1 attack/month), amyloidosis in 6, injection site reaction to anakinra in 5, oligospermia in one and myopathy in one patient, both being adverse effects of colchicine in 2. The mean age of the patients was 34.67 ± 13.45 years, the disease duration was 16.75 ± 9.42 years, the mean injection number was 7.00 ± 3.62 and the mean duration of canakinumab therapy was 10.98 ± 6.06 months. Twenty of the patients had no attacks after canakinumab, six patients’ attack frequency was reduced more than %50 while two patient’s attack frequency did not change. In 6 cases with FMF amyloidosis, proteinuria decreased in 2 (from 15020 mg/dl to 9160 mg/dl, and from 6135 mg/dl to 4610 mg/dl), increased in 2 (from 1700mg/dl to 4700mg/dl and from 5001 mg/dl to 7061 mg/dl), and did not change in the other 2. Eleven of the 24 patients with severe myalgia and calf pain unresponsive to colchicine treatment, improved significantly on canakinumab. According to patient global assessment the mean score decreased from 7.9 ± 2.6 to 2.1 ± 2.9 (p<0.001). Canakinumab was stopped because of remission (no attacks for at least 3 months) in 5 and for pregnancy demand in one. The treatment was also stopped in the patient with oligospermia after being fertile, and he is without attacks for 5 months. Attacks recurred after 4, 6, 12 months from discontinuation of the therapy in 3 patients, and 3 patients are attack-free for 5, 6 and 13 months till now. None of the patients had injection site reactions. The patient with psoriasis reported a flare in psoriatic plaques, which responded to local treatment. Therapy was discontinued temporarily in one patient who developed mild leukopenia, which did not recur on a 2-monthly regimen. Treatment was switched to another biological agent in 2 patients with amyloidosis because of increasing proteinuria. One other patient with amyloidosis whose proteinuria was stable, developed lichen planus lesions and the treatment had to be stopped. One patient had pneumonia, also he was attack-free for three months until last dose. The patient with psoriasis reported a flare in psoriatic plaques which responded to local treatment.

Conclusion: Canakinumab is effective in controlling the attacks in patients with inadequate response to colchicine. In a selected group of FMF patients, Canakinumab may serve as a treatment alternative with a favorable side effect profile. For better understanding the drug’s efficacy and safety in the long term there is a need for controlled trials.

References:

Disclosure: S. Ugurlu, None; E. Seyahi, None; G. Hatemi, None; A. Hacioglu, None; F. N. Akkoc, None; H. Ozdogan, None.

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Tocilizumab (TCZ) in the Treatment of AA Amyloidosis in Patients with Familial Mediterranean Fever. Huri Ozdogan, Serdal Ugurlu, Aysa Hacioglu, Yasamin Adibnia and Vedat Hamuryudan. Cerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: AA amyloidosis is the major long-term complication of various chronic inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, FMF and other autoinflammatory syndromes. Treatment of the underlying disease decreases the frequency of this complication however, if it develops there is no established treatment of AA amyloidosis. Recently there are few reports pointing out that tocilizumab (TCZ), an anti IL-6 agent may be effective in controlling resistant AA amyloidosis.

We aim to demonstrate our data on the effect of TCZ in patients with AA amyloidosis secondary to FMF.

Methods: The follow-up data of FMF patients with histologically proven AA amyloidosis, treated with TCZ (8 mg/kg per month) is evaluated by assessing the changes in creatinine, creatine clearance, the amount of 24-hour urine protein, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values measured before and throughout the treatment period. A diverse and side effects of the treatment were closely monitored.

Results: TCZ was given to 13 patients (8 female, 5 male) with AA amyloidosis secondary to FMF who were also on Colchicine (2.28 mg/d per month). Two patients had coexisting ankylosing spondylitis, one had systemic lupus erythematosus and one other had Crohn’s disease. The mean age was 36.46 ± 9.96 years, while the mean disease duration of FMF was...
23.15 ± 7.65 years and of amyloidosis was 4.52 ± 4.98 years. The mean follow-up period on TCZ treatment was 8.76 ± 5.59 months. The mean creatinine levels decreased from 1.21 ± 0.93 mg/dl to 1.05 ± 0.65 mg/dl (p = 0.001), mean creatine clearance increased from 102.34 ± 53.95 ml/min to 109.08 ± 60.23 ml/min (p < 0.001). Renal function was improved in 3 of the 13 patients who improved significantly on TCZ therapy (serum creatinine from a mean of 2.64 ± 0.57 mg/dl to 1.97 ± 0.46 mg/dl, p = 0.018; creatinin clearance from a mean of 36.2 ± 4.51 to 45.3 ± 5.35 ml/min, p = 0.005). The median of 24-hour urinary protein excretion for the whole group was reduced from 3038.55 mg/dl (IQR 1827-7061) to 1155mg/dl (IQR 802-4707) (p = 0.013). A significant decrease in acute phase reactants was also recorded. The mean level of CRP was reduced from 19.43 ± 18.75 mg/l to 8.74 ± 4.8 mg/dl (p = 0.004) as the mean ESR was reduced from 45.41 ± 26.68 mm/h to 27.63 ± 29.25 mm/h (p < 0.001).

Twelve of the patients did not experience any FMF attack under TCZ treatment. In one patient TCZ was switched to canakinumab because of an increase in the frequency of attacks associated with erysipelas-like erythema and no decrease in proteinuria. One other patient with FMF and AS had 2 attacks of acute saccroilitis during the follow-up. Increased blood pressure (220/120 mm Hg) was noted 5 days after the single infusion in one patient who was an illicit user of synthetic cannabinoid. TCZ was stopped in one other patient with underlying Sle and APLS who developed ischemic chest pain.

Conclusion: TCZ improves the acute phase response and the renal function impaired by amyloidosis secondary to FMF. Among this patient group TCZ treatment is well tolerated and not associated with serious side effects. Further studies are warranted to test the efficacy and safety of TCZ in AA amyloidosis secondary to FMF as well as other inflammatory conditions.

Disclosure: H. Ozdogan, None; S. Ugurlu, None; A. Hacioglu, None; Y. Adilbina, None; V. Hamuryudan, None.

1234 Periodic Fever Syndromes in an Academic Medical Center. Mark Cervinski1 and Daniel Albert1. 1Dartmouth Hitchcock Medical Center, Lebanon, NH, 2The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH.

Background/Purpose: Most published clinical data on this rapidly evolving group of diseases are from highly specialized centers and do not reflect what is commonly seen in academic rheumatology practices. This retrospective case series examines the breadth and phenotypic variation seen in our medical center over the last two years.

Methods: Case acquisition was achieved by three methods: review of ICD 9 code for periodic fever [277.31 - Familial Mediterranean Fever]; laboratory test requests for periodic fever genetic screening; and, clinic records.

Results: 30 cases were obtained. The age range was 2m to 54 years old. 13 were female, 17 male. All but 3 were seen by a rheumatologist. Of the rheumatology patients 1 was cared for by an adult only rheumatologist and 1 by a rheumatologist who predominantly cares for adult patients and the remainder (25) by a rheumatologist who cares for children (DA). 11 patients had the periodic fever, aphthous stomatitis, pharyngitis, adenopathy syndrome (PFAPA) and all responded to abortive therapy with predniione 1-2mg/kg at the onset of symptoms. 9 patients had an unknown syndrome predominantly abdominal pain and fever with a negative screen for common mutations associated with Familial Mediterranean Fever and other periodic fever syndromes (GeneDX). 5 patients with the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) were diverse ranging from asymptomatic relatives to classical presentations including fever, abdominal pain, myalgias, arthritides and conjunctivitis. Only one of TRAPS patients received Etorinacet and had a partial response but developed systemic lupus when given Infliximab. Two of the three Familial Mediterranean patients responded to colchicine. The single patient with Hyper IgD Syndrome (HIDS) did not respond to either prednisone or anakinra. One child is a compound heterozygote with a mutation in the C1AS1 gene and the MEV gene. This patient presented with urticaria, abdominal pain, and fever reflecting an overlap syndrome as did one of the other FMF patients.

Conclusion: Patients with Periodic Fever Syndromes have a variable clinical presentation and response to therapy and are predominantly cared for by rheumatologists. Familiarity with these disorders is essential for trainees and practicing rheumatologists. Expertise in pediatric rheumatology is useful to distinguish these patients from those with systemic juvenile rheumatoid arthritis and to appropriately treat this population that predominantly present in childhood.

Disclosure: M. Cervinski, None; D. Albert, None.

1235 Recovery of Renal Function after Corticosteroid Therapy for IgG4-Related Kidney Disease. Takako Saeki1, M. Ishihoro Kawano1, Ichiro Mizushima1, Motohisa Yamamoto1, Yoshiyumi Ubara1, Hitoshi Nakashima3, Yoko Wada1, Tomoyuki Ito1, Hajime Yamazaki4, Ichie Narita5 and Takao Saito1. 1Nagakko Red Cross Hospital, Nagakko, Japan, 2Kanazawa University Hospital, Kanazawa, Japan, 3Sapporo Medical University School of Medicine, Sapporo, Japan, 4Toranomon Hospital, Tokyo, Japan, 5Fukuoka University, Fukuoka, Japan, 6Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background/Purpose: In our earlier study of IgG4-related kidney disease (IgG4-RKD), we found that renal dysfunction, which was mostly attributable to IgG4-related tubulo-interstitial nephritis, was significantly improved at 1 month after the start of corticosteroid therapy, but reached a plateau thereafter, and renal atrophy developed in many patients (Saeki, et al. Kidney Int 2013). Little is known about the appropriate initial corticosteroid dose for induction therapy or the long-term renal outcome in IgG4-RKD with renal dysfunction.

Methods: This retrospective cohort analysis evaluated the recovery of renal function during the initial 1 month of corticosteroid therapy, and the long-term course of renal function after treatment, in 41 patients with confirmed IgG4-RKD in whom the eGFR before corticosteroid treatment had been less than 60 ml/min. The patients were collected from 16 collaborating institutions in Japan between 2004 and 2013, and divided into two groups (group L, initial prednisolone dose < 0.6 mg/kg/day; group H, > 0.6 mg/kg/day).

Results: Among the patients, 88% were male, and the mean age at the time of diagnosis of renal disease was 66.6 ± 9.3 years. Renal pathology data were available for 38 of the 41 patients, and all of them had tubulo-interstitial features characteristic of IgG4-RKD. One patient with renal failure in group L showed no recovery of renal function and maintenance hemodialysis became necessary within 1 month after the start of treatment. Except for this patient, eGFR data at 1 month after treatment were available for 31 patients (group L 17; group H 14). The initial prednisolone dose was 0.47 ± 0.12 mg/kg/day in group L and 0.84 ± 0.16 mg/kg/day in group H, being significantly lower (P < 0.001) in the former. There was no significant inter-group difference in patient age, sex or pretreatment eGFR. In both groups, the pretreatment eGFR was significantly improved at 1 month after the start of corticosteroid therapy [30.5 ± 15.7 to 41.8 ± 14.9 ml/min in group L (p < 0.05) and 32.7 ± 13.8 to 46.6 ± 17.0 ml/min in group H (p < 0.05)], and the degree of improvement showed no significant inter-group difference. Fifteen of the 41 patients were followed up for over 36 months (39 – 210 months, median 56 months), and all of them have been maintained on low-dose prednisolone (5.1 ± 2.1 mg/day) at the last review. No patient showed progression to end-stage renal disease, and there was no significant difference in eGFR at the last review (45.1 ± 11.3 ml/min) in comparison to that at 1 month after the start of treatment (42.5 ± 12.8 ml/min).

Conclusion: In IgG4-RKD, prednisolone 0.5 mg/kg daily is sufficient for induction therapy, and the recovery of renal function during the first month of this treatment can be maintained for a long period on low-dose corticosteroid maintenance therapy.

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1236 IgG4 Immunostaining Is Common but Not Specific in Orbital Inflammation Diseases. James T. Rosenbaum1, Amanda Wong2, Patrick Stauffer2, Megan Troxell3, Donald Houghton2, Dongseok Choi3, Christine Harrington2, David Wilson2, Hans Grossniklaus4, Roger Dailey2, John Ng2, Eric Steele2, Patrick Yeatts5, Peter Dolman6, Valerie White6, Craig Czyz7, Jill Foster7, Eric Steele2, Patrick Yeatts5, Peter Dolman6, Valerie White6, Craig Czyz7, Jill Foster7, Deepak Edward8, Hind Alkatan8, Don Kikkawa9, Bobby Korn9, Dinesh Selva9, Gerald Harris10, Michael Kazim11, Raye Patel12 and Stephen R. Planck1. 1OHsu, Portland, OR, 2Oregon Health & Science University,
Background/Purpose: IgG4-related disease is an emerging clinical entity which frequently involves tissue within the orbit. In order to appreciate the implications of IgG4 immunostaining, we analyzed gene expression and the prevalence of IgG4-immunostaining among subjects with orbital inflammatory diseases.

Methods: We organized an international consortium to collect orbital biopsies from 109 subjects including 22 with no known orbital disease, 42 with nonspecific orbital inflammatory disease (NSOI), 27 with thyroid eye disease (TED), 12 with sarcoidosis, and 6 with granulomatosis with polyangiitis (GPA). Lacrimal gland and anterior orbit adipose tissue biopsies were immunostained for IgG4 or IgG secreting plasma cells. RNA transcripts were quantified by Affymetrix microarrays.

Results: None of the healthy controls or subjects with TED had substantial IgG4 staining. Among the 63 others, the prevalence of significant IgG4-immunostaining ranged from 11 to 39% depending on the definition for subjects with GPA and less commonly in tissue from subjects with sarcoidosis or NSOI. The detection of IgG4+ cells correlated with inflammation in the lacrimal gland based on histology. Subjects with NSOI and IgG4 staining did not have multisystem disease. IgG4 staining tissue expressed an increase in transcripts associated with inflammation, especially B cell-related genes. Functional annotation analysis confirmed this.

Conclusion: IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA, or NSOI and do not consistently indicate a multisystem disease. Even using the low threshold of 10 IgG4+ cells/high powered field, IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression.

Disclosure: J. T. Rosenbaum, Genentech and Biogen IDEC Inc., 2; A. Wong, None; P. Stauffer, None; M. Troxell, None; D. Houghton, None; D. Choi, None; C. Harrington, None; D. Wilson, None; H. Grossniklaus, None; R. Dailey, None; J. Ng, None; E. Steele, None; P. Yettts, None; P. Dolman, None; V. White, None; C. Czyz, None; J. Foster, None; D. Edward, None; H. Alkataan, None; D. Kikawa, None; B. Korn, None; D. Selva, None; G. Harris, None; M. Kazim, None; P. Patel, None; S. R. Planck, None.

1237 Retroperitoneal Fibrosis and IgG4 Disease: Response to Immunosuppressive Therapy - A Single Centre Retrospective Study. Shirish Sangle1, Pamela Lutalo, Louise Ne9, James Patterson, Tim OBrien and David P. D’Cruz2. 1Louse Coote Lupus Unit, Guy’s and St Thomas’ Hospital, London, UK, 2Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan. 3Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory disease with multisystem involvement. Affecting patients frequently have a history of bronchial asthma and allergic rhinitis. The reported pathogenesis of IgG4-RD describes the clear involvement of excessive Th2 cells and regulatory immune reaction in addition to plasma cells 1). However, peripheral immune cell phenotype, which reflects disease status, has not been comprehensively evaluated. Our aim was to definitively determine peripheral blood cell abnormalities and their correlation with disease activity in patients with IgG4-RD.

Methods: Peripheral blood samples were obtained from active untreated IgG4-RD patients (n=11) and healthy controls (n=16). Comprehensive immunophenotyping assay with information on activation status was done by multi-color flow cytometry, and the proportion of peripheral blood mononuclear cells (PBMCs), including T cells (naive/memory, Th2/Th1, Reg and Thf), B cells (naive/memory, plasmablast, Breg), monocytes (classical, intermediate, non-classical) and dendritic cells (myeloid, plasmacytoid), and their activity status were precisely defined. Disease activity was measured using the IgG4-RD responder index (RI). Statistical analysis was done using the Mann-Whitney U test and Spearman rank correlation coefficient test.

Results: The proportion of plasmablasts (CD19+CD20+CD27-CD38+), memory Th2 cells (CD3+CD4+CXCR3-CCR6+CD45RA-), Tregs (CD3+CD4+CD25+CD127low), Tfh (CD3+CD4+CXCR5+), and mDCs (CD3+CD19-DLHA-DR+CD1c+CD303-) in peripheral blood was significantly increased in IgG4-RD patients compared with HC, whereas the proportion of pDCs (CD3+CD19-DLHA-DR+CD1c+CD303-) was significantly decreased. Interestingly, the proportion of pDCs in total DCs was negatively correlated with IgG4-RD RI (r = -0.778, p = 0.005) while the proportion of plasmablasts in CD19+ cells was positively correlated with RI (r = 0.701, p = 0.016). Further, the increased proportion of plasmablasts was positively correlated with serum IgG4 level (r = 0.718, p = 0.013).
while the decreased proportion of pDCs tended to be negatively correlated with the number of affected organs (r = −0.518, p = 0.061).

**Conclusion:** Our comprehensive analysis identified distinct proportional changes in PBMCs in IgG4-RD. In particular, the decrease in pDCs and increase in plasmablasts were strongly linked with disease activity. These combined measurements are expected to be clinically useful surrogate cell markers. This newly identified decrease in circulating pDCs may be involved in the pathogenesis in IgG4-RD via the recently described role in the enhancement of Th2 response 2).

Reference:
2) Maazi H et al. Allergy 2013;68:695-701

Disclosure: M. Akiyama, None; K. Suzuki, None; Y. Kassai, Employee of Takeda Pharmaceutical Company Limited; T. Miyazaki, Employee of Takeda Pharmaceutical Company Limited; R. Morita, None; A. Yoshimura, None; T. Takeuchi, Grant/research support: Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Takeda Pharmaceutic K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc, Sanofi–Aventis K, 2.

1239

**Is Lymphocytic Sialadenitis IgG4-Related?** Nathalie Shehwaro1, Marie Houstseau2, Thomas Papo3 and Karim Sacre3. 1University Paris-7, APHP, 2Bichat Hospital, Paris, France, 3University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France.

**Background/Purpose:** To assess the prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on labial salivary gland biopsy.

**Methods:** All labial salivary gland biopsies (LSGB) performed in a French University Hospital Center over a one-year period (2012) were retrospectively screened. IgG4 immunostaining was performed on all LSGB showing lymphocytic sialadenitis defined by a Chisholm score > 3. Histopathological criteria for IgG4-related disease according to international criteria and final diagnosis associated with lymphocytic sialadenitis were analyzed in all cases.

**Results:** Three hundred and fifty patients had a labial salivary gland biopsy (LSGB). Among them, 79 (23%) had a lymphocytic sialadenitis. Mean age at diagnosis was 55.5 ± 15.7 years old. Female/Male Sex ratio was 2.3/2.0. LSGB was performed because of sicca symptoms in most cases (48/79, 60.8%). Only one (1/79, 1.3%) LSGB showed histopathological features of IgG4-related disease in a patient who otherwise displayed obvious extra-salivary features of IgG4-related disease. Overall, the diagnoses associated with lymphocytic sialadenitis were Sjögren’s syndrome (29/79, 36.7%), other autoimmune disorders (besides Sjögren’s syndrome) (17/79, 21.5%), idiopathic pulmonary fibrosis (5/79, 6.3%), sarcoidosis (3/79, 3.8%), B-cell hemopathy (3/79, 3.8%), hepatitis C infection (2/79, 2.5%), unclassified arthritides (1/79, 1.3%), idiopathic uveitis (1/79, 1.3%), multiple sclerosis (1/79, 1.3%) and tuberculosis (1/79, 1.3%). In 15 cases (19%), no diagnosis could be obtained despite extensive work-up. Of note, IgG4 staining was negative in all patients with unexplained lymphocytic sialadenitis.

**Conclusion:** The prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on LSGB is very low. Systematic IgG4 immunostaining has no diagnostic value in patients with lymphocytic sialadenitis. On the other hand, lip biopsy, by being simple and safe, can be useful for a definite diagnosis when IgG4-related disease is suspected.

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1240

**Efficacy of Anakinra in Refractory Adult-Onset Still’s Disease: Multicenter Study of 41 Patients.** Leyre Blancho-Zarrabatia1, Ricardo Blanco2, Alejandro Oliver2, Anne Rivers-Frutos2, Santos Castañeda3, Maria Luisa Veloso Feijoo4, Javier Narvaez2, Inmaculada Jimenez–Moleon5, Olga Maza-Alonso6, Maria Carmen Ordóñez7, Jose Antonio Bernal8, M. Victoria Hernández9, Alberto Šifuentes Giraldo10, Catalina Gomez–Gay11, Hospital Universitario Marques de Valdecilla. IDIVAL, Santander. Spain, Santander, Spain, 2Hospital Universitario Germans Trias i Pujol, Badalona, Spain, 3Hospital Universitario de La Princesa, HSP, Madrid, Spain, 4H Valme, Sevilla, Spain, 5Hospital Universitario de Bellvitge, Barcelona, Spain, Barcelona, Spain, 6Hospital San Cecilio, Granada, Spain, 7HU Donostia, San Sebastián, Spain, 8Hospital Regional Universitario Carlos Haya, Málaga, Spain, 9HGU, Alicante, Alicante, Spain, 10Hospital Clinico, Barcelona, Barcelona, Spain, 11HU Ramón y Cajal, Madrid, Spain, 12Hospital Universitario Basurto, Bilbao, Spain, 13Hospital General, Granollers, Granollers, Spain, 14H Sant Jaume, Calella, Spain, 15HU Alava, Vitoria, Spain, 16University Hospital Parc Taulí, Sabadell, Spain, 17HU Son Espases, Palma de Mallorca, Palma de Mallorca, Spain, 18Hospital Universitario 12 de Octubre, Madrid, Spain, 19Hematology Unit. Hospital Jerez, Jerez, Spain, 20Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

**Background/Purpose:** A dult-onset Still’s disease (AOSD) is frequently refractory to standard therapy. Anakinra (ANK), an interleukin-1 (IL-1) receptor antagonist, has demonstrated efficacy in single cases or in small series of AOSD. We assessed the efficacy of ANK in a large series of AOSD patients.

**Methods:** Multicenter retrospective open-label study of 41 patients with AOSD from 19 hospitals. ANK was used due to lack of efficacy to standard synthetic immunosuppressive drugs and some cases also due to lack of adequate response to at least 1 biologic agent.

**Results:** 41 Patients (26 women/15 men) had a mean age of 34.4 ± 14 years and a median (interquartile range) age of 2.2 [1–24] years before ANK onset.

Besides oral steroids, patients had previously received the following drugs: Methotrexate (32 patients), Leflunomide (7), Etanercept (10), Infliximab (9) and Adalimumab (6). ANK standard dose was 100 mgsciday.

**Table**

<table>
<thead>
<tr>
<th>Table</th>
<th>Month 6</th>
<th>Month 12</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N = 41</td>
<td>N = 82</td>
</tr>
<tr>
<td>Patients with joint manifestations, %</td>
<td>87.8</td>
<td>29.6</td>
</tr>
<tr>
<td>Patients with fever, %</td>
<td>78.0</td>
<td>37.4</td>
</tr>
<tr>
<td>Patients with cutaneous manifestations, %</td>
<td>58.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**Conclusion:** ANK is associated with rapid and maintained clinical and laboratory improvement, even in cases that are refractory to other biologic agents. However, joint manifestations seem to be more refractory than systemic manifestations.
**Disclosure:** L. Riancho-Zarrabéitía, None; R. Blanco, None; A. Oliveira, None; A. Riveros-Frutos, None; S. Castañeda, None; M. L. Veloso Feljo, None; J. Navarz, None; I. J. Jiménez-Méndez, None; O. Maíz-Alonso, None; M. C. Ordóñez, None; J. A. Bernal, None; M. V. Hernández, None; A. Sifuentes Giraldo, None; C. Gómez Arango, None; E. Galindo-Agirregoitia, None; V. Ortiz-Santamaria, None; J. del Blanco, None; J.-R. De Dios, None; M. Moreno, None; J. Fiter, None; M. de los Ricos, None; P. Carreira, None; M. J. Rodriguez Valls Sr., None; F. Ortiz-Sanjuán, None; T. Pina Murcia, None; M. Santos-Gómez, None; M. A. González Gay, None.

**1241**

**Efficacy of Tocilizumab Therapy in Korean Patients with Adult Onset Still’s Disease: Multicenter Retrospective Study of 20 Cases.** Jin Ju Kim1, Joo Hyun Lee2, Chang-Nam Son3, Hyoun-Ah Kim4, Kwang-Hoon Lee5, Sang Tae Choi6, Eun Young Lee7, Ki Chul Shin8, Hoon-Suk Cha9 and Dae-Hyun Yoo10. 1Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 2IlSan Paik Hospital, Inje University, Goyang, South Korea, 3Kemgyung University School of Medicine, Daegu, South Korea, 4Aju University School of Medicine, Suwon, South Korea, 5Dongguk University Ilsan Hospital, Goyang, South Korea, 6Chung-Ang University College of Medicine, Seoul, South Korea, 7Seoul National University College of Medicine, Seoul, South Korea, 8Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

**Background/Purpose:** Adult onset Still’s disease (AOSD) is a rare inflammatory disorder of unknown etiology. Refractory cases to conventional therapy require biologic agents. Although IL-1 blockade may be more effective in patients with chronic articular disease than patients with CAD. Different pathogenic mechanisms underlying SD and SD* are not easily available. In this study, we assessed the efficacy of TCZ in multicenter retrospective fashion.

**Methods:** We retrospectively collected clinical data of AOSD patients who were treated with in Korea. The response to TCZ was defined as decreased modified Pouchot’s score more than 2 score with decreased acute phase reactants compared to initial treatment of TCZ at least two consecutive months.

**Results:** Patients (15 women/5 men) had a mean age of 42.5 ± 18.8 years and the age of diagnosis was 37.3 ± 21.2 years old. The mean disease duration before TCZ treatment was 40.7 ± 33.6 months. Ten patients (52.6%) had polyarticular systemic pattern and 9 patient had chronic articular pattern, but 1 patient was no classified due to short disease duration. Immune modulating agents before TCZ therapy were as follows: methotrexate (n=18), leflunomide (n=12), cyclosporine (n=9), azathioprine (n=8) and hydroxychloroquine (n=7). Biologic agents before TCZ therapy were etanercept (n=7), infliximab (n=4), adalimumab (n=3), abatacept (n=2) and anakinra (n=1). TCZ at the onset, the most frequent clinical manifestations were joint manifestations (80.0%), rash (50.0%), myalgia (35.0%), fever (25.0%) and sore throat (25.0%) (Table 1). The baseline laboratory parameters such as leucocytosis, ESR, CRP and serum ferritin showed high level (Table 1). The mean dose of TCZ was 7.8 mg/kg (4–8 mg/kg) per 4 weeks and mean duration of TCZ administration was 7.9 ± 6.7 months. The 90.0% of patients showed clinical and laboratory improvement after TCZ therapy (Table 1). The median dose of prednisolone was also significantly reduced from 10.1 mg/day at TCZ onset to 7.5 ± 3.9 mg/day at 12 months (Table 1). The 35% of patients had side effects during TCZ treatment as follows: leukopenia (n=2), hypertension (n=2), alopecia (n=2), pneumonia (n=1). Four patients (20%) relapsed after 5.0 ± 3.6 months of discontinuation of TCZ.

**Conclusion:** TCZ was effective in Korean AOSD patients refractory to conventional therapy and/or other biologic agents. Larger and prospective study is needed for further investigation.

Table 1. Change of clinical manifestations and laboratory parameters before and after TCZ treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N=20)</th>
<th>After 6 months (N=12)</th>
<th>After 12 months (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (n, %)</td>
<td>25.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>1.0 ± 1.4</td>
</tr>
<tr>
<td>Sore throat (n, %)</td>
<td>25.0 ± 1.8</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Rash* (n, %)</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

**Upcoming: Switching Biologic Agents in Refractory Adult-Onset Still’s Disease: Efficacy and Safety in a Cohort of 20 Patients at a Single Referral Center.** Giulio Cavalli1, Stefano Franchini1, Corrado Campochiaro2, Elena Baldissera3, Lorenzo Dagna4 and Maria Grazia Sabbadini5. 1Vita-Salute San Raffaele University, Milan, Italy, 2Clinical immunopathology and advanced medical therapeutics, San Raffaele Scientific Institute, Milan, Italy, 3Vita-Salute San Raffaele University, Milan, Italy.

**Background/Purpose:** No data is available on the long-term clinical outcome of AOSD patients treated with biologic drugs, nor on the efficacy and safety of switching biologics in the management of refractory cases. We aimed to evaluate the efficacy and safety of switching biologic agents in a large, monocentric cohort of 20 patients with refractory AOSD.

**Methods:** Twenty Italian AOSD patients treated with biologic agents were followed-up at our Institution for at least 24 months. For each case we retrospectively evaluated the disease course, the efficacy of treatment, and the potential adverse effects. Efficacy was evaluated as “Complete response” (CR: absence of articular and systemic manifestations, normalization of inflammatory indexes, >50% reduction in the corticosteroid dosage); “Partial response” (PR: clinical improvement without normalization of inflammatory markers, <50% reduction in the dose of steroids); or “Treatment failure” (TF: persistence/worsening of disease manifestations, persistent elevation of inflammatory markers, or need for an increased dose of corticosteroids despite 2 months of treatment).

**Results:** The median duration of follow-up was 5 years. In 12 patients a single biologic drug induced a clinical response. Five patients were switched to a different biologic because of lack of efficacy. In 3 patients, a third biological was necessary to achieve disease control. Biologics eventually determined a clinical response in all patients. Anakinra was used in all 20 patients; etanercept, tocilizumab and adalimumab was used in 6, 4, and 1 patient, respectively. Sixteen patients responded to anakinra (80%; CR 70%; PR 10%). Four patients (20%) did not respond to anakinra, and of these three responded to tocilizumab, and one responded to adalimumab. Tocilizumab was used unsuccessfully in six patients. Patients with systemic manifestations had better responses than patients with chronic articular disease (p<0.05). Overall, biologic agents determined a significant reduction in the dose of the associated therapy with corticosteroids (p<0.0001) and DMARDs (p<0.05).

**Conclusion:** Biologic agents represent a pivotal therapeutic resource for AOSD patients refractory to conventional treatment. Although the biologic drug of choice may prove ineffective, switching between biologics ultimately resulted in a clinical response in all patients without significant adverse effects, hence the importance of pursuing a tailored treatment approach. Athough IL-1 blockade with anakinra represents the mainstay of treatment, IL-6 blockade may be more effective in patients with chronic articular involvement. Both anakinra and tocilizumab were more effective than TNF-α blockers. Patients with SD are more likely to respond favorably to biologics than patients with CAD. Different pathogenic mechanisms underlying SD and
MACROPHAGE ACTIVATION SYNDROME (MAS) CAN BE A SERIOUS COMPLICATION OF AOSD AND MAY Co-exist WITH ITS ONSET. IN CONJUNCTION WITH LITERATURE, THIS STUDY OF A RELATIVELY LARGE CASE SERIES SUGGESTS THAT TREATMENT WITH A TRIPLE COMBINATION OF AN IL-1 RECEPTOR ANTAGONIST, A CALCINEURIN INHIBITOR AND SYSTEMIC GLUCOCORTICOIDS MAY HAVE FAVORABLE OUTCOMES.

**Disclosure:** R. Chavda, None; M. R. Bussey, None; R. Tehrani, None; R. A. Ostrowski, None.

**1245**

**LONG TERM OUTCOME OF INFLIIXIMAB IN SEVERE AND REFRACTORY SYSTEMIC SARCOIDOSIS: REPORT OF 16 CASES.** Catherine Chapelon,1 David Saadoun,2 Lucie Biard,3 Mathieu Resche-Rigon,4 Baptiste Herrier,5 Nathalie Costedoat-Chalumeau,6 Aurélie Dries,6 Jean-Marc Léger6 and Patrice Ca-doch7.1DHU 218 Internal Medicine Referral Center for Autoimmune diseases Pitie Hospital, Paris, France. 2Hôpital Saint-Louis, Paris, France. 3Hôpital Pité-Salpêtrière University Hospital, PARIS, France. 4Assistance Publique - Hôpitaux de Paris, Pité-Salpêtrière University Hospital, PARIS, France. 5Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France. 6Hôpital Saint-Louis, Paris, France. 7Assistance Publique - Hôpitaux de Paris, Hopital Pitié-Salpétrière, PARIS, France. 8Hôpital Pitié-Salpétrière, Neurology, Paris, France. 9Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, PARIS, France. 10Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Neurology, PARIS, France.

**Background/Purpose:** Infliximab (IFX) appears to be effective in refractory sarcoidosis. However, data are lacking regarding its efficacy in severe sarcoidosis (i.e. with cardiac and/or neurological involvement).

**Methods:** Retrospective single-center study including 16 unselected consecutive patients with biopsy proven, severe and resistant sarcoidosis, who were treated by infliximab (3 or 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks) between 2005 and 2013.

**Results:** Following IFX therapy we observed an improvement in 92% of cases, with a marked decrease of the severity score [median score 6 (3–12) vs. 2 (1–8), p<0.0001] and trend toward steroid sparing effect [12.5 (0–40) vs. 0.5 mg/d (0–30), p=0.11] between baseline and the end of follow-up, respectively. Regarding the index organ response, we observed a remission of cardiac and central nervous system involvements in 4 out of 4 and 11 out of 12 cases, respectively. Thirty-eight percent of patients experienced a relapse. After a median follow-up of 57 months (2 to 91), we observed 7 (44%) infectious complications, 1 paradoxical cutaneous granuloma and 1 leuco-
cephalopathy. Infectious complications were mostly observed in male (6/7 (86%), p = 0.06), with a longer duration of steroids (108 vs. 39 months, p = 0.11) and immunosuppressant use prior IFX (42 vs. 24 months, p = 0.08) compared to their negative counterpart, respectively.

**Conclusion:** IFX was efficient in severe and refractory sarcoidosis. Infectious complications were frequent and occurred mainly in male patients with longer duration of steroids and immunosuppressant use prior IFX.

**Disclosure C. Chapelon, None; D. Saadoun, None; L. Biard, None; M. Resch-Rigon, None; B. Hervier, None; N. Costeodat-Chalumeau, None; A. Drier, None; J. M. Léger, None; P. Cacoub, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Glaxo Smith Kline, Xience, Janssen, Merck Sharp Dohme, Roche, Servier, Vifor., 5.**

**1246**


**Method:** A retrospective chart review of biopsies-diagnosed patients with sarcoidosis for > 1 year extracted and compared variables of prevalence, age (at chart review), sex, race, smoking status and designation of BMD defined as osteopenia or osteoporosis with a T-score of ≤ -1 on DXA. Calculations were performed by non-parametric analyses using Fisher’s exact for categorical data and Mann Whitney tests for continuous variables.

**Results:** 269 charts were reviewed and 109 had documentation of biopsy. Of these 109, 61 patients (85.9% Black) had documentation of DXA, 38 (62.3%) with BMD (30 with osteopenia and 8 with osteoporosis). Although patients with BMI ≥ 30 had a significantly lower incidence of BMD vs. those with BMI < 30, BMD incidence exceeded reported in CDC data for overweight subjects. No differences (table) were seen in incident BMD in patients age ≥ vs < 65, in ever vs never smokers (no significant age difference between groups), nor in males vs females (despite females being significantly older than males with median 54 and 48 respectively).

**Table 1.** Comparison of Factors Influencing Bone Mineral Density within a New Orleans Sarcoidosis Population

<table>
<thead>
<tr>
<th>Low BMD</th>
<th>Normal BMD</th>
<th>Odds Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 Y ears Old</td>
<td>26 (10/38)</td>
<td>3.75 (95% CI 1.74 to 8.196)</td>
<td>0.11</td>
</tr>
<tr>
<td>% Male</td>
<td>13% (5/38)</td>
<td>0.43 (95% CI 0.11 to 1.61)</td>
<td>0.30</td>
</tr>
<tr>
<td>% BMI ≥ 30</td>
<td>18% (7/38)</td>
<td>0.21 (95% CI 0.06 to 0.66)</td>
<td>0.01</td>
</tr>
<tr>
<td>% Smoker</td>
<td>32% (12/37)</td>
<td>0.48 (95% CI 0.14 to 1.59)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Conclusion:** Factors protective against BMD in the general population were not demonstrated in this retrospective sarcoidosis predominantly black cohort. A lower risk of BMD was not conferred by age < 65, male gender, or non-smoking status. While BMI appeared to confer protection, the prevalence in obese sarcoidosis patients supersedes that in CDC reported data. These trends suggest an abnormal signal of incident BMD in this population differing from the general population. Lack of uniformity of documentation inherent in retrospective methods limits the assessment of important associative and causative influences such as duration and dose of GCs, biomarkers of bone metabolism (e.g. calcium, calcitriol, etc) and fracture risk which will be examined in our prospective sarcoid registry. Nevertheless these findings are important and support increased vigilance in GC use and perhaps consideration to initiate GC sparing agents earlier in the disease course, as well as routine DXA screening in sarcoidosis.

**Disclosure** M. Walker, None; H. K. Grewal, None; A. J. Janot, None; M. Yu, None; S. Cenac, None; M. R. Lamm, None; L. A. Saketkoo, None.

**1247**

The Prevalence of Sacroiliitis and Spondyloarthropathy in Patients with Sarcoidosis. Senol Kobak, Fidan Sever, Ozlem Inci, and Mehmet Orman.

**Background/Purpose:** Sarcoidosis is a chronic granulomatous disease, which can involve different organs and systems. Coexistence of sarcoidosis and spondyloarthropathy has been reported in numerous case reports. **Purpose:** To determine the prevalence of sarcoidosis and spondyloarthropathy in patients previously diagnosed with sarcoidosis, and to investigate any possible relation with clinical findings.

**Methods:** Forty-two patients with sarcoidosis were enrolled in the study. Any signs and symptoms in regard to spondyloarthropathy (i.e. existence of inflammatory back pain, gluteal pain, uveitis, enthesitis, dactylitis, inflammatory bowel disease, psoriasis) were questioned in details and biochemical tests were evaluated. Sacroiliac joint imaging and lateral heel imaging were performed in all patients. The existence of active sarcoidosis was confirmed by magnetic resonance imaging of sacroiliac joint with short time inversion recovery (STIR) method.

**Results:** Sacroiliitis was found in 6 of the 42 (14.3%) sarcoidosis patients and all of these patients were female. The average age of the patients with sarcoiditis was 55 years, while the average duration of the disease was 17.8 months. Common features of the disease in these six patients were inflammatory back pain as the major clinical complaint, stage 2 sacroiliitis as revealed by radiological staging and the negativity of HLA B-27 test. These six patients with sarcoidosis were diagnosed as spondyloarthropathy according to the criteria of ASAS and of ESSG.

**Conclusion:** We found spondyloarthropathy in patients with sarcoidosis at a higher percentage rate than in the general population (1–1.9%). Controlled trials involving large series of patients are required for the confirmation of the data.

**Disclosure** S. Kobak, None; F. Sever, None; O. Inci, None; M. Orman, None.

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SeroLogic and Clinical Overlap Between Sarcoidosis and the Rheumatic Autoimmune Diseases. Sabrina Qazi and Marie Claire Maroun. Wayne State University, Detroit, MI.

**Background/Purpose:** Sarcoidosis is a systemic inflammatory disorder of unknown etiology, characterized pathologically by noncaseating epithelioid cell granulomas, primarily affecting the lungs, the eye, the skin, and the lymphatics. Musculoskeletal manifestations and the immunologic profile in sarcoidosis may mimic those seen in the rheumatic autoimmune diseases. Hyperg lobulinemia and autoantibodies including rheumatoid factor [RF] and anti-nuclear antibodies [ANA] have been reported. Citrullination is a post-translational modification of proteins, in which the amino acid arginine is enzymatically converted to citrulline. Citrullinated peptides can be found at the site of chronic inflammation and, in the appropriate genetic setting, can elicit an autoimmune response. Anti-citrullinated peptide antibodies [ACPA] are thought to be a new and more specific marker than RFs in rheumatoid arthritis [RA] and have been added to the new RA classification criteria. The occurrence of ACPA in sarcoidosis has not previously been described.

**Objectives:** The aim of this study was to investigate the serologic profile, in particular the serum RFs, ANAs and ACPAs in patients with sarcoidosis attending the rheumatology and/or pulmonary clinics.

**Methods:** We retrospectively reviewed the charts of 73 patients with the diagnosis of sarcoidosis and recorded the clinical manifestations and the immunological profile including ANA, RF, and ACPA.

**Results:** Forty one percent of patients with sarcoidosis [30/73] had a positive ANA, with titers ranging from weakly positive [1/40] to high positive [1/1280]. RF and ACPA were not available on all patients. RF was found in 22 % of patients [13/59] while ACPA was found positive at moderately elevated titters in 8% of patients [2/24] in the absence of RA. One patient with RA with positive CCP was excluded from the analysis. One patient had Sjogren syndrome and one had systemic lupus erythematosus. In addition, 22% of the patients had sarcoid arthropathy.

**Conclusion:** ANAs, RFs and ACPAs were found in sarcoidosis patients at titters within the range found in the rheumatic A Ds. ACPA was present in 8% of sarcoidosis patients in the absence of RA. We suggest that investigation of the autoantibody signatures responsible for the serologic overlap between sarcoidosis and the rheumatic A Ds, especially ACPA may be of great interest.
since, since inflammation is central in the immune-pathogenesis of sarcoidosis.

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Efficacy of Tocilizumab in Patients with Uveitis Refractory to Other Biologic Drugs: A Multicenter Study on 31 Cases. Leyre Riancho-Zarrabezudo1, Vanesa Calvo-Rio1, Ricardo Blanco1, Inmaculada Calvo2, Emma Beltrán-Catalán3, Alfredo Ader4, M. aria M esquida5, M aria Victoria Hernández6, M aria hernández7, A ntonio Anes-Sandoval8, Luis Francisco Linares Ferrando9, Olga M aiz Alonso9, Ana Blasco10, Beatriz Bravolo11, Gisela Díaz-Cordovez12, Trinitario Pina13, Montserrat Santos-Gómez14 and Miguel Ángel González-Gay15.

Background/Purpose: To evaluate the clinical response and safety of Tocilizumab (TCZ) in a series of patients with non-infectious uveitis refractory to other biologic drugs.

Methods: Multicenter study of patients studied in the Uveitis Units of 14 hospitals from Spain. All patients had experienced inadequate response to at least one biologic agent. Intracocular inflammation, macular thickness, visual acuity, steroid sparing effect and immunosuppression load score were the outcome variables. Comparisons were made between baseline and 1st week, 1st month, 6th month and 12th year.

Results: We studied 31 patients/58 affected eyes (7 men/24 women) with a mean age of 31.7 ± 17.2 years (range 8–70). Uveitis was bilateral (n = 27 cases) or unilateral (n = 4). The pattern of ocular involvement was anterior uveitis (n = 11 cases), panuveitis (n = 6), posterior (n = 4), intermediate (n = 3), panuveitis + retinal vasculitis (n = 3), retinal vasculitis without uveitis (n = 2) and panuveitis + retinal vasculitis + papillitis (n = 1). Uveitis was acute (n = 1), chronic (n = 26) or recurrent (n = 4).

The main underlying diseases were: Juvenile Idiopathic Arthritis (n = 13), Behçet disease (n = 5), idiopathetic uveitis (n = 5), Birdshot retinopathy (n = 3); idiopathic retinal vasculitis (n = 2); spondyloarthritides (n = 2) and rheumatoid arthritis (n = 1).

Besides oral steroids and before TCZ onset they had received: intraocular corticosteroids (n = 21), intravenous methylprednisolone pulses (n = 9), methotrexate (n = 25), cyclosporine A (n = 20), azathioprine (n = 3), other synthetic immunosuppressive drugs (n = 9), adalimumab (n = 25), infliximab (n = 12), etanercept (n = 7), abatacept (n = 6), rituximab (n = 2), golimumab (n = 2) and anakinra (n = 1). TCZ was started because inefficacy (n = 28) and/or toxicity (n = 3) to other biologics. TCZ was used as monotherapy (n = 10) or in combination with methotrexate (n = 12), leflunomide (n = 4), cyclosporine A (n = 4) and mycophenolate (n = 1). After one year of TCZ therapy all the following variable improved statistically (p < 0.05) (TABLE): a) mean best corrected visual acuity (from 0.46 ± 0.3 at baseline to 0.58 ± 0.3); b) anterior chamber and vitreous inflammation (from 58% and 60% of eyes, to 15.3% and 34%, respectively); c) cystoid macula edema (OCT > 300 μm) (from 66.6% to 21%); d) the mean OCT (from 389.1 ± 197.2 to 261.8 ± 46.1 μm); and e) the median IQR (Q3) of prednisone (from 30 [10–90] to 5 [5–5] mg/day).

A non-statistically reduction in the mean of the immunosuppression load score were the outcome variables were bullous impetigo (n = 1), mild thrombotic occlusion (n = 1), pneumonia (n = 1) and infectious reaction (n = 1).

Conclusion: Our results indicate that TCZ is an effective and safe therapy for patients with non-infectious uveitis refractory to other biologic agents.

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Background/Purpose: To evaluate the clinical response and safety of golimumab (GLM) in a series of patients with non-infectious uveitis refractory to other anti-TNFα drugs. GLM was given at the standard dose of 50 mg/sc/month. The main outcome measures were degree of anterior and posterior chamber inflammation, visual acuity, and macular thickness.

Methods: Multicenter study of 29 patients with uveitis that was refractory to previous standard synthetic immunosuppressive drugs and at least 1 anti-TNFα drug. GLM was given at the standard dose of 50 mg/sc/month. The main outcome measures were degree of anterior and posterior chamber inflammation, visual acuity, and macular thickness.

Results: A total of 29 patients (44 affected eyes) (21 men/8 women) with a mean age of 34.6 ± 9.5 years (range 11–48) were studied. Uveitis was bilateral (n = 15 cases) or unilateral (n = 14). The pattern of ocular involvement was anterior uveitis (n = 19), panuveitis (n = 6) and intermediate, anterior + intermediate, anterior + posterior and intermediate + posterior (one case each). Uveitis was acute (n = 1), chronic (n = 16) or recurrent (n = 12). The underlying diseases were spondyloarthritides (n = 9), psoriatic arthritis (n = 5), juvenile idiopathic arthritis (n = 4), Behçet disease (n = 4), sarcoidosis (n = 3), uveitis associated with HLA-B27 and ulcerative colitis (n = 1), undifferentiated arthritis (n = 1), pars planitis (n = 1) and Vogt-Koyanagi-Harada (n = 1).

Besides oral steroids and before GLM onset they had received: intraocular corticosteroids (n = 11), intravenous pulses of methylprednisolone (n = 6), methotrexate (n = 23), cyclosporine A (n = 6), azathioprine (n = 7), adalimumab (n = 17), infliximab (n = 15), abatacept (n = 2) and certolizumab (n = 1). GLM was started because inefficacy (n = 27) and/or toxicity (n = 2) to other biologics. GLM was used as monotherapy (n = 11) or in combination with methotrexate (n = 10), azathioprine (n = 4), leflunomide (n = 2), and mycophenolate (n = 2).

After one year of GLM therapy all the following variables improved significantly (p < 0.05) (TABLE): a) the mean best corrected visual acuity (from 0.68 ± 0.3 at baseline to 0.75 ± 0.3); b) anterior chamber and vitreous inflammation (from 62.7% and 40.4% of eyes, to 12.5% and 0% respectively); c) cystoid macula edema (OCT > 300 μm), (from 50% to 0%); d) the mean OCT (from 318.9 ± 74 to 244.2 ± 43.2 μm); and e) the mean dose of prednisone (from 24 ± 20.1 to 7.7 ± 6.7 mg/day).

A mean follow-up of 13.1 ± 8.5 (range 2–30) months the most important side-effects observed were injection site erythema (n = 3) and herpes zoster (n = 1).

Conclusion: Our results suggest that GLM may be an effective and safe treatment for patients with uveitis refractory to other anti-TNFα drugs.
Observation during follow-up.

Edema was present in 4 eyes (3 patients) at baseline. The mean OCT 0.34 logMAR visual acuity improved significantly from 0.41 (Table).

To our knowledge, information on Certolizumab Pegol (CZP) in patients with uveitis refractory to other anti-TNF-α drugs is scarce. Due to this, we assessed the efficacy of CZP in a series of patients with uveitis refractory to other anti-TNF-α drugs.

Methods: Study from 3 tertiary referral centers that included patients with uveitis that had been refractory to previous standard synthetic immunosuppressive and at least 1 anti-TNF-α drug. For the inclusion in the assessment, a follow-up of at least 6 months was required.

Outcome was measured according to SUN criteria (abs et al. 2005) for anterior chamber inflammation (0 to 4+) and scale (0 to 4+) for vitreous haze (Bloch-Michel 1997). Best corrected visual acuity (BCVA) was measured by Snellen charts and converted to logarithm (LogMAR) (Jabs 2005). Macular thickness was defined by OCT.

Results: We studied 7 patients (14 affected eyes) (4 men/3 women) with a mean age of 42.4 ± 8.8 years. The main underlying diseases were: Behçet disease (3 cases), idiopathic retinal vasculitis (1 case), ankylosing spondylitis (1 case), psoriatic arthritis and Crohn’s disease (1 case) and relapsing polychondritis (1 case). All patients suffered from long-lasting chronic relapsing ocular inflammation with a median evolution time until CZP onset of 108 (range 68–302) months.

Table

<table>
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<tr>
<th>Case</th>
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<th>Disease</th>
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Background/Purpose: Treatment with high-dose intravenous methylprednisolone (IVMP) pulse therapy has proved to be effective in different inflammatory conditions. Since severe ocular inflammation can lead to rapid and irreversible structural and functional eye damage, we aimed to assess the efficacy of IVMP pulse therapy as a remission induction therapy in patients with severe ocular inflammation.

Methods: Multicenter study of patients with severe ocular inflammation attended at 11 Uveitis Units from Spain. All patients were treated with IVMP pulse therapy for 2–5 consecutive days. MP dose ranged from 0.25 to 1 gram per day. Patients were evaluated at baseline and on days 2–5, 7, 15 and 30 after treatment with IVMP.

Results: 104 patients (59 women/45 men; mean age of 42.27 ± 14.42 years (range 8–76 years) with severe ocular inflammation were included in the study. The most frequent underlying conditions were: idiopathic uveitis (n = 21), Vogt-Koyanagi-Harada (n = 26), Behçet disease (n = 19), spondyloarthritis (n = 4), Sjögren syndrome (n = 2), psoriatic arthritis (n = 2) and multiple sclerosis (n = 2). All the patients had active and severe intraocular inflammation at baseline. The inflammatory ocular patterns were: panuveitis (n = 61), posterior uveitis (n = 35), anterior uveitis (n = 3), scleritis (n = 3) and intermediate uveitis (n = 2). Bilateral ocular involvement was observed in 65 patients (62.5%). Following IVMP pulse therapy inflammation in the anterior chamber, vitreitis and visual acuity experienced rapid and statistically significant improvement. It was already seen 2 days after the onset of IVMP therapy. Improvement of retinal vasculitis, choroiditis/chorioretinitis and macular edema was achieved more gradually, reaching statistical significance from the first week. Optical coherence tomography (OCT) showed a macular thickening (>250μm) in 30 eyes at baseline, with normalization in 30% of the affected eyes at day 15 and in 50% of the affected eyes at day 30 (p<0.05). IVMP pulse therapy was well tolerated without remarkable side effects.

Conclusion: Treatment with IVMP pulse therapy decreases rapidly the ocular inflammation, leading to an improvement of all the ophthalmological measurements without important side effects.
Anakinra for the Management of Resistant Idiopathic Recurrent Pericarditis in Adults. Dimitrios Vassilopoulos 1, Panagiota Vasilieou 2, Christos Koutsianas 2, Katerina Antnatoou 2, Christina Tsalapaki 2, Dimitrios Pectasides 2 and George Lazaros 2. 1 University of Athens Medical School, Athens, Greece, 2 Hippokration General Hospital, Athens, Greece.

Background/Purpose: Recurrent idiopathic pericarditis is currently considered as an autoimmune inflammatory disorder which is frequently either resistant to standard therapy (with NSAIDs, colchicine or corticosteroids-CS) or requires long term treatment with high doses of CS. Interleukin-1 (IL-1) inhibition has shown encouraging results in pediatric cases and a few adult cases. The aim of our study was to explore the efficacy and safety of anakinra in adult patients with recurrent idiopathic pericarditis.

Methods: In this open label study, ten patients with idiopathic recurrent pericarditis were included. All were resistant and/or intolerant to previous treatment with aspirin and/or NSAIDs, colchicine and CS while two (20%) had failed azathioprine therapy. Patients were initially treated with daily subcutaneous injections of anakinra (100 mg) with gradual tapering of the administered dose. Recurrences as well as adverse events were recorded in all patients during the follow-up period (24 ± 16 months).

Results: Among the 10 patients included (5 females/5 males, mean age = 42 ± 18 years, mean disease duration = 37 ± 22 months), the mean number of recurrences despite standard therapy was 8 ± 3.7 while the baseline mean daily dose of prednisolone was 14.1 ± 7.9 mg. All patients treated with anakinra demonstrated a rapid clinical response with resolution of symptoms and normalization of CRP (mean time = 5.9 ± 2.3 days). All patients receiving CS at baseline (n=8) were able to gradually discontinue them (mean time to discontinuation = 53 ± 44 days). Among 7 patients who discontinued anakinra, 5 (70%) relapsed after a mean time of 18 ± 9 days; in 4/5, anakinra was restarted leading again to clinical remission while one was successfully treated with NSAIDs and colchicine. One patient discontinued therapy due to transient elevation of aminotransferases while 6 (60%) demonstrated mild skin reactions at the injection site.

Conclusion: Our study shows that IL-1 inhibition with anakinra is a highly efficacious, safe and steroid-sparing strategy for treatment-resistant recurrent idiopathic pericarditis in adults. Further studies need to be clarified to the appropriate dose and duration of therapy in these patients.

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Pathogenic Role of Tyrosyl-Transfer RNA Synthetase in Anti-Synthetase Syndrome. Yuko Okamoto 1, Yasuhiro Katsumata 2, Yasushi Kawauchi 3, Manabu Kawamoto 3, Ken Ikawa 3, Miki Miyakoshi 3, Hiromichi Wakasugi 3, Koji Tahara 3, Kaori Ito 3, Hiroaki Hatton 3, Takahisa Gono 3, Masanori Hanagata 3, Tomoki Higuchi 3, Hidenaga Kawasumi 3 and Hisashi Yamanaka 3. 1 Tokyo Women's Medical University, Tokyo, Japan, 2 The University of Tokyo, Tokyo, Japan, 3 BML, Saitama, Japan, 4 Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Autoantibodies directed against the aminocyl transfer RNA (tRNA) synthetases are associated with myositis, arthritis, Raynaud's phenomenon, mechanic's hands, fever, and interstitial lung disease, clinically referred to as anti-synthetase syndrome. Targoff and his colleagues reported a case with an autoantibody to tyrosyl-tRNA synthetase (TyrRS) with features of anti-synthetase syndrome at the 2005 ACR meeting. At the 2013 ACR meeting, we reported three more patients with anti-TyrRS autoantibodies in the setting of anti-synthetase syndrome using other assays than previously reported methods: enzyme-linked immunosorbent assay, Western blot, and immunoprecipitation assay. In addition, one of the authors of this abstract reported that TyrRS can be split into two fragments with distinct chemotactic activities: an interleukin-8 (IL-8)-like cytokine, and an...
endothelial-monocyte-activating polypeptide II (ELAM II)-like cytokine (Science, 1999). We aimed to further elucidate the pathogenic role of TyrRS in anti-synthetase syndrome.

Methods: Previously defined anti–TyrRS antibody–positive patients with features of anti-synthetase syndrome were the study subjects. Anti–TyrRS antibody–positive and control sera were tested for the ability to inhibit TyrRS aminoacylation by preincubation of the enzyme source with the sera. Recombinant human TyrRS and histidyl–tRNA synthetase (HisRS; j=1) proteins were generated. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood of an anti–TyrRS or an anti–HisRS antibody–positive patient by density gradient centrifugation. Then, PBMCs were cultured and stimulated with TyrRS, HisRS, or phytomenadion (PHAs). Antibody–specific cell proliferation was analyzed using tetrazolium salt as a chromogenic indicator for nicotinamide adenine dinucleotide dehydrogenase.

Results: Anti–TyrRS sera significantly inhibited the in vitro enzymatic function of TyrRS (aminoacylation of tRNA Tyr) compared with normal control serum. In the cell proliferation assay using PBMCs from an anti–TyrRS patient, the O.D. values of the TyrRS–stimulated cells were significantly higher than those of the unstimulated cells and HisRS–stimulated cells. Immunohistochemical analyses demonstrated that C–C chemokine receptor type 1 (CCR1) and type 2 (CCR2) which are the receptor of IL–8, and type 3 (CCR3) which is the receptor of EMAP II, were expressed in degenerating muscle fibers, vascular endothelial cells, and infiltrating mononuclear cells in muscle tissue from an anti–TyrRS antibody–positive patient. Conclusion: This study showed that anti–TyrRS sera can function as an enzyme inhibitor. TyrRS may also play some pathogenic roles in anti-synthetase syndrome by recruiting leukocytes to inflammatory cites and eliciting adaptive immune responses.

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Background/Purpose: Anti jo-1 antibodies are the main marker of the antisyntethetase syndrome (AS), a connective tissue disease chiefly characterized by arthritis (A), myositis (M) and interstitial lung disease (I). These manifestations may occur concomitantly but incomplete clinical pictures have been described. Aim of this study is to further characterize clinical presentation and course of anti jo-1 positive AS.

Methods: Data from multicentre, multinational series of patients diagnosed with anti jo-1 positive AS were retrospectively collected and analyzed. Anti jo-1 antibodies were tested in all cases by commercially available ELISA techniques.

Results: 146 patients were included (Table 1). Median follow up was 91 months (IQR 40.25–153.75). At the onset, a complete clinical picture (AM) was present in 26 patients (18%). Seventy-two patients (49%) had monosymptomatic presentation (A 36, 24.5%; M 20, 14%; I 16, 11%), 19 AM (13.5%), 19 MI (13.5%) and 10 AI (7%). Arthritis was the most frequent feature at the onset, the only detectable in 24.5% of patients. Many patients meet the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA). Rheumatoid factor, anti citrullinated peptide antibodies and RA typical radiographic erosions were not a rare finding. Time from clinical onset to diagnosis was different in incomplete forms (p<0.001). During the follow up, 69 patients (57.5%) developed additional features (median time to progression: 17 months, IQR 7.5–43.5). Progression rate was significantly higher in patients with single feature onset (57/72) with respect to those with two features (12/48) (p<0.001). At the last follow-up, 69 patients (47%) had AM, 23 (15.5%) AM, 23 (15.5%) MI, 16 (11%) AI, 8 (5.5%) I, 4 (3%) A and 3 (2%) M. Twenty-five patients (17.5%) died, 7 (5%) due to AS progression. First line treatment was based on corticosteroids (140 patients, 96%) and immunosuppressants (112, 77%; hydroxychloroquine, HCQ, 30; methotrexate, MTX, 24; IV cyclophosphamide, CYC, 20; cyclosporine, Cs, 20; azathioprine, Aza, 17; mycophenolate mofetil, MMF, 4; tacrolimus, TC, 3; other not listed). Globally, MTX was prescribed in 58 patients (40%, 22 withdrawn for side effects/ineffectiveness), Cys in 47 (32%, 10), Aza 36 (24.5%, 21), CYC 34 (23%, 21), HEC 34 (21%, 21), MMF in 17 (11.5%, in 5), TC in 9 (6.5%, 5).

Conclusion: The diagnosis of anti jo-1 positive AS may be delayed in incomplete forms, which are the vast majority at presentation. Joint involvement may be very similar to RA, adding further challenges to differential diagnosis. Clinical picture evolution is common in patients presenting with incomplete forms and it may occur even after several years from disease onset. Treatment appears heterogeneous and with high drop-out rates in both first and second line. This suggests the need of better strategies supported by specific recommendations.

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A New Multianalyte Assay for Detection of Dermatomyositis-Specific Autoantibodies Undetectable By Commercially Available Immunassays.

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Background/Purpose: The disease expression of dermatomyositis (DM) is highly variable among patients, ranging form those with severe muscle weakness in the absence of internal organ involvement to those with clinically amyopathic DM (CADM) complicating fatal rapidly progressive interstitial lung disease. A series of serum autoantibodies have been identified in DM patients, and are useful in diagnosis as well as disease subsetting. These antibodies to dsDNA, Sm, Jo-1, U1RNP, and anti-SRP are currently available. However, many DM-specific antibodies are still undetectable. As a result, a multianalyte line-blot assay that detects Mi-2, Ku, PM-Scl, Jo-1, SRP, PL-7, PL-12, EJ, OJ, MDA5, MDA5, and KU (Mysitis Profile 3 EUROLINE, EUROMIMUN) is commercially available. However, many DM-specific antibodies are still undetectable by these convenient assays. In this study, we have developed a new multianalyte assay for detection of DM-specific antibodies undetectable by current commercial assays, using a principle of IP combined with immunoblotting.

Methods: We enrolled 116 patients with DM, including 52 with CADM, 23 with clinically amyopathic DM (CADM) and 70 with polymyositis. Serum samples were obtained from242 patients with idiopathic inflammatory myopathy (IIM) who were followed up at 8 medical centers across Japan. IIM patients included 104 with classic DM, 68 with clinically amyopathic DM (CADM) and 70 with polymyositis. Serum samples from 190 patients with other connective tissue diseases (CTDs) including 45 with rheumatoid arthritis, 67 with systemic lupus erythematosus, 43 with systemic sclerosis, 30 with mixed connective tissue disease, 8 with Sjogren’s syndrome, and 7 with others. 123 healthy individuals were also assessed.

Full-length TIF-1y and Mi-2 proteins were produced by a baculovirus expression system. Purified proteins were respectively coated on ELISA plates, on which serum antibody levels were examined. To assess the crossreactivity, partial-length Mi-2 proteins with or without mutations were produced and processed similarly, before subjected to ELISA.

Results: Cutoff levels for anti-TIF-1y and anti-Mi-2 ELISAs were calculated using Receiver Operating Characteristic analysis based on the results of the gold standard IP assay of 242 IIM samples. When compared with IP assay, anti-TIF-1y ELISA showed 100% sensitivity and 99.6% specificity, while anti-Mi-2 ELISA showed 100% sensitivity and 99.6% specificity.

Conclusions: A TIF-1y Ab was positive in 30 (28.8%) with classic DM and 4 (5.9%) with CADM, whereas 14 (13.5%) with classic DM, but none with CADM, were positive for anti-Mi-2 Ab. Anti-TIF-1y and anti-Mi-2 Abs were both positive in 2 (1.1%) with CTDs other than IIM, respectively. Of 30 anti-TIF-1y-positive DM patients, 23 (76.7%) and 5 (14.7%) had malignancy and interstitial lung disease (ILD), respectively. By contrast, 3 (21.4%) had malignancy in 14 anti-Mi-2 positive DM patients, but none had ILD. Both Abs were negative in normal subjects.

Although no samples positive for anti-Mi-2 Ab exceeded the cutoff level of anti-TIF-1y Ab, they showed substantially higher levels than those negative for anti-TIF-1y Ab. ELISA analyses after absorption with various truncated Mi-2 proteins with and without inserted mutations identified that anti-Mi-2 Ab weakly crossreacted with the 896-930 amino acid sequence (gpdilcic) within an Plant Homeodomain of TIF-1y protein, due to the sequence homology with Mi-2B protein (458-465, gpdilcic).

Conclusion: The current study demonstrates the utility of newly established ELISAs for anti-TIF-1y and anti-Mi-2 Abs, which can serve as effective detection systems for routine testing. Developing these ELISAs needs attention to crossreactivity of anti-Mi-2 Ab with TIF1 antigen.

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Enzyme-Linked Immunosorbent Assays for Detection of Anti-Transcriptional Intermediary Factor 1 Gamma and Anti-Mi-2 Autoantibodies in Dermatomyositis: Utility and Crossreactivity.

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Background/Purpose: Anti-transcriptional intermediary factor 1 (TIF-1) and anti-Mi-2 antibodies (Abs) are myositis-specific autoantibodies (MSA) selectively detected in dermatomyositis (DM) patients. Anti-TIF-1 Ab is frequently found in juvenile DM and cancer-associated adult DM. Anti-Mi-2 Ab is predominantly detected in patients with classic DM with favorable prognosis. TIF-1 and Mi-2 Abs are both positive in 1.1% with CTDs other than IIM, respectively. Of 30 anti-TIF-1y-positive DM patients, 23 (76.7%) and 5 (14.7%) had malignancy and interstitial lung disease (ILD), respectively. By contrast, 3 (21.4%) had malignancy in 14 anti-Mi-2 positive DM patients, but none had ILD. Both Abs were negative in normal subjects.

Although no samples positive for anti-Mi-2 Ab exceeded the cutoff level of anti-TIF-1y Ab, they showed substantially higher levels than those negative for anti-TIF-1y Ab. ELISA analyses after absorption with various truncated Mi-2 proteins with and without inserted mutations identified that anti-Mi-2 Ab weakly crossreacted with the 896-930 amino acid sequence (gpdilcic) within a Plant Homeodomain of TIF-1y protein, due to the sequence homology with Mi-2B protein (458-465, gpdilcic).

Conclusion: The current study demonstrates the utility of newly established ELISAs for anti-TIF-1y and anti-Mi-2 Abs, which can serve as effective detection systems for routine testing. Developing these ELISAs needs attention to crossreactivity of anti-Mi-2 Ab with TIF1 antigen.

Disclosure: M. Fujimoto, None; A. Murakami, Medical & Biological Laboratories Co., Ltd., 3; S. Kure, Medical & Biological Laboratories Co., Ltd., 3; A. Kuwajima, employee of Medical & Biological Laboratories Co., Ltd., 3; Y. Fujisawa, None; A. Kawakami, None; M. Mishima, None; S. Sato, None; M. Seishima, None; T. Suda, None; T. Mimori, None; K. Takehara, None; M. Kuwana, None.
Background/Purpose: A nti-Melanoma Differentiation-Associated Gene 5 (MDA5) antibody is found specifically in patients with dermatomyositis (DM). This autoantibody is associated with clinically amyopathic DM (CADM) and rapidly progressive interstitial lung disease (RP-ILD) especially in eastern Asian population. An association between anti-MDA5 antibody titer measured by in-house enzyme-linked immunosorbent assay (ELISA) and disease activity has been also reported. Recently, we have established an ELISA system for detection of anti-MDA5 antibody for clinical practice use. Objectives: To verify utility of our anti-MDA5 ELISA in a multi-center study.

Methods: Sera and clinical information were obtained from 432 patients with connective tissue disease (CTD) and 154 with Idiopathic interstitial pneumonia (IIP), who were followed at 8 participating hospitals. CTD patients included 104 with classic DM, 68 with CADM, 70 with polymyositis (PM), 43 with systemic sclerosis, 67 with systemic lupus erythematosus, 45 with rheumatoid arthritis (RA) and 20 with mixed connective tissue disease. 8 with Sjögren syndrome, and 7 with other CTD. IIP was defined as interstitial lung disease of unknown cause, in which patients did not fulfill classification criteria for any specific CTD or vasculitis. A healthy control included 123 volunteers. Anti-MDA5 ELISA utilized a recombinant protein encompassing the entire amino acid sequence of MDA5, which was expressed and purified using a baculovirus expression system. Antibody levels were shown in an index, which was calculated by optical density (OD) at 450 nm according to the following formula: (sample OD – blank OD/positive reference OD – blank OD) × 100. Immunoprecipitation (IP) assay was also conducted in patients with PM/DM (including classic DM, CADM, and PM). Comparisons between two groups were made using the chi-square test.

Results: Of 242 PM/DM samples, 10 (9.6%) with classic DM and 46 (67.6%) with CADM were positive for anti-MDA5 antibody by the gold standard IP assay. When a cutoff of the anti-MDA5 ELISA was set at 32 index based on receiver operating characteristics curve analysis in comparison with results of IP assay, analytical sensitivity and specificity of the ELISA were 98.2% and 100%, respectively. The ELISA showed an extremely high specificity, since anti-MDA5 antibody was detected in none of the patients with other CTD (including PM), those with IIP, or healthy controls. RP-ILD was more frequently found in classic DM (CADM patients with anti-MDA5 than in those without (83.6% versus 14.5%, P < 0.001).

Conclusion: This multi-center study has confirmed that a newly established ELISA for anti-MDA5 antibody is as efficient as the IP assay. This system enables easier and wider use in the detection of anti-MDA5 antibody in patients suspected to have DM and/or RP-ILD.

Disclosure: S. Sato, Holding a patent on anti-MDA5 antibody-measuring kit, 7; A. Murakami, employee of Medical & Biological Laboratories Co., Ltd., 3; A. Kuwajima, employee of Medical & Biological Laboratories Co., Ltd., 3; K. Takehana, None; T. Mitusaka, None; M. Nakai, None; M. Mishima, None; T. Suda, None; M. Sashima, None; M. Fujimoto, None; M. Kuwana, Holding a patent on anti-MDA5 antibody-measuring kit, 7.

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Background/Purpose: The Early Use of Cyclosporine Is Beneficial for Long-Term Prognosis in Patients of Polymyositis/Dermatomyositis-Associated Interstitial Lung Disease with Anti-Synthetase Antibodies. Objective: To evaluate the role of early use of cyclosporine on the long-term prognosis of patients with polymyositis/dermatomyositis (PM/DM)-associated interstitial lung disease (ILD). Methods: Patients with PM/DM-associated ILD were categorized into early-use group and delayed-use group. Early use group was defined as treatment with cyclosporine within 3 months after the initial hospitalization. The statistical significance was evaluated by log-rank test and Cox's proportional hazards model.

Results: Sixty-eight patients (33 with PM and 35 with DM) were positive for anti-synthetase antibody (Ab) against aminoacyl-tRNA synthetase (Ab). Among them, 64 patients with positive Ab response were treated with cyclosporine for a median of 6 months. The primary outcome of this study was to compare the prevalence of anti-MDA5 antibody in patients with PM-Scl to that in the general population. The prevalence of anti-MDA5 antibody in patients with PM-Scl was significantly higher than that in the general population (P<0.05 by log-rank test). Conclusion: The prevalence of anti-MDA5 antibody in patients with PM-Scl was significantly higher than that in the general population. This finding suggests that patients with PM-Scl may have a higher prevalence of anti-MDA5 antibody than the general population, and that this finding should be further studied in a larger population. Additionally, cyclosporine use at early stage in PM/DM-associated ILD with anti-synthetase Ab is beneficial for long-term prognosis.
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Evidence for the Involvement of NK Cells in Antisynthetase Syndrome.

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Background/Purpose: Antisynthetase syndrome (aSS) is characterized by the association of interstitial lung disease and myositis with anti-cytoplasmic antibody autoantibodies. Its pathogenesis remains unknown, especially regarding the involvement of innate immune cells, including natural killer (NK) cells. Here, we describe the first phenotypic and functional characterization of NK cells in this context.

Methods: A total of 20 patients with inactive and active aSS were included (women-men = 9, median age = 50 years), and compared to 20 healthy controls. Freshly isolated NK cell phenotype was performed by Flow cytometry. Polyfunctional assays were performed to measure degranulation and intracellular production of TNFα and IFNγ, spontaneously or after stimulation by interleukin(IL)-12 and IL18, in the presence of K562 target cells. The presence and the localization of NK cells in primary human specimens of lung (n=3) and muscle (n=3) target tissue were studied by immunohistochemistry, using anti-NKp46 monoclonal antibody.

Results: NK cells from inactive patients showed normal phenotype, whereas active aSS revealed a differentiated NK cell profile, as indicated by a increased level of CD57 (p=0.09) and ILT7 (p=0.016) associated with decreased CD161 (p=0.052) and NKp30 (p=0.009), compared to healthy donors. This is consistent with the inability of circulating NK cells of active aSS patients to produce IFNγ (p=0.0017) after IL12 plus IL18 stimulation, compared to healthy controls. More importantly, our in-depth analysis reveals that NKp30 down-modulation strongly correlated with the loss of NK cell functions (Spearman coefficient r=0.57, p=0.009), and could be a surrogate marker of aSS activity. Histological studies reveal for the first time the presence of small numbers of NK cells in the muscles, as well as a massive infiltration of NK cells inside the lungs of aSS patients.

Conclusion: Taken as a whole, NK cell phenotypic and polyfunctional changes as well as infiltration of target tissue argue for an involvement of NK cells in aSS pathogenesis.

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Analysis of Clinical Manifestations and Myositis-Specific Autoantibodies in PM/DM Patients with Severity of Physical Dysfunction:

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Background/Purpose: Many patients with PM/DM have trouble with daily living even after disease activity has been adequately controlled. However, details regarding the clinical factors that are associated with the disability of physical function after treatment in PM/DM remain unclear. The aim of our study was to clarify the clinical manifestations and myositis-specific autoantibodies (MAAs) that are associated with the severity of physical dysfunction after treatments in PM/DM.

Methods: In the present study, Seventy seven patients who were diagnosed with PM, DM or clinically amyopathic DM (CADM) were retrospectively enrolled. They were admitted to our hospital from December 1991 to February 2013 because of initial treatment for PM/DM/CADM. Diagnoses were made based on the criteria of Bohan and Peter or those of Sontheimer. We obtained clinical data from their medical records, including age of disease onset, gender, and disease duration. We also obtained laboratory data prior to initial treatment, such as CK, LD, antinuclear
antibodies and MSA, the content of treatment, and the presence of relapse. We evaluated the physical dysfunction of each patient after treatment from August to October 2013 using the Japanese version of the Health Assessment Questionnaire Disability Index (J-HAQ-DI). We retrospectively analyzed the clinical data prior to the initial treatment as predictors for the severity of physical dysfunction after treatment.

Results: Of the 77 patients with PM/DM/CADM, the median age of disease onset was 46 years old, and 79% of the patients were female. The number of PM/DM, and CADM cases were 40, 30, and 7, respectively. Anti-aminocarboxyl-tRNA synthetase antibody (anti-ARS), anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5), and anti-signal recognition particle antibody (anti-SRP) were identified in 25, 7, and 9 patients, respectively. Anti-M-I-2, anti-TIF1-γ, and anti-NXP-2 were also identified in a few patients. The median dose of prednisolone (PSL) at the initial treatment was 0.125 (range 0–2.75). In a multivariate analysis, the age of disease onset (t value = −4.72, p < 0.0001), female status (t = −2.80, p = 0.01), and the initial doses of PSL (t = 1.83, p = 0.073) were associated with the severity of the J-HAQ-DI score after treatment. The serum levels of CK prior to treatment were not associated with the severity of the J-HAQ-DI scores after treatment. The clarification of MSA is useful for predicting treatment was 0.125 (range 0–2.75). In a multivariate analysis, the age of disease onset (t value = −4.72, p < 0.0001), female status (t = −2.80, p = 0.01), and the initial doses of PSL (t = 1.83, p = 0.073) were associated with the severity of the J-HAQ-DI score after treatment. The serum levels of CK prior to treatment were not associated with the severity of the J-HAQ-DI scores after treatment. The view from the viewpoint of MSA, anti-SRP positivity was associated with more severe physical dysfunction after treatment than other MSA cases. However, anti-MDA-5-positivity was associated with better physical function after treatment than other MSA cases.

Conclusion: The age of disease onset, gender, and the initial dose of PSL were significant factors associated with the severity of physical dysfunction after treatment in PM/DM. The clarification of MSA is useful for predicting the severity of physical dysfunction after treatment in PM/DM.

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Diabetes and Atorvastatin Are Potential Risk Factors for Statin-Associated Myopathy with Autoantibodies Against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase. Pari Basharat1, Araz Lahouti H1, Andrew L. Mammen1, Iago Pinal-Fernandez1, Tanmayee Bichile1, Thomas E. Lloyd1, Sonye K. Danoff1, Livia Casciola-Rosen2 and Lisa Casciola-Rosen1

Background/Purpose: The idiopathic inflammatory myopathies (IIM) comprise a group of autoimmune disorders that target skeletal muscle. Some IIM cases may be associated with an autoantibody against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR), especially in statin exposed patients. The purpose of our study was to characterize the disease course, prevalence of comorbidities and detailed statin history in HMGR antibody positive (HMGR+) IIM patients, as compared to statin exposed HMGR antibody negative (HMGR-) IIM patients. We also aimed to distinguish differences between statin exposed vs statin naive HMGR+ patients.

Methods: From 5/1/02 to 1/1/14, 1687 suspected myopathy patients evaluated at the Johns Hopkins Myositis Center were enrolled in a longitudinal study. Serum and DNA samples were available for 1083 patients. Patients were included in our analysis if they met Bohan and Peter (B and P) criteria for definite/probable polymyositis or dermatomyositis. HMGR autoantibodies were tested for via immunoprecipitation and ELISA. Patients in the comparator group were selected from the large cohort of myositis patients if they were HMGR-, fulfilled the aforementioned B and P criteria, and had a documented statin history including exact statin name, dose, and start/stop dates. We performed a retrospective chart review of data from time of first clinical visit until 01/31/2014 or last clinical encounter.

Results: There were 77 HMGR+ patients, 19 statin naive. Data was compared between 58 statin exposed HMGR+ IIM patients and 39 statin exposed HMGR- IIM patients. HMGR+ patients were slightly older (mean age 59.9 ± 35; p = 0.013) but otherwise had similar baseline characteristics. HMGR+ patients had higher mean creatine kinase (CK) values (p < 0.001), and greater hip flexor weakness at presentation (p = 0.033). IVIG (p = 0.036) and Rituximab (p = 0.018) were used more in HMGR+ patients. More HMGR+ patients had interstitial lung disease (ILD) (p = 0.003). There was no difference in the prevalence of dysphagia.

Conclusion: Compared to statin exposed HMGR- patients, statin exposed HMGR+ patients had a higher prevalence of type II diabetes, a high number of cancers, increased exposure to atorvastatin prior to symptom onset, less prevalence of ILD, and greater treatment with IVIG and Rituximab.

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Background/Purpose: Miositis-specific auto-antibodies (Ab) include those directed against aminoacyl-tRNA synthetases (ARS), signal recognition particle (SRP), and nuclear helicase M-I-Z. A nti-SRP Ab are among the most abundant and best characterized miositis-specific Ab. Patients diagnosed with myositis associated with anti-SRP Ab are mainly associated with aggressive disease and poor prognosis and are refractory to glucocorticoids/To determine the clinical features, serological features and long-term prognosis among patients with anti-SRP Ab.

Methods: We retrospectively analyzed 8 patients with positive anti-SRP Ab, detected between 2000 and 2013 in our hospital (Tertiary, referral: 850,000 inhabitants). Medical records of patients with polymyositis (PM) or dermatomyositis according to the Bohan and Peter criteria, and patients with anti-cytoplasmic Ab, were reviewed regardless of diagnosis. Past and current status were assessed from hospital records. A post-questionnaire, personal interview and electromyography (EMG) test were performed in patients without myositis. Anti-nuclear Ab and anti-tissue Ab (A MA, L C, LKM) were tested at diagnosis by indirect immunofluorescence on Hep-200 cells (Immunoccepts®) and in-house tissue, respectively. Miositis-specific Ab: anti-ARS (J o-1, PL7, PL12) and anti-SRP were tested by immunoblot (Orcetec®). In addition, levels of creatine kinase (CK) were measured by turbidimetry (Roche®).

Results: Patients with anti-SRP Ab were 6 Caucasians and 2 north-African women, mean age 63 years; three (37.5%) had PM (1 associated with systemic sclerosis). At diagnosis, muscle weakness was severe in 2 patients (defined as < 3 of manual muscle strength testing), associated with dysphagia and respiratory muscle involvement. Season of onset of muscle weakness: 2 in spring and 1 in winter. All 3 patients were treated with glucocorticoids; 2 required immunosuppressive agents (methotrexate, azathioprine, rituximab or intravenous immunoglobulin). Histological study of biceps brachii showed histological changes consistent with necrotising myopathy with scarce inflammatory cells. Five (62.5%) patients showed no features of myositis after a follow-up of 6 months to 3.5 years; 4 had a normal EMG and normal CK levels. Their diagnoses: rheumatoid arthritis, Sjögren’s syndrome, autoimmune hepatitis, and primary biliary cirrhosis (pure and associated with systemic sclerosis). There were no deaths or history of malignancy among the 8 anti-SRP patients.

Conclusion: Although anti-SRP remains a specific Ab for PM, it is occasionally detected in patients with other rheumatic diseases and autoimmune hepatitis in the absence of myositis.

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Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of autoimmune disorders characterized by muscle inflammation, progressive weakness with a combination of clinical, electromyography and laboratory findings, which includes the expression of autoantibodies. In the last few years there has been an increasing interest to study IIM in different geographic populations. The objective of the study was to identify ANA, the myositis specific antibodies (MSA) and the myositis associated antibodies (M A A) in a cohort of Mexican IIM patients.

Methods: Serum samples from 77 IIM patients were collected from five participating centers in Mexico. ANA were detected by indirect immunofluorescence (IIF) on HEp-2 cells (Antibodies Inc., Davis, CA, USA). MSA and MAA were tested by two different methods: Luminex ENA (FIDIS: Thera-Diag, Paris, France) kit (ALBIA), and EUROL ine Autoimmune Inflammatory Myopathies 15 A nalyte kit (Eu roimmun, Luebeck, Germany, line immunoassay).

Results: Of the 77 IIM patients, 55 (71%) had dermatomyositis (DM), 13 (17%) polymyositis (PM) and 9 (12%) juvenile dermatomyositis (JDM). The mean age was 40 years (6-69 years), 67 (87%) were female. The frequency of ANA by IIF was 81%, the most common IIF patterns were homogeneous and speckled representing close to 60%, the second most common pattern was cytoplasmic speckled 13% and then nucleolar 10%. The most frequently MSA detected by FIDIS ALBIA was Ro52/TRIM21 (16.9%) followed by Ku and TIF-1-gamma (9%), and MDA-5 (7.8%); with less than 4% attributed to PM/Scl-100, NXP-2 and SAE-1. Ro52/TRIM21 (16.9%) was detected by FIDIS ALBIA. Of the 16.9% of positive Ro52/TRIM21 patients, 30% were also positive for Jo-1 (LIA), and 54% for M2-ε (LIA).

Conclusion: The study of ANA, MSA and MAA in a cohort of Mexican IIM patients from 5 different centers. We observed a high prevalence of IIF ANA (81%) which is consistent with some previous reports. Homogeneous and speckled pattern represented approximately...
60% of the ANA and the second most common pattern was cytoplasmic and nucleolar (13 and 10%, respectively). Regarding the analysis of the MSA and MAA we found an increased prevalence of anti-Mi2 antibodies (32.5%) in an autoantibody typically associated with DM which was even higher frequency (~40%) when the two α and β isoforms of anti-Mi2 were analyzed. This is in contrast to many other geographic studies were anti-synthetase antibodies tend to be the most common IIM autoantibody. The most common MAA antibody was anti-Ro52/TRIM21, an autoantibody that has been associated with pulmonary fibrosis and polyautoimmunity. It is worth noting that up to 46% of the positive Ro52/TRIM21 patients did not share any MSA or MAA which may indicate that it is an independent marker in IIM sera.

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Epidemiology and Characteristics of Antisynthetase Syndrome in the African Descent Population of Martinique

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Background/Purpose: There is no population based epidemiologic studies of antisynthetase syndrome (ASS). We described characteristics and epidemiology of this disease in Martinique, populated by an African descent population.

Methods: Incidence was calculated including incident cases prospectively identified from 2006 to 2013 by 3 sources in Martinique (1) competence center for rare systemic autoimmune diseases, (2) national referral center for rare neuromuscular disorders, (3) the only respiratory medicine department, all located in the academic hospital of Fort de France. We included to describe biological and clinical characteristics, more patients from the rheumatology, internal medicine and respiratory medicine units of the 2 others French American regions (Guadeloupe and French Guiana). Inclusion criteria were: presence of one of the antisynthetase antibodies associated to muscular, rheumatological involvement or interstitial lung disease.

Results: In the 3 regions, 41 patients (all of African descent) were found (31 from Guadeloupe and 5 from French Guiana): 31 females, 10 males. The mean age at diagnosis was 44.1 yo (range: 25-82). Three patients were lost to follow up (none in Martinique) and 5 deceased (2.06 dead/100 patients-year). The mean follow up time was 72.3 months. Fifty one percent had anti-j1 antibody, 44% anti-PL12, 5% anti-PL7. Initially, the clinical picture was: 15% and 57% muscular (p<0.05), 60 and 38% pulmonary (p>0.05), 50 and 23.8% rheumatologic (p>0.05). In comparison with anti-PL7/PL12 and anti-j1 respectively. Cumulative characteristics in 41 patients showed: Interstitial lung disease 82.9% (PL7/12: 90%, Jo1: 76.2%; p>0.05), arthritis 63.4% (PL7/12: 65%, Jo1: 62.9%; p>0.05), mechanic hands 51.2% (PL7/12: 36.8%, Jo1: 71.4%; p=0.05), fever 51.2% (PL7/12: 60%, Jo1: 42.9%; p=0.05). Clinical myopathy was found for 43.9% (PL7/12: 25%, Jo1: 61.9%; p< 0.05) and 56.1% were considered as amyopathic (34.1% PL7/12: 45%, Jo1: 23.8%) or clinically amyopathic (22% PL7/12: 30%, Jo1: 14.3%). Main histologic pattern at the chest CT scan were: non specific interstitial pneumonia (52.9%), usual interstitial pneumonia (23.5%), cryptogenic organizing pneumonia (5.9%), diffuse alveolar damage (3%). Myocarditis was present in 3 patients. Associated diseases were: rheumatoid arthritis (5), juvenile idiopathic arthritis (1), systemic sclerosis (1), antiphospholipid syndrome (1), Evans syndrome (3), Pulmonary hypertension was found in 5. Myocarditis was found in 3 patients. For 5 patients were considered as incident cases in Martinique during the 2006-2013 period, allowing a mean annual incidence of 5.3/100000 (PL7-12: 2.5; Jo1: 3.1). In December 31, 2013, the prevalence of ASS in Martinique was 67.5/100000 (PL7-12: 30; Jo1: 37.5).

Conclusion: We provide the first population based epidemiology of ASS, moreover in an African origin population. We confirm the elevated proportion with anti-PL7/12 close to anti-j1 in our black patients from the French West Indies. This initial clinical profile, frequently mimicking infectious pneumonia with fever and high blood c reactive protein level without clinical myopathy, can explain difficulties in the diagnosis.

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Distinctive Muscle Histopathological Features of Anti-Synthetase Syndrome.

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Background/Purpose: As supported by recent studies, anti-histidyl tRNA synthetase (anti-j1) antibodies are specific for clinico-biological features and outcomes. Though, anti-j1 synthetase syndrome is a clinical distinct entity among idiopathic inflammatory myopathies and among other anti-synthetase syndromes, its pathological features are poorly described.

Methods: This study was performed to define the histological characteristics of the associated myopathy, as well as to immunophenotype the inflammatory infiltrates, in a series of 53 anti-j1-positive patients with antist synthetase syndrome.

Results: Myopathic changes in myofibers were observed with predominant perifascicular topography: these changes included a characterized,istro peripheral necrosis (66%), or atrophy (45%). A perimysial fragmentation, seen with a trichrome coloration or with histochemical staining for alkaline phosphatases was commonly noted (90%). C5b9 membrane-attack-complex staining showed a sarcolemmal perifascicular expression in 57% of the biopsies. Human-leucocyte antigen class-I (HLA I) expression was enhanced at the periphery of the fascicles in 60% of the cases. A perimysial inflammatory infiltrate was present in 90%, extending to endomy she sheets in 83%.

Conclusion: This largest study to date is highlighting that anti-j1 synthetase syndrome is a distinct histological entity within the spectrum of myositis, with a particular perifascicular necrotizing involvement, associated with a perimysial fragmentation, and a striking membrane-attack-complex perifascicular sarcolemmal expression.

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Myocarditis in Antisynthetase Syndrome.

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Background/Purpose: Antisynthetase syndrome (ASS) corresponds to an overlapping inflammatory myopathy identified by different myositis specific autoantibodies (directed against tRNA-synthetases). Myocardial involvement in this condition is poorly described.

Methods: From a 342 ASS patient registry, nine cases of myocarditis were identified on the basis of an unexplained increased in cardiac troponin I levels associated with either suggestive cardiac magnetic resonance imaging (MRI) findings, normal coronary artery explorations, and/or positive endomyocardial biopsy.

Results: The prevalence of myocarditis in ASS is 2.6% (n=9) and was not linked to any autoantibody specificity: anti-j1 (n=5), anti-PL7 (n=3) and anti-PL12 (n=1). Myocarditis was an inaugural presentation in 44% of the
cases and was asymptomatic (n=1) or revealed by an acute (n=4) or subacute (n=4) cardiac failure. Of note, myocarditis was always associated with an active myositis. When performed (n=8), cardiac MRI revealed a late hypersignal in the T$_1$-images in 87% of the cases (n=7). Four patients (44%) required intensive care. Seven patients (78%) received dedicated cardiotoxic drugs. Steroids and at least one immunosuppressive drug were given in all cases. After a median follow-up of 23 months (range 2-51), six (67%) patients recovered whereas three (33%) developed chronic cardiac insufficiency. No patient died.

Conclusion: The prevalence of myocarditis in aSS is similar to that reported in other inflammatory myopathies. Although it has a relatively good prognosis, myocarditis is a severe condition and should be carefully explored in active aSS patients.

Disclosure: C. Dieval, None; O. Benveniste, None; C. Deligny, None; A. Meyer, None; G. Lefèvre, None; Y. Schoindre, None; A. Rigolet, None; B. Hervier, None.

1272

Musculoskeletal and Myositis Associated Autoantibodies in Indian Patients with Inflammatory Myositis. Puja Srivastava, Ramnath Misra, Abhijit Lawrence, Armita Aggarwal and Vikas Agarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Recently, idiopathic inflammatory myositis (IIM) has been categorised into distinct subsets based on myositis specific autoantibodies (M Sa) and myositis associated autoantibodies (M A A). However, there is little data on prevalence of these autoantibodies from Indian subcontinent. Hence, we studied the prevalence and clinical associations of MS As and MA As in Indian patients with IIM.

Methods: Clinical data and sera were collected from patients with IIM (November 2012-May 2014). Sera were analysed for antibodies against SRP, Mi2, Jo1, PL 7, PL 12, EJ, Oj, Ro 52, Ku, PM-scl 75 and PM-scl 100, using line immunoblot assay (Euroimmun).

Results: During 18 months there were 124 patients with IIM. ANA positivity was found in 84 (68.9%). The distribution of different autoantibodies in different subset is given below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DM</th>
<th>PM</th>
<th>IIM</th>
<th>JDM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>55</td>
<td>22</td>
<td>22</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Female: Male</td>
<td>40:15</td>
<td>24:1</td>
<td>22:0</td>
<td>11:11</td>
<td>97:27</td>
</tr>
<tr>
<td>Mean age</td>
<td>34.4</td>
<td>35.2</td>
<td>34.4</td>
<td>10.1</td>
<td>30.4</td>
</tr>
<tr>
<td>Mean disease duration</td>
<td>8.3 + 11.2</td>
<td>11.4 + 16.7</td>
<td>7.6 + 7</td>
<td>20.6 + 25.1</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Musculoskeletal specific antibodies (number positive)
- Mi2: 21
- SRP: 3
- Anti-Jo1: 3
- Other Anti-synthetase: 7

Myositis associated antibodies (number positive)
- Ro52: 14
- Ku: 7
- PM-scl 100: 3
- PM-scl 75: 3

All antibody negative: 13

10 | 33

Thirty eight (30.6%) patients had two autoantibodies and 7(5.6%) patients had 3 autoantibodies.

Anti-Jo1 showed positive association (r = 0.31) while anti-Mi2 showed negative association (r = -0.26) with anti-Ro52 antibody. Anti-Mi2 antibodies were strongly associated with adult DM (p<0.0001) as well as it was associated with decreased risk for I LD (p=0.001) and increased risk for pharyngeal weakness (p=0.006). ILD and mechanics hands were strongly associated, both with anti-Jo1 and anti-synthetase antibodies (p<0.0001).

Four of the six patients with anti-SRP antibody had poor response to multiple drugs.

Conclusion: Higher prevalence of anti-Mi2 is probably related to higher proportion of patients with DM. We found absence of ILD in patients with anti-Mi2 antibody suggesting that it may protect against ILD. In Indian population also anti-synthetase antibodies are associated with ILD and anti-SRP with poor response to treatment.

Disclosure: P. Srivastava, None; R. Misra, None; A. Lawrence, None; A. Aggarwal, None; V. Agarwal, None.

1273

Assessment of the Effect of Rituximab in the Treatment of Interstitial Lung Disease associated with the Antisynthetase Syndrome. Tracy Doyle1, Juan Osorio2, Eduarda Nilo DeFragal3, Rachna M adan4, Fernanda Cabral5, Ivan Rossas6 and Paul Dellaria4.

1 Brigham and Women’s Hospital, Boston, MA, 2 Brigham and Women’s Hospital, Boston, MA, 3 Harvard Medical School, Boston, MA, 4 Brigham and women’s Hospital, Boston, MA, 5 Brigham and women’s Hospital, Boston, MA.

Background/Purpose: To assess clinical outcomes including pulmonary function and radiographic imaging in patients with ILD and the antisyntethetase syndrome who were treated with Rituxan (RTX).

Methods: We retrospectively identified all patients at one institution with the antisyntethetase syndrome who presented with ILD and were treated with RTX. Data regarding demographics, serologic status, muscle disease, concomitant steroid use, pulmonary function testing and chest CT scans were assessed before and after the use of RTX. Serial assessments with PFTs were performed using standardized methods. Two radiologists independently evaluated axial chest CT scans using a standardized scoring system (Oda et al. Respiratory Research 2014, 15:10) and made a subjective assessment of the type of ILD pattern at 0 and 6 months and the scores of the two radiologists were averaged.

Results: 12 patients were identified who were treated with RTX for the anti-synthetase syndrome. Anti-synthetase antibodies were identified in all patients (5 PL-12, 4 J-1, 3 PL-7). 11 patients (92%) were females and the mean age was 54. Three patients (25%) had been smokers. The diagnosis of antisyntethetase syndrome followed the diagnosis of ILD in 8 patients (67%) by a mean of 14.5 years. 7 of the patients had myositis. In 9 cases (75%), the principal indication for use of RTX was recurrent or progressive ILD due to failure of other agents. Mean time to initiation of RTX after identification of ILD was 5.4 years. One patient discontinued RTX in this time due to aphthous ulcers. One patient proceeded to lung transplant, and 2 patients had serious gastrointestinal complications requiring surgery but subsequently resumed RTX therapy.

Comparing pre and post RTX PFTs at 3-12 months for the 10 patients with adequate follow-up, FVC% and TLC% were stable or improved in 70% and 80% of subjects, and DLCO% increased in 38% (Table 1). The average individual change was 12%, 13%, and −6%, respectively. CT score was stable or improved in 83% of subjects where followup CT was available. Eight CTs were consistent with non-specific interstitial pneumonia (NSIP) and 2 had components of both cryptogenic organizing pneumonia (COP) and NSIP. Steroid dose decreased in 88% of subjects with an average decrease in dose of 6mg.

Conclusions: Use of RTX was well tolerated in the majority of patients who had ILD and the anti-synthetase syndrome. Stability or improvement in pulmonary function or CT imaging was seen in most patients. RTX may play a therapeutic role in patients with ILD associated with the antisyntethetase syndrome and further clinical investigation is warranted.

Table 1: Comparison of pre and post RTX pulmonary function test measurements, CT scan score at 0 and 6 months, and prednisone dose (mg) with individual values and % change

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FEV1%</th>
<th>FVC%</th>
<th>TLC%</th>
<th>DLCO%</th>
<th>CT Score</th>
<th>Prednisone Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Pre-RTX</td>
<td>55.3 (15%)</td>
<td>55.6 (15%)</td>
<td>42.3 (10%)</td>
<td>38.9 (8%)</td>
<td>171.9 (5%)</td>
<td>19 mg</td>
</tr>
<tr>
<td>Average Post-RTX</td>
<td>62.3 (20%)</td>
<td>62.6 (20%)</td>
<td>63.5 (15%)</td>
<td>45.9 (13%)</td>
<td>162.7 (3%)</td>
<td>12 mg</td>
</tr>
<tr>
<td>Subjects Stable or Improved</td>
<td>70.7 (90%)</td>
<td>70.8 (90%)</td>
<td>45.7 (80%)</td>
<td>38.8 (38%)</td>
<td>51.6 (36%)</td>
<td>71 (88%)</td>
</tr>
<tr>
<td>Average individual %</td>
<td>15%</td>
<td>12%</td>
<td>13%</td>
<td>6%</td>
<td>8%</td>
<td>37%</td>
</tr>
<tr>
<td>Subject Off-follow-up</td>
<td>FEV1% (%Δ)</td>
<td>FVC% (%Δ)</td>
<td>TLC% (%Δ)</td>
<td>DLCO% (%Δ)</td>
<td>CT Score (%Δ)</td>
<td>Prednisone Dose (mg)</td>
</tr>
<tr>
<td>Subject 1</td>
<td>84 (77%)</td>
<td>95 (90%)</td>
<td>-</td>
<td>87</td>
<td>117.5 (9%)</td>
<td>5</td>
</tr>
<tr>
<td>Subject 2</td>
<td>61 (65)</td>
<td>62 (65)</td>
<td>40</td>
<td>125.1 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 3</td>
<td>72 (80)</td>
<td>75 (80)</td>
<td>56 (40)</td>
<td>138.3 (11%)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Subject 4</td>
<td>54 (43)</td>
<td>53 (43)</td>
<td>36</td>
<td>237.4 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 5</td>
<td>64 (60)</td>
<td>64 (60)</td>
<td>26 (20)</td>
<td>216.6 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 6</td>
<td>56 (50)</td>
<td>50 (50)</td>
<td>39</td>
<td>182.4 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 7</td>
<td>63 (56)</td>
<td>49 (49)</td>
<td>24 (24)</td>
<td>182.4 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 8</td>
<td>47 (40)</td>
<td>43 (43)</td>
<td>39</td>
<td>222.2 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 9</td>
<td>47 (40)</td>
<td>43 (40)</td>
<td>28 (20)</td>
<td>186.6 (10)</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Subject 10</td>
<td>48 (48)</td>
<td>-</td>
<td>181.6 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects Stable or Improved</td>
<td>60 (80)</td>
<td>76 (80)</td>
<td>40 (38)</td>
<td>124.8 (31%)</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

S557
Patients with Osteoarthritis Do NOT Have Increased Risk of Cardiovascular Disease in Ullensaker Community in Norway.

Methods: The Musculoskeletal Study (MUST) is a cross-sectional investigation comprising a thorough clinical examination, recording of CV risk factors in addition to radiographic evaluation of hands, hips and knees of persons with self-reported OA (The MUST-Heart study). Of the 604 persons examined, 438 fulfilled the ACR classification criteria for OA in the hand, knee and/or hip joints. The study population was divided into: (i) generalized OA, defined as bilateral hand OA or involvement of > 3 out of 6 sites (bilateral hand/hip/knee); (ii) focal OA; and (iii) non-OA. CV risk was calculated by the SCORE algorithm for persons without CV disease, not using lipid lowering and/or antihypertensive medication (OA n = 200 and non-OA n = 87). An estimated CV risk ≤ 5% for a fatal myocardial infarction coming 10 years is defined as low to medium risk, while > 5% is the cut off for initiation of CV preventive pharmacotherapy. Comparisons between groups were done by using independent samples T-test, Mann Whitney-U test for non-parametric data, and Pearson’s correlation coefficient. Multivariate analyses were made by using linear or logistic regression model.

Results: The median CV risk for patients with OA [1.40 (IQR 0.65, 2.92)] was higher compared to non-OA [0.99 (IQR 0.52, 1.92)] (p = 0.02). The difference in the CV risk was related to higher age (p < 0.001), but not to total cholesterol (p = 0.07), systolic blood pressure (p = 0.13) or to the OA diagnosis. Only 17/200 (8.5%) of the OA patients and 3/87 (3.4%) of the non-OA patients had a CV risk > 5% (p = 0.12) (Table). The presence of established CV disease was comparable for those with (n = 72/438, 16.8%) and without OA (n = 34/166, 21.1%) (p = 0.23). Dividing the OA group into focal and general OA, did not reveal any further differences regarding estimated CV risk or CV disease compared with non-OA. Inflammatory biomarkers (erythrocyte sedimentation rate and C-reactive protein) were in the normal range for the whole study population, with no difference between OA and non-OA (p = 0.30 and 0.10, respectively) (Fig 1a&b).

Conclusion: Inhabitants with OA in a Norwegian municipality had an overall low risk of CV disease and did not have higher prevalence of established CV disease compared to non-OA.

Table. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>OA</th>
<th>Non-OA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>469</td>
<td>157</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular disease n (%)</td>
<td>77 (16.4)</td>
<td>33 (21.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>260 (57.4)</td>
<td>93 (59.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>71 (15.1)</td>
<td>21 (13.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>126 (26.9)</td>
<td>66 (42.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age mean ± SD</td>
<td>64.1 ± 8.6</td>
<td>63.3 ± 9.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Systolic blood pressure mean ± SD</td>
<td>136.2 ± 17.4</td>
<td>134.4 ± 16.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Total cholesterol mean ± SD</td>
<td>5.90 ± 1.15</td>
<td>5.60 ± 1.18</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL-c mean ± SD</td>
<td>1.38 ± 0.48</td>
<td>1.62 ± 0.49</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Disclosure: T. Doyle, None; J. Osorio, None; E. Nilø DeMagaldi, None; R. Madan, None; F. Cabral, None; I. Rosas, None; P. Dellaripa, None.

ACR/ARHP Poster Session B
Osteoarthritis - Clinical Aspects: Epidemiology and Pathogenesis
Monday, November 17, 2014, 8:30 AM - 4:00 PM

1275

Association Between Cardiometabolic Disorders and Hand Osteoarthritis Severity: A Cross-Sectional and Longitudinal Study.

Methods: This is an ancillary study from an international 3-year, randomized, placebo-controlled phase III trial designed to evaluate strontium ranelate on the X-ray progression of knee OA (SEKOIA trial). A clinical assessment at baseline and at 3 years was performed. Hand radiographs were scored by 2 reproducible readers (ICCs >0.8) for Kellgren-Lawrence (KL) and Verbruggen anatomical phase (Verb) scores. We included subjects with radiographic HOA defined by at least 2 joints with KL ≥ 2. Symptoms were assessed using the overall Australian/Canadian (AUSCAN) score (normalized at 300) and the criterion hand pain and Functional index for HOA (FIHOA) ≥5. Radiographic HOA severity at baseline was assessed by global KL and Verb scorings. The longitudinal analysis was performed on the placebo group only to avoid potential biases due to a treatment effect. The clinical and radiographic progressions were defined as the changes of AUSCAN, KL or Verb scores between baseline and endpoint. Baseline age, gender, body mass index (BMI), clinical features and cardio-metabolic parameters were included in a multivariate linear or logistic regression model.

Results: At baseline, 869 subjects (72 % women) with mean ± SD age of 64 ± 7 years and BMI 29.6 ± 4.7 kg/m2 had radiographic HOA. Multivariate analyses indicated that AUSCAN level was associated with menopause (p < 0.0005), depression (p < 0.01), a history of ischemic cardiopathy (p < 0.05) and radiographic severity (p < 0.0005) (Table). A similar association was found for "FIHOA ≥ 5 and pain" criterion (p < 0.05 for all analyses). A combination of metabolic factors (hypertension, dyslipidemia, diabetes mellitus and obesity (BMI ≥ 30 kg/m2) was associated with the AUSCAN score (β = 5.5 [0.3;10.9]; p < 0.05). Radiographic severity was associated with age, obesity, menopause as well as knee KL grade after adjustment on confounders (Table). Similar associations were found for Verb score (p < 0.05 for all.

Table S558
analyses), 307 HOA patients from the placebo group were followed for a mean duration of 31.5 ± 8.5 months. Obesity independently predicted Verb score variation (β = −1.3 [−2.2; −0.45]; p < 0.01). Baseline KL score was the main factor associated with radiographic progression (KL or Verb). Baseline AUSCAN score was the main factor associated with subsequent clinical progression (β = −0.39 [−0.55; −0.03]; p < 0.0001).

**Conclusion:** In HOA, obesity and ischemic cardiopathy are associated with structural damages and symptoms respectively. Such results further delineate the metabolic OA phenotype.

**Table.** Factors associated with baseline HOA symptoms and radiographic severity. NT: not tested; NS: not significant.

<table>
<thead>
<tr>
<th>Corrected AUSCAN score</th>
<th>Hand KL score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average (± SD)</td>
<td>95.4 ± 79.9</td>
</tr>
<tr>
<td></td>
<td>214 ± 13.1</td>
</tr>
<tr>
<td>β (95% CI) p-value</td>
<td>β (95% CI) p-value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.18 (−0.95–0.59) 0.64 0.46 (0.34–0.58) -0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>Male Ref Ref</td>
</tr>
<tr>
<td>Female with menopause</td>
<td>27 (10.57–43.44) 0.001 2.79 (0.12–5.47) 0.04</td>
</tr>
<tr>
<td>Female without menopause</td>
<td>27.11 (14.37–39.86) &lt;0.0001 3.65 (1.69–5.61) 0.0003</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>BMI &lt;30 Ref Ref</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>0.973 (−9.6–11.59) 0.36 1.94 (0.32–3.67) 0.02</td>
</tr>
<tr>
<td>Ischemic cardiopathy</td>
<td>24.4 (5.67–43.23) 0.01 NS</td>
</tr>
<tr>
<td>Depression</td>
<td>30.91 (13.07–48.75) 0.0007</td>
</tr>
<tr>
<td>Knee KL Score</td>
<td>NT 1.77 (0.03–3.51) 0.04</td>
</tr>
<tr>
<td>Verbrugen score</td>
<td>1.259 (0.91–1.61) &lt;0.0001 NT</td>
</tr>
<tr>
<td>KL score</td>
<td>1.42 (1–1.84) &lt;0.0001</td>
</tr>
<tr>
<td>Number of joints with KL ≥2</td>
<td>3.48 (2.33–4.64) &lt;0.0001</td>
</tr>
<tr>
<td>Number of Erosive joints</td>
<td>9.646 (6.53–12.76) &lt;0.0001</td>
</tr>
</tbody>
</table>


1276


UCSF (University of California, San Francisco), San Francisco, CA, 2Boston University School of Medicine, Boston, MA, 3The University of Alabama at Birmingham, Birmingham, AL, 4University of Iowa, Iowa City, IA, 5Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA.

**Background/Purpose:** Osteoarthritis (OA) is reported to be more prevalent in individuals with diabetes mellitus (DM). Potential etiologies include advanced glycation endproducts, which reduce cartilage integrity, and obesity which increases the mechanical load on the knee. We further explored the relationship of abnormal glucose metabolism and incident knee OA in a community based cohort with 84 months of follow up.

**Methods:** The Multicenter Osteoarthritis Study Group (MOST) is an NIH-funded longitudinal study of risk factors for knee OA in people age 50-79 years, with or at high risk of knee OA. Subjects were eligible for this ancillary study if they did not have RKOA at baseline (Kellgren and Lawrence (KL) grade <2 bilaterally). Subjects were excluded if they lacked follow up x-ray radiographs or if their baseline blood sample was not available. A random sample diverse in baseline body mass index (BMI) of 1000 subjects (out of 1280 eligible subjects) was selected. Fasting glucose (Unichal DxC 800 A Auto-analyser (Beckman Coulter, Fullerton, CA, USA) and free insulin (Lumines M II/plex Analyzer Model XYP 100/200 S, Austin, Texas) levels at baseline were measured on all subjects. Subjects were categorized as DM based on any of the following: self-report DM, use of anti-diabetic medications or a fasting glucose at baseline of > 126 mg/dL.

The outcome was the cumulative incidence of RKOA between baseline and the 84-month follow-up visit, defined by either a KL grade > 2 or total knee replacement. Knee-level pooled binary regression analysis was performed in men and women separately. GEE (to account for within-subject correlation) was used to obtain risk ratios (95% CI) and diabetes status. Subjects who were taking insulin were excluded from models in which insulin resistance was analyzed.

**Results:** Among the 1000 subjects (mean age 61.6±7.8 years, 59% women, mean BMI at baseline 29.1±4.9 kg/m²), there were 107 subjects with DM. DM subjects were more likely to be male, non-white and have higher BMI. Over the 84 months of follow-up, incidence of RKOA did not differ between diabetics compared to non-diabetics. In men, both elevated fasting glucose and HOMA-IR were associated with an increased risk of incident RKOA, but this effect did not persist after adjustment for BMI. In women, HOMA-IR levels were associated with a decreased risk of incident RKOA after adjustment for BMI (Table).

**Conclusion:** DM at baseline was not associated with incident RKOA in this cohort. However, insulin resistance in women may be protective against the development of RKOA once the effect of high BMI is accounted for. This finding needs to be replicated in additional studies.

**Table.** Risk Ratio for Incident Knee Osteoarthritis, stratified by sex

<table>
<thead>
<tr>
<th>Gender</th>
<th>Men 580 subjects</th>
<th>150 knee/278 events</th>
<th>Women 420 subjects</th>
<th>80 knee/137 events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Ratio (95% CI) p-value</td>
<td>Risk Ratio (95% CI) p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unadjusted Model</td>
<td>BMIA-Adjusted Modela</td>
<td>Unadjusted Model</td>
<td>BMIA-Adjusted Modela</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>1.00 (0.96–1.02) 0.2</td>
<td>0.93 (0.81–1.07) 0.3</td>
<td>1.04 (0.98–1.23) 0.7</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR (per SD)</td>
<td>1.05 (0.93–1.19) 0.4</td>
<td>0.81 (0.71–0.93) &lt;0.01</td>
<td>1.03 (0.84–1.27) 0.8</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.92 (0.59–1.40) 0.7</td>
<td>0.63 (0.38–1.06) 0.08</td>
<td>1.04 (0.62–1.70) 0.7</td>
<td></td>
</tr>
</tbody>
</table>

1Adjusted for age, race, clinic site, visit, and body mass index.


1277

**Retinal Arteriolar Narrowing and Incidence of Knee Replacement for Osteoarthritis: A Prospective Cohort Study.** Sultana Monira Hussain1, Y Yungioo Wang1, Jonathan E. Shaw2, Dianna J. Maglione2, Tien Y. Wong1, Anita W. Luka3, Stephen Graves3, Robyn J. Tapp4 and Flavia Cicuttini5.

1School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, 2Baker IDI Heart and Diabetes Institute, Melbourne, Australia, 3Singapore Eye Research Institute, Singapore, Singapore, 4Asian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia, 5The University of Melbourne, Melbourne, Australia.

**Background/Purpose:** Epidemiological studies suggest that macrovascular disease is involved in the pathogenesis of osteoarthritis (OA) possibly through reduced nutrition to the joint. However, the role of the microcirculation in the pathogenesis of OA remains unclear. The retinal vasculature provides a unique window to assess the microcirculation noninvasively and directly. This study examined the association between retinal vascular caliber and incidence of knee replacement for OA.

**Methods:** 1838 participants of the Australian Diabetes, Obesity and Lifestyle Study - a population-based, national prospective cohort study who had retinal caliber measured in 1999-2000 using a nonmydriatic digital fundus camera and a validated computer-based program. Participants were aged >40 years at joint replacement data collection commencement. The incidence of knee replacement for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry. Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the incidence of knee replacement due to OA associated with retinal vascular caliber, with age as the time scale. Follow-up for joint replacement (calculation of person-time) began 1 January 2002, and ended at the date of first knee replacement for OA or date of censoring. Retinal vascular caliber was standardized so that HR represents the effect of a one-standard-deviation difference in caliber. Retinal vascular caliber was also categorized into tertiles based on the analysis sample. The widest tertile was used as the referent category. Each analysis was adjusted for sex and body mass index (BMI), and further adjusted for physical activity, HbA1c, and cardiovascular risk factors (systolic blood pressure, total cholesterol and microalbuminuria).

**Results:** 77 participants underwent knee replacement for OA. At baseline, these participants had narrower retinal arteriolar calibre than those who did not need knee replacement (166.1±24.8 μm vs. 174.3±24.5 μm, p = 0.004). Narrower retinal arteriolar caliber was associated with an increased risk of knee replacement (HR 1.25, 95%CI 1.00–1.56, per 1 standard deviation decrease in retinal arteriolar...
ol ar caliber); and participants with arteriolar caliber in the narrower two-thirds of the cohort had twice the risk of knee replacement compared with those in the widest one-third (HR 2.00, 95% CI 1.07–3.74, p=0.03) after adjustment for sex, BMI, physical activity and HbA1c. Further adjustment for the cardiovascular risk factors did not change the associations. There was no association for retinal venular caliber.

Conclusion: Persons with narrower retinal arteriolar caliber had a higher risk of knee replacement for OA, suggesting a role of microvascular disease in the pathogenesis in the disease of knee OA.

Disclosure: S. M. Hussain, None; Y. Wang, None; J. E. Shaw, None; D. J. Magliano, None; T. Y. Wong, None; A. Wluka, None; S. Graves, None; R. J. Tapp, None; F. Cicuttini, None.

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1School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, 2Baker IDI Heart and Diabetes Institute, Melbourne, Australia, 3Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia.

Background/Purpose: Low birth weight and preterm birth have been associated with adverse adult outcomes including hypertension, insulin resistance, cardiovascular disease and reduced bone mass. It is unknown whether low birth weight and preterm birth affect the risk of osteoarthritis (OA). This study aims to examine whether low birth weight and preterm birth were associated with the incidence of knee and hip arthroplasty for OA.

Methods: 3,604 participants of the Australian Diabetes, Obesity and Lifestyle Study - a population-based, national prospective cohort study, who reported their birth weight and history of preterm birth and were aged more than 40 years at the commencement of arthroplasty data collection. The incidence of knee or hip arthroplasty for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry. Cox proportional hazard regression models were used to estimate the hazard ratios (HR) and 95% confidence interval (CI) for knee or hip arthroplasty for OA associated with low birth weight and preterm birth. Follow-up for arthroplasty (i.e. calculation of person-time) began in January 1, 2002, and ended at the date of first arthroplasty for OA or date of censoring. Each analysis was adjusted for age, sex, and body mass index (BMI), in model 1, as these are established risk factors for arthroplasty for OA. In model 2, the analyses were further adjusted for hypertension, diabetes, smoking status and physical activity. Associations of low birth weight and preterm birth with arthroplasty risk were modified by obesity (BMI ≥ 30 kg/m2) and sex, interactions were fitted, and tested using the likelihood ratio test.

Results: One hundred and sixteen participants underwent knee arthroplasty and 75 underwent hip arthroplasty for OA. Low birth weight (yes vs. no, HR 2.04, 95% CI 1.11–3.75, p=0.02) and preterm birth (yes vs. no, HR 2.50, 95% CI 1.29–4.78, p=0.007) were associated with increased incidence of hip arthroplasty independent of age, sex, BMI, education level, hypertension, diabetes, smoking and physical activity. No significant association was observed for knee arthroplasty.

Conclusion: Although these findings will need to be confirmed, they suggest that individuals born with low birth weight or preterm are at increased risk of hip arthroplasty for OA in adult life. The underlying mechanisms warrant further investigation.

Disclosure: S. M. Hussain, None; Y. Wang, None; A. Wluka, None; J. E. Shaw, None; D. J. Magliano, None; T. Y. Wong, None; A. Wluka, None; S. Graves, None; R. J. Tapp, None; F. Cicuttini, None.

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Pre-Operative Musculoskeletal Comorbidities Limit Improvement in Functional Outcomes and Hip Pain in Total Hip Arthroplasty Patients. Scott Pascal, David Ayers, Wenjun Li, Leslie Harold, Jerom Allison and Patricia D. Franklin.

University of Massachusetts Medical School, W oces-ter, MA.

Background/Purpose: Identifying clinical factors predictive of total hip arthroplasty (THA) outcomes is valuable for clinicians and patients to make a data-driven surgical decision. While factors such as age, weight, and medical comorbidities have been shown to affect post-operative pain and/or functional gains following THA, musculoskeletal comorbidities have not been investigated. We evaluated whether lumbar pain and pain in the knees and non-operative hip joints predict poorer 6 month pain relief and functional gains.

Methods: Data were collected from 2,848 patients enrolled in FORCE-TJR, a national prospective cohort of patients who underwent a primary unilateral total hip replacement due to osteoarthritis. Data include patient demographics, medical comorbidities, emotional health (SF/MCS), low back pain ( Oswestry), pain in both hips and knees (HOOS/KOOS pain score), and pre-operative and post-operative function (SF/PCS) were collected pre-operatively and six months post-operatively. Post-THA pain relief and functional gains were analyzed using descriptive statistics as well as linear mixed regression models, in relation to musculoskeletal comorbid conditions and traditional patient and clinical factors.

Results: This cohort was 59% female, with a mean age of 65.4 years and mean BMI of 28.9 (kg/m2). Out of the 2,848 patients, 992 (34.8%) reported moderate to severe low back pain pre-operatively. In addition, 264 (9.3%) reported moderate to severe pain in at least two non-operative hip or knee joints. After adjusting for gender, age, BMI, emotional health and medical co-morbidities, moderate to severe pre-THA back pain and pain in one or more non-operative hip or knees was significantly correlated (p=0.001) with a smaller improvement in hip pain and function after THA. Additionally, the greater the number of nonsurgical hip and knee joints with pain pre-operatively, the stronger the negative effect on pre-to-6 month post-THA gain in pain and function outcomes.

Conclusion: The presence of low back pain and pain in non-operative hip and knee joints has a significant negative impact on post-THA pain relief and functional outcome. In addition to traditionally reported clinical factors (i.e. age, weight and medical co-morbidities) the burden of musculoskeletal co-morbidity is an important consideration in predicting post-THA gains.

Table 1. Predictors of pre-to-6 month post-THA change in HOOS ADL/Function Score

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.136***</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.109*</td>
</tr>
<tr>
<td>Female</td>
<td>0.326</td>
</tr>
<tr>
<td>pre SF/S6 MCS</td>
<td>0.190***</td>
</tr>
<tr>
<td>Baseline Hip Function</td>
<td>0.886***</td>
</tr>
<tr>
<td>pre HOOS ADL</td>
<td></td>
</tr>
<tr>
<td>pre HOOS Pain</td>
<td></td>
</tr>
<tr>
<td>Basline Medial Co-Morbidities</td>
<td></td>
</tr>
<tr>
<td>pre MCCOM =1</td>
<td>-1.068</td>
</tr>
<tr>
<td>pre MCCOM =2</td>
<td>-3.219**</td>
</tr>
<tr>
<td>pre MCCOM =3</td>
<td>-4.453**</td>
</tr>
<tr>
<td>Baseline Low Back Pain</td>
<td></td>
</tr>
<tr>
<td>Pre OSW LB Pain = Mild</td>
<td>-1.207</td>
</tr>
<tr>
<td>Pre OSW LB Pain = Moderate</td>
<td>-2.709***</td>
</tr>
<tr>
<td>Pre OSW LB Pain = Severe</td>
<td>-3.737***</td>
</tr>
<tr>
<td>Other hip or knee joints with pain</td>
<td></td>
</tr>
<tr>
<td>Pre Pain HK Joint = 1</td>
<td>-2.571***</td>
</tr>
<tr>
<td>Pre Pain HK Joint = 2</td>
<td>-5.860***</td>
</tr>
<tr>
<td>Pre Pain HK Joint = 3</td>
<td>-7.422***</td>
</tr>
<tr>
<td>Constant</td>
<td>86.19***</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001.

Disclosure: S. Pascal, None; D. Ayers, None; W. Li, None; L. Harold, None; J. Allison, None; P. D. Franklin, None.

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Relationship of Buckling and Knee Injury to Pain Exacerbation in K ee Osteoarthritis: A Web-Based Case-Crossover Study. Isabelle Zobel3, Tahereh Efrani2, Kim Bennell5, Joanna Makovey4, Ben Met- calf7, Jian Sheng Chen5, Lynn Arch1, Yiqing Zhang5, Felix Eckstein1 and David J. Hunter2.

1Institute of Bone and Joint Research, Kolding
Background/Purpose: Knee osteoarthritis (OA) pain is neither constant nor stable, nor do exacerbations of pain are disabling. We examined whether knee injury and buckling (giving way) are triggers for exacerbation of pain, also defined as flare, in persons with symptomatic knee OA.

Methods: We conducted a web-based case–crossover study with all data collected via the Internet. Participants with painful radiographic knee OA were recruited and followed at 10-day intervals for 3 months (control periods). Participants were instructed to additionally record knee pain exacerbations during the 3 months interval. Pain exacerbation was defined as an increase of 20mm from baseline on VAS knee pain score (VAS 0–100). Information about triggers occurring during “control periods” (without pain exacerbation) and “hazard periods” (immediately preceding the pain exacerbation) was collected. Two potential triggers by asking for acute knee injuries in the previous seven days. Similarly we asked about knee buckling events, defined as giving way in the previous two days (i.e., date of pain exacerbation for hazard period, and date of data assessment for control periods). The relationship of knee injury and buckling to the risk of pain exacerbation was examined using conditional logistic regression models.

Results: Of the 297 participants (women: 61%, mean age: 62 years, mean BMI: 29.3 kg/m²) recruited, 157 (53%) had both hazard and control periods and were included in the data analysis. Sustaining a knee injury increased the likelihood of experiencing a pain flare (odds ratio (OR) 10.2; 95% CI 5.4, 19.3) compared to no injury (Table). An event of knee buckling increased the likelihood of experiencing a pain exacerbation (OR 4.0; 95% CI 2.6, 6.2) compared to no buckling and the risk increased with a greater number of buckling events (for ≥ 6 buckling events, OR 20.1; 95% CI 3.7, 110).

Conclusion: Knee injury and buckling are associated with knee pain exacerbation. Reducing the likelihood of knee injury and buckling through avoidance of particular activities and/or appropriate rehabilitation programs may decrease the risk of pain exacerbation.

Table. Association of knee injury and risk of knee pain exacerbation

<table>
<thead>
<tr>
<th>Knee injury</th>
<th>Case periods</th>
<th>Control periods</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>329</td>
<td>820</td>
<td>1.02 (0.87, 1.20)</td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
<td>31</td>
<td>10.2 (5.4, 19.3)</td>
</tr>
</tbody>
</table>

Association of knee buckling and risk of knee pain exacerbation.

<table>
<thead>
<tr>
<th>Number of episodes</th>
<th>No Frequent Knee Pain</th>
<th>Frequent Knee Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>259</td>
<td>743</td>
</tr>
<tr>
<td>2-5</td>
<td>141</td>
<td>108</td>
</tr>
<tr>
<td>≥6</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Conclusion: Knee injury and buckling are associated with knee pain exacerbation. Reducing the likelihood of knee injury and buckling through avoidance of particular activities and/or appropriate rehabilitation programs may decrease the risk of pain exacerbation.

Table 1. Descriptive Baseline Characteristics of the Study Samples in Primary and Secondary Analyses

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Full OAI Cohort (n = 4,435)</th>
<th>ROA at Baseline (n = 1,443)</th>
<th>No ROA at Baseline (n = 1,863)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean (sd))</td>
<td>61.2 (9.2)</td>
<td>63.0 (8.8)</td>
<td>59.2 (9.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m², mean (sd))</td>
<td>28.6 (4.8)</td>
<td>30.2 (5.0)</td>
<td>27.2 (4.5)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>2591 (58.4%)</td>
<td>905 (62.7%)</td>
<td>1095 (58.8%)</td>
</tr>
<tr>
<td>WO MAC right knee pain score (%)</td>
<td>1639 (37.0%)</td>
<td>683 (47.3%)</td>
<td>543 (29.2%)</td>
</tr>
<tr>
<td>Frequent left knee pain (%)</td>
<td>1582 (35.7%)</td>
<td>658 (45.6%)</td>
<td>537 (28.9%)</td>
</tr>
<tr>
<td>WO MAC left knee pain score (%)</td>
<td>1349 (30.4%)</td>
<td>609 (42.2%)</td>
<td>412 (22.1%)</td>
</tr>
</tbody>
</table>

Note. ROA = radiographic osteoarthritis.

Table 2. Frequent Knee Pain and History of Injury Predict a New Knee Injury within 12 Months

<table>
<thead>
<tr>
<th>Frequency of Injuries/ Total Observations</th>
<th>Adjusted Odds Ratio for Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Osteoarthritis Initiative (4,435 participants, 875 injuries)</td>
<td></td>
</tr>
<tr>
<td>No Frequent Knee Pain</td>
<td>422/21312 (2.0%)</td>
</tr>
<tr>
<td>Frequent Knee Pain</td>
<td>453/10118 (4.5%)</td>
</tr>
<tr>
<td>No Frequent Contralateral Knee Pain</td>
<td>502/21311 (2.4%)</td>
</tr>
<tr>
<td>Frequent Contralateral Knee Pain</td>
<td>373/10119 (3.7%)</td>
</tr>
<tr>
<td>No History of Knee Injury</td>
<td>433/22275 (2.0%)</td>
</tr>
<tr>
<td>History of Knee Injury</td>
<td>432/9155 (4.7%)</td>
</tr>
<tr>
<td>No History of Contralateral Knee Injury</td>
<td>518/22275 (2.3%)</td>
</tr>
<tr>
<td>History of Contralateral Knee Injury</td>
<td>357/9155 (3.9%)</td>
</tr>
</tbody>
</table>

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Knee Pain and a Prior Injury Are Associated with Increased Risk of a New Knee Injury: Data from the Osteoarthritis Initiative. Jeffrey B. Driban, Grace H. Lo, Lori Lyn Price, Charles Eaton, Bing Lu and Timothy E. McAlindon. "Tufts Medical Center, Boston, MA; "Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX. "Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI; "Bingham and Women’s Hospital, Foxboro, MA.

Background/Purpose: A knee injury increases the risk for early-onset osteoarthritis (OA) and accelerated knee OA progression but little is known about risk factors for injuries among adults. Knee pain and a history of knee injury may be key risk factors because both can lead to altered joint biomechanics. Therefore, we explored if knee pain or a history of knee injury was associated with a knee injury in the subsequent 12 months.

Methods: We conducted longitudinal knee-based analyses among participants in the Osteoarthritis Initiative, a longitudinal observational study. We included both knees of all participants who attended baseline and had at least one follow-up visit with complete data. Our first set of exposures were knee pain (frequency and severity) at baseline, 12-month, 24-month, and 36-month visits. We defined frequent knee pain as pain on most days of a month in past 12 months. Knee pain severity was based on the WOMAC pain subscale, which we dichotomized as no-to-light pain (0 to 2) or knee pain (≥ 3). Another exposure was a history of injury, which we defined as a self-reported injury at any time prior to baseline, 12-month, 24-month, or 36-month visits. The outcome was self-reported knee injury during the past year at 12-month, 24-month, 36-month, and 48-month OAI visits. We conducted secondary analyses based on the bilateral absence or presence of knee OA at baseline, which we defined as Kellgren-Lawrence Grade ≥ 2. We evaluated the association between knee pain or history of injury (in both knees) and a new knee injury within 12 months of the exposure by performing repeated measures random intercept models to adjust for correlations within person observations over time and between knees. A nales were adjusted for sex, age and body mass index at each visit.

Results: The baseline characteristics of the samples are presented in Table 1. In our primary analyses, individuals who reported frequent knee pain or an injury in either knee were more likely to experience a new knee injury in the following 12 months (Table 2) than individuals without frequent knee pain or prior injury. These findings were supported when we evaluated knee pain severity and in our secondary analyses. The only exception was that a history of a contralateral knee injury was not related with a new knee injury among those without radiographic OA at baseline.

Conclusion: Knee pain and a history of injury are associated with new knee injuries in the following 12 months. This may identify a group of people at higher risk for accelerated knee OA. It may be beneficial for individuals with knee pain or a history of pain to participate in injury prevention programs.
S562


Background/Purpose: A variety of pain and function instruments are often measured in osteoarthritis (OA) clinical trials. Instruments with maximal sensitivity to change are preferred as the primary measure in trials. Shown to be sensitive to change in rheumatoid arthritis, patient preference instruments, in which a patient nominates a painful activity to track, have not been tested in OA trials. Ideally, to compare the sensitivity to change of outcome measures, trials with a positive result need to be studied. We compared the sensitivity to change of pain and function self-report outcomes in 2 OA trials that reported statistically significant improvements in pain/function status outcomes.

Methods: We used data from a controlled trial of a knee brace (BRACE; n = 126) and an uncontrolled trial of intra-articular steroid injection (TASK; n = 120). For both trials, eligible subjects had to meet ACR criteria for knee OA and have significant knee pain. In addition to completing KOOS and WOMAC questionnaires, and questions about overall knee pain, subjects were asked to nominate an activity that commonly caused them knee pain, and to rate pain during that activity throughout the trial. Standardised response mean (SRM) was generated for multiple time points in both trials, in the active treatment group alone, and comparing treatment to control, where possible. Additionally, we tested correlations between the study outcomes and an anchor variable: a 5-point Likert scale of patient-perceived change in pain, using ordinal regression to determine the odds of an improvement in pain for a 1 SD increase in each pain outcome.

Results: Both trials reported a positive effect of the intervention on pain and function. Pain on nominated activity visual analogue score (VAS) produced SRMs that were at least as high as other pain outcomes, and usually higher (table 1). Sensitivity to change of the other outcomes was less consistent. Patient perceived improvement in pain was more strongly associated with pain on nominated activity than the other pain or function outcomes (table 2).

Conclusion: Pain on nominated activity may be an extremely sensitive outcome for OA trials, and appears more strongly associated with perceived pain improvement than other currently used outcome measures.

Table 1: Standardised Response Means (SRMs) for the TASK and BRACE Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BRACE 6 week active vs. control treatment difference: SRMs</th>
<th>BRACE 6 week active treatment only: SRMs</th>
<th>BRACE 12 week active treatment only: SRMs</th>
<th>TASK Study - Change at 1 week after intra-articular steroid: SRMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on nominated activity VAS</td>
<td>-0.31</td>
<td>-0.85</td>
<td>-0.95</td>
<td>-1.13</td>
</tr>
<tr>
<td>Pain in last week VAS</td>
<td>-0.25</td>
<td>-0.86</td>
<td>-0.73</td>
<td>-1.07</td>
</tr>
<tr>
<td>Global pain VAS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KOOS pain subscale</td>
<td>-0.16</td>
<td>-0.53</td>
<td>-0.73</td>
<td>-1.12</td>
</tr>
<tr>
<td>KOOS symptom subscale</td>
<td>-0.20</td>
<td>-0.62</td>
<td>-0.61</td>
<td>-0.94</td>
</tr>
<tr>
<td>KOOS activities of daily living subscale</td>
<td>-0.12</td>
<td>-0.54</td>
<td>-0.77</td>
<td>-1.04</td>
</tr>
<tr>
<td>WOMAC pain subscale</td>
<td>-0.13</td>
<td>-0.47</td>
<td>-0.63</td>
<td>-1.06</td>
</tr>
<tr>
<td>WOMAC stiffness subscale</td>
<td>-0.19</td>
<td>-0.53</td>
<td>-0.51</td>
<td>-1.17</td>
</tr>
<tr>
<td>WOMAC function subscale</td>
<td>-0.12</td>
<td>-0.54</td>
<td>-0.77</td>
<td>-1.04</td>
</tr>
</tbody>
</table>

Table 2: Association between Different Pain Outcomes and Patient Perceived Improvement in Pain. Odds Ratios Indicate Odds of Improvement in Patient Perceived Pain, for a 1 SD Improvement in the Outcomes Listed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BRACE Study - 6 week change, all persons pooled</th>
<th>BRACE Study - 12 week change, all persons pooled</th>
<th>TASK Study - Change at 1 week follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on nominated activity VAS</td>
<td>2.09</td>
<td>2.57</td>
<td>6.12</td>
</tr>
<tr>
<td>Pain in last week VAS</td>
<td>1.94</td>
<td>2.15</td>
<td>4.45</td>
</tr>
<tr>
<td>Global pain VAS</td>
<td>-</td>
<td>-</td>
<td>2.36</td>
</tr>
<tr>
<td>KOOS pain subscale</td>
<td>1.63</td>
<td>1.79</td>
<td>1.87</td>
</tr>
<tr>
<td>KOOS symptom subscale</td>
<td>1.64</td>
<td>1.62</td>
<td>1.88</td>
</tr>
<tr>
<td>KOOS activities of daily living subscale</td>
<td>1.67</td>
<td>1.70</td>
<td>1.86</td>
</tr>
<tr>
<td>WOMAC pain subscale</td>
<td>1.60</td>
<td>1.71</td>
<td>1.84</td>
</tr>
</tbody>
</table>
Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the long established first-line treatment for the management of pain associated with rheumatic diseases but carry a risk of gastrointestinal (GI) disturbance. The recognized GI risk factors are age > 60 years; concomitant use of acetylsalicylic acid (ASA), oral corticosteroids or anticoagulants; previous history of ulcer, bleeding, or dyspepsia; and use of two NSAIDs or high dose of one NSAID. Evidence-based guidelines recommend the concomitant use of gastroprotective agents (GPAs) in NSAID users with one or more risk factors. Current evidence suggests that a significant proportion of patients at risk for GI events do not receive a GPA.

Methods: The RATIONAL study was conducted in Asia, Russia and Latin America and had an observational, multicenter, cross-sectional design to evaluate the prevalence of GI risk factors in patients with osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS). The single study visit was part of standard practice. Patients were aged >21 years with a documented diagnosis of RA (ACR/EULAR 2010 criteria), OA (ACR 1991 criteria) or AS (New York 1984 criteria or ESSG 2002 criteria) and had taken at least one dose of NSAIDs in the 15 days before enrolment. Information collected included NSAID treatment over the year preceding the study visit, GPA use, and occurrence of any of a defined range of GI events.

Results: The distribution of rheumatic disorders in the 5373 patients was OA 2996 (55.8%), RA 1882 (35.0%), AS 283 (5.3%), and a combination of these 212 (3.9%). One or more GI risk factors were present in 87.7% of patients. The prevalence of individual risk factors and treatment with GPAs is shown in Table 1. GPA use was higher in patients aged >60 years or concomitantly using anticoagulants was close to the study average (57.9%). A modest numerical increase from this mean value was observed in patients taking concomitant ASA (63.8%) or high doses of an NSAID (64.1%). A greater numerical increase in this percentage was seen for all of the other risk factors with values of 96.6% and 93.3% for those with histories of GI complications and GI ulcer, respectively. There was a strong preference for using proton pump inhibitors as the class of GPA and the most commonly used individual treatment was omeprazole (36.4% of total patients).

Table 1: Prevalence of risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk factor present</th>
<th>Receiving a GPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years</td>
<td>2627</td>
<td>1534</td>
</tr>
<tr>
<td>History of GI complications</td>
<td>1058</td>
<td>636</td>
</tr>
<tr>
<td>History of complicated ulcer</td>
<td>1202</td>
<td>850</td>
</tr>
<tr>
<td>Concomitant anticoagulants</td>
<td>120</td>
<td>53</td>
</tr>
<tr>
<td>Concomitant ASA</td>
<td>564</td>
<td>360</td>
</tr>
<tr>
<td>History of dyspepsia</td>
<td>569</td>
<td>351</td>
</tr>
<tr>
<td>History of complicated ulcer</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>High dose NSAID</td>
<td>120</td>
<td>77</td>
</tr>
<tr>
<td>More than one NSAID</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

Conclusion: Risk factors that appeared to influence the provision of treatment with a GPA were those related to a previous history of GI-related symptoms or events and concomitant use of corticosteroids. Most of the other risk factors appeared to have little influence on the prescription of a GPA. Although 87.8% of the study population had one or more GI risk factors, only 57.9% received any form of GPA. Age does not appear to be recognized as a risk factor for GI symptoms and GPAs are under prescribed.

Study identifier [NCT01375653]


Background/Purpose: Longitudinal studies of people with knee osteoarthritis (OA) have reported stable or improved physical function, contrary to the progressive degenerative nature of OA. The early improvement may be from regression to the mean, because subjects enroll when they are in pain. Limitations to current studies are exclusion of subjects with missing data, and of total knee replacements (TKRs). Little is known when including imputation of missing values and pre-TKR physical function data. The aim of this study was to describe physical function over 7 years among subjects with symptomatic knee OA before and after imputation of missing values, and inclusion of pre-TKR physical function values.

Methods: Participants from the Osteoarthritis Initiative (OAI) with symptomatic knee OA at baseline were included, excluding those with hip replacement, those that died, and with TKR at baseline. We defined symptomatic knee OA when at least one knee showed Kellgren and Lawrence grade ≥1 by x-ray and pain on most days the last month. WOMAC physical function (pf) (0–68) was assessed annually over 7 years in clinic visits. We set the reference for pre-TKR values to missing. For all, missing WOMAC-pf values were imputed using the multiple imputation method. For the TKR group, time from the last clinic visit prior to TKR was regressed on WOMAC-pf using a fitted LOESS curve. Then, new predicted WOMAC-pf values were assigned to the existing pre-TKR values, to provide values close to the actual time of the TKR. Mixed effect models were used to compare original WOMAC-pf values against adjusted values (after imputation and prediction of pre-TKR values) (grey vs. red lines in the figure).

Results: Of 4344 eligible people in OAI, 1065 (24.5%) had symptomatic knee OA at baseline (age: 61.3±8.9 years, women: 58.4%, BMI: 30.3±5.0). There were 163 unilateral and 45 bilateral TKRs (19.5%). There was no significant difference in WOMAC-pf between original values and adjusted values, although incorporating data on missing and predicted pre-TKR values left WOMAC-pf worse on average (figure, red and grey lines), and created a larger sample followed over time than original analyses in which pre-TKR and missing values were excluded.

Conclusion: Physical function over time is sensitive to missing values when excluding people who go through TKR and missing clinic visits. Including imputation of missing visit and adjusted pre-TKR values better depicts physical function in persons with symptomatic OA, and permits the evaluation of function in many persons left out of current studies.

Figure. WOMAC physical function over 7 years among people with symptomatic knee osteoarthritis.
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Patient Perspective of the Main Health Concerns and Needs of Living with Hand Osteoarthritis.

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Background/Purpose: Hand OA (HOA) is associated with substantial pain, joint stiffness, functional impairment and disability, and cosmetic concerns. Data regarding patients’ perspective on living with these consequences is limited. We aimed to explore the experiences of HOA patients of different phenotypes and explored their perspectives in the symptom, function, and aesthetic domains.

Methods: Unrelated patients ≥45 years of age with clinical and radiographic idiopathic HOA (distal interphalangeal (DIP) and/or carpometacarpal (CMC) joints) from our registry were recruited and consented for a 45-minute, face-to-face semi-structured interview by a trained medical anthropologist. We assessed symptomatology, HOA, functional and aesthetic domains. Interviews were audiorecorded and interview notes and tapes were reviewed using a content analysis approach.

Results: 14 (11 women and 3 men) patients were interviewed. 10 of 14 were ≥60 years with a median age of 70 years. 5 had erosive disease, of whom 3 also had CMC involvement, 3 had CMC only disease, 6 had non erosive HOA, of whom 4 had CMC disease as well. Median age of 14 had 60 years with a median score of 6 out of 10 with 0=none and 10=maximum possible) and stiffness. Many described different adaptations to address pain, discussed their fears of future disease progression and their reluctance to medication for HOA, and accepted pain as part of the aging process. The participants claimed the worst part of having HOA was decreased functionality and potential loss of independence (median score=5). They discussed how HOA limited daily activities, hobbies, and work, leading to frustration. Those with HOA in multiple joint areas reported the most limitations; those with DIP joint involvement reported worse function vs. those with CMC only disease. Whether it was erosive or non-erosive did not make much difference.

Participants rated how much the appearance of their hands affected them (median score=2). Most related HOA to aging However, of those bothered by their appearance (all female), they reported being very troubled. Important issues of concern to the patients also emerged and were discussed. Coping strategies, self-reliance and personal strength, lessons learned, and worry and fears for the future, given this chronic illness. They also commonly articulated their desire to receive more counseling and information, including non-medical healing approaches, from their rheumatologists.

Conclusion: Patients with more joint area involvement suffered the most functional loss. IP involvement led to more severe functional limitations compared to CMC OA but erosive disease did not compound functional disability. Patients experienced frustration over functionality loss and potential loss of future independence since many either experienced or anticipated living alone. Other areas of concern not traditionally assessed or considered by physicians, including coping, lessons learned from the disease, fears for the future, and desire for non-drug approaches were identified. Understanding the impact of HOA on patient perception may identify new opportunities for targeted intervention outside of traditional methods.

Disclosure: M. L. Ishimori, None; G. Racaza, None; M. Wither, None; M. Weisman, None.

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Older Adults with Osteoarthritis Do Not Have an Increased Risk of Cognitive Impairment.

Bansari Gujrati, Ann Gruber-Baldini, Moni Baumgarten, William Hawkes, Michael C. Nevitt, Kristine Yaffe, Tamara Harris and Marc C. Hochberg.
1 University of Maryland School of Medicine, Baltimore, MD, 2UCSF (University of California, San Francisco), San Francisco, CA, 3National Institute on Aging, National Institutes of Health, Bethesda, MD.

Background/Purpose: A prior study showed an association between osteoarthritis (OA) and increased mortality from dementia. Recent preclinical studies suggest a possible association between OA and the development of dementia. The objective of this analysis was to determine if older adults with OA have a higher risk of cognitive impairment (CI). Method: We used data from the Health And Body Composition (HABC) study, a multicenter prospective cohort study of community dwelling adults, ages 70–79, to determine if participants with OA at baseline (self-reported OA or OA defined by HABC prevalent disease algorithm) have an increased risk of developing CI. CI was defined as a Modified Mini-Mental State examination (3MS) score<80. Participants with 3MS scores of ≥80 at baseline were excluded. Baseline and year 3, 5, 8, and 10 scores were analyzed.

Results: There were 2577 participants with 3MS scores of ≥80 at baseline (n=1277 with OA, n=1300 without OA). The OA group had more women (54% vs 44%, p<0.001), higher baseline CES-Depression scores (4.9 SD 5.4 vs 4.2, SD 4.9, p=0.003) and hypertension (46% vs 40%, p=0.028). There was no significant difference in development of CI after 9 years amongst those with OA (n=165, 12.9%) versus without OA (n=197, 15.1%), χ^2 (1, n=2577)=2.66, p<0.01. The results of the multiple variable logistic regression analysis (adjusted for age, race, education and gender) suggest a protective effect that did not reach statistical significance (odds ratio=0.8, 95% CI 0.6–1.0; P-value=0.10). There was no significant association between baseline OA and the development of CI at the 3, 5, 8 and 10 year time point. No differences were found upon sensitivity analysis using race and education adjusted cut-points for 3MS scores.

Conclusion: These results do not support the hypothesis that there is a causal association between OA and CI.

Disclosure: B. Gujrati, None; A. Gruber-Baldini, None; M. Baumgarten, None; W. Hawkes, None; M. C. Nevitt, None; K. Yaffe, None; T. Harris, None; M. C. Hochberg, None.

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Classification of Osteoarthritis Phenotypes By Metabolomics Analysis.

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Background/Purpose: Osteoarthritis (OA) is a group of heterogeneous conditions consisting of different subgroups or phenotypes that continuously evolve, eventually leading to common clinical manifestations. Identifying OA subphenotypes and uncovering their different mechanisms of pathogenesis is of fundamental importance for the development of appropriate therapies and diagnostic tools. The aim of this study was to identify metabolic markers that can classify OA patients into subgroups.

Methods: A case-only study design was utilized in this study. Patients undergoing total hip/knee joint replacements due to primary OA were recruited and their synovial fluid samples were collected during their joint surgeries. Metabolic profiling was performed on the synovial fluid samples by the targeted metabolomics approach using the Biocrates AbsoluteIDQ p180 kit. Various analytic methods including principal component analysis (PCA), hierarchical clustering (HCL) method, and partial least squares discriminant analysis (PLS-DA) were utilized to identify metabolic markers for classifying subgroups of OA patients. Potential confounders such as age, sex, body mass index (BMI), and comorbidities were considered in the analysis.

Results: A total of 80 OA patients were included in the study. 38 were males and 42 were females with an average age of 65.2 ± 8.7 years. Two distinct patient groups, A and B, were clearly identified. Patients in group A had significant higher concentration on 39 acylcarnitines in their synovial fluids than the patients in group B. Patients in group B were further subdivided into five subgroups, i.e., B1-1, B1-2, B2-1, B2-2, and B2-2. The corresponding metabolites that contribute to the grouping were 14 amino acids, 24 glycerophospholipids, 12 acylcarnitines and 1 biogenic amine. The grouping was not associated with any known confounders including age, sex, BMI, and comorbidities. The corresponding metabolites involved in these clusters are carnitine, lipid, and collagen metabolism, respectively.

Conclusion: The study demonstrated that OA consists of metabolically distinct subgroups. Identification of these distinct subgroups will help to unravel the pathogenesis and develop targeted therapies for OA.
Background/Purpose: Single Nucleotide Polymorphisms (SNPs) are inherited genetic variations that can predispose or protect individuals against clinical events. Osteoarthritis (OA) has a multifactorial etiology with a strong genetic component. Genetic factors influence not only knee OA onset, but also disease progression. The aim of the Arthritis study was to develop a genetic prognostic tool to predict radiologic progression towards severe disease in primary knee OA (KOA) patients.

Methods: Cross-sectional, retrospective, multicentric, association study with Spanish KOA patients. 595 patients from 31 sites were selected. Inclusion criteria: Caucasian patients aged ≥40 years at the time of diagnosis of primary KOA (according to the ACR criteria), for whom two anteroposterior X-rays were available, one corresponding to the time of OA diagnosis with Kellgren-Lawrence grade ≥2 or 3 and the other to the end of the follow-up period. Patients who progressed to KL score 4 or were referred for total knee replacement in ≤8 years since the diagnosis were classified as progressors to severe disease. A unique expert viewer measured radiologic progression from all X-rays. A candidate gene study analyzing 774 SNPs was conducted. SNP genotyping was performed with Illumina Golden gate technology or KASP chemistry. Clinical variables of the initial stages of the disease (gender, BMI, age at diagnosis, OA duration in the contralateral knee and OA in other joints) were registered as potential predictors. Univariate analysis was done to identify associations between the baseline clinical variables or SNPs and KOA progression. SNPs and clinical variables with an association of p<0.05 were included on the multivariate analysis using forward logistic regression.

Results: 282 patients fulfilled DNA and X-ray quality control criteria (220 in the exploratory cohort and 62 in the replication cohort). The univariate association analysis showed that one of the clinical variables and 23 SNPs were significantly associated to KOA severe progression in the exploratory cohort (p<0.05). The predictive accuracy of the clinical variable was limited, as indicated by the area under the ROC curve (AUC = 0.66). Combining only genetic variables, a predictive model with a good accuracy (AUC = 0.78) was obtained. When genetic variables were added to the clinical model (full model) the prediction of KOA progression was improved and the AUC increased to 0.82. The predictive ability for KOA progression of the full model was confirmed on the replication cohort (two-sample Z-test p=0.190). The full final model developed combines the clinical variable age at KOA diagnosis and 8 SNPs (rs2073508, rs10845493, rs2206593, rs10519263, rs874692, rs7342880, rs12009 and rs780094 - located in GCKR2 gene -).

Conclusion: Genetic polymorphisms predict radiologic progression more precisely than clinical variables. An accurate prognostic tool to predict primary KOA progression has been developed based on genetic and clinical information from OA patients.

Disclosure: Disclosure: Disclosure: W. Zhang, None; S. Likhodi, None; Y. Zhang, None; E. Aref-Eshghi, None; P. E. Harper, None; E. Randell, None; R. Green, None; G. Martin, None; A. Furey, None; G. Sun, None; P. Rahman, None; G. Zhai, None.

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Knee Osteoarthritis Progression Is Predictable By Genetic Polymorphisms. Results from a Multicenter Association Study. Francisco J Blanco1, Ingrid Möller2, Nerea Bartolome3, Marta Artieda4, Diego Tejedor5, Antonia Martinez6, Eulália M onter1, Helena Martinez1, Marta Herrero5, and Josep Verges5. 1INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, 2Bioiberica, 3; 3Progenika, a Grifols Company, Derio, Bizkaia, Spain, 4Progenika, a Grifols Company, Verge´s, Bioiberica, 3; 5Hospital for Special Surgery, New York, NY.

Background/Purpose: The presence of calcium crystals (CC) in synovial fluid (SF) of osteoarthritis (OA) is a well known and frequent feature (1). However, their role in the pathogenesis of OA is still unclear and matter of discussion, in particular as regard the local inflammation (2). The objective of the study was to evaluate the presence of the most common CC, calcium pyrophosphate (dihydrate) (CPP) and basic calcium phosphate (BCP), in SF of the symptomatic knee OA (KOA), particularly in early disease stage (<3yrs) and to investigate their association with local inflammation, disease severity and speed. We performed an ultra-sensitive analysis of SF crystals using the scanning electron microscopy (SEM) and the routine method by compensated polarized light microscopy (CPLM) and alizarin red staining.

Methods: Seventy-four (48 F, mean age 64.84±3.93 yrs, range 50–89 yrs) consecutive outpatients attending the Rheumatology Unit, University of Padova with symptomatic KOA (according to the American College of Rheumatology criteria) underwent knee arthrocentesis. After optical and Alizarin Red Staining (ARS), the SF was analysed by SEM. Total white blood cell (WBC) count was performed and a cut-off of total WBC was established in ≤<1000/mm³.

Results: CPP crystals were identified in 32.4% by CPLM and in 31.1% by SEM. A lizarin was positive in 36.5% of the samples. BCP were found in 13.5% by SEM. CPP and BCP crystals were simultaneously positive in 8.1% of the samples by SEM.

Conclusion: The presence of CC in SF, also when detected in early OA stages, was associated with a higher degree of local inflammation, so suggesting that they may play a role in eliciting an inflammatory reaction, which may be crucial in OA pathogenesis.

Disclosure: Disclosure: W. Zhang, None; S. Likhodi, None; Y. Zhang, None; E. Aref-Eshghi, None; P. E. Harper, None; E. Randell, None; R. Green, None; G. Martin, None; A. Furey, None; G. Sun, None; P. Rahman, None; G. Zhai, None.

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Relationships Between Inflammation, Disease Severity and Synovial Fluid Calcium Crystals Detected By Scanning Electronic Microscopy in Early Osteoarthritis. Paola Frallonardo1, Francesca Oliviero1, Luca Peruzzo1, Assunta Pozzuoli3, Ambrogio Fassina1, Ermanno Martucci1, Leonardo Tauro1, Paola Frallonardo2, Leonardo Punzi2 and Roberta Ramonda1. 1University of Padova, Padova, Italy, 2Center for Science and Earth Resources IGG-CNRS, Padova, Italy.

Background/Purpose: The study was conducted in the context of a three-year project funded by the Italian Ministry of Health (Ricerca Finalizzata - Giovani Ricercatori - project code: GR-2010-2317593), which maintains extensive records of preclinical, intraoperative and post-operative data so far for 58 patients who have undergone meniscectomy for both degenerative and traumatic meniscal tear. Synovial biopsies were collected in suprapatellar area during arthroscopic surgery and processed for histology. Synovial features of
inflammation were assessed using an histological synovial scoring based on perivascular mononuclear cell infiltration as follows: grade 0 = none, grade 1 = mild (0-1 perivascular aggregates per low-power field); grade 2 = moderate (>1 perivascular aggregate per low power field with or without focal interstitial infiltration); grade 3 = marked aggregates (both perivascular and interstitial) (Scanzello CR, Arthritis Rheum. 2011). The following clinical data were collected: age, sex, BMI, date of injury and time to surgery, pre-operative VAS and KOOS, 3–6 months KOOS and meniscal tear characteristics. Cartilaginous defects and meniscal pathologies were assessed intraoperatively using the Outerbridge scoring system.

Results: In the series of 58 patients, males were predominant (72%) with median ages of 43.6 and 50 years, respectively. Meniscal tear were traumatic in 50% of patients. KOOS at 3–6 months after meniscectomy statistically improved compared with the baseline (p < 0.0001). No association was observed between traumatic or degenerative meniscal tear and age, BMI, KOOS, frequency of cartilage defects or macroscopic synovitis score. Of 26 patients age and BMI.

Discussion: In our study, we observed an high percentage of low-grade synovitis (88%), and/or cartilage defects (82.7%) in patients undergoing partial meniscectomy for meniscal tear. Microscopic synovial inflammation correlate with the grade of cartilage defect confirming that synovitis play a role in the progression of the disease.

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Identification of an Inflammation-Driven Phenotype of Osteoarthritis By Quantification of Synovial Inflammation Ex Vivo and in Serum from Patients With Knee Osteoarthritis

Methods: Synovial membrane explants (SMEs): Synovial membrane from 4 OA patients undergoing total knee replacement at Gentofte Hospital, Copenhagen, were cultured as SMEs (30–270mg) for 3 weeks with media alone (w/o), 10 ng/mL TNFα, IL-1β or TGFβ-2, or metabolic inactivated, supernatant was collected 3 times a week and stored at -20°C. In-house neo-epitope biomarkers; C1M, C3M, and active MMP-3 were assessed by ELISA. The aim of the study was to investigate if C1M and C3M were associated with joint inflammation in OA, by i) measuring the release of the biomarkers in response to pro-inflammatory factors in an ex vivo human OA synovial explant model and ii) investigate the level of the biomarkers in patients in association with radiographic and inflammatory knee OA.

Results: SME: C1M and C3M were increased (10 and 100-fold, respectively) at day 7 in response to TNFα compared to w/o (C1M: p < 0.0001, C3M: p < 0.0001). IL-1β showed similar pattern. TGFβ-2 did not affect C1M or C3M. A activated MPP-9 and activated MPP-3 (p < 0.0001) was increased in SMEs treated with IL-1β or TNFα throughout the study for SMEs, while activation of MPP-2 was not affected. Knee OA cohort: Serum C1M were significant elevated in the Terminal group compared to the Moderate (p < 0.0001) and Severe OA (p < 0.01) groups, but no significant difference in serum C3M. Patients with inflammatory OA (high hsCRP and pain) had a higher level of C1M and C3M as compared to non-inflammatory patients (table). There was no difference in KL between the two groups.

Conclusion: In OA patients with the same KL score, C1M and C3M were significantly higher in those with an inflammation-driven phenotype. C1M and C3M were released from the SMEs upon treatment with the pro-inflammatory cytokines IL-1β and TNFα, but not TGFβ-2, which indicates that C1M and C3M are direct measures of synovial turnover and inflammation. This was supported by the detection of active MPP-3 and -9, which act downstream of the cytokines and upstream of the biomarkers. These biomarkers may be part of the identification of the important and possibly treatable inflammation-driven OA phenotype.

Table

<table>
<thead>
<tr>
<th></th>
<th>Non-inflammatory OA</th>
<th></th>
<th>Inflammatory OA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95%-CI</td>
<td>Mean</td>
</tr>
<tr>
<td>KL</td>
<td>2.3</td>
<td>2.2–2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>C1M, ng/mL</td>
<td>49.0</td>
<td>46.8–51.2</td>
<td>94.2</td>
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<tr>
<td>C3M, ng/mL</td>
<td>17.7</td>
<td>16.9–18.4</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Disclosure: C. F. Kjeldgaard-Petersen, None; A. S. Siebuhr, Nordic Bioscience A/S; K. K. Petersen, None; L. Arendt-Nielsen, None; T. Eskehave, CCBR-Synarc; H. C. Hoeck, CCBR-Synarc; O. Simonsen, None; T. Christiansen, None; L. L. Egggaard, None; M. A. Karsdal, Nordic Bioscience Holding, 1; Nordic Bioscience Diagnostic, 3; A. C. Bay-jensen, Nordic Bioscience Holding A/S, 1; Nordic Bioscience Diagnostic, 3.

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Gender Differences in the Lupus Nephritis Biomarkers in Children.

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Background/Purpose: Lupus nephritis (LN) is frequently associated with a poor long-term prognosis. The non-invasive traditional measures of LN (LN-TM) currently used to monitor LN have limited responsiveness to change. Though the discovered and initially validated promising LN biomarkers (i.e. the LN-Panel) accurately reflect LN activity & chronicity as seen on kidney biopsy, and can forecast LN flares, however, there remains an important unknown in regards whether the LN-Panel biomarkers are influenced in their levels by patient gender. The objective of this study is to assess the gender and age specific differences in the levels of the LN-Panel biomarkers and to establish normative values of the combinatorial biomarkers in healthy children.

Methods: Urine concentrations of the LN biomarkers Neutrophil gelatinase associated lipocalin (NGAL), Monocyte chemoattractant protein-1 (MCP-1), Cereuloplasmin (CP), Alpha-acid glycoprotein (AGP), Transferrin (TF) and Lipocalin-like prostaglandin-D Synthase (LPDGS) were measured by nephelometry or ELISA in select male and female pediatric LN patients. All the biomarkers were logarithmically transformed and standardized to urinary creatinine concentration. Student t test was used to compare means of the LN panel biomarkers between female and male active LN patients. A fixed effects model was used to compare means after adjusting for differences in clinical measures of LN activity using the Renal SLEDAI domain scores. P value of < 0.05 was considered statistically significant.

Results: In a sample of 64 females and 12 males with childhood LN, the means of urinary M CP-1 was significantly elevated in females compared to males (table 1). A similar tendency of urinary LPGDS is significantly elevated in females compared to males (table 1).
in 27 female patients who had histological feature of Epimembranous deposits compared to 6 males (table 2). There were also significant gender differences in select LN Panel biomarkers when looking at the activity and chronicity of LN on kidney biopsy (see Table 3).

**Conclusion:** This study supports that there are gender differences in select LN-Panel markers. Aiso these differences can be seen with certain type of underlying histological features of LN.

**Table 1:** Gender related differences in LN-Panel with LN adjusted for differences in clinical measures of LN activity using the Renal SLEDAI domain scores.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Female (n=64)</th>
<th>Male (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAG</td>
<td>3.50 ± 1.18</td>
<td>2.83 ± 1.68</td>
<td>0.097</td>
</tr>
<tr>
<td>MCP1</td>
<td>0.00 ± 1.10</td>
<td>−0.95 ± 0.89</td>
<td>0.013</td>
</tr>
<tr>
<td>CP</td>
<td>8.91 ± 1.47</td>
<td>8.42 ± 1.24</td>
<td>0.299</td>
</tr>
<tr>
<td>ACG</td>
<td>10.60 ± 1.41</td>
<td>10.34 ± 1.52</td>
<td>0.584</td>
</tr>
<tr>
<td>TF</td>
<td>1.83 ± 1.43</td>
<td>1.36 ± 1.19</td>
<td>0.328</td>
</tr>
<tr>
<td>LPGDS</td>
<td>−0.59 ± 0.90</td>
<td>−1.10 ± 2.23</td>
<td>0.103</td>
</tr>
<tr>
<td>Bp(sysp)</td>
<td>129.03 ± 215.88</td>
<td>138.17 ± 23.60</td>
<td>0.189</td>
</tr>
</tbody>
</table>

**Table 2:** Some LN Panel biomarkers show gender differences with the activity and chronicity of LN on kidney biopsy.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Absent</th>
<th>Present</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAG</td>
<td>1.00</td>
<td>0.69</td>
<td>0.017</td>
</tr>
<tr>
<td>MCP1</td>
<td>0.02</td>
<td>0.18</td>
<td>0.177</td>
</tr>
<tr>
<td>CP</td>
<td>7.00</td>
<td>2.00</td>
<td>0.001</td>
</tr>
<tr>
<td>ACG</td>
<td>10.43</td>
<td>3.03</td>
<td>0.001</td>
</tr>
<tr>
<td>TF</td>
<td>1.59</td>
<td>0.84</td>
<td>0.044</td>
</tr>
<tr>
<td>LPGDS</td>
<td>−0.74</td>
<td>−0.98</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Table 3:** Some LN Panel biomarkers show gender differences with the activity and chronicity of LN on kidney biopsy.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Female (n=37)</th>
<th>Male (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAG</td>
<td>3.51 ± 1.25</td>
<td>3.19 ± 1.81</td>
<td>0.574</td>
</tr>
<tr>
<td>MCP1</td>
<td>0.02 ± 1.11</td>
<td>−0.97 ± 0.81</td>
<td>0.093</td>
</tr>
<tr>
<td>CP</td>
<td>8.70 ± 1.66</td>
<td>8.33 ± 1.63</td>
<td>0.600</td>
</tr>
<tr>
<td>ACG</td>
<td>10.43 ± 1.32</td>
<td>10.17 ± 1.67</td>
<td>0.703</td>
</tr>
<tr>
<td>TF</td>
<td>1.59 ± 1.51</td>
<td>1.40 ± 0.85</td>
<td>0.801</td>
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<tr>
<td>LPGDS</td>
<td>−0.74 ± 0.98</td>
<td>−0.87 ± 1.22</td>
<td>0.777</td>
</tr>
</tbody>
</table>

**Results:** 155 patients had biopsy-proven PLN between 1983-2013. Mean age at PLN diagnosis was 12.6±3.4 years old, and 80% were female. The cohort's ethnic heritage was 38% Asian, 28% Caucasian, 19% Black, and 15% other. 47 (30%) patients had class III, 85 (55%) had class IV, 5 (3.2%) had III/V, and 11 (7.1%) had class IV/V. 34 (22%) patients developed acute renal failure. Other phenotypic features included malar rash (71%), arthritis (74%), fever (65%), and photosensitivity (28%). At baseline, mean C3 was 0.72, and mean C4 was 0.11. Overall, 61% had CR and 15% had PR at 6 months, while 68% had CR and 7.5% had PR at 12 months (see Table 2 for complete results). We found that the rate of CR at 6 and 12 months was significantly higher in Era 1 (aza) than in Era 2 (MMF).

**Table 2:** Response rates

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<tr>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=150)</td>
<td>(N=86)</td>
<td>(N=64)</td>
<td>(N=63)</td>
</tr>
</tbody>
</table>

**Conclusion:** The majority of patients showed a complete response to treatment at 6 months, with 68% of patients demonstrating complete response by one year. Partial response rates at both 6 and 12 months were comparably lower. Interestingly, CR rates at 6 and 12 months were higher in the aza-prednisone era as compared to the MMF-prednisone era.

**Disclosure:** A. Human, None; S. Y. Tian, None; E. D. Silverman, None; D. M. Levy, None.

**1295**

**Childhood-Onset Systemic Lupus Erythematosus: Short-Term Treatment Response Rates in Proliferative Lupus Nephritis.** Andrea Human1, Simon Yiu Tian2, Earl D. Silverman3 and Deborah M. Levy4. 1The Hospital for Sick Children and University of Toronto, Toronto, ON, 2The Hospital for Sick Children, Institute of Medical Science, University of Toronto, Toronto, ON, 3The Hospital for Sick Children, Toronto, ON.

**Background/Purpose:** Proliferative Lupus Nephritis (PLN) occurs in up to 50% of patients with childhood-onset systemic lupus erythematosus (cSLE). PLN is a significant source of morbidity and can lead to end-stage renal disease. Our objectives were to examine rates of complete and partial response to treatment in the first year in a large multiethnic cohort using non-cyclophosphamide induction strategies.

**Methods:** A single-centre retrospective cohort study at the Hospital for Sick Children examined partial and complete response rates at 6 and 12 months following the diagnosis of biopsy-proven PLN (WHO Class III or IV) in SLE patients. Patients with PLN and concomitant Class V lupus nephritis were included. Urine protein/creatinine ratio (uPCR) and serum creatinine (Cr) were used as core renal parameters. Urinary sediment was not included due to lack of available data. Criteria for complete (CR) and partial response (PR) were adapted from the American College of Rheumatology consensus guidelines, and from the outcome measures defined in Wofsy et al. (Table 1). All data were collected prospectively on standardized clinic forms and maintained in a clinical database. Demographic, clinical, pathologic and laboratory data were analyzed. As therapeutic options have evolved over the past 30 years, results were stratified into two treatment eras, the 1st era when prednisone and azathioprine (aza) were routinely used in the first year, and the 2nd era when prednisone and mycophenolate mofetil (MMF) were more commonly used.

**Table 1:** Renal Response Definitions

<table>
<thead>
<tr>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with abnormal Cr,</td>
<td>For patients with normal Cr,</td>
</tr>
<tr>
<td>Normalization of Cr</td>
<td>Maintenance of a normal Cr within 50% of baseline value</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>uPCR&lt;25μmol</td>
<td>CR or OR 50% improvement in Cr</td>
</tr>
<tr>
<td>CR or OR 50% improvement in Cr</td>
<td>CR or OR 50% improvement in Cr</td>
</tr>
</tbody>
</table>

**Disclosure:** K. Abulaban, None; E. D. Silverman, None; D. M. Levy, None.

**1296**

**Pulse-Pediatric Update on Lupus in South Africa: Epidemiology and Management.** Laura Lewandowski1, Laura Schanberg2, Nathaniel Thielman3 and Christiaan Scott. 1Duke University Medical Center, Durham, NC, 2Duke Hubert Yeuran Center for Global Health, Durham, NC, 3Red Cross War Memorial Children’s Hospital, Cape Town, South Africa.

**Background/Purpose:** In developed nations, SLE is more common and severe in people of African extraction than in Caucasians; however, the epidemiology of SLE in Africa is largely understudied. Historically, the incidence of SLE in Africa was presumed to be low, but recent studies challenge this theory. In general, children present with higher disease activity, require more therapy, and accrue more organ damage than adult-onset patients. Although African children with SLE may be at high risk for poor outcomes, little research has investigated this population. We have initiated the first prospective study of this high risk pediatric SLE (pSLE) population. Here, we...
report the initial findings of the South African pSLE patients (PULSE cohort).

Methods: We conducted a retrospective chart review of pediatric and adult rheumatology and nephrology patients seen at 2 centers in Cape Town, South Africa from 1988–2014 meeting American College of Rheumatology criteria for pSLE. Patient age, gender, race, and presenting features were recorded for the PULSE cohort and compared to previously described pSLE cohorts in South Africa and worldwide.

Results: Initial review of patients yielded 68 patients (age 12.2; 83% female). The racial distribution was 65% colored, 26% black, 3% white, and 3% Asian/Indian. A much larger proportion of patients in our cohort are of colored or black race compared to a previously published South African cohort. Most patients presented with severe lupus nephritis (LN) (renal biopsy performed in 49%). Of patients with LN, 83% presented with ISN class IV or higher. Pediatric LN cohorts from developed nations report 6–7% progressing to end stage renal disease (ESRD), and reports from developing nations report 8–12%. Within the cohort, 13% went on to develop ESRD requiring transplant, strikingly higher than previously reported cohorts. Our cohort had severe disease at diagnosis (mean SLEDAI 20.4), compared to previously reported pSLE cohorts (SLEDAI 4–13). Also, the PULSE cohort had end organ damage with 63% of the cohort having a SLICC score > 0 (mean SLICC 1.9), compared to only 23% in a previously reported US cohort of 221 pSLE patients.

Table 1. Demographic Information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12 months</th>
<th>p-value, Student’s t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid dose (n = 48)</td>
<td>31.7 ± 23.4</td>
<td>8.8 ± 12.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C3 (n = 29)</td>
<td>70.4 ± 39.8</td>
<td>115 ± 41.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C4 (n = 29)</td>
<td>11.6 ± 16.5</td>
<td>25.6 ± 15.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESR (n = 47)</td>
<td>57.4 ± 37.7</td>
<td>37.2 ± 28.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Hemoglobin (n = 48)</td>
<td>10.9 ± 1.6</td>
<td>12.0 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine (n = 48)</td>
<td>1.0 ± 2.0</td>
<td>0.84 ± 1.1</td>
<td>0.143</td>
</tr>
<tr>
<td>Albumin (n = 48)</td>
<td>3.7 ± 0.76</td>
<td>4.2 ± 0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine protein:creatinine ratio (n = 40)</td>
<td>0.96 ± 2.0</td>
<td>0.75 ± 1.8</td>
<td>0.548</td>
</tr>
<tr>
<td>dsDNA (n = 37)</td>
<td>860 ± 330</td>
<td>85 ± 301</td>
<td>0.128</td>
</tr>
<tr>
<td>Physician global (n = 41)</td>
<td>35.2 ± 19.2</td>
<td>14.3 ± 12.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2. Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class of Lupus Nephritis</th>
<th>PULSE cohort South Africa 2014</th>
<th>Toronto Cohort N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Minimal Change</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>II Mesangial</td>
<td>3 (9%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>III Focal Proliferative</td>
<td>2 (6%)</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>IV Diffuse Proliferative</td>
<td>17 (53%)</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>V Membranous</td>
<td>7 (21%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>VI Advanced Sclerosis</td>
<td>3 (9%)</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

Conclusion: The PULSE cohort is the largest registry of pSLE patients in Africa to date. Preliminary findings show these children present with high disease activity and progress to end organ damage at higher rates than pSLE cohorts in developed nations.

Disclosure A. Lewandowski: None; L. Schanberg: None; N. Thielman: None; C. Scott: None.

1297


Background/Purpose: Rituximab (RTX) is a chimeric monoclonal antibody that specifically targets CD20 positive B cells and is used successfully for a variety of pediatric rheumatologic conditions. One pediatric autoimmune disease for which RTX has gained particular interest is systemic lupus erythematosus (SLE). Herein, we report on the safety and effectiveness of use of RTX in 104 subjects with a variety of pediatric autoimmune diseases, with a focus on SLE.

Methods: This was a retrospective study of children treated by 1 or more pediatric rheumatologists at Children’s of Alabama (CoA) with at least 1 course (2 doses of 750 mg/m²; maximum of one gram, 2 weeks apart) of RTX between August 1, 2007 and April 1, 2014. To evaluate effectiveness, we documented for all patients the MD Global assessment of disease activity and corticosteroid dosage at baseline (just prior to RTX) and at 12 months of follow-up. For SLE patients, we additionally documented complement levels, ESR, CBC, creatinine, albumin, urine protein, and anti-DNA levels. For safety outcomes, we documented infusion reactions and severe adverse events. Comparisons were performed with the Student’s t-test.

Results: 104 children were included in the study. The single most common diagnosis was SLE (n = 50), and the next most common diagnosis was dermatomyositis (n = 11). In total, 464 RTX infusions were administered during the study period. A total of 251.4 person-years of follow-up was available (median 2.4 years; range 1 month – 6.4 years). A mong patients with one-year follow-up data available, mean daily corticosteroid dose decreased from 29.8 ± 25.7 mg to 8.7 ± 13.1 mg (n = 98; p < 0.001) and mean MD global assessment of disease activity decreased from 34.4 ± 19.2 to 15.7 ± 12.3 (n = 98; p < 0.001). A mong SLE patients with data available at 12 months of follow-up, significant improvements were observed in corticosteroid dosage and MD global assessment of disease activity, as well as in multiple SLE-associated markers of disease activity (Table). Overall, RTX was well-tolerated. There were no infusion reactions requiring emergent intervention. The incidence of hospitalized infections among the cohort as a whole (83/51,000 person-years) and among the 50 SLE patients (92/21,000 person-years) is similar to previous studies of children with SLE treated with cyclophosphamide. One patient died after transition to adult care.

Conclusion: RTX can be safely administered to children with a variety of rheumatic conditions and appears to contribute to decreased disease activity and steroid burden.

Disclosure A. Tambralli: None; Beulke: Novartis Pharmaceutical Corporation, M. R. Pereira: University of Sao Paulo, Sao Paulo, Brazil. 2 F. de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.
macrophage hemophagocytosis. cSLE patients had higher SLEDAI-2K at AP diagnosis (22[8–41] vs. 10[0–40], p=0.007), fever (p=0.002), anti-dsDNA antibodies (p=0.002) and death by MAS complication (31% vs. 0%, p=0.017) than aSLE. No differences were evidenced in glucocorticoid use in both groups (p=0.394). Further analysis of MAS patients showed that the median of ferritin [1804(28–24.511) vs. 409[25–4.282] ng/ml, p=0.041], aspartate aminotransferase (AST) [121(23.156) vs. 30[13–4.464] U/L, p=0.018] and triglyceride [285(163–526) vs. 172(61–357) mg/dL, p=0.005] were significantly higher in AP patients with MAS compared those without this complication. Fever (94% vs. 38%, p=0.001), leucopenia (82% vs. 19%, p=0.0001), thrombocytopenia (65% vs. 19%, p=0.013), hypertriglyceridemia (87% vs. 42%, p=0.037) and hyperferritinemia (39% vs. 37%, p=0.011) were also more frequently observed in AP patients with versus without MAS. Of note, acute infections were alike in both groups (p=0.438).

Conclusion: This study provides novel data demonstrating that MAS occurs in the majority of cSLE with AP with a higher mortality compared to those without MAS. In addition, we identified in AP patients, a cluster of MAS clinical and laboratory parameters more associated with this complication.

Disclosure: N. W. Spelling, None; C. I. Otouzi, None; D. L. Barros, None; M. A. da Silva, None; R. M. R. Pereira, Federico Foundation and CNPq 300559/2009-7, 2; L. M. A. Campos, None; E. F. Borba, Federico Foundation and CNPq 303135/2008-1; 2; E. Bonfa, Federico Foundation and CNPq 301411/2009-3-2, C. A. Silva, Federico Foundation and CNPq 302724/2011-7, 2.

1299

A Cross-Sectional Study of Mental Health Symptoms and Mental Health Care in Pediatric SLE/MCTD Patients and Their Peers. Andrea K Night1, Michelle Vickery1, Pamela Weiss1, K mashawn M ora12 and Ron Keren2. 1Children’s Hospital of Philadelphia, Philadelphia, PA, 2University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Mental health problems are prevalent in pediatric systemic lupus erythematosus (SLE). We aimed to compare the rates of mental health problems and mental health services use for children and adolescents with SLE and mixed connective tissue disease (MCTD) to healthy peers and those with other chronic disease.

Methods: In a cross-sectional analysis, 40 children and adolescents with SLE/MCTD were matched according to sex and age with 40 healthy and 40 type 1 diabetic controls. Subjects were consecutively recruited and consented at outpatient clinic visits. We screened for symptoms of depression, suicidal ideation and anxiety using the Patient Health Questionnaire 9 (PHQ-9) and the Screen for Child Anxiety Related Disorders (SCARED), respectively. We also assessed for use of mental health services in the previous 12 months by parent report. We used matched pair analysis to compare the rate of mental health symptoms, and the Fisher’s exact test to compare rates of mental health services use among the groups.

Results: Mental health symptoms were prevalent in all groups with 33% (13) of SLE/MCTD, 30% (12) of healthy controls and 43% (17) of diabetic controls screening positive for any symptom. Compared to the 10% prevalence in the matched controls, there was a trend towards higher prevalence in the SLE/MCTD group at 23% (RR = 2.3, 95%CI 0.8–6.6) and statistically higher prevalence in the diabetes group at 30% (RR = 2.5, 95%CI 1.2–5.3). Compared to the 5% prevalence of suicidal ideation in the healthy controls, there was a trend towards higher prevalence in the SLE/MCTD group at 18% (RR = 3.5, 95%CI 0.7–16.8) and in the diabetes group at 18% (RR = 2.5, 95%CI 0.9–7.3), but these were not statistically significant. There was no difference in depression or suicidal symptoms between the SLE/MCTD and diabetes groups. Anxiety was prevalent among all groups, but there was no difference between the groups. In those with any symptom, previous mental health care had been obtained in none (0/12) of the healthy controls, 23% (3/13) of the SLE/MCTD and 53% (9/17) of the diabetes groups. Compared to healthy controls, the diabetes group had a statistically significant higher rate of mental health care in those with symptoms (p=0.003), but there was no difference for the SLE/MCTD group (p=0.12). There was no statistically significant difference in mental health care rates between SLE/MCTD and diabetic patients with symptoms (p=0.14).

Conclusion: Mental health symptoms were common in pediatric SLE/MCTD patients, and their peers, but there was a trend towards more frequent depression and suicidal ideation in the SLE/MCTD and diabetes groups, implicating chronic disease as a risk factor for these symptoms. The majority of those with symptoms had no previous mental health care, although those with diabetes had a significantly higher rate of mental health care compared to healthy peers. Further study of the risk factors for mental health problems in chronic illness and factors affecting mental health care may improve overall care for pediatric SLE/MCTD patients.

Disclosure: A. K. Night, None; M. Vickery, None; P. Weiss, None; K. Morales, None; R. Keren, None.

1300

Subclinical Right Ventricle Systolic Dysfunction By Two-Dimensional Speckle-Tracking Echocardiography in Childhood-Onset Systemic Lupus Erythematosus Patients. Gabriela N Leal1, Kellen F Silva1, Camilla M. P. Franca1, Alessandro C. Lianza2, José L. Andrade2, Lucía M. A. Campos3, Eloisa Bonfa1 and Clovis A. Silva1. 1Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 2University of São Paulo, São Paulo, Brazil, 3Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Evaluation of right ventricle (RV) systolic function by standard echocardiogram remains a challenge because of the complex geometry of this chamber. Recently, two-dimensional Speckle-tracking derived strain (2DST) was proven to have a better accuracy in detecting subtle RV dysfunction in children with congenital heart diseases, however this new technique was not systematically studied in childhood-onset SLE patients. Therefore, the aim of this study was to evaluate strain imaging by 2DST in cSLE patients and healthy controls and possible association of RV dysfunction with demographic data, clinical manifestations, laboratory and treatment.

Methods: A cross-sectional study was conducted at our Pediatric Rheumatology Unit from September 2012 to September 2013. Exclusion criteria were: heart failure, congenital heart disease, pericardial effusion, history of infectious myocarditis or pulmonary obstructive diseases and poor quality echocardiographic imaging. Thirty-five cSLE patients and 33 healthy volunteers were submitted to standard echocardiogram, and 2DST. Conventional parameters included: RV diastolic diameter (RVD), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic wave velocity (S), Tei index and the presence of pulmonary hypertension (velocity of tricuspid regurgitation (Vt) > 2.5 m/s). 2DST analyzed global systolic longitudinal strain and strain rate of RV. Demographic data, clinical features, SLEDAI-2K, SLICC/ACR-DI and treatment were also assessed.

Results: The median current age was similar in cSLE patients and controls (14.75 vs. 14.88 years, p=0.62). Standard echocardiogram analysis revealed that cSLE patients had a significant increase RVD (14.65 vs. 13.68 mm/m² vs. 12.31±2.43 mm/m², p=0.031) and Tei index compared to controls (0.3±0.19 vs. 0.3±0.20, p=0.001). They also had reduced S wave velocity (0.13 [0.09–0.2] vs. 0.16 [0.13–0.23] m/s, p<0.0001) and TAPSE (1.84±0.26 vs. 2.59±0.41 cm, p<0.0001). Four patients had mild pulmonary hypertension. Further evaluation of function by 2DST showed that RV longitudinal peak systolic strain was significantly reduced in cSLE (−24.5±5.69 vs. −27.62±3.02% p=0.003). The same finding was observed with the exclusion of four patients with mild pulmonary hypertension (−24.62 ± 4.87 vs. −27.62 ± 3.02, 0.0041, p=0.0041). RV longitudinal peak systolic strain was positively correlated with TAPSE (r=0.49, p=0.0027) and negatively correlated with Tei index (r=−0.34, p=0.04) in cSLE patients. Further analysis of cSLE patients revealed higher frequencies of neuropsychiatric manifestations (35% vs. 0%, p=0.007) and antiphospholipid antibodies (55% vs. 18%, p=0.035) in those with reduced strain (<= −23.7%) compared to high strain values (>-23.7%). No differences were evidenced in demographic data, disease activity/damage and treatments (p>0.05).

Conclusion: This is the first study to identify, using a more accurate methodology, subclinical RV systolic dysfunction in cSLE patients. The novel association of symptomatic cardiac dysfunction with neuropsychiatric manifestations and antiphospholipid antibodies may suggest a common underlying mechanism.

Disclosure: G. N. Leal, None; K. F. Silva, None; C. M. P. Franca, None; A. C. Lianza, None; J. L. Andrade, None; E. Bonfa, None; C. A. Silva, FAPESP 2009/51897-5, CNPq 301411/2009-3 and Federico Foundation, 2; C. A. Silva, FAPESP 2009/51897-5, CNPq 302724/2011-7 and Federico Foundation, 2.

1301

Background/Purpose: The three-dimensional evaluation of bone by HR-pQCT has the advantage to provide assessment to not only bone density, but also to a noninvasive evaluation of bone structure and bone strength. Information about changes in bone microarchitecture in juvenile-onset SLE (JoSLE) with and without fractures is lacking and they may improve future strategies of therapy and prediction of fracture risk in these patients. The objective of this study was, therefore, to analyze bone microarchitecture in JoSLE with and without vertebral fractures (VF).

Methods: Twelve consecutive JoSLE female patients with VF according to Vertebrae fracture assessment (VFA) by dual-energy X-ray absorptiometry (DXA) were selected and compared to 44 female JoSLE patients without VF. Demographic, anthropometric, clinical and laboratory data were recorded by interview and electronic chart review. Bone microarchitecture was evaluated by High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) at the distal radius.

Results: Patients with and without VF had comparable age (18.0±2.73 vs. 18.5±3.35 years, p=0.0636), BMI (23.03±3.49 vs. 23.15±3.67 kg/m², p=0.927), disease duration (38.24±52.03 vs. 71.39±48.57 months, p=0.043), SLEDAI (4.14±4.04 vs. 4.73±5.92, p=0.744), GC cumulative dose (860.72±18448.35 vs. 6291.54±6737.18 mg, p=0.454), current GC dose (16.04±14.44 vs. 15.97±17.95 mg/day, p=0.990), maximum GC dose (34.17±26.53 vs. 29.20±31.35 mg/day, p=0.466) and 25-hydroxyvitamin D (22.25±6.93 vs. 23.38±6.90 ng/ml, p=0.610). In spite of these comparable parameters, Table 1 illustrates significant differences in HR-pQCT in distal radius findings in the two groups of patients analyzed. Patients with vertebral fractures had reduced density parameters, particularly related to D100 (p=0.011) and D trab (p=0.024), suggesting a predominant trabecular bone involvement. Structural evaluation in patients with VF revealed a significant reduction in BV/TV (p=0.023) and Tb.Th (p=0.033), both parameters associated with trabecular erosion. Finally, a significant decrease in apparent modulus was observed in patients with VF (p=0.018) indicating a bone strength impairment of VF group.

Table 1: Density and Structural parameters of distal radius assessed HR-pQCT in JoSLE patients with and without vertebral fractures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Vertebral Fractures (n=44)</th>
<th>Vertebral Fractures (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density Parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D 100, mg HA/ccm</td>
<td>275.93 ± 56.87</td>
<td>272.95 ± 56.87</td>
<td>0.011*</td>
</tr>
<tr>
<td>D trab, mg HA/ccm</td>
<td>163.77 ± 35.45</td>
<td>136.96 ± 35.45</td>
<td>0.024*</td>
</tr>
<tr>
<td>D comp, mg HA/ccm</td>
<td>787.67 ± 105.84</td>
<td>742.83 ± 87.41</td>
<td>0.122</td>
</tr>
<tr>
<td>Structural Parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV/TV</td>
<td>0.114 ± 0.03</td>
<td>0.136 ± 0.03</td>
<td>0.023*</td>
</tr>
<tr>
<td>Tb.N, 1/mm</td>
<td>2.123 ± 0.28</td>
<td>1.986 ± 0.31</td>
<td>0.165</td>
</tr>
<tr>
<td>Tb.Th, mm</td>
<td>0.057 ± 0.01</td>
<td>0.064 ± 0.01</td>
<td>0.033*</td>
</tr>
<tr>
<td>Tb.Sp, mm</td>
<td>0.461 ± 0.11</td>
<td>0.416 ± 0.07</td>
<td>0.129</td>
</tr>
<tr>
<td>Ct.Th, mm</td>
<td>0.428 ± 0.17</td>
<td>0.520 ± 0.22</td>
<td>0.189</td>
</tr>
</tbody>
</table>

Biomorphological Properties

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Vertebral Fractures (n=44)</th>
<th>Vertebral Fractures (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness, kN/mm</td>
<td>61999.99 ± 34636.81</td>
<td>61814.79 ± 13493.61</td>
<td>0.071</td>
</tr>
<tr>
<td>Estimated Failure Load</td>
<td>3005.72 ± 619.73</td>
<td>3196.70 ± 2435.13</td>
<td>0.059</td>
</tr>
<tr>
<td>Apparent Modulus, N/mm²</td>
<td>1236.36 ± 334.85</td>
<td>1523.70 ± 367.14</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

D100=average bone density; D trab=trabecular bone density; D comp=compact bone density; HA=hydroxyapatite; BV/TV=trabecular bone volume to tissue volume; Tb.N=trabecular number; Tb.Th=trabecular thickness; Tb.Sp=trabecular separation; Ct.Th= cortical thickness.

Conclusion: The novel identification by a non-invasive technique (HR-pQCT) that JoSLE patients with vertebral fractures have trabecular bone alterations with a significant reduction in bone strength opens a new perspective to define in future prospective studies the utility of this method for fracture prediction in this disease.

Disclosure: J. T. Jones, None; N. Cunningham, None; J. L. Huggins, None; S. Kashkar-Zuck, None; H. I. Brunner, TMA and NIEHS, 9.

1303


Background/Purpose: Childhood-onset lupus (cSLE) is a chronic autoimmune disease and its effect on health-related quality of life (HRQoL) has not been fully established, but, disease activity alone does not solely account for the impact on HRQoL. Gaps in the literature exist around the impact of potentially modifiable factors (pain, sleep, fatigue, pain coping, mood, anxiety) in relation to HRQoL. Disease activity measures are often unrelated to psychological factors associated with cSLE. Chronic disease and its related psychological factors can impact participation in developmentally appropriate activities in adolescents, leading to chronically poor HRQoL. Objectives of this study were to evaluate psychological factors in patients with cSLE and the degree of HRQoL impairment in cSLE due to psychological factors commonly associated with chronic diseases.

Methods: As part of an ongoing study, a population-based cohort of cSLE patients (n= 20; 8–18 years) from Cincinnati Children’s Hospital and University of Cincinnati were asked to complete brief measures of pain (Pain visual analog scale [Pain VAS]), sleep (A Sleepless Adolescent Sleep Wake Scale), fatigue (PedQOL Multidimensional Fatigue Scale), pain coping (Pain Coping Efficacy Questionnaire), mood (Children’s Depression Inventory [CDI]), anxiety (Screen for Child Anxiety Related Disorders [SCARED]), and HRQoL (PedQOL Generic Core scale and Rheumatology Module). Measures of disease activity (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]) and physician complete visual analog scale of cSLE disease activity (MD Global, 0-10; 0=inactive) were also obtained.

Results: Subjects were 90% female with mean age of 15.5 years (SD 1.5) and mean SLEDAI score of 7.8 (SD 6.1). Of the subjects, 60% had fatigue and 87% had bone density less than or equal to VAS (≤ 3), and 40% reported feeling fatigued the next morning. Also, 25% had clinically significant anxiety symptoms (SCARED ≥ 25), and 30% had mild-to-moderate depressive symptoms (CDI1 ≥ 10). The average HRQoL score for cSLE patients was well below the reported healthy mean, and the presence of fatigue, anxiety, and decreased mood correlated highly with HRQoL (Pearson’s r ≥ 0.70). Consequently, none of the HRQoL measures correlated with SLEDAI score or MD global (r < 0.25; see Table 1). Regression demonstrated HRQoL was most impacted by fatigue (p < 0.05) when evaluating all factors concurrently.

Conclusion: cSLE is often associated with decreased HRQoL, despite comprehensive treatment provided at a tertiary pediatric rheumatology center. Our data suggests that psychological aspects of health (pain, mood, fatigue and anxiety) contribute substantially to diminished HRQoL in cSLE patients, whereas, measures of cSLE activity are not related to HRQoL outcomes. Psychological factors, and especially fatigue, need to be addressed to achieve optimal health outcomes with cSLE.

Table 1: Pearson Correlation Coefficients

<table>
<thead>
<tr>
<th>Psychological Variables</th>
<th>HRQoL Measures</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VAS</td>
<td>Pain</td>
<td>Mood</td>
</tr>
<tr>
<td>PedQOL GC</td>
<td>0.466</td>
<td>0.35</td>
</tr>
<tr>
<td>PedQOL RM</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>PedQOL VAS</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Mood</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Pain Coping</td>
<td>0.55</td>
<td>0.36</td>
</tr>
<tr>
<td>Pain Catastrophizing</td>
<td>0.55</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Denotes p-value < 0.05. **Denotes p-value < 0.01.

Disclosure: J. T. Jones, None; N. Cunningham, None; J. L. Huggins, None; S. Kashkar-Zuck, None; H. I. Brunner, TMA and NIEHS, 9.
Background/Purpose: LN is common in childhood-onset Systemic Lupus Erythematosus (cSLE). Kidney biopsies are impractical to assess the course of LN given their invasiveness and cost. Therefore, traditional laboratory measures (GFR, complement levels, anti-dsDNA antibodies, serum creatinine and urinary protein/creatinine ratio) are used and several clinical indices (Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS), renal domain score of the BILAG (BILAG-R) and SLEDAI (SLEDAI-R)) have been developed: The objective of this study was to validate these traditional non-invasive measures of LN activity in cSLE, using histological activity & severity of LN as criterion standard.

Methods: The traditional laboratory measures were measured in 83 children with LN at the time of biopsy. The biopsy specimens were rated by a single nephropathologist for LN severity as per International Societies for Nephrology & Renal Pathology (ISN/RPS) class, the NIH glomerular activity index (GLAI; range 0-24) and the tubulointerstitial activity index (TIAI, range 0-21). For the statistical analysis, LN severity is categorized as Class I/II vs. III/IV vs. V; GLAI score (activity index (TIAI, range 0–21). For the statistical analysis, LN severity is categorized as Class I/II vs. III/IV vs. V; GLAI score (activity index (TIAI, range 0–21). For the statistical analysis, LN severity is categorized as Class I/II vs. III/IV vs. V; GLAI score (activity index (TIAI, range 0–21).

Results: Of the 83 kidney biopsies, 12%, 60% and 28% of the patients had class I/II, III/IV and V, respectively. The median scores of the GLAI and TIAI were summarized (Table 1). SLEDAI-R and SLICC-RAS, but not BILAG-R, was positively associated to the ISN/RPS classification (Table 2). In particular, higher SLEDAI-R and serum creatinine level and lower GFR level was found in patients with LN inflammatory activity (GLAI > 10 or TIAI > 5). Similar patterns were also noticed in patients with ISN/RPR Class V being compared against those with ISN/RPR Class V.

Table 1. Summary of GLAI, TIAI and ISNPR Class in cSLE Cohort

<table>
<thead>
<tr>
<th>Score</th>
<th>Stat Type</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLAI</td>
<td>median (range)</td>
<td>60 (4, 22)</td>
</tr>
<tr>
<td>TIAI</td>
<td>median (range)</td>
<td>27 (71) (36.0%)</td>
</tr>
<tr>
<td>ISNPR Class</td>
<td>&lt;10</td>
<td>10 (12.05%)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>50 (60.24%)</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>23 (27.71%)</td>
</tr>
</tbody>
</table>

Table 2. Traditional LN measures validated by LN biopsy

<table>
<thead>
<tr>
<th>Traditional LN measures</th>
<th>ISNPR Class</th>
<th>GLAI Score</th>
<th>TIAI Score</th>
<th>ISNPR Class</th>
<th>TIAI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td></td>
<td></td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td></td>
<td></td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td></td>
<td></td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>SLEDAI-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BILAG-R</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SLICC-RAS</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein/ Cr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Injury Molecule-1</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 2. Traditional LN measures validated by LN biopsy

Results: The means and percentages of the values of the LN-TM and RMB levels are summarized (Table 1). Based on multivariate logistic regression modeling levels of TGBF, NGAL and GFR (or serum creatinine) but not protein excretion (urinary protein/creatinine ratio) were found to be combinatorial biomarkers of LN damage. Results on the RMB liver-type fatty acid binding protein (LFABP), Kidney Injury Molecule-1 (KIM1) and the receptor operating characteristic curve analyses will be presented.

Conclusion: NGAL, TGBF and GFR are good potential components for Children a Lupus Nephritis Index for Damage (C-LID) to non-invasively measure chronic histological changes in LN in the glomeruli, interstitium and tubules. Further studies with larger numbers of patients are required for further evaluation and confirmation of our finding.

Table 1. Comparison of LN biomarkers between NIH CI Groups

<table>
<thead>
<tr>
<th>LN biomarkers</th>
<th>NIH CI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein/ Cr</td>
<td>1.85 (1.32, 2.59)</td>
</tr>
<tr>
<td>GFR*</td>
<td>104.39 (90.12, 120.91)</td>
</tr>
<tr>
<td>Serum Cr*</td>
<td>0.70 (0.62, 0.81)</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.33 (0.21, 0.53)</td>
</tr>
<tr>
<td>CP</td>
<td>1.75 (102.30)</td>
</tr>
<tr>
<td>MCP1</td>
<td>11.37 (7.22, 17.00)</td>
</tr>
<tr>
<td>AGP</td>
<td>929 (416, 2.075)</td>
</tr>
<tr>
<td>TGF-B1*</td>
<td>0.69 (0.49, 0.96)</td>
</tr>
<tr>
<td>ADI</td>
<td>0.17 (0.07, 0.42)</td>
</tr>
<tr>
<td>HEPCIDIN</td>
<td>0.62 (0.33, 1.17)</td>
</tr>
<tr>
<td>LPDGS</td>
<td>3.76 (2.30, 6.15)</td>
</tr>
</tbody>
</table>

Note: Values in the cells are mean (95% CI).
Outcome of Lupus Nephritis in Children Less Than 12 Years Old from North-India.

Anjul Gupta, Bonnie Abujam, Deepit Suri, Amit Rawat and Surjit Singh. Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Background/Purpose: Studies on lupus nephritis in young children below 12 years of age from developing countries are limited. This study looks at long-term outcome in North-Indian children.

Methods: This was a single-center retrospective study from a University referral hospital that provides specialized treatment. Children seen in the center during the last 25 years were included if they had been diagnosed with systemic lupus erythematosus (as per the ACR 1997 criteria) and lupus nephritis (proteinuria >500mg/d or hematuria (>5RBC/HFP) or any cellular cast) before their 12th birthday. Initial presentation, laboratory data and treatment received was obtained from the file. Renal biopsy data was classified as per the WHO classification. The primary endpoint was survival with functioning kidneys (absence of death or ESRD). Patients were followed up till January 2012. Kaplan-Meier analysis was used for survival and log-rank test was used to compare different classes. Definitions used: Chronic kidney disease = elevated serum creatinine (>1.5mg/dl) at least 3 months. End-stage renal disease = need for renal replacement therapy > 3 months.

Results: This study included 72 children (F: M 3:2:1). The mean± SD age at onset of lupus was 9.3±2.4 years and the duration of disease before presentation was 9.2±12.6 months. Majority of the children (76%) had nephritides at presentation. Renal biopsy was done in 54 children. The histological class was class II in 9, class III in 1, class IV in 35 and class V in 7. Biopsy was not done in the remaining 18 patients due to poor general condition in 7, ongoing anticoagulation in 5, thrombocytopenia, uncontrolled hypertension and refusal by caregivers in 2 children each. The most common induction treatment was monthly pulses of cyclophosphamide (6-12 pulses) followed by maintenance with azathioprine or quarterly pulses of cyclophosphamide. At 1 year of follow up, 11 (15%) children had died (all in 1st admission), 11 (15%) were lost to follow up, 36 (50%) were in complete remission and 5 each (6.9%) were in partial remission and active disease. Data for 4 children at 1 year could not be retrieved. Another 11 (15%) children died after the 1st year. The common causes of mortality was infection, disease activity and renal failure. (Table 1). The mean duration of follow up was 4 ± 4.4 years (0.2-20 years) with a total follow up of 287 patient years. Survival with functioning kidneys was seen in 71% at 3 years, 68% at 5 years and 60% at 10 years. There was no difference in survival among various histological classes.

Conclusion: We found a majority of young children presented with lupus nephritis. There was a high mortality at initial presentation. The long term outcome is still much lower as compared to those from the developed nations. Majority of deaths occur in the initial presentation due to infections, severe disease activity and renal failure.

Table 1: Causes of death

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Initial visit</th>
<th>Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septicemia</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Severe disease activity</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Disseminated kochs with shunt malfunction</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary thrombosis</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive intracranial bleed</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Myocarditis with left ventricular failure</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Unknown cause (died at home)</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>22 (30)</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Disclosure: A. Gupta, None; B. Abujam, None; D. Suri, None; A. Rawat, None; S. Singh, None.

Monitoring of Mid-Interval Plasma Levels of Mycophenolic Acid in Pediatric Lupus Nephritis Patients.

Joyce S Hui-Yuen, Kristi Truong, Lisa Mardel-Bernandez-Santiago, Amy J. Staw, Andrew Eichenfield, Lisa F. Imuno and Anca Askanase. 1Morgan Stanley Children's Hospital of New York Presbyterian, Columbia University Medical Center, New York, NY, 2St John's University, Queens, NY, 3Columbia University Medical Center, New York, NY, 4Children's Hosp of New York, New York, NY.

Background/Purpose: Mycophenolate mofetil (MMF) is often used to treat lupus nephritis (LN) and extra-renal lupus in children with SLE. Plasma levels of mycophenolic acid (MPA) are used in clinical practice to determine absorption of MMF and compliance. However, data are equivocal in the use of plasma MPA levels as a measure of efficacy or a predictor of prognosis in pediatric LN patients. This study was initiated to evaluate the use of MPA levels in routine care of children with LN.

Methods: This was a retrospective study of pediatric LN patients treated with MMF. Data were collected on demographic and disease characteristics, concomitant medications, and treatment outcomes. Complete renal remission (CR) was defined as proteinuria <500mg/24h, and no other clinical manifestations of renal disease. Mid-interval MPA plasma levels were drawn
during routine follow-up. Calculated steady-state concentrations can predict plasma MPA levels at peak, trough, or any time during the dosing interval. Steady-state levels of MPA were calculated using basic pharmacokinetics and compared to routine mid-interval plasma MPA levels. Student t-tests were used when appropriate.

Results: We describe 17 patients with pediatric lupus nephritis treated with MMF that have plasma MPA levels available from our cohort. The mean duration of SLE was 5 years, and LN was 3.3 years. Ten LN patients were in CR at the time of this study; 5 had mixed proliferative/membranous nephritis and 5 had proliferative disease alone. All 7 patients not in CR had some component of membranous LN. MMF was dosed at 600mg/m²/dose for all patients. The mean dose of corticosteroids was 23.75mg prednisone equivalent/day in patients in CR compared with 62.5mg prednisone equivalent/day in patients with persistent disease (p = 0.06). The mean mid-interval levels of MPA were 1.69 µg/ml (range <0.5 to 8 µg/ml) in patients in CR and 2.04 µg/ml (range <0.5 to 6 µg/ml) in patients with persistent active disease (p = NS). Of note, 3 patients in each group had undetectable MPA levels. Based on dose, the calculated mid-interval steady-state level was 13.62 ± 3.67 mg·h/L and did not reflect the observed mid-interval levels.

Conclusion: This is the first study to investigate the correlation between mid-interval levels of MPA and predicted steady-state serum levels in patients with lupus nephritis. Our data suggest a large inter-individual variability but also clearly raise concerns about compliance with MMF regimens and emphasize the need to more precisely monitor MPA levels with peak, trough, and area-under-the-curve, as well as the need to discuss with patients and families the reason(s) for non-compliance.


1308 Antinucleosome Antibodies As Potential Diagnostic and Prognostic Biomarkers in Childhood Onset Systemic Lupus Erythematosus. Thaschawee Arkachaisri, Joo Guan Yeo, Justin Hung Tiong Tan, Sook Fun Hoh, Lena Das and Jing Yao Leong. KK Women’s and Children’s Hospital, Singapore, Singapore.

Background/Purpose: The role of antinucleosome antibodies (ANuA) in the immunopathogenesis of SLE is evident. ANuA was shown to be a good, if not better than anti-dsDNA antibody, diagnostic and prognostic biomarkers in adult SLE pts of different ethnicities. Such evidence is scarce in childhood onset SLE (cSLE). We aim to explore the role of ANuA as potential diagnostic and prognostic biomarker in our ASEAN cohort.

Methods: 68 cSLE pts (onset < 18) were recruited and 55 pts with 180 patient-visits with complete clinical data/blood samples were studied. Disease activity (DA) indices: SLEDAI-2K, SLAM and BILAG were recorded. Anti-dsDNA, ANuA (H1-stripped) and anti-C1q were measured by ELISA. AIU was calculated using basic pharmacokinetics and compared to routine mid-interval plasma MPA levels. Student t-tests were used when appropriate.

Results: 55 cSLE (84% female) with median age of 15.9 (14.4–18.2) and median disease duration of 54.7 (29.4–76.2) mo were included. Majority were Chinese and Malay (38%, 33%). Hematologic disorder (90%), arthritis (58%), malar rash (47%) and renal disease (44%) were among most common manifestations. All cSLE had positive ANA at onset. The median (IQR) of SLEDAI-2K, SLAM and BILAG for each disease activity groups were as follows: ID-2.0 (0.0–2.0), 1.0 (0.0–3.0), 1.0 (0.0–1.0); MD-4.0 (3.0–8.0), 3.0 (2.0–4.0), 2.0 (2.0–4.0) and AD-8.0 (4.0–12.0), 6.0 (3.0–9.0), 5.0 (3.0–12.0). ANuA titers among cSLE disease groups and controls were shown in Table 1. ANuA level did not fluctuate with renal DA (p = 0.601) or associated with the presence of nephritis (p = 0.58), so did anti-dsDNA A b (p = 0.587). ANuA showed good and reasonable diagnostic properties, moderate – strong correlations with laboratory parameters but rather weak correlation with DA indices.

Table 1. Antinucleosome antibodies (ANuA) as diagnostic biomarkers* Parameters cSLE (n = 180) Controls (n = 116)

<table>
<thead>
<tr>
<th>ANuA titers (nil &lt; 20 U/ml)</th>
<th>No activity (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>66.67</td>
</tr>
<tr>
<td>Specificity</td>
<td>100.00</td>
</tr>
<tr>
<td>Likelihood ratio (+ LR)</td>
<td>NA as specificity 100.00%, very large</td>
</tr>
<tr>
<td>Likelihood ratio (− LR)</td>
<td>0.33</td>
</tr>
<tr>
<td>Predictive value (+ PPV)</td>
<td>100.00</td>
</tr>
<tr>
<td>Predictive value (− PPV)</td>
<td>92.80</td>
</tr>
</tbody>
</table>

Diagnostic odd ratio (DOR) NA as specificity 100.00%, very large

Conclusion: ANuA has a good diagnostic property with high specificity and high PPV suggesting that it could be a compliment biomarker in cSLE diagnosis. The levels fluctuated with DA with moderate – strong correlation with lab parameters despite weak correlation with clinical index, for which a larger validation study is needed.


1309 Does Anti-C1q Antibody Have Diagnostic and Prognostic Roles in Childhood - Onset Systemic Lupus Erythematosus? Thaschawee Arkachaisri, Joo Guan Yeo, Justin Hung Tiong Tan, Sook Fun Hoh, Lena Das and Jing Yao Leong. KK Women’s and Children’s Hospital, Singapore, Singapore.

Background/Purpose: Biomarkers proven to be effective in aSLE patients may not directly apply to cSLE unless validation is done. Existing...
evidences have shown immunopathogenic roles of C1q and anti-C1q antibody (aC1qA) in SLE both in vitro and in vivo. The latter are strongly associated with the development of lupus nephritis especially in aSLE but evidences of its role in cSLE are rare. We aim to explore the role of aC1qA in our Southeast Asian cSLE cohort in regard to its diagnostic and prognostic properties as our proof-of-concept study.

Methods: Sixty-eight cSLE patients were recruited and 55 patients with 180 patient-visits with complete clinical data/blood samples were studied. Disease activity indices including SLEDAI-2K, SLAM and BILAG were recorded. Anti-dsDNA, antinucleosome Abs (ANuA, H1-stripped) and aC1qA were measured by ELISA. Patients were evaluated at 1-3 mo intervals depending on their disease severity. Patients were grouped into 3 disease activity groups: no activity (ID), minimal activity (MĐ) = mild activity with no therapeutic intervention or activity with improvement from previous visit and active disease activity (AD) = new case or flare or persistent activity/refractory to treatment. 72 JIA, 6 JD, 5 MCTD/UCTD, 11 vasculitides, 5 ANA-positive and 17 other inflammatory conditions composed 116 controls (female 45%, median age (IQR) 13.6 (10.3–16.6) years). Descriptive statistics were used to describe data. Mann Whitney/Kruskal-Wallis tests were used to compare data and Spearman’s rho for correlation studies.

Results: 55 cSLE (84% female) with median age of 15.9 (14.4–18.2) yrs and median disease duration of 54.7 (29.4–76.2) mo were included. Majority were Chinese and Malay (38% and 33%). Hematologic disease (96%), arthritis (58%), malar rash (47%) and renal disease (44%) were among most common manifestations. All patients had ANA positivity at onset. Fig 1 shows significant differences in A C1qA levels between controls vs. cSLE and among disease activity groups (p < 0.001). Table 1 reveals strong diagnostic properties of aC1qA. aC1qA was also associated with the presence of nephritis (p = 0.034). Correlation analysis showed moderate to good correlations with ESR, C3, C4, anti-dsDNA and ANuA and SLEDAI.

Conclusion: Our initial findings showed a strong diagnostic and possible, prognostic properties of aC1qA in our cSLE cohort. The presence of aC1qA was associated with lupus nephritis and it’s levels seem to fluctuate with global, if not only renal disease activity. A longer term and prospective study is needed to validate these initial findings in our region.

Disclosure: T. Arkachaisri, None; J. G. Yeo, None; J. H. T. Tan, None; S. F. Hoh, None; L. Das, None; J. Y. Leong, None.

1310
Predicting Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus Patients at Diagnosis. Maya Gerstein1, Roberto Ezquezile Borja2, Brian Feldman3, Deborah M. Levy2, Sharon Sukhdeo4, Susanne M. Benseler4, Lawrence W.K. Ng1, Mohamed Abdelhaleem5, Earl D. Silveman6 and Linda T Hiraki1. 1The Hospital for Sick Children, Toronto, ON, 2The Hospital for Sick Children and University of Toronto, Toronto, ON, 3The Hospital For Sick Children, Toronto, ON, 4Alberta Children’s Hospital, University of Calgary, Calgary, AB.

Background/ Purpose: It can be difficult to differentiate macrophage activation syndrome (MAS) from active pediatric systemic lupus erythematosus (pSLE). However, this differentiation is in determining correct treatment decisions. The purpose of this study is to generate a decision tree for the recognition of MAS in newly diagnosed pSLE and test the performance of these proposed criteria in an independent pSLE cohort.

Methods: A retrospective cohort study of consecutive patients requiring admission to SickKids Hospital with newly diagnosed, active pSLE between January 2002 and July 2007 (training cohort) was performed. All patients met ≥4 ≥1 ACR criteria. Data collection on: 1) Clinical features including fever, CNS dysfunction, splenomegaly, hepatomegaly and hemorrhage; 2) Laboratory parameters: CBC, ESR, CRP, C3, C4, ferritin, AST, ALT, LDH, albumin, bilirubin, triglycerides, LDL, HDL, urea, creatinine, sodium, coagulation parameters including INR, PTT, fibrinogen and D-Dimer, and soluble IL-2 receptor (sIL-2R) and CD163. Patients were assigned to one of 2 cohorts exclusively (MAS/non-MAS). Putative predictor variables were compared between cohorts. A decision tree analysis for diagnosis of MAS in pSLE was constructed using recursive partitioning, and decision rules were subsequently applied to an independent cohort of newly diagnosed, active pSLE diagnosed and admitted to SickKids between July 2007 and July 2013 (testing cohort) to determine the sensitivity and specificity of the proposed criteria.

Results: The training cohort consisted of 56 pSLE patients: 9 (16%) diagnosed with MAS and 47 non-MAS patients. Splenomegaly was more common in the non-MAS cohort, with no other differences in clinical characteristics between cohorts. Of all the available laboratory data, ALT > 45 units/L, neutrophils < 1.65 x 10^9/mm^3 and ferritin > 836 µg/L identified 55% of the patients with MAS (R^2 = 0.75) with 100% specificity. The testing cohort consisted of 9 (20%) MAS and 32 non-MAS pSLE patients. The proposed thresholds for ALT, neutrophil count and ferritin demonstrated a sensitivity of 67% and specificity of 94% in discriminating MAS from non-MAS patients.

Conclusion: None of the clinical features differentiated pSLE patients with and without MAS. Using all laboratory data proposed to be elevated in MAS and decision tree analysis demonstrated that ALT, neutrophil count and ferritin had excellent specificity and adequate sensitivity for distinguishing MAS from active SLE at diagnosis in both the testing and validation

Table 1. Anti-C1q antibody as diagnostic biomarker

<table>
<thead>
<tr>
<th>Properties</th>
<th>%</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>48.15</td>
<td>28.67–68.05</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.41</td>
<td>92.63–99.46</td>
</tr>
<tr>
<td>+ Likelihood ratio</td>
<td>18.62</td>
<td>5.70–60.80</td>
</tr>
<tr>
<td>– Likelihood ratio</td>
<td>0.53</td>
<td>0.37–0.77</td>
</tr>
<tr>
<td>Predictive value</td>
<td>81.25</td>
<td>82.20–93.84</td>
</tr>
<tr>
<td>Predictive value</td>
<td>88.98</td>
<td>88.98–93.84</td>
</tr>
</tbody>
</table>

Table 2. Anti-C1q antibody in cSLE and Controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>cSLE (n=180)</th>
<th>Controls (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aC1q titers (n &lt; 10 U/ml)</td>
<td>4.03 (2.78–6.97)</td>
<td>No activity (n=106)**</td>
</tr>
</tbody>
</table>
cohort. This is a first step in improved recognition of MAS among pSLE patients. Future analyses are planned to further refine methods in distinguishing these two groups.

Disclosure: M. Gerstein, None; R. E. Borgia, None; B. Feldman, None; D. M. Levy, None; S. Sukhdeo, None; S. M. Benser, None; L. W. K. Ng, None; M. Abdelhameen, None; E. D. Silverman, None; L. T. Hiraki, None.

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Background/Purpose: Incidence and disease pattern of childhood-onset systemic lupus erythematosus (SLE) is reported to differ among ethnic groups. Lupus nephritis (LN) strongly affects the outcome in children with LES systemic lupus erythematosus (SLE). There are lack of data on the clinical course, long-term outcome and predictors of disease progression in Mexican children. This study reports the results and outcomes of a cohort of Mexican patients with LN.

Methods: To describe lupus nephritis pattern and follow-up of a cohort of 61 Mexican children with SLE in the Hospital Infantil de Mexico Federico Gomez during a 18-month period in 2013–2014. Descriptive data, parametric, non parametric statistics and Kaplan-Meier graphs was used to analyze disease remission.

Results: The mean age at diagnosis was 12.4 years (SD = 2.6), most of them was female (85%) and 51 (83%) presented nephritis at the time of LES diagnosis. The mean plasma creatinine was 0.8 (SD 0.4) and 24 (39%) patients presented with nephritic syndrome. Renal function was reported with a median proteinuria 41 mg/m2TBS/h (0 - 735) and 53 (86.9%) presented with positive urinary sediment. Complement was diminished in the most of the patients. Class IV LN was the most prevalent (62%). Treatment was based on cyclophosphamide IV pulses alone or combined with oral either azathioprine or MMF. The patients completed a mean follow-up of 8 months, 26 (42.6%) patients were in complete remission and 15 (24.6%) were in partial remission. Two patients needs to move to rituximab treatment.

Conclusion: The current study provides outcome data on a mexican pediatric population with LN and underlines the importance of prescribing appropriate induction treatment to all children, also we identify that class II LN presents the best outcome in our patients.

Results: The current study provides outcome data on a mexican population with LN and underlines the importance of prescribing appropriate induction treatment to all children, also we identify that class II LN (Figure, P = 0.13).

Conclusion: The current study provides data on the clinical and laboratory characteristics of Mexican children with LN and underlines the importance of prescribing appropriate induction treatment to all children, also we identify that class II LN presents the best outcome in our patients.

Clinical Features of MAS n (%)

Table: Clinical and Laboratory characteristics:

<table>
<thead>
<tr>
<th>Clinical Features of MAS n (%)</th>
<th>SLE ACR Classification Criteria n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Malar rash</td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>Arthritis</td>
</tr>
<tr>
<td>CNS dysfunction</td>
<td>Ulcers</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Serositis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>CNS disease</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Anti-cardiolipin</td>
</tr>
</tbody>
</table>

MAS Laboratory Parameters mean (±/ SD)

| WBC (mm3) | 2.56 (1.87) |
| Neutrophils (mm3) | 1.32 (1.01) |
| HGB (g/L) | 95 (16.04) |
| PLT (mm3) | 134,000 (79.94) |
| AST (units/L) | 249 (301) |
| ALT (units/L) | 161 (259) |
| LDH (IU/L) | 2,728 (3,655) |
| Ferritin (µg/L) | 6,310 (11,091) |
| Fibrinogen (g/L) | 2,86 (1.04) |
| aPTT | 37 (8) |
| D-Dimer (ng/mL) | 1,923 (5,709) |
| Triglycerides (mmol/L) | 2.78 (1.19) |
| Sodium (mmol/L) | 135 (4.61) |

Disclosure: M. D. R. Maldonado-Velázquez, None; E. Faugier, None; F. García-Rodríguez, None; P. Lara, None; A. Flores, None; J. Tomala-Haz, None; D. Salinas-Encinas, None.

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Features, Treatment and Outcome of Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus. Roberto Ezequiel Borgia1, Maya Gerstein2, Deborah M. Levy3, Earl D. Silverman3 and Linda T Hiraki4. 1The Hospital for Sick Children, Toronto, ON, 2The Hospital for Sick Children and University of Toronto, Toronto, ON.

Background/Purpose: Macrophage activation syndrome (MAS) is a life-threatening inflammatory complication of pediatric systemic lupus erythematosus (pSLE). There are few reports of the presentation, treatment and outcome of MAS in pSLE. Our objective is to describe the presentation and treatment of pSLE-MAS patients seen at a single tertiary centre.

Methods: Our retrospective review included all patients seen at the Hospital for Sick Children, Toronto, diagnosed with pSLE (≥ 4/11 ACR classification criteria) and MAS (by Pediatric Rheumatologist expert opinion) between January 2002 and December 2012. We collected data on: 1) Demographics: Sex, ethnicity, age of diagnoses; 2) MAS clinical features (fever, hepatosplenomegaly, lymphadenopathy, hemorrhages, CNS involvement); 3) SLE ACR classification criteria; 3) Additional laboratory, pathological and genetic parameters including autoantibodies and bone marrow aspiration (BMA); 4) Treatment; 5) Frequency of hospitalization, PICU admission and death.

Results: We identified 34 patients diagnosed with pSLE and MAS. The majority were female (70%). The most common SLE features were malar rash, arthritis and anti-dsDNA antibodies (Table). Mean age at SLE diagnosis was 13.4 years (SD: 3.0), the average interval between SLE and MAS diagnosis was 1.5 months (SD: 0.54), with the majority (76%) of patients diagnosed with MAS concomitantly with their SLE diagnosis. 4 patients had documented concomitant infections: 2 bacterial, 1 EBV and 1 HSV1. All patients had fever (Table). 6/23 patients (26%) who underwent BMA demonstrated hemophagocytosis. Targeted gene sequencing of HLA genes perform and syntaxin 11 was performed in 5 patients with the only abnormality a silent heterozygous polymorphism in perforin coding region detected in one patient. All patients were treated with corticosteroids with the majority (59%) receiving IV pulse of methylprednisolone (average 3 pulses/patient). Concomitant medications: IVIG in 59%, calcineurin inhibitor in 32%, and etoposide in 6%. All the patients required hospital admission, 6 required PICU admission and there were no deaths from MAS.

Conclusion: To our knowledge this is the largest cohort of patients with diagnosis of MAS in pSLE reported in a single center. We observed that MAS is most likely to develop concomitantly with pSLE diagnosis. The majority of the patients were successfully treated with corticosteroids and IVIG with complete recovery in all.

Table: Clinical and Laboratory characteristics:

<table>
<thead>
<tr>
<th>Clinical Features of MAS n (%)</th>
<th>SLE ACR Classification Criteria n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Malar rash</td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>Arthritis</td>
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<td>CNS dysfunction</td>
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<td>Lymphadenopathy</td>
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<td>Serositis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>CNS disease</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Anti-cardiolipin</td>
</tr>
</tbody>
</table>

Antibodies n (%)

| WBC (mm3) | 2.56 (1.87) |
| Neutrophils (mm3) | 1.32 (1.01) |
| HGB (g/L) | 95 (16.04) |
| PLT (mm3) | 134,000 (79.94) |
| AST (units/L) | 249 (301) |
| ALT (units/L) | 161 (259) |
| LDH (IU/L) | 2,728 (3,655) |
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| Triglycerides (mmol/L) | 2.78 (1.19) |
| Sodium (mmol/L) | 135 (4.61) |

Disclosure: M. D. R. Maldonado-Velázquez, None; E. Faugier, None; F. García-Rodríguez, None; P. Lara, None; A. Flores, None; J. Tomala-Haz, None; D. Salinas-Encinas, None.
Comorbidity Patterns in Children with Juvenile Idiopathic Arthritis and Systemic Lupus Erythematosus: The Childhood Arthritis and Rheumatology Research Alliance Registry, Marc D. Natter1, Mei-Sing Ong2, Kenneth D. Mandl2, Laura Schanbergen, Yukiko Kimura4, Norman Ilowite5, and the CARRA Registry Investigators. 1Children’s Hospital Boston, Boston, MA, 2University of New South Wales, Sydney, Australia, 3Duke University, Durham, NC, 4Hackensack Univ Medical Ctr, Hackensack, NJ, 5Children’s Hospital Montefiore, Bronx, NY.

Background/Purpose: Knowledge of co-occurring disease processes (comorbidities) is important for understanding disease pathogenesis, refining disease classifications, developing appropriate screening and prevention strategies, and determining overall burden of disease. We analyze prevalence and patterns of comorbidities in children with JIA and SLE in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

Methods: We analyzed cross-sectional data from the CARRA Registry across 60 sites between 2010 and 2013. Patterns of comorbidities in children with JIA and SLE were assessed. Network analysis of disease co-occurrence was carried out to identify clusters of comorbidities that are likely to present in the same individual.

Comorbidities were present and captured (1 or more) for subjects in the registry according to disease type:

**JIA**: uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, type 1 diabetes (T1D), type 2 diabetes (T2D), malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, seizure, pulmonary hypertension, psoriasis, IBD, interstitial lung disease.

**SLE**: chronic vasculitis, autoinflammatory disease, uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, T1D, T2D, malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, coronary heart disease.

Results: 6,150 children with JIA and 1,067 children with SLE were enrolled in the CARRA registry. 20.5% of JIA and 11.5% of SLE patients had at least 1 comorbidity (Table 1). Multiple co-occurring co-morbidities were individually much less common (0.6% or less), including in known associations (e.g. JIA with Down’s syndrome and hypothyroidism or congenital heart disease).

Conclusion: The prevalence of comorbidities in children with JIA and SLE in the CARRA Registry is in accordance with ranges reported in other studies. We analyzed multiple co-occurring co-morbidities, including a network clustering analyses, which showed established and potential associations that are candidates for further evaluation in larger, population-based data sets.

Table 1. Number of comorbidities in JIA and SLE patients

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JIA*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1153 (18.7)</td>
</tr>
<tr>
<td>2</td>
<td>95 (1.5)</td>
</tr>
<tr>
<td>3</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>4</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>At least one</td>
<td>1258 (20.5)</td>
</tr>
</tbody>
</table>

*Comorbidities considered included: uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, type 1 diabetes, type 2 diabetes, malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, seizure, pulmonary hypertension, psoriasis, IBD, interstitial lung disease.

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Health, London, United Kingdom, 2 Great Ormond Street Hospital for Children, London, United Kingdom, 3 Novartis Pharmaceutical Corporation, 2 UCB Pharma, 5, Eli Lilly and Company, 5 Novartis, Janssen, 5.

Comparison of the Utility and Validity of Three Scoring Tools to Detect Skin Disease in Patients with Juvenile Dermatomyositis. Y. Kimura, M. S. Ong, None; B. Almeida, None; K. Arnold, None; K. Nistala, None; C. A Pilkington, None; L. R. Wedderburn, None.

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Comparison of the Utility and Validity of Three Scoring Tools to Detect Skin Disease in Patients with Juvenile Dermatomyositis. Raquel Campaniho-Marques1, Beverley Almeida2, Katie Arnold1, Kiran Nistala3, Clarissa A Pilkington4, and Lucy R Wedderburn5. 1 UCL Institute for Child Health, London, United Kingdom, 2 Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, 3 University College London, London, United Kingdom.

Background/Purpose: Juvenile dermatomyositis (JDM) is a rare condition affecting 3 children/million/year. Muscle and skin involvement are key features. The muscle symptoms are frequently the main initial focus: formal measures (Childhood Myositis Assessment Scale - CMAS and M Anual Muscle Test - MMT8) exist to routinely and accurately assess this component of the disease. However, the involvement of skin, and its assessment, is a vital aspect. The abbreviated Cutaneous Assessment Tool (CAT) encompassing active skin disease and skin damage, Disease Activity Score (DAS) and Myositis Intention to Treat Activity Index (MITAX), both with skin components, have all been suggested to measure skin disease in JDM; however the optimal tool is unknown. The aim was to compare 3 tools for assessment of skin disease in JDM and correlate them with the physician’s 10cm skin visual analogue scale (physician’s skin VAS) to define which tool best assesses skin disease.

Methods: Patients recruited to the UK JDM Cohort & Biomarker Study who fulfil Bohan-Peter criteria for JDM were included. Each patient was assessed for skin disease using the CAT, DAS, MITAX and an overall physician’s skin VAS. Markers of muscle disease (CMAS, MMT8, CK U/L), inflammatory markers (CRP mg/l, and ESR mm/hr) and overall physician’s global score were also recorded. Spearman’s correlations (rs) were used to correlate categorical and continuous variables and a relationship >0.75 was considered strong. A p-value <0.05 was considered significant.

Results: Between 2012 and 2014, 67 JDM patients were assessed. 59.7% were female. The mean (±SD) age of the patients was 9.86 ± 3.37 years, with mean age at diagnosis 6.59 ± 3.42 years and mean disease duration of 3.26 ± 3.08 years. The skin section of the DAS had the strongest correlation with the physician’s skin VAS (Table 1). The skin section of the MITAX and the CAT activity scores were significantly correlated with the physician’s skin VAS. DAS skin, MITAX skin and CAT Activity scores were all negatively correlated with CMAS and MMT8 scores; no significant correlations were noted with the CK. DAS skin scores were significantly correlated both with the CRP and ESR, while the MITAX skin was significantly correlated only with the ESR, and CAT Activity only with the CRP.

Table 1. Spearman’s correlation between items shown as rs and corresponding p value.

<table>
<thead>
<tr>
<th>Skin tool</th>
<th>n</th>
<th>CMAS</th>
<th>MMT8</th>
<th>CK</th>
<th>CRP</th>
<th>ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS skin</strong></td>
<td>67</td>
<td>rs 0.795</td>
<td>rs 0.242</td>
<td>rs 0.176</td>
<td>rs 0.280</td>
<td>rs 0.311</td>
</tr>
<tr>
<td><strong>MITAX skin</strong></td>
<td>52</td>
<td>rs 0.594</td>
<td>rs 0.453</td>
<td>rs 0.208</td>
<td>rs 0.281</td>
<td></td>
</tr>
<tr>
<td><strong>CAT Activity</strong></td>
<td>54</td>
<td>rs 0.623</td>
<td>rs 0.428</td>
<td>rs 0.300</td>
<td>rs 0.164</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: These data demonstrate the potential application of using a skin assessment tool to evaluate and monitor skin involvement in JDM patients. It also demonstrates that the DAS skin section appears to be the best of the tools using the physician’s skin VAS as the gold standard. The DAS skin tool was concise, quick to use and easy to score.

Disclosure: R Campaniho-Marques: None; B. Almeida: None; K. Arnold: None; K. Nistala: None; C. A Pilkington: None; L. R. Wedderburn: None.

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Background/Purpose: Hydroxychloroquine is an antimalarial agent commonly used in the treatment of rheumatologic diseases. Data on the use of HCQ in JDM is limited, primarily based on anecdotal experiences and two small, retrospective reviews. As a result, there is no current consensus on the utility of HCQ in the management of JDM. Our objective was to investigate the use of HCQ treatment in JDM using a large, national, multi-center registry.

Methods: Subjects meeting Bohan and Peter criteria for definite or probable JDM were enrolled into the CARRA registry between 2010 and 2013. Cross sectional analysis of data regarding demographics, disease characteristics, measures of disease activity, diagnostic assessments, medications and long term complications were examined. Bivariate analysis was performed evaluating the use of HCQ with clinical variables of interest. Variables with biologic relevance or statistically significant associations (p<0.25) were selected for inclusion into a multivariate logistic regression model examining independent predictors of HCQ use.

Results: Baseline information was available for 604 patients. Information on HCQ treatment was available for 565 patients (93.5%). 295 (52.2%) patients had current or prior treatment with HCQ and 270 (47.8%) patients had never been treated with HCQ. In bivariate analysis, an association was found between the use of HCQ and age at first rheumatology visit (p=0.02), disease duration (p=0.001), abnormal CHAQ (p=0.001), symmetric proximal muscle weakness (p=0.002), large joint arthritis (p=0.002), malar erythema (p=0.04) and calcinosis (p=0.012). In multivariate analysis,
patients with symmetrical proximal muscle weakness or an abnormal CHAQ score were less likely to be on HCO therapy; whereas patients with any rash (malar erythema, heliotrope rash, V-sign orshawl sign), calcinosis or arthritis had a higher likelihood to be on current or prior HCO therapy (Table 1).

Table 1. Multivariable model using logistic regression predicting use of HCO (n=496)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetrical muscle weakness</td>
<td>0.46 (0.28–0.74)</td>
<td>0.002</td>
</tr>
<tr>
<td>Abnormal CHAQ</td>
<td>0.66 (0.44–0.99)</td>
<td>0.044</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>1.93 (1.08–3.45)</td>
<td>0.027</td>
</tr>
<tr>
<td>Rash</td>
<td>1.65 (1.11–2.46)</td>
<td>0.014</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.56 (1.05–2.31)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

**Conclusion:** The CARRA registry represents one of the largest ongoing multi-center JDM registries. This data aids our understanding of which clinical characteristics may predict HCO use in JDM. Prior evidence in other rheumatologic conditions suggests that HCO improves arthritis and skin manifestations. As expected, patients with these characteristics were more likely to be on HCO. Patients with muscle weakness and abnormal CHAQ were less likely to be on HCO. We speculate these patients had a more severe disease course and likely treated with aggressive immunosuppression. Due to the design of this study as a cross-sectional analysis, we are unable to determine the causal association of these results. Further longitudinal data is needed to examine the benefits of HCO in these patients.

Funded by the NIAMS, Friends of CARRA, CARRA Inc., and the Arthritis Foundation.

Disclosure Y. Sterba None; D. Wahezi None; F. the CARRA investigators None.

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A Hybrid Conjoint Analysis Model Is Proposed As the Definition of Minimal, Moderate and Major Clinical Improvement in Juvenile Dermatomyositis Clinical Trials.

Lisa G. Rider1, Rohit Aggarwal2, nastaran Bayat3, Brian Erman4, Brian M. Feldman5, Adam M. Huber6, Rolando Cimat7, Ruben J. Cuttica8, Sheila K. Feitosa de Oliveira9, Carol B. Lindsley10, Clarissa A Pilkington11, Marilynn G. Punaro12, Angelo Ravelli13, Ann M. Reed14, Kelly A. Rouster-Stevens15, Annet van Royen-Kerkhof16, Luca Villa17, M ariangela Rinaldi18, Angela Pistorio19, Howard Rockette20, Peter A. Lachenbruch21, Frederick W. Miller22, Jiri Vencovsky23 and Nicolino Ruperto24.

1Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD; 2University of Pittsburgh, Pittsburgh, PA; 3Social and Scientific Systems, Inc., Durham, NC; 4The Hospital for Sick Children, Toronto, ON; 5IWK Health Centre, Halifax, NS; 6University of Firenze, Firenze, Italy; 7Hospital de Niños Pedro de Elizalde - University of Buenos Aires, Buenos Aires, Argentina; 8Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; 9Univ Kansas City Med Ctr, Kansas City, KS; 10Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; 11University of Texas Southwestern Medical Center, Dallas, TX; 12University of Genova, Genova, Italy; 13Mayo Clinic, Rochester, MN; 14Emory University School of Medicine, Atlanta, GA; 15University Medical Centre Utrecht - Wilhelminalia Children's Hospital, Utrecht, Netherlands; 16IRCCS Istituto G. Gaslini, Genova, Italy; 17Istituto Giannina Gaslini, Genova, Italy; 18NIEHS, NIH, Bethesda, MD; 19Charles University, Prague, Czech Republic; 20Istituto Giannina Gaslini, Genova, Italy.

**Background/Purpose:** Preliminary definitions of improvement (DOIs) for juvenile dermatomyositis (JDM) combining IMACS or PRINTO core set activity measures (CSMs) have been used as a responder index in clinical trials. However, these DOIs defined only minimal clinical improvement and are in need of further validation.

**Methods:** Using natural history study data, JDM experts rated patient profiles containing IMACS or PRINTO CSMs and achieved consensus (≥ 70% agreement) in 98% (247 minimal, 174 moderate and 84 major improvement). Conjunct analysis was performed on forced-choice surveys (by using 1000Minds software) administered to myositis experts. Candidate DOIs based on changes in core set measures (CSMs) were generated as follows: A) 23 published DOIs were restested; B) 436 DOIs developed using expert survey and variations of published DOIs; C) 56 DOIs derived from logistic regression analysis; D) 6 DOIs derived from a conjoint analysis survey that yielded scores with different levels of improvement in different CSMs; E) 8 DOIs drafted by combining changes in each CSM with respective conjoint analysis weights; and F) 194 DOIs drafted by applying weights from conjoint analysis to the base DOIs. Relative and absolute % change DOIs were tested. The consensus patient profiles were then used to test DOIs for their validity, including sensitivity, specificity, kappa, OR and area under the curve (AUC). High performing DOIs were externally validated using Rituximab in Myositis (RIM) trial data (N=48) and PRINTO JDM (n=139) trials.

**Results:** The 14 highest performing candidate DOIs with AUC ≥ 0.90 in profile data for minimal, moderate and major improvement, and comparable results for the RIM trial, were discussed among 12 JDM experts for their performance characteristics and clinical face validity at a consensus conference using Nominal Group Technique (NGT). Many DOIs had significant discriminant validity in the PRINTO trial. A final ranking of the pediatric experts’ top DOIs yielded 92% consensus for a conjoint analysis hybrid model DOI using absolute % change in CSMs with different cut points for minimal, moderate and major improvement (Table 1). NGT discussion with the pediatric and adult working groups yielded consensus (91% agreement) in use of this hybrid DOI for adult DM/PM and JDM.

**Conclusion:** A conjoint analysis-driven hybrid definition with a continuous score of improvement based on absolute % change in CSMs with different cut points for minimal, moderate and major improvement was selected by a data- and consensus-driven process as a final DOI to be used for JDM and adult DM/PM clinical trials. ACR and EULAR funding support was received for this project, and their approval will be sought for these as new criteria for clinical response.

**Table 1.** Preliminary definitions of improvement (DOIs) for JDM.

<table>
<thead>
<tr>
<th>DOI</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Kappa</th>
<th>OR</th>
<th>Area under the curve (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>Minimal improvement</td>
<td>87%</td>
<td>96%</td>
<td>0.72</td>
<td>5.8</td>
<td>0.77</td>
</tr>
<tr>
<td>10%</td>
<td>Moderate improvement</td>
<td>80%</td>
<td>93%</td>
<td>0.61</td>
<td>3.7</td>
<td>0.72</td>
</tr>
<tr>
<td>20%</td>
<td>Major improvement</td>
<td>70%</td>
<td>88%</td>
<td>0.47</td>
<td>2.3</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Disclosure:** L. G. Rider, NIEHS-NIH, 2; NIAIMS-NIH, 2; National Center for Translational Science-NIH, 2; Cure JM Foundation, 2; American College of Rheumatology, 2; R. Aggarwal, Questcor, 2; Pfizer Inc, 2; NIEHS-NIH, 2; Questcor, 5; Aty Pharma, 5; N. Bayat, Cure JM Foundation, 2; B. Erman, NIEHS-NIH, 3; B. M. Feldman, None; A. M. Huber, None; R. C.reeze, None; R. J. Cuttica, None; S. K. Feitosa de Oliveira, Novartis Pharmaceutical Corporation, 2; Roche Pharmaceuticals, 2; C. B. Lindsley, None; C. A. Pilkington, None; M. G. Punaro, None; A. Ravelli, None; A. M. Reed, None; K. A. Rouster-Stevens, None; A. van Royen-Kerkhof, None; L. Villa, None; M. Rinaldi, None; A. Pistorio, None; H. Rockette, NIEHS-NIH, 5; P. A. Lachenbruch, NIEHS-NIH, 5; F. W. Miller, NIEHS-NIH, 2; NIAIMS-NIH, 2; National Center for Advancing Translational Science-NIH, 2; J. Vencovsky, European League Against Rheumatism, 2; J. A. Lindsley, Myositis Support Group, 2; The Myositis Association, 2; R. L. Ruperto, European League Against Rheumatism, 2.
Anti-p155/140 Autoantibodies and Selected Features at Illness Onset Are Associated with a Chronic Course of Illness in the Juvenile Idiopathic Inflammatory Myopathies. G. Esther A. Habers 1, Adam M. Huber 2, Gulnara Mamyrova 3, Ira Targoff 4, Chantal Boonacker 5, Richard Targoff 4, Frederick W. Miller 2, Lisa G. Rider 2 and Annet van Royen-Kerkhof 7. 1Child Development and Exercise Center, Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, Netherlands, 2IWK Health Centre, Halifax, NS, 3George Washington University, Washington, DC, 4Oklahoma Medical Research Foundation, Oklahoma City, OK, 5Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands, 6Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, 7University Medical Centre Utrecht - Wilhelmina Children’s Hospital, Utrecht, Netherlands.

Background/Purpose: Three types of disease courses can be distinguished in patients with juvenile idiopathic inflammatory myopathies (JIIM), namely monomorphic (M), polymorphous (P), and chronic (C). This study explored the association of demographics, clinical onset features and myositis autoantibodies with disease course in a large JIIM cohort.

Methods: In the present study, we included 365 patients with JIIM (295 dermatomyositis, 28 polyMyositis, and 42 overlap myositis) who were enrolled into IRB-approved studies in the US and Canada and had a disease duration >2 years from diagnosis. Blood samples and physician questionnaires with demographics and clinical onset features were obtained. Myositis autoantibodies were determined by immunoprecipitation and blotting methods. Follow-up information was performed through medical record review. The disease course classification was: M - no active disease and off medication within 2 years of diagnosis (n = 88); P - disease recurrence after definite remission (n = 86); and C - persistent disease or continuation of medication for > 2 years (n = 191). Parameters with p < 0.10 in univariate analysis were analyzed by multinomial logistic regression.

Results: Factors significant only in univariate analysis were cuticular overgrowth (M < P and C), V- and/or shawl-sign rash (M and P < C), contractures (P < C and M), photosensitivity (M < C), dyspnea at rest (P < C), palpatory and/or syncope (M and C < P), geoclimatic zone, and anti-Ro autoantibodies (M < C). An abnormal aldolase was more frequent in P compared to M and C, but not included in multivariable analysis due to missing values. Two different multinomial logistic regression analyses with non-overlapping parameters were performed (see Table 1 for results). Myositis-specific and -associated autoantibodies were more frequent in P versus C than in M, with the anti-p155/140 autoantibody as the most significant (p = 0.0001). Documented infections within 6 months prior to illness onset were also more frequent in the P and C compared to M. P had less early illness signs and symptoms (–lower clinical symptom score) compared to M and C. A more severe illness onset was present in C compared to M and P. Compared to M, mucous membrane involvement was less frequent in C and distal weakness was less frequent in P and C. Weight loss was more frequent in C compared to P.

Conclusion: Myositis-specific and -associated autoantibodies (especially the anti-p155/140 autoantibodies) and selected features at illness onset were associated with a chronic course of illness in patients with JIIM. These findings suggest that certain predictors of poor prognoses can be identified that might influence treatment options at illness onset.

Table 1: Results of 2 separate multinomial logistic regression analyses.

<table>
<thead>
<tr>
<th>Significant parameters</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant parameters</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>Any myositis specific autoantibodies</td>
<td>0.0001</td>
</tr>
<tr>
<td>Any myositis associated autoantibodies</td>
<td>0.01</td>
</tr>
<tr>
<td>Any infection 6 months prior to illness onset</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical symptom score</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data was adjusted for date of diagnosis and for the significant parameters in the analysis. *p < 0.05. †p < 0.10. ‡p < 0.001.

Disclosure: G. E. A. Habers, None; A. M. Huber, None; G. Mamyrova, Cure JM Foundation, 2; I. Targoff, None; C. Boonacker, None; M. van Brussel, None; F. W. Miller, None; L. G. Rider, None; A. van Royen-Kerkhof, None.

1318 Illness Onset Features and Misdiagnosis in Juvenile Idiopathic Inflammatory Myopathies (JIIM) Differ Among Clinical and Autoantibody (Ab) Subgroups. Gulnara Mamyrova 3, Lan Wu 2, Adam Huber 3, Ira N. Targoff 4, Frederick W. Miller 2 and Lisa G. Rider 2. 1George Washington University, Washington, DC, 2Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, 3IWK Health Centre, Halifax, NS, 4Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: To evaluate features of JIIM clinical and Ab subgroups at illness onset.

Methods: Physician-completed questionnaires illness onset features were reviewed in 465 JIIM pts (381 juvenile dermatomyositis (JDM), 33 polymyositis, 17 PM, and 51 JIIM) associated with other autoimmune diseases (JCTM) meeting probable or definite Bohan and Peter criteria. Myositis Abs were tested by standard immunoprecipitation and blotting methods. Univariate analysis was performed using GraphPad Prism 5.0.

Results: The first weakness was proximal in all clinical and Ab subgroups (86–90%). Gottron’s papules were most often the first rash in JDM and JCTM (48% and 47%), followed by heliotrope (45% and 29%), and malar rash (30% and 14%). Gottron’s papules were also the first rash in 57% of pts with anti-p155/140, 50% of anti-Mi2, 40% of anti-MJ and 32% of pts with anti-SRP Abs (p < 0.04). Heliotrope was most often the first rash in pts with anti-M (52%) and anti-ARS (47%). Both Gottron’s papules and heliotrope were present at diagnosis in 72% of JDM and 58% of JCTM pts. Gottron’s papules or heliotrope alone were seen in 18% and 9% of JDM pts at diagnosis, yet 1.7% of JDM patients did not have either rash at diagnosis. 81% of pts with anti-p155/140 Abs had both Gottron’s and heliotrope at diagnosis. Rash before weakness was seen in 54% of JDM and 74% of JCTM pts. Weakness before rash was seen in 23% of JDM and 14% of JCTM pts; 23% of JDM and 12% of JCTM pts developed rash and weakness simultaneously. Rash before weakness was observed in 73% of pts with anti-p155/140, 67% of anti-Mi2, 39% of anti-MJ, and 39% of anti-ARS Ab pts (p < 0.04). Weakness before rash was observed in 33% of anti-ARS, 31% of anti-MJ, 17% of anti-M12 and 12% of anti-p155/140 pts (p < 0.02). All JIIM pts had a median delay to diagnosis of 4.1 mo and JCTM pts had delay of 7.1 mo (p < 0.03); pts with anti-p155/140 had a median delay of 4.8 mo, anti-ARS 6.6 mo, and anti-SRP Abs 2.0 mo between first symptom and diagnosis. The median time between rash and diagnosis was 2.5 mo in JDM, 6.1 mo in JCTM, 4.0 mo in anti-p155/140 and 1 mo in anti-ARS Ab groups (p < 0.007). Twenty-three percent of JIIM pts had one and 5.7% had ≥ 2 misdiagnoses. Common misdiagnoses included infections (9.6%), other autoimmune diseases (4.6%), musculoskeletal (2.4%) and dermatologic conditions (17.6%), neurologic diseases (1.5%), and psychiatric disorders (0.7%). JPM and pts with anti-SRP Ab were often misdiagnosed with hepatitis (15.2–28.6%) and neurologic conditions (9.1%) including Guillain-Barre (3–14%). Pts with JDM and JCTM, including those with p155/140 and M Abs, were often misdiagnosed with other skin conditions (11–21%), including eczema (11–21%).

Conclusion: JIIM clinical and Ab groups vary in their type of rash and weakness and misdiagnosis at illness onset. Most present with rash before weakness, and with Gottron’s papules first. Better recognition of these varied presentations of illness should enhance recognition of JIIM phenotypes and help decrease delay in diagnosis and therapy.

Disclosure: G. Mamyrova, Cure JM Foundation, 2; L. Wu, None; A. Huber, None; I. N. Targoff, Consultant for the Oklahoma Medical Research Foundation Clinical Immunology Laboratory, 5; F. W. Miller, None; L. G. Rider, None.

1319 Safety of Rituximab in Treating Pediatric Rheumatic Disease, Arunima Agarwal1, Anusha Ramanathan2 and Rhina Castillo3. 1Children’s Hospital of Los Angeles, Los Angeles, CA, 2Children’s Hospital Los Angeles, Los Angeles, CA, 3Children’s Hospital Los Angeles, Los Angeles, CA.

Background/Purpose: Rituximab is a chimeric human/murine monoclonal antibody directed against the B cell specific antigen CD20. There is growing evidence that suggests Rituximab may also influence T cell immu-
nity and thus predispose patients to opportunistic infections by this mechanism as well. Rituximab use, both as monotherapy and in combination with other immunosuppressants, is increasing in the pediatric population. Data regarding infection associated with Rituximab is limited and inconsistent. The most concerning side effect is the development of progressive multifocal leukoencephalopathy (PML), a fatal condition which has been reported rarely with Rituximab use. This study seeks to report adverse events associated with Rituximab use in the pediatric rheumatologic population.

Methods: From January 2007 and April 2014 was conducted. All patients received Rituximab and incidence of infection was assessed for a follow-up period of 6 months to 7 years following first Rituximab course.

Results: The majority of patients were female (55%) and Hispanic (70%), with 3 African American, 2 Caucasian and 1 Asian patient. The most common diagnoses were lupus (35%), dermatomyositis (30%), or overlap syndrome (20%). Sixty percent of patients received only one course of Rituximab and most (65%) received high dose glucocorticoids concurrently with their first course of Rituximab. Other immunosuppressants included methotrexate (55%), cyclophosphamide (CYC) (15%), with an average cumulative dose of 6g/m2), and anti-TNF therapy (15%). One patient each was on concurrent therapy with cyclosporine or azathioprine. There were 15 total infections in 9 patients during a mean follow up of 16.2 months (range 6 to 45 months) occurring on average 4.5 months (range 1 to 19 months) following Rituximab. Two infections (bacterial pneumonia and cellulitis) requiring hospitalization occurred in one patient who had received CYC as well. The remainder of infections were minor, 11 required outpatient antibiotics and 2 self-resolved. The majority of infections (87%) occurred in patients with lupus or an overlap syndrome. Only 1 patient developed prolonged hypogammaglobulinemia requiring supplemental IVIG. There were no cases of infection related adverse events or PML in this cohort.

Conclusion: Overall the occurrence of significant adverse events following Rituximab was low in this pediatric cohort. Serious infections may be increased in those receiving combination therapy with CYC. Larger studies are needed to determine the attributable risk for infection from Rituximab alone versus that associated with underlying diagnosis or combination therapy. However, our results suggest that Rituximab use is safe and well-tolerated in a variety of pediatric rheumatologic conditions.

Disclosure: A. Agarwal, None; A. Ramanathan, None; R. Castillo, None.

1320
Analysis of Risk Factors for Thrombosis in Pediatric Patients with Systemic Lupus Erythematosus. Kyla D. Driest1, Mollie S. Sturm2, Sarah H. O'Brien3, Charles H. Spencer3 and Stacy P. Ardoin4. 1OSU Pediatrics, Nationwide Children's Hospital, Columbus, OH; 2Nationwide Children's Hospital, Columbus, OH; 3Nationwide Childrens Hospital, Columbus, OH, 4Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at high risk for thrombotic risk compared to the general population, and arterial and venous thromboses impart substantial morbidity and mortality. Few studies have focused on thrombotic risk within the pediatric SLE (pSLE) population. We sought to better characterize the risk factors for thrombosis in patients with pSLE utilizing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) registry.

Methods: The CARRA registry contains 979 patients with pSLE. Pediatric patients with a history of thrombosis were compared to those with no history of thrombosis. A history for thrombosis was defined as any patient within the SLE registry who had a history of arterial or venous thrombotic event as reported by the treating pediatric rheumatologist. For continuous variables, the Wilcoxon Mann-Whitney test was used to compare patients with pSLE utilizing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) registry.

Results: Of the 979 patients in the registry, 974 had data recorded for thrombosis and were included in the analysis. The majority of these patients were female (82.4%), non-Hispanic (72.8%) and white (44.7%). Of the 974 patients, 24.2% had history of arterial thrombosis and 35.6% of venous thrombosis. Odds ratios for thrombosis were calculated for gender, ethnicity, BMI, race, Raynaud’s phenomenon, vasculitis, avascular necrosis (AVN), renal disease, positive antiphospholipid antibody (APLA), thrombocytopenia, and hydroxychloroquine use. Utilizing a p value of < 0.05 as significant, the odds ratios of having a thrombotic event were significantly higher in patients with vasculitis [3.11, 95% CI: (1.60, 6.01)], history of AVN [3.08, 95% CI: (1.24, 7.67)], or APLA [3.03, 95% CI: (1.45, 6.36)]. Odds ratios for other variables were not statistically significant.

Conclusion: Our study of 974 patients with pSLE including 59 with a history of thrombotic event suggests that pSLE patients with a history of vasculitis, positive APLA, and AVN are at a greater risk for thrombotic events than those without. Odds ratios for gender, race, ethnicity, hydroxychloroquine use, renal disease, history of Raynaud’s phenomenon, and thrombocytopenia were not found to be statistically significant within this subset of patients.

Disclosure: K. D. Driest, None; M. S. Sturm, None; S. H. O’Brien, None; C. H. Spencer, None; S. P. Ardoin, None.

1521
A Pilot Study to Evaluate the Feasibility of Conducting Juvenile Localized Scleroderma Comparative Effectiveness Treatment Studies. Suzanne C. Li1, Kathlyn S. Torok2, Mara L Becker2, Fatma Dedegolu3, Polly J. Ferguson4, Robert C. Fuhlbrigge5, Gloria C. Higgins6, Sandy D. Hong7, Maria F. Illera8, Ronald M. Laker9, Thomas G. Mason II11,12, Elena Pope12, Marianna S. Pildal12, C. Elia Rabinovich13, Katie G. Stewart14 and Brian Feldman11. 1Joseph M Sanzari Children’s Hospital, Hackensack University Medical Center, Hackensack, NJ, 2Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA, 3Children’s Mercy Hospital, Kansas City, MO, 4Boston Children’s Hospital, Boston, MA, 5University of Iowa Carver College of Medicine, Iowa City, IA, 6Brigham and Women’s Hospital, Boston, MA, 7Nationwide Childrens Hosp, Columbus, OH, 8U of Iowa Childrens Hosp, Iowa City, IA, 9The Hospital for Sick Children, University of Toronto, Toronto, ON, 10Mayo Clinic Rochester, Rochester, MN, 11The Hospital for Sick Children, Toronto, ON, 12Texas Scottish Rite Hospital, Dallas, TX, 13Duke Univ Med Ctr, Durham, NC.

Background/Purpose: Juvenile localized scleroderma (jLS) often causes severe morbidity in the developing child, including growth defects and disfigurement. Optimal therapy is not known. The LS Children’s Arthritis and Rheumatology Research Alliance (CARRA) subgroup has been working towards improving long-term outcome for these patients. Towards this end, we have developed standardized treatment regimens based upon best available evidence and consensus methodology (consensus treatment plans, CTPs), and clinical tools to use in comparative effectiveness treatment studies. We are currently conducting a pilot study to evaluate the feasibility of conducting jLS comparative effectiveness treatment studies. Additional analyses will include evaluating performance characteristics of developed tools.

Methods: Fifteen physicians from 10 CARRA centers have been conducting a prospective observational cohort study of jLS subjects initiating systemic immunosuppressive treatment. Inclusion criteria include diagnosis of jLS by pediatric rheumatologist or dermatologist, and presence of active disease according to delineated activity criteria generated by the group. Participants criteria include treatment with methotrexate (MTX) within the prior 3 months or corticosteroids (CS) within prior 2 weeks. Subjects were treated with one of three MTX-based CTPs (MTX alone, MTX with intravenous CS (IV CS), or MTX with oral CS), determined by treating physician, and evaluated at 6 visits over 1 year. At the start of the study, a workshop meeting was held to standardize evaluation.

Results: The targeted enrollment (50 subjects) was reached. All sites enrolled subjects, with enrollment taking approximately 23 months to complete following study initiation at the first site. Subjects were enrolled in all 3 CTPs, with half enrolled in MTX + IV CS CTP. Over 40% of subjects deviated from their initial treatment regimen, with persistent activity a frequent reason. Over 80% of subjects agreed to participate in the optional sample collection and banking sub study.

Study Subject Features
Gender
35 Females (73%)
Race
12.7 yr (3 - 21 yr)
43 White
1 Black
2 Asian
unknown
Ethnicity
39 non-Hispanic: 9 Hispanics
Treatment Regimen
MTX alone
12 (25.5%)
MTX + intravenous CS
24 (51%)
MTX + oral CS
11 (23%)
Conclusion: This is the first study to explore the feasibility of conducting comparative effectiveness treatment studies in JLS. We achieved our target enrollment of 50 subjects, with subjects enrolled in all 3 standardized treatment regimens. Biological samples have been collected from the majority of subjects, which will enable future translational studies. This study will enable us to evaluate and refine clinical tools needed for treatment studies based upon study data, and identify issues related to conducting JLS treatment studies. Further analyses of these data once completed will also include clinical effectiveness and tolerability of the 3 different treatment regimens in JLS subjects.

Disclosure: S. C. Li None; K. S. Torkk None; M. L. Becker None; F. Dedegoli None; P. J. Ferguson None; R. C. Fuhlbrigge None; G. C. Higgins None; S. D. Hong None; M. F. Ibarra None; R. M. Laxer None; T. G. Mason II None; E. Pope None; M. G. Punaro None; C. E. Rabinovich None; K. G. Stewart None; B. Feldman None.

1323

Gastrointestinal Involvement in Juvenile Systemic Sclerosis: Development of Recommendations for Screening and Investigation. Ivan Foeldvari1, Claire Pain1, Tamás Constantin2, Eileen Baildam3, Henning Lenhartz2, Michael Blakley5, Dana Nemkova7 and Clarissa A Pilkington8. 1Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendheumatologie, Hamburg, Germany, 2University Children’s Hospital, Liverpool, United Kingdom, 3University Childrens Hospital, Budapest, Hungary, 4Alder Hey Children’s Foundation NHS Trust, Liverpool, United Kingdom, 5Pediatric Cardiology, Hamburg, Germany, 6Indiana University School of Medicine and Riley Hospital for Children at IU Health, Indianapolis, IN, 7Pediatric Rheumatology, Prague, Czech Republic, 8Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom.

Background/Purpose: There are currently no agreed recommendations on how to investigate children for gastrointestinal involvement in Juvenile Systemic Sclerosis (JSSc). The aim of screening is to detect disease early to facilitate early aggressive therapy and improve outcomes. Gastrointestinal involvement is the leading cause of death in JSSc and gastrointestinal involvement at diagnosis incurs a worse outcome (1). Most deaths occur early in the disease course (1, 2).

Objectives: To develop recommendations for investigation of gastrointestinal involvement in JSSc, based on paediatric evidence and where this was lacking, consensus expert agreement.

Methods: Members of the PRES Scleroderma Working Group were invited to participate; additionally a paediatric cardiologist and paediatric gastroenterologist were invited. A nominal group technique was used. 75% consensus was defined as agreement.

Results: Table 1 shows the recommendations for screening for gastrointestinal and GI involvement at baseline and at defined time points from diagnosis. Other recommendations agreed by the group which are relevant at any stage in the disease course are as follows:

1. If there are any concerns or signs of pulmonary hypertension then right heart catheterisation should be undertaken.
2. Any child with exertional chest pain or abnormality on 24hr ECG should undergo exercise ECG (if old enough to comply).
3. Those with worsening PFTs or clinical deterioration should have HRCT thorax repeated sooner (particularly, FVC <70% or DLCO <80% or drop in values by 20% of baseline).
4. Recommendations are based on low grade evidence and in the most part from expert consensus opinion with extrapolation from adult studies.

Table 1. Recommendations for screening for gastrointestinal and GI involvement in JSSc at baseline and follow-up (75% consensus defined as agreement)

Cardiopulmonary | Baseline
---|---
All patients should undergo: | 
- 6MWT
- ECHO with Doppler
- Cardiac M R I with gadolinium
- HRCT thorax
- PFT with DLCO

Follow-up screening (for first 5 years from diagnosis)
- 6 monthly: 12 lead ECG
- ECHO with doppler
- 6MWT

6 monthly: PFT with DLCO

A annual: 24hr ECG

Repeat HRCT

Conclusion: JSSc has a significant mortality particularly early on in the disease course. The objective of an aggressive screening program is to identify gastrointestinal and GI involvement at a stage which may be amenable to treatment. The recommendations developed by this group aim to standardise care and improve outcomes in this rare disease.

Disclosure: I. Foeldvari, Novartis Pharma AG, A. bellow, Chugui, Genzyme, S. C. Pain, None; T. Constantin, None; E. Baildam, None; C. Beyer, None; M. Blakley, None; D. Nemkova, None; C. A. Pilkington, None.
Conclusion: JSSc has a significant mortality particularly early on in the disease course. The objective of an aggressive screening program is to identify GI involvement at a stage which may be amenable to treatment. The recommendations developed by this group aim to standardize care and improve outcomes in this rare disease.


Disclosure: I. Foeldvari, Novartis Pharma AG, Abbott, Chugai, Genzyme, 5; C. Pain, None; T. Constantin, None; E. Baldain, None; H. Lenhardt, None; M. Blakley, None; D. Nemikova, None; C. A. Pinkerton, None.

1324
Predictors of Disease Relapse in Juvenile Localized Scleroderma. Kathryn S. Torok1, Katherine Kurzinski2 and Christina Kelsey3. 1Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA, 2Univ of Pittsburgh Med Ctr, Pittsburgh, PA, 3University of Pittsburgh/UPMC, Pittsburgh, PA.

Background/Purpose: Localized scleroderma (LS) is an autoimmune disease characterized by inflammation of the skin and underlying tissue leading to tissue damage including atrophy, dyspigmentation, and fibrosis. More recent literature supports childhood-onset LS as a chronic relapsing condition which may cause significant physical and psychological disability into adulthood. Often, initial control of the disease is obtained using systemic therapy regimens including methotrexate (MTX) combined with a corticosteroid (CS). For unknown reasons, patients may exhibit a relapse of LS activity following a period of disease remission. This study was designed to evaluate the clinical characteristics of patients exhibiting LS flares after an initial disease response (inactive disease) to a standardized MTX and CS regimen with the goal of identifying predictors of LS activity relapse.

Methods: Pediatric-onset LS patients at a single scleroderma center with at least 2 years of follow-up and three or more clinical visits were included in the analysis. Clinical data, including patient demographics, laboratory parameters, and treatment regimens were evaluated. Flare of LS was defined as a relapse of disease activity from inactive disease, as determined by the modified Localized Scleroderma Severity Index (mLoSSI) and the Physician Global Assessment of Disease Activity. Chi-square and Fisher’s Exact tests were used to compare rates of categorical variables, and independent sample t-tests were used to compare continuous variables between groups (α< 0.05).

Results: Seventy-seven patients were followed for greater than two years and 33 patients (46%) were found to experience LS flare after an initial response to MTX and CS. Demographic and laboratory data are summarized in Table 1. Patients that flared were significantly older at age of onset and were more likely to be ANA positive. Unexpectedly, flare patients were less likely to have an extracutaneous manifestation (ECM).

Table 1. Patient characteristics

<table>
<thead>
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<th>Flare (n=33)</th>
<th>No Flare (n=42)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (74)</td>
<td>28 (62)</td>
</tr>
<tr>
<td>LS Subtype</td>
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<td></td>
</tr>
<tr>
<td>Circumscribed Superficial</td>
<td>10 (29)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Circumscribed Deep</td>
<td>4 (11)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Generalized M orphaea</td>
<td>6 (17)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Linear Trunk/Limb</td>
<td>20 (57)</td>
<td>22 (52)</td>
</tr>
<tr>
<td>Linear Face</td>
<td>3 (9)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Mixed Nodule</td>
<td>6 (17)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Pansclerotic M orphaea</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Esophagitis + Fasciitis</td>
<td></td>
<td></td>
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<tr>
<td>Age Onset (years), mean (SD)</td>
<td>10.0 (3.9)</td>
<td>6.7 (3.7)</td>
</tr>
<tr>
<td>Time Onset to Diagnosis (mos), mean (SD)</td>
<td>13.8 (18.5)</td>
<td>22.4 (31.4)</td>
</tr>
<tr>
<td>Follow-up Duration (years), mean (SD)</td>
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<td>4.9 (2.8)</td>
</tr>
<tr>
<td>Laboratory Evaluation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA Positive</td>
<td>18/30 (60)</td>
<td>8/33 (24)</td>
</tr>
<tr>
<td>ssDNA Positive</td>
<td>13/32 (41)</td>
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<tr>
<td>AHA Positive</td>
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</tr>
<tr>
<td>CKP Elevated</td>
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<td>8/37 (22)</td>
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Disclosures: K. S. Torok, None; K. Kurzinski, None; C. Kelsey, None.

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Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE): Evidence Based Recommendations for Diagnosis and Treatment of Juvenile Localized Scleroderma and Juvenile Systemic Sclerosis. Bas Vastert1, Roberta Culpo2, Jordi Anton1, Tadej Avcin3, Eileen Baldain3, Christina Boros4, Tamás Constantin5, Jeff Chaitow6, Pavela Dolezalova7, Ozgur Kasapcopur8, Sheila Oliveira9, Clarissa Pilkington10, Annet van Reenen-Kerkhof11, Ricardo A. C. Russo12, Claudia Saad-Magalhães13, Natasa Toplak14, Angelo Ravelli15, Nico Wulfraat16, Ivan Foeldvari17 and Francisco Zulian18. 1University Medical Center Utrecht, Utrecht, Netherlands, 2University of Padua, Padua, Italy, 3Pediatric Rheumatology Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain, 4University Children’s Hospital, Ljubljana, Slovenia, 5Alder Hey Children’s Foundation NHS Trust, Liverpool, United Kingdom, 6University of Adelaide, Adelaide, Australia, 7University Children’s Hospital, Budapest, Hungary, 8The Children’s Hospital Westmead, Sydney, Australia, 9Charles University, Prague, Czech Republic, 10University Cerrahpasa Faculty of Medicine, Istanbul, Turkey, 11Universidade F Rijo De Janeiro, Rio De Janeiro, Brazil, 12Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, 13University Medical Center Utrecht - Wilhelmina Children’s Hospital, Utrecht, Netherlands, 14Hospital de Pediatría Garrahan, Buenos Aires, Argentina, 15Facultad de Medicienda de Botucatu, Botucatu, Brazil, 16University Medical Center, Ljubljana, Slovenia, 17Istituto Giannina Gaslini and University of Genova, Genoa, Italy, 18Wilhelmina Children’s Hospital/ UMC Utrecht, Utrecht, Netherlands, 19Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany.

Background/Purpose: Juvenile Localized Scleroderma (JLS) and Juvenile Systemic Sclerosis (JSSc) form a group of rare pediatric diseases that can lead to significant morbidity. Evidence-based guidelines are sparse and management is mostly based on physician’s experience. In 2012, a European initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Purpose: to provide evidence based recommendations for diagnosis and treatment of Juvenile Localized Scleroderma.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric rheumatologists and experts in Juvenile Scleroderma. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement during the online survey were reformulated. Subsequently, all
recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

**Results:** The literature search yielded 1550 articles for JLS and 8562 for JSSc, of which 52 and 37, respectively (25 for diagnosis and 27 for treatment of JLS, 21 for diagnosis and 16 for treatment of JSSc) were considered relevant and therefore scored for validity and level of evidence. 42 articles (15 for diagnosis and 14 for treatment of JLS, 6 for diagnosis and 7 for treatment of JSSc) were scored valid and used in the formulation of the recommendations. Eleven recommendations for diagnosis and 7 for treatment were suggested on the online survey on JLS. Ten recommendations for diagnosis and 6 for treatment were accepted with more than 80% agreement after the consensus meeting. Six recommendations for diagnosis and 5 for treatment were suggested in the online survey on JSSc. Six recommendations for diagnosis and 4 for treatment were accepted with more than 80% agreement after the consensus meeting. Topics covered for diagnosis and for treatment are shown in Table 1.

**Table 1: Diagnosis and Treatment for JLS and JSSc**

<table>
<thead>
<tr>
<th>Diagnosis/Assessment</th>
<th>JLS</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity assessment and response to therapy</td>
<td>Clinical scores</td>
<td>Topical treatment</td>
</tr>
<tr>
<td>Thermography</td>
<td>Ultrasound</td>
<td>Systemic treatment</td>
</tr>
<tr>
<td>Disease severity and damage assessment</td>
<td>Clinical scores</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Extra-cutaneous involvement</td>
<td>Clinical assessment</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>MRT</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Brain MRT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** The SHARE initiative provides recommendations for diagnosis and treatment for juvenile Scleroderma and thereby facilitates improvement and uniformity of care throughout Europe.

**Disclosure:** B. Vastert, None; R. Culo, None; J. Anton, None; T. Avrin, None; E. Baildam, None; C. Boros, None; T. Constanti, None; J. Chatow, None; P. Dolezalova, None; O. Kasapcopur, None; S. Oliveira, None; C. Pilkington, None; A. van Royen-Kerkhof, None; R. A. G. Russo, None; C. Saad-Maghales, None; N. Toplak, None; A. Ravelli, None; B. N. Wulffraat, None; I. Foedilvar, None; Pharma A.G. Abbott, Chugai, Genzyme, P. Zulian, None.

**1326**

**Transition of Care and Long-Term Outcomes of Juvenile Systemic Sclerosis during Adulthood: Results from a French Single-Center Case-Control Study.** François-Xavier Mauvais, Brigitte Bader-Meurin, Alize Berenne, Guillaume Busson, Christèle Bodemer, Loïc Guillevin, Pierre Quartier, and Luc Mouton.

**Methods:** In the juvenile SSc group, 10/20 (80%) for female and 11/20 (55%) presented a diffuse SSc. Mean age for diagnosis was 11.9 years (5.1–15.9). One patient had anti-centromere, 4/20 (20%) anti-Scl70 and 11/20 (55%) presented a diffuse SSc. Mean age for diagnosis was 11.9 years (5.1–15.9). One patient had anti-centromere, 4/20 (20%) anti-Scl70 and 11/20 (55%) presented a diffuse SSc.

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**1327**

**Decreased CD3-CD16CD56+ Natural Killer Cell Counts Are Associated with Disease Activity in Children with Orbital Myositids.** Melissa R. Bussey, Gabrielle A. M.organ, Maria C. A. Amoroso, Bahram Rahmani, and Lauren M. Pachman.

**Methods:** After obtaining IRB approval, a retrospective review was performed of all patients with a diagnosis of OM presenting between 2006 and 2012 to the Cure-JM Program of Excellence of The Ann and Robert H. Lurie Children’s Hospital of Chicago. Duration of untreated disease (DUD) was defined as the time, in months, from onset of symptoms to the date of the first medication. Data for muscle enzymes, neopterin, and absolute level of CD3-CD56/16+ natural killer cells (NK) via flow cytometry were determined using standard methods in the Diagnostic Immunology Laboratory. In addition, frozen sera were tested for immunoglobulin G (IgG) levels.

**Results:** Of the 4 cases, 2 were female and all were Caucasian; the mean age of onset of the first symptom was 14.4 ± 1.2 years, and the mean DUD was 0.28 ± 0.26 months. One child was seen after diagnosis, treatment, and resolution of disease. At diagnosis/first visit of the 3 active children, muscle enzyme tests were performed and the results are as follows (n = 3 except where noted): CPK: 97.3 ± 44.2, aldolase: 8.5 ± 2.8 (n = 2), ALT: 13 ± 2.8 (n = 2), AST: 21 ± 3.9, LDH: 176 ± 52.4. Their mean WBC was 10.4 ± 1.3 (n = 2), mean ESR 6 ± 4, mean neutrophil 63 ± 0.14 (n = 2); mean Von Willebrand Factor Antibodies: 133 ± 141 (n = 2). The mean for IgG1 was 87.7 ± 66 (normal range=8–89 mg/dl). The mean NK was 96.7 ± 27.8 at diagnosis/first visit of the 3 active subjects (lower limit of normal = 138) which increased to normal range 163 ± 57.2 with resolution of active disease. Computed tomography studies with contrast document involvement of left superior oblique, right superior oblique, left medial rectus, left lateral rectus, and right lateral rectus muscles in all 4 children. Only 1 child had multiple orbital muscles involved simultaneously. Treatment was initiated with high dose intravenous pulse methylprednisolone supplemented by daily oral prednisone (0.5 mg/kg) on non-IV days as well as methotrexate (n = 2) and other steroid-sparing agents.

**Conclusion:** The SHARE initiative provides recommendations for diagnosis and treatment for juvenile Scleroderma and thereby facilitates improvement and uniformity of care throughout Europe.

**Disclosure:** B. Vastert, None; R. Culo, None; J. Anton, None; T. Avrin, None; E. Baildam, None; C. Boros, None; T. Constanti, None; J. Chatow, None; P. Dolezalova, None; O. Kasapcopur, None; S. Oliveira, None; C. Pilkington, None; A. van Royen-Kerkhof, None; R. A. G. Russo, None; C. Saad-Maghales, None; N. Toplak, None; A. Ravelli, None; B. N. Wulffraat, None; I. Foedilvar, None; Pharma A.G. Abbott, Chugai, Genzyme, P. Zulian, None.

**Background/Purpose:** Orbital myositid (OM), an inflammatory disease affecting the extra-ocular muscles, typically presents in the third decade. It more commonly affects females and is extremely rare in children. Pediatric orbital inflammatory disorders account for 6–17% of the total orbital inflammatory disorders and OM specifically makes up about 8% of pediatric orbital inflammatory disease. Because of the rarity of pediatric OM, many questions remain unanswered and specific laboratory markers of disease activity have not yet been identified, often resulting in a protracted course.

**Methods:** After obtaining IRB approval, a retrospective review was performed of all patients with a diagnosis of OM presenting between 2006 and 2012 to the Cure-JM Program of Excellence of The Ann and Robert H. Lurie Children’s Hospital of Chicago. Duration of untreated disease (DUD) was defined as the time, in months, from onset of symptoms to the date of the first medication. Data for muscle enzymes, neopterin, and absolute level of CD3-CD56/16+ natural killer cells (NK) via flow cytometry were determined using standard methods in the Diagnostic Immunology Laboratory. In addition, frozen sera were tested for immunoglobulin G (IgG) levels.

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Conclusion: OM does occur in children and disease activity was not associated with creatine kinase, aldolase, neopterin, sedimentation rate, or C reactive protein values, which typically remained within normal range. In contrast, initially decreased absolute NK trended toward normal ranges as the inflammation improved. We speculate that this lymphocyte subset may contribute to the inflammatory myopathy.

Disclosure: M. R. Bussey, None; G. A. Morgan, None; M. C. Amoruso, None; B. Rahmani, None; L. M. Pachman, None.

1328

Modulation of Natural IgM-Autoantibodies to Oxidative Stress-Related Neo-epitopes on Apoptotic Cells in Newborns of Mothers with Anti-Ro Autoimmunity. Caroline Grönwall1, Robert M. Clancy1, Lelise Getu2, Don L. Siegel2, Joanne Reed3, Jili P. Buyon4 and Gregg J. Silverman1.

1New York University School of Medicine, New York, NY; 2Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background/Purpose: At birth, the human immune system expresses substantial circulating levels of polymeric IgM that include autoantibodies to oxidation-associated epitopes on apoptotic cells. This study addressed whether the neonatal IgM-repertoire may be affected by exposure to anti-Ro/La IgG-autoantibodies of maternal origin, which in some offspring leads to development of neonatal lupus.

Methods: Levels of IgM-specificities were compared in 43 healthy adults, and in umbilical cord blood (CB) from 31 unaffected newborns of non-autoimmune mothers and 103 newborns of mothers from the Research Registry for Neonatal Lupus. All mothers enrolled in the Registry have anti-Ro (Ro60 and/or Ro52). In this cohort, 56 fetuses developed cardiac neonatal lupus, 4 neonates had rash, while 40 were clinically unaffected. Sandwich ELISA used phosphorylcholine (PC16):BSA, malondialdehyde (MDA):BSA or Ro60, with anti-IgM detection.

Results: IgM-antibodies to oxidation-associated MDA-determinants were relatively more highly represented in control newborns compared to adults (IgM anti-MDA/total IgM 7.2 ±3.6 vs 1.7 ±1.0; p=0.001). CB levels of IgM anti-MDA directly correlated with IgM binding to apoptotic cells. In neonates exposed to IgG anti-Ro, total IgM and IgM anti-Ro60 were significantly elevated compared to control neonates (41.39 RU/ml vs 27.16, p=0.008; 218.230 RU/ml vs 129.115 RU/ml, p=0.003, respectively). Similarly, the ratio of IgM anti-Ro60 was higher in these newborns compared to controls (8.6 ±9.6 vs 5.0 ±2.8, p=0.001). No correlation between IgM and IgG anti-Ro60 or RF IgM in CB could be detected. In contrast, the proportion of IgM anti-MDA was significantly lower in CB from neonates exposed to IgG anti-Ro60 mothers compared to controls (4.8 ±4.7 vs 7.2 ±3.6, p=0.004). Neither the development of heart block, nor the disease status of the mothers, was associated with differences in neonatal IgM levels.

Conclusion: These findings document the relative dominance in the neonate of specificities of IgM-autoantibodies to oxidation-associated neo-determinants associated with protective properties in other settings. These data suggest that early immune development of the natural IgM-repertoire may become imprinted by maternally transferred anti-Ro60 IgG-autoantibodies.

Disclosure: C. Grönwall, None; R. M. Clancy, None; L. Getu, None; D. L. Siegel, None; J. Reed, None; J. P. Buyon, None; G. J. Silverman, None.

1329

Comparison of Clinical and Serological Features of Childhood Sjögren Syndrome Based on the Presence or Absence of Parotitis. Jay Mehta1, Namrata Singh2 and Scott Lieberman3.

1Children’s Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, NY; 2University of Iowa, Iowa City, IA; 3University of Iowa Children’s Hospital, Iowa City, IA.

Background/Purpose: Sjögren syndrome is a complex autoimmune disease that affects lacrimal and salivary glands with the potential to cause damage to other organs. Diagnosis of childhood Sjögren syndrome (cSS) is currently based on expert opinion due to the lack of childhood specific diagnostic criteria. Children do not typically present with sicca symptoms characteristic of adult Sjögren syndrome. While they most commonly present with recurrent parotitis, some children present with other organ involvement in the absence of parotitis. The goal of this study was to compare clinical and serological profiles of cSS patients presenting with or without parotitis as a first step towards defining cSS diagnostic criteria.

Methods: We reviewed cSS cases from a single center as well as those in the published English literature with individual patient data. We collected available data on sicca symptoms, serologies (ANA, anti-SSA/B, RF), lacrimal and salivary gland function, imaging, and histopathology as well as extraglandular clinical features. For analyses of laboratory, serologic, imaging, pathology, and functional data, cases were excluded if specific data were not explicitly reported.

Results: We reviewed 26 cases of cSS diagnosed and followed at The Children’s Hospital of Philadelphia and 196 cases in the literature that contained information on individual children. Parotitis status was clearly indicated for 162 cases which were considered further. Parotitis was a main feature in presentation in 131 (81%) cases. Comparing the cases with parotitis (n=131) to those without (n=31), there were no differences in sex (78% vs 87% females, respectively, p=0.448) or positive serologies: 87% and 90% ANA +, respectively (p=0.768), 72% and 63% RF + (p=0.405), 86% and 90% SSA + (p=0.761), 69% and 64% SSb + (p=0.649). 53% of children had sicca symptoms regardless of parotitis status (p=1). A mong extrav glandular features, children without parotitis developed more joint symptoms (58% vs 33%, p=0.012), CNS symptoms (32% vs 7%, p=0.0003), Raynaud Phenomenon (16% vs 5%, p=0.048), and renal tubular acidosis (16% vs 4%, p=0.032). Non-significant extraglandular features included fever, rash, lymphadenopathy, fatigue, other renal manifestations, myositis, vaginal dryness, serositis, and transaminitis.

Conclusion: While the majority of childhood Sjögren syndrome (cSS) patients have parotitis, a significant percentage do not. Those who do not differ in their clinical features, with a significantly higher incidence of joint symptoms, RF, renal tubular acidosis, neuroimyelitis optica, and all CNS manifestations. A large majority of all cSS patients have positive ANA and/or anti-SSA/B, and the serologic profiles do not significantly differ based on parotitis status. Thus, testing for ANA and anti-SSA/B is warranted in the diagnostic workup of any child suspected of having Sjögren syndrome, especially in patients who do not present with parotitis. Given the selection bias inherent in this approach, development of cSS-specific diagnostic criteria are needed for future prospective studies to better characterize the prognosis and optimal therapies for this potentially devastating disease.

Disclosure: J. Mehta, None; N. Singh, None; S. Lieberman, None.

ACR/ArHP Poster Session B Pediatrics (ArHP) Monday, November 17, 2014, 8:30 AM-4:00 PM

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The efficacy of a multidisciplinary intervention strategy for the treatment of Benign Joint Hypermobility Syndrome (B)HS) in childhood. a Randomised, Single Centre Parallel Group Trial. Peter Bates1, Vicky Holman1, Holly Bacon2, Emma Jerman3, Kate Armstrong4 and Alex J Magrnie5.

1University of East Anglia, Norwich, United Kingdom; 2Norfolk and Norwich University Hospital, Norwich, United Kingdom; 3Occupational Therapist, Norwich, United Kingdom.

Background/Purpose: Joint hypermobility is common in childhood and can be associated with musculoskeletal pain and dysfunction. Current management is delivered by a multidisciplinary team but evidence of efficacy is limited. This clinical trial aimed to determine whether a structured multidisciplinary intervention resulted in improved clinical outcomes compared with standard care.

Methods: A prospective randomised, single centre parallel group trial comparing an 8-week individualised multidisciplinary intervention programme with current standard management (advise and a physiotherapy appointment). Children and young people (CYP) were assessed for pain, function, coordination and strength. However, no added benefit could be shown from the intervention (Table 1). The number of CYP showing significant pain reduction (≥ 40%) was 27 (50.0%) (I) vs 21 (41.1%) (S). Those pain free at 12 months were 29 (56.9%) (I) vs 20 (45.5%) (S). The response was independent of the degree of hypermobility.

Disclosure: P. Bates, None; V. Holman, None; H. Bacon, None; E. Jerman, None; K. Armstrong, None; A. J Magrnie, None.

1258
Conclusion: This is the first RCT to compare a structured multidisciplinary intervention with standard care in symptomatic childhood hypermobility. The study demonstrates significant improvement among subjects but no additional benefit from targeted intervention. The findings emphasise the benefit of information and physiotherapy, but highlight the difficulty in demonstrating subtle benefit from specific interventions without better tools for case definition and outcomes assessment.

Table 1. The rate of change in primary and secondary outcomes over 12 month follow-up period, this data includes analysis from multi-level modelling.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Baseline (SD)</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child pain assessment ( Wong-Baker Faces pain scale, 0-3, zero is the best )</td>
<td>2.31 (1.55)</td>
<td>1.42 (-1.78 to -1.06)</td>
<td>1.31 (-1.75 to -0.85)</td>
</tr>
<tr>
<td>Parent observed pain assessment ( VAS, zero is the best )</td>
<td>35.90 (26.46)</td>
<td>6.09 (12.90 to 0.73)</td>
<td>6.22 (-13.62 to 1.13)</td>
</tr>
<tr>
<td>Child health questionnaire (CHQ-1) (0-3, zero is the best )</td>
<td>0.82 (0.63)</td>
<td>0.02 (-0.12 to 0.14)</td>
<td>0.03 (-0.12 to 0.04)</td>
</tr>
<tr>
<td>Child health # of days sick (CHQ-1) (0-14, zero is the best )</td>
<td>0.85 (0.11)</td>
<td>0.02 (-0.01 to 0.04)</td>
<td>0.002 (-0.02 to 0.03)</td>
</tr>
<tr>
<td>Moemount of pain assessment battery for children (WASCO-D, zero is the world n = 104)</td>
<td>34.56 (28.61)</td>
<td>2.60 (-2.82 to 1.11)</td>
<td>2.61 (2.57 to 2.66)</td>
</tr>
<tr>
<td>Grip Strength (Newton) = 104</td>
<td>57.29 (28.30)</td>
<td>4.55 (0.16 to 8.94)</td>
<td>6.75 (2.85 to 10.66)</td>
</tr>
</tbody>
</table>

Disclosure: P. Bale, None; V. Easton, None; H. Bacon, None; E. Jerman, None; K. Armon, None; A. J. Macgregor, None.

1331
Factors Associated with Pain in Children with Hypermobility - a Pilot Study, Susan Maillard1, Clarissa Pilkington1, Richard Howard1, Christine Liossi1 and Suellen Walker2.

Background/Purpose: The rate of change over 12 months (95% CI)

<table>
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Disclosure: P. Bale, None; V. Easton, None; H. Bacon, None; E. Jerman, None; K. Armon, None; A. J. Macgregor, None.

1332
From Social Support to Information Sharing, How Are Persons with Rheumatoid Arthritis Using Disease-Specific Facebook Communities? A Content Analysis. Cheryl Crow and Kristin Jones. Samuel Merritt University, Oakland, CA.

Background/Purpose: High perceived social support is associated with better quality of life and lower rates of depression for persons with rheumatoid arthritis (Minnock, et al 2003 and Zyrianova, et al, 2006), yet pain, fatigue and the invisible nature of the disease can lead to social isolation. Disease-specific Facebook communities have become thriving, accessible platforms for information sharing and social support. However, little is understood about the content of patient engagement on this medium.

Methods: The 4 largest patient-driven Facebook community pages devoted to rheumatoid arthritis were identified. Text from 10 sequential “wall posts” from May-June 2013 by members each community and ensuing discussion posts were thematically coded and aggregated into a database. Multiple codes were allowed for each post. Members self-identified as persons with rheumatoid arthritis, loved ones, caregivers, or did not specify. Providing advice, sharing a personal story and providing support were predominant themes. Content coded as “providing advice” and “personal story” was further categorized based on areas of occupation according to the Occupational Therapy Practice Framework. Patient-provider interactions were coded under “Health Management and Maintenance” and then further sub-categorized to be of relevance to rheumatology professionals.

Results: 1066 posts were thematically coded. In 73% of posts, information was provided (44% of which involved a personal story, 29% of which involved advice). In 20% of posts, support was provided. Instrumental activities of daily living (such as home, medical and financial management) were the most frequently discussed topics. Health management was the most frequently discussed instrumental activity of daily living (which included pain management, medication management, nutrition and fitness, and patient-provider interactions).

Conclusion: Participants primarily use rheumatoid arthritis-specific Facebook pages to share stories, advice and support about health management and maintenance. While this medium allows for many potential positive effects such as increased social support and the sharing of effective daily living strategies, potential drawbacks include frequent medical advice given by individuals with unknown qualifications. It would behoove healthcare professionals to understand and address the role of this medium in social participation for their clients.

Disclosure: C. Crow, None; K. Jones, None.

1333

Background/Purpose: Social support is instrumental in the mental and physical well-being of people with systemic lupus erythematosus (SLE). Research has demonstrated that strengthening social ties can potentially reduce the negative influences of biology, genetics and environment. For instance, positive social integration has been found to be associated with both reduced mortality and improved health outcomes in people with SLE. This study assessed the social support needs among a socioeconomically disadvantaged cohort of African American women with SLE and investigated the ways in which a low-cost high-impact chronic disease self-management program (CDSMP) met these needs.

Methods: Participants were validated SLE patients receiving care at a lupus clinic at a public hospital. Qualitative data were gathered via focus groups with 27 of the 45 participants who completed the CDSMP, and with one-on-one interviews with two CDSMP leaders. The purport of focus groups and interviews was to gain insight into the acceptability of the CDSMP and the relevance and usefulness of its components. In addition, we surveyed
participants regarding the number of close relatives and friends, and CDMP satisfaction.

Thematic analysis methods were used to analyze qualitative data; codes were developed using the data and the study’s theoretical framework, including Cohen’s definitions of social relationships and resources. Descriptive statistics were used to analyze survey data. Data sources and methodologies were triangulated.

**Results:** Six key themes emerged that depicted the types of social support needs: mental health (stress, depression, coping), personal empowerment (motivation), person-centered (care, “self-love”), interpersonal relationships, communication, and physical health (exercise, nutrition, pain management, stress). Survey data showed an average CDMP satisfaction score of 4.8 (range 4 [agree] to 5 [strongly agree]). The most frequent memorable program opportunities were being involved personally, social support, and interpersonal interactions, respectively. There was no significant change in the number of close relatives and friends before and after the program. The emotion- and problem-focused channels of the CDMP offered the supportive resources to satisfy participant needs. The data and methodological triangulation demonstrated a consistency across data sources and approaches.

**Conclusion:** This qualitative study provided a greater understanding of the role of social support among African American women with SLE and the ways in which the CDMP might help develop, enhance and utilize social support resources. Healthy social relationships were found to have significant impact in SLE women’s ability to cope with stress and self-manage this disease. The influences of stress were revealed in both the mental health and physical health themes. The CDMP offered the resources needed to enhance resilience, healthy behaviors, and overall well-being.

**Disclosure:** C. M. Dunlop-Thomas, NIH, 2; GlaxoSmithKline, line 2; H. Cooper, None; T. Barham, None; C. M. Drenkard, NIH, 2; GlaxoSmithKline, line 2.

**1334**

Social Support and Suicidal Ideation in Systemic Lupus Erythematosus: Georgians Organized Against Lupus Cohort. Charmayne M. Dunlop-Thomas, Gasbin Bao, S. Sam Lim and Cristina M. Drenkard. Emory University, Atlanta, GA. Emory University School of Medicine, Division of Rheumatology, Atlanta, GA.

**Background/Purpose:** Social support (SS) is instrumental in the mental and physical well-being of people with systemic lupus erythematosus (SLE). Moreover, SS contributes to overall health by providing a buffer from the adverse effects of stress. This is especially salient for people with SLE who may experience a wide-range of physical and psychological disease stressors. These stressors combined with other risk factors can contribute to suicidal ideation (SI). We examined the impact of perceived social support on suicidal ideation in SLE patients from the Georgians Organized Against Lupus (GOAL) Cohort.

**Methods:** We examined cross-sectional data from the GOAL Cohort, a large population-based cohort of validated SLE patients from metropolitan Atlanta, Georgia. GOAL participants responded to a variety of validated self-administered health outcomes. The Systemic Lupus Aactivity Questionnaire assessed disease activity. The Patient Health Questionnaire-9 assessed depression severity, including the presence and duration of SI during the preceding two weeks. The emotional support question from the Behavioral Risk Factor Surveillance System assessed the perceived adequateness of SS received. Those who responded positively for SI were further contacted, provided with depression management resources, and probed for current SS resources. Logistic regression was used to examine the factors associated with SI.

**Results:** Of 600 SLE patients studied (93.3% women, mean age 48.8 [SD 12.8], 78.3% Black, mean disease duration 16 years [SD 12.8], 78.3% Black, mean disease duration 16 years [SD 12.8], and 68% uninsured), the average PHQ-9 score was 7.8 (SD 6.2), indicating mild to moderate depression. SI was present in 67 (11%) of GOAL participants. Logistic regression was used to examine the factors associated with SS. After controlling for other risk factors, such as socio-demographics and disease status, those with perceived inadequate social support, living in poverty, or with greater disease activity were at higher risk for SI. Further development and recognition of SS resources to which SLE patients can be referred are warranted, especially in socioeconomically disadvantaged communities.

**Disclosure:** C. M. Dunlop-Thomas, NIH, 2; GlaxoSmithKline, line 2; G. Bao, GlaxoSmithKline, line 2; S. S. Lim, NIH, 2; GlaxoSmithKline, line 2, Emory University, 3; C. M. Drenkard, NIH, 2; GlaxoSmithKline, line 2.
Conclusion: In contrast to the general population, RA patients with an evening preference did not report worse emotional health or higher pain and fatigue, compared to intermediate or morning chronotypes. RA patients with evening chronotypes did report sleeping more hours than subjects with morning or intermediate chronotypes, despite similar sleep adequacy scores. Additional studies are needed to determine whether morning/evening preference can be used to identify subgroups of RA patients at increased risk for sleep problems. Table 1. Adjusted mean values for sleep, fatigue, pain and emotional well-being among RA patients with clinically significant sleep problems.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Morning* (N = 43)</th>
<th>Intermediate* (N = 81)</th>
<th>Evening 7:16 (p&lt;0.51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Quantity (hours)</td>
<td>6.4 (p = 0.26)</td>
<td>6.1 (p = 0.01)</td>
<td>6.8</td>
</tr>
<tr>
<td>Sleep Adequacy (0-100 scale, higher = better sleep adequacy)</td>
<td>41.9 (p = 0.11)</td>
<td>37.1 (p = 0.49)</td>
<td>34.5</td>
</tr>
<tr>
<td>Somnolence Scale (0-100 scale, higher = more somnolence)</td>
<td>28.9 (p = 0.25)</td>
<td>31.8 (p = 0.51)</td>
<td>34.4</td>
</tr>
<tr>
<td>Sleep Disturbance Scale (0-100 scale, higher = more disturbance)</td>
<td>45.0 (p = 0.86)</td>
<td>48.5 (p = 0.52)</td>
<td>45.8</td>
</tr>
<tr>
<td>MDHAQ Fatigue Scale (0-100 scale, higher = more fatigue)</td>
<td>53.6 (p = 0.93)</td>
<td>52.2 (p = 0.87)</td>
<td>53.0</td>
</tr>
<tr>
<td>MDHAQ Pain Scale (0-100 scale, higher = more pain)</td>
<td>40.6 (p = 0.60)</td>
<td>39.7 (p = 0.65)</td>
<td>37.5</td>
</tr>
<tr>
<td>Mental Health Index - 5 (0-100 scale, higher = better mental well-being)</td>
<td>77.3 (p = 0.07)</td>
<td>71.6 (p = 0.51)</td>
<td>69.3</td>
</tr>
</tbody>
</table>

*p-values are for comparison between morning chronotypes and evening chronotypes and the comparison between intermediate chronotypes and evening chronotypes.

Disclosure: A. Wolfsahl, None; J. Culi, None; M. A. Frits, None; C. K. Iannaccione, None; J. S. Coblyn, CVS Caremark, 3; M. E. Weinblatt, UCB, 2, Bristol-Myers Squibb, 2, Crescendo, 2, Amgen, 2, UCB, 2, Abbvie, 2, Bristol-Myers Squibb, 2, Genentech, 2; Y. C. Lee, Forest Research Institute, 2, Merck Pharmaceuticals, 1, Cubist Pharmaceuticals, 1, Perrigo, 1, Express Scripts, 1.

1336

Associations of Physical and Mental Factors with Outcome Expectations for Exercise in a Clinical Trial. ShaoYu Chang, Lori Lyn Price, Jeffrey Driban, William F. Harvey and Chenchen Wang. Tufts Medical Center, Boston, MA.

Background/Purpose: In exercise intervention trials, higher outcome expectancy can predict stronger adherence. Such expectancy is known to be associated with gender, age, marital status, physical and mental health, and self-efficacy. However, it remains unclear whether specific disease conditions may help discriminate high expectancy individuals from those with moderate or lower expectancy participants for clinical trials. This study aimed to explore whether physical and mental health factors are associated with outcome expectations for exercise among patients with knee osteoarthritis (KOA) participating a large clinical trial.

Methods: We conducted a secondary analysis of baseline data from a randomized clinical trial comparing Tai Chi to aerobic exercise in fibromyalgia patients as defined by the ACR criteria. At their baseline evaluation, they completed the PROMIS Pain Impact Short Form (PROMIS pain), Symptom Severity Scale, and the revised Fibromyalgia Impact Questionnaire (FIQR). We calculated Pearson’s correlation coefficients to assess associations between mindfulness and measures of fibromyalgia pain impact and symptom severity. We determined an overall mindfulness score by calculating a mean of the five facets of mindfulness (observing, describing, acting with awareness, non-judging, and non-reacting) in order to explore higher levels of mindfulness.

Results: Our analysis included data from rounds 1–4 (160 participants) with a mean age of 51.9 (SD = 12.2) years; 92% women, mean BMI 29.5 kg/m²; and 83% completed at least some college. Higher global mindfulness scores were associated with lower symptom severity and pain intensity as measured by the PROMIS Pain Impact, Symptom Severity, and FIQR (see Table). These relationships were also significant for most of the sub-facets of mindfulness with the exceptions of observing and non-reacting.

BMI. We found that Beck II score and self-efficacy were significantly associated with OES.

Conclusion: The participants with worse depression symptoms and lower confidence in coping chronic pain tended to have lower outcome expectations. We observed trends that more severe self-reported symptoms and worse radiographic KOA severity were associated with higher outcome expectancy, although the statistical tests failed to reach significance. Such relationship may be confirmed by a larger sample size. Our results showed that in the clinical trials settings, high outcome expectancy populations may be identified through physical and psychological measurements, though further research is needed to determine their predictive ability.

Table 1. Odds ratios for high outcome expectations (OES = 4) by physical and psychological parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertile</th>
<th>OR (95% CI)</th>
<th>Global p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC Pain</td>
<td>Best</td>
<td>Reference</td>
<td>0.2328</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.57</td>
<td>(0.78, 3.14)</td>
<td>0.2037</td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>1.83</td>
<td>(0.88, 3.80)</td>
<td>0.1042</td>
<td></td>
</tr>
<tr>
<td>WOMAC Function</td>
<td>Best</td>
<td>Reference</td>
<td>0.9788</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.00</td>
<td>(0.50, 2.01)</td>
<td>0.9998</td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>0.94</td>
<td>(0.46, 1.92)</td>
<td>0.8581</td>
<td></td>
</tr>
<tr>
<td>BECK II</td>
<td>Best</td>
<td>Reference</td>
<td>0.0462</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>0.57</td>
<td>(0.30, 1.10)</td>
<td>0.0920</td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>0.43</td>
<td>(0.22, 0.85)</td>
<td>0.0347</td>
<td></td>
</tr>
<tr>
<td>ANXIETY</td>
<td>Best</td>
<td>Reference</td>
<td>0.3908</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.52</td>
<td>(0.80, 2.90)</td>
<td>0.2044</td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>1.46</td>
<td>(0.75, 2.85)</td>
<td>0.2649</td>
<td></td>
</tr>
<tr>
<td>Keligren-Lawrence (K L)</td>
<td>0-2</td>
<td>Reference</td>
<td>0.1469</td>
<td></td>
</tr>
<tr>
<td>(collapsed)</td>
<td>3</td>
<td>1.62</td>
<td>(0.87, 3.00)</td>
<td>0.6807</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.01</td>
<td>(0.89, 4.56)</td>
<td>0.2416</td>
</tr>
<tr>
<td>Self Efficacy</td>
<td>Worst</td>
<td>Reference</td>
<td>0.0464</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.83</td>
<td>(0.97, 3.45)</td>
<td>0.0605</td>
<td></td>
</tr>
<tr>
<td>Best</td>
<td>2.22</td>
<td>(1.14, 4.34)</td>
<td>0.0193</td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: S. Chang, None; L. L. Price, None; J. Driban, None; W. F. Harvey, None; C. Wang, None.

1337

Mindfulness Is Associated with Symptom Severity and Pain Impact in Patients with Fibromyalgia. Emily Wolcott, William F. Harvey, Lori Lyn Price, Jeffrey Driban, Nani Morgan, Lucas Morgan and Chenchen Wang. Tufts Medical Center, Boston, MA; University of Hawaii, Honolulu, HI.

Background/Purpose: Mindfulness is attention to and awareness of present experiences (e.g., physical sensations, emotions, thoughts) in a nonjudgmental way. Initial evidence suggests that increased mindfulness may be associated with less pain intensity and catastrophizing among some people with chronic pain. However, this has not been confirmed among people with fibromyalgia. We evaluated whether greater mindfulness is associated with less pain and severity of associated symptoms in people with fibromyalgia.

Methods: We performed a secondary analysis of baseline data from a randomized clinical trial comparing Tai Chi to aerobic exercise in fibromyalgia patients as defined by the ACR criteria. At their baseline evaluation, subjects completed the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item, self-report questionnaire that measures five facets of mindfulness: observing, describing, acting with awareness, non-judging, and non-reacting to inner experience. Higher scores in each facet indicate higher levels of mindfulness. Subjects also completed validated symptom measures including the PROMIS Pain Impact Short Form (PROMIS pain), Symptom Severity Scale, and the revised Fibromyalgia Impact Questionnaire (FIQR). We calculated Pearson’s correlation coefficients to assess associations between mindfulness and measures of fibromyalgia pain impact and symptom severity. We determined an overall mindfulness score by calculating a mean of the five facets for each participant. We also conducted a multivariate regression analysis to control for age, gender, body mass index, and education.

Results: Our analysis included data from rounds 1–4 (160 participants) with a mean age of 51.9 (SD = 12.2) years; 92% women, mean BMI 29.5 kg/m²; and 83% completed at least some college. Higher global mindfulness scores were associated with lower symptom severity and pain intensity as measured by the PROMIS Pain Impact, Symptom Severity, and FIQR (see Table). These relationships were also significant for most of the sub-facets of mindfulness with the exceptions of observing and non-reacting.

M mindfulness...
remained independently associated with PROMIS pain, Symptom Severity, and FIQR after adjusting for confounders.

**Conclusion:** Our results suggest that greater mindfulness is associated with less pain impact and severity of associated symptoms in people with fibromyalgia. Thus, mindfulness-based interventions may have the potential to improve the way those with fibromyalgia relate to their symptoms, by increasing non-judgmental acceptance of their experience, resulting in a reduction of their perception of pain intensity. Longitudinal studies are in progress to assess whether the cultivation of mindfulness alters the severity and prevalence of associated symptoms and experience of pain in people with fibromyalgia amongst those with other chronic pain disorders.

**Table 1:** Association between the Facets of Mindfulness and Measures of Symptom Severity and Pain Impact

<table>
<thead>
<tr>
<th>FFMQ Variable (range: m.s.s)</th>
<th>PROMIS Pain (r-p-value)</th>
<th>Symptom Severity (r-p-value)</th>
<th>FIQR (r-p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFMQ-Describing (15–40; 29.8±5.7)</td>
<td>.36 (&lt;0.001)</td>
<td>.32 (&lt;0.001)</td>
<td>.25 (&lt;0.001)</td>
</tr>
<tr>
<td>FFMQ-Observing (15–40; 27.7±8.2)</td>
<td>.09 (0.25)</td>
<td>.03 (0.75)</td>
<td>0.01 (0.95)</td>
</tr>
<tr>
<td>FFMQ-Non-judging (8–38; 24.5±4.9)</td>
<td>.32 (0.01)</td>
<td>.20 (0.014)</td>
<td>.18 (0.02)</td>
</tr>
<tr>
<td>FFMQ-Acknowledging (13–40; 21.5±5.1)</td>
<td>.28 (0.01)</td>
<td>.37 (0.01)</td>
<td>.24 (0.01)</td>
</tr>
<tr>
<td>FFMQ-Overall Mindfulness (16–56; 26.2±4.6)</td>
<td>.31 (0.01)</td>
<td>.33 (0.01)</td>
<td>.30 (0.001)</td>
</tr>
<tr>
<td>FFMQ-Non-reacting (9–35; 21.5±7.6)</td>
<td>.27 (0.01)</td>
<td>.16 (0.05)</td>
<td>0.14 (0.08)</td>
</tr>
</tbody>
</table>

Note: FFMQ = Five Facet Mindfulness Questionnaire. PROMIS = PROMIS Pain Impact Short Form. FIQR = revised Fibromyalgia Impact Questionnaire.

**Disclosure** E. Wolcott, None; W. F. Harvey, None; L. L. Price, None; J. B. Driban, None; N. Morgan, None; L. Morgan, None; C. Wang, None.

### 1338

**Correlates of Body Image Dissatisfaction in Patients with Limited and Diffuse Systemic Sclerosis**


**1SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, 2San Diego State University, San Diego, CA, 3University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 4University of Michigan Health System, Ann Arbor, MI.**

**Background/Purpose:** Little research has evaluated body image dissatisfaction (BID) in Systemic Sclerosis (SSc). What has been conducted shows that BID is common and associated with worse psychosocial functioning. Additionally, age, upper-body telangiectasias, fingertip-to-palm distance, and facial skin involvement have been shown to be associated with Dissatisfaction with Appearance and Social Discomfort, two components of BID. However, it remains unclear if these factors relate to BID in the same way across disease classification (i.e., limited versus diffuse disease). Because limited and diffuse patients may have very different physical disease manifestations, the current study aimed to determine if sociodemographic and medical correlates of BID differed for patients with limited versus diffuse SSc, and identify which variables related to the two components of BID for each disease classification.

**Methods:** Participants were adults participating in the UCLA Scleroderma Quality of Life Study with rheumatologist-diagnosed limited (n = 101) or diffuse (n = 82) SSc. The Brief-Satisfaction with Appearance Scale (Brief-SWAP), which is comprised of two subscales measuring Dissatisfaction with Appearance and Social Discomfort, evaluated BID. The present analysis 1) examined if the relationships of sociodemographic (i.e., age, gender, race, education, and marital status) and medical (i.e., disease duration, presence of telangiectasia, presence of hyper/hypo-pigmentation, and facial, hand/foot skin involvement) variables to the Brief-SWAP subscales were equivalent for limited and diffuse SSc, and 2) identified which of these variables were associated with each of the two Brief-SWAP subscales. Structural Equation Modeling evaluated both of these research questions. Both statistical and practical indicators of model fit were considered.

**Results:** There were similarities and differences in how sociodemographic and medical variables related to BID for limited versus diffuse SSc (S-B² [143] = 181.42, p = .02; RMSEA = .06, CFI = .91, SRMR = .06). Greater Dissatisfaction with Appearance was associated with younger age (b = -.02, SD = .01) and being unmarried (b = -.64, SE = .30) for limited patients, and with younger age (b = -.02, SE = .01) and increased finger/hand skin involvement (b = .69, SE = .15) for diffuse patients (p < .05). Greater Social Discomfort was associated with younger age (b = -.02, SE = .01) and being unmarried (b = -.46, SE = .22) for both subtypes (p < .05).

**Conclusion:** Both sociodemographic (i.e., age, marital status) and medical (i.e., finger/hand skin involvement) variables were related to BID. This is consistent with prior research and underscores the complex nature of BID in SSc. The present analysis suggests that young, unmarried patients may be at greatest risk for BID across disease subtypes. However, these factors may be more important for patients with limited disease, and finger/hand skin involvement may also be important for patients with diffuse disease. These findings can inform development of optimal, targeted interventions to diminish BID in SSc.

**Disclosure** R. S. Fox, Rheumatology Research Foundation; S. D. Mills, None; S. Gholidahi, None; E. L. Mertz, None; S. C. Roesch, None; P. J. Clements, None; S. Kafaja, None; D. K. Hannon, Actelion, Bayer, Biogen-Idec, BMS, DIGNA, Genentech/Roche, Gilead, InterMune, Merck, Sanofi-Aventis, United Therapeutics, 5, Patient Health Organization, 6, Scleroderma Foundation, 6; D. E. Hurst, Abbott, Actelion, Amgen, BMS, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB; 5, V. L. Malcangio, None.

### 1339

**Is Psychological Status Related to Symptom Experience in Behçet’s Syndrome?**

Robert Moots¹ and Sophie Campbell², 1University of Liverpool, Liverpool, United Kingdom, 2Aintree University Hospital, Liverpool, United Kingdom

**Background/Purpose:** Little is known about the impact of Behcet’s Syndrome (BS) within the UK. The recent establishment of National Centres of Excellence now allows a systematic and holistic investigation of both physical and psychological effects of BS. This study investigates the relationship between disease characteristics and psychological status reported by attendees at one Centre.

**Methods:** Psychological questionnaires measuring depression, anxiety, pain, fatigue and condition intrusion were sent to all patients with a diagnosis of BS and attending a Behcet’s Centre of Excellence (N = 106). A associations between psychological scores and responses from the Behcet’s Disease Activity Index (BDAI), a subjective measure of BS symptoms, were analysed using Spearman’s correlat.

**Results:** Response rate was 51%. A high proportion of patients scored above the clinical cut off for depression (88.9%) and anxiety (74.1%). High levels of pain, fatigue and condition intrusion were also recorded. Female patients reported higher scores on all measures. On average, 4 out of 12 active BS symptoms were reported.

Overall, whilst psychological scores and BDAI responses indicated statistically significant positive correlations, associations were only moderate or low. Surprisingly of the 12 BS symptoms measured by the BDAI, headache, arthralgia, arthritis, nausea, diarrhoea and erythema were significantly associated with higher psychological scores with no association between psychological scores and mouth ulcers, genital ulcers or skin pustules. Certain symptoms domains were not reported to be important by the majority of patients, notably eye, nervous system or major vessel problems, reflecting the spectrum of disease observed in the UK.

**Table 1:** Summary of results

<table>
<thead>
<tr>
<th>Psychological measure</th>
<th>BDAI Total Score</th>
<th>BDAI subscore</th>
<th>Correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>-.02</td>
<td>-.04</td>
<td>-.02</td>
<td>.06</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-.03</td>
<td>-.04</td>
<td>-.03</td>
<td>.07</td>
</tr>
<tr>
<td>Pain</td>
<td>-.03</td>
<td>-.04</td>
<td>-.03</td>
<td>.07</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-.03</td>
<td>-.04</td>
<td>-.03</td>
<td>.07</td>
</tr>
<tr>
<td>Condition intrusion</td>
<td>-.03</td>
<td>-.04</td>
<td>-.03</td>
<td>.07</td>
</tr>
</tbody>
</table>


**Disclosure** R. Moots, None; S. Campbell, None.
Choosing Subserologies Wisely: An Opportunity for Rheumatologic 
Healthcare Resource Savings. 

Background/Purpose: In March 2013, the American College of Rheumatology published its Top 5 List of Things Physicians and Patients Should Question as part of the American Board of Internal Medicine’s Choosing Wisely campaign. First on the list was “Don’t test ANA subserologies without a positive ANA and clinical suspicion of immune-mediated disease.” Previously, we examined positive subserologies when the ANA was negative, and were surprised to find that rheumatologists were frequently ordering subserologies when the ANA was negative. The present study was undertaken to elucidate the extent of this ordering pattern and understand the providers’ rationales. The ultimate goal is to develop a quality improvement program to support cost effective utilization of subserologies.

Methods: We conducted a retrospective study of the Geisinger Health System that includes 2198 providers; 342 in primary care and 14 in rheumatology. We looked at the incidence of subserologies ordered simultaneously with an ELISA ANA when the ANA result was normal. Data from 2011–2012 was collected via the Sunquest lab system and EPIC electronic health record. Subserologies included were ELISA dsDNA, Anti-Smith/RNP, SSA/SSB, SCL70 and Jo-1 antibodies. Since anti-Smith/RNP, SCL70, and dsDNA should be negative when the ANA screen is negative, those testing instances represent unnecessary utilization. A six question survey was sent to providers who ordered ANA negative subserologies more than twice in an attempt to determine the providers’ ordering rationale and to ascertain if they had quality improvement educational preferences. Finally, a cost analysis was done totaling the allowed reimbursement of unnecessary subserology tests based on the Medicare fee schedule.

Results: 22596 ANA tests were ordered from 2011–2012. 2246 ANA’s were ordered at the same time as subserologies when all tests were negative (9.4%). 32.8% were ordered by Rheumatologists. Out of 440 unique ordering providers, 183 ordered testing more than twice. 130 were sent the survey and 47 completed it. The primary reasons for ordering ANA’s in conjunction with subserologies were an unclear diagnosis based on history and physical (16) and patient convenience (7). Providers were asked about opportunities for quality improvement, 10 preferred monetary incentives, 18 were interested in educational materials, 28 favored reflex testing, and 10 would want training through the EHR.

In our cost analysis we found that, excluding SSA/SSB and Jo-1, the estimated total cost of subserologies ordered with a negative ANA from 2011–2012 was $39,091.

Conclusion: In the Geisinger Integrated Health System, Rheumatologists frequently did not choose subserologies wisely. No specialty was immune from ordering ANA’s and subserologies simultaneously. Responding physicians were most receptive to educational materials and reflex testing to help eliminate superfluous subserologies. If reflex testing had been available in 2011–2012, Geisinger would have saved close to $40,000 in unnecessary tests. We will be implementing an ANA/reflex subserology option combined with directed provider education about ordering patterns to improve utilization.

Disclosure: D. Bulbin, None; A. Meadows, None; S. Kelsey, None; H. Harrison, None; A. E. Denio, None.

Choosing Not so Wisely: The Tale of Antinuclear Antibody Testing. 

Tejas Sheth1 and David Alcid2. 1Albert Einstein College of Medicine / Yeshiva University, Bronx, NY, 2Drexel University College of Medicine / St Peter’s University Hospital, New Brunswick, NJ.

Background/Purpose: Choosing Wisely campaign aims to promote evidence based care that is truly necessary and not duplicative. ACR has furnished guidelines for use of ANA and ANA subserologies (ANAS): First, repeat testing of ANA is not indicated in patients with established diagnosis of SLE. Second, ANAS should not be ordered along with initial ANA testing. Third, ANA should not be used as a screening test in patients with nonspecific symptoms. The study objective was to identify occasions where ANA testing does not reflect high-value, cost-conscious care.

Methods: All patients having ANA test done at St Peter’s Hospital lab from 4/1/2012 to 3/31/2014 were included. Retrospective chart review was done for demographics, indication of testing and outcomes. Inferential analysis and logistic regression were done by SAS 9.0.

Results: Total 851 patient encounters were found with mean age of 46.9 years and M:F ratio of 1:3.3. In 91 encounters, ANA testing was done despite a history of SLE. In 223 encounters, ANAS were ordered along with initial ANA. Of 223 ANAS ordered, only 15 were positive; all of which had positive ANA results. Female patients (OR 2.92, 95% CI 1.86–4.59) and those with history of autoimmune disease (AID) (OR 6.76, 95% CI 4.37–10.44) were more likely to have a positive ANA result. Patients with history of AID (OR 7.87, 95% CI 1.72–35.95) and those with a positive ANA results (p<0.001) were more likely to have positive ANAS. Age (OR 0.99, 95% CI 0.98–1.01) and location of patient (p=0.48) did not show association with ANA results. ANA testing ordered in family medicine, pediatrics and gastroenterology were more likely to have negative results (OR 2.61, 2.3 and 5.04 respectively) as compared to rheumatology. Follow up visits were available in 587 encounters; on 12 occasions (2.07%) a positive ANA result translated in a change in management.

Conclusion: A significant amount of clinically done ANA testing does not reflect high value care and is associated with significant economic burden (>150,000 USD/yr).

Table 1: ANA testing behavior of different specialties in patients with history of SLE

Table 2: ANAS testing behavior of different specialties along with initial ANA testing

Table 3: Clinical situations where ANA testing does not reflect high-value care
Improving Serologic Testing for Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus. Arshad Mustafa¹, Kara Prescott², Una Makris³, and E. Blair Solow⁴. ¹UT Southwestern Medical Center at Dallas, Dallas, TX, ²Dallas VA Medical Ctr, Dallas, TX, ³UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: Antiphospholipid antibodies (APL) in patients with Systemic Lupus Erythematosus (SLE) are common. Persistent positivity is known to increase the risk of thrombosis and pregnancy morbidity and predicts early damage in patients with SLE. Testing for APL is part of the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) immunologic criteria for SLE. The purpose of the Quality Improvement (QI) project was to determine the percentage of SLE patients in whom APL were checked before and after intervention at the Parkland Rheumatology Clinic—the largest urban safety net hospital in Dallas, Texas.

Methods: Initially, 150 Parkland Rheumatology charts with an International Classification of Disease (ICD)-9 code of 710.0 were selected at random and reviewed for the presence of APL (lupus anticoagulant, anticardiolipin, and beta 2 glycoprotein I). Patients who met the ACR or SLICC classification criteria were included. APL testing done before July 2012 was recorded. Charts with ≥2 APL were counted as "Yes" and <2 APL were counted as "No". The intervention consisted of a 6 month education period focusing on the impact of APL in SLE. This consisted of a series of case presentations and journal club by the fellows, guest speakers with expertise on Antiphospholipid Syndrome, and a QI related SLE-APL literature review. Verbal reminders were made to the providers on their clinic days. Subsequently, another 150 Parkland charts with an ICD-9 code of 710.0 were selected at random and reviewed for the presence of APL. Patients not seen in the clinic after July 2012 were excluded, as changes after intervention could not be applied to these patient's charts. Fisher's exact test was used to investigate the change in APL testing in SLE patients before and after the intervention.

Results: Pre-intervention data showed that in 95 (64%) charts APL were checked, and in 54 (36%) charts APL were not measured. Post-intervention, in 93 (77%) charts, APL were checked and in 27 (23%) charts APL were not measured, see Figure. The intervention was significant for a change in APL testing in SLE patients before and after the intervention. 

Conclusion: Routine APL testing in patients with SLE is often overlooked. It is important to identify APL in SLE patients for diagnostic, therapeutic and prognostic purposes. In this QI project provider education significantly improved the testing for APL in patients with SLE. Future interventions include ongoing education strategies and creating rheumatology template notes with smartphrases in the electronic medical record.

Disclosure: A. Mustafa, None; K. Prescott, None; U. Makris, None; E. B. Solow, None.
Conclusion: A QI strategy involving an educational session along with distribution of a pocket-sized vaccination guide significantly increased the rate of being up-to-date with pneumococcal vaccination among immunosuppressed patients in our academic rheumatology practice.

Disclosure: M. Bussey, None; R. A. Ostrowski, None.

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Electronic Medical Record-Based Best Practice Alert Used by Clinical Staff Improved Pneumococcal Vaccination and Documentation Among Immunosuppressed Rheumatoid Arthritis Patients. Heena Sheth, Larry W. Moreland, Hilary J. Peterson and Rohit Aggarwal. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The Centers for Disease Control and American College of Rheumatology guidelines recommend pneumococcal vaccination for all immunosuppressed patients, specifically those taking disease modifying antirheumatic drugs (DMARDs) or biologic agents. Despite these guidelines, the rates of pneumococcal vaccination are very low in RA patients. The aim of this study was to improve the rate of administration and documentation of pneumococcal vaccine in rheumatoid arthritis (RA) patients taking DMARDs and biologic agents at rheumatology outpatient clinics.

Methods: An automated electronic medical record (EMR)-based best practice alert (BPA) intervention was designed to be used by clinical staff and to provide user-friendly interface to remind, document and order pneumococcal vaccine for eligible patients. EMR determined the eligibility of the patients at the time of rooming by medical assistant (MA) or nurse, and the BPA appeared for eligible patients. MA confirmed eligibility, documented prior vaccination or patient refusals and ordered the vaccine using the BPA if the patient agreed. Physicians reviewed and verified orders, and the patient either received the vaccination or a written prescription based on clinic/patient preferences. If the patient was unsure, the BPA was passed on to the physician for further discussion. The process continues at each visit until patient is vaccinated or documentation occurs. The study was designed as a pre- and post-intervention comparison. Clinical staff and physicians were educated on the guidelines and intervention. Patient education about vaccination was performed during clinic visit and educational materials was also provided. Eligibility for pneumococcal vaccine was all RA patients on immunosuppressant medications (DMARDs or biologics) who have not completed pneumococcal vaccination. Vaccination and documentation rates for the pre-intervention period (July 2012-June 2013) were compared with post-intervention period rates (2/17/2014 – 5/17/2014) using chi square test.

Results: 3285 and 1949 patients were analyzed for baseline and intervention data, respectively. Demographic characteristics were similar in both groups. Vaccination and documentation rates increased significantly from 44.4% and 51.4% in pre-intervention phase to 50.8% and 58.4%, respectively within 3 months of intervention phase (p<0.0001). Approximately 3% of patients refused vaccination, and for 4% of patients, physicians noted deferral during both study phases.

Conclusion: Pneumonia vaccination administration rates in immunosuppressed patients with RA are low. Implementation of an automated EMR and clinical staff-based BPA intervention significantly improved vaccination rates without the need for considerable physician input. The project is ongoing and will become standard of practice in our rheumatology clinics.

Disclosure: H. Sheth, None; L. W. Moreland, Pfizer Inc, 9; H. J. Peterson, None; R. Aggarwal, Questcor, 2, Pfizer Inc, 2, NIEHS-NIH, 2, Questcor, 5, aTyr Pharma, 5.

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Improving Pneumococcal Immunization Rates for Patients on Immunosuppressive Medications at an Academic Rheumatology Clinic. Lauren Dudley, Stephen Liu, Krista Mattiello, Jocelyn Verrell and Lin Brown. Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background/Purpose: Patients with rheumatologic diseases are frequently placed on immunosuppressive medications which increase their risk of developing Streptococcus pneumoniae infections. The Advisory Committee on Immunization Practices recommends that all immunosuppressed adults receive the 13-valent pneumococcal conjugate vaccine (PCV-13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) but many specialty clinics lack processes of care that facilitate immunization. The objective of this study was to improve pneumococcal immunization rates for patients on immunosuppressant medications in the adult rheumatology clinic.

Methods: Immunization rates for PCV-13 and PPSV-23 were defined as the proportion of visits in which patients were up to date on their immunization. Data obtained from the electronic health record from May 2011 to April 2014 was analyzed using statistical process control methods. Rates over time were tracked using p-charts. Semi-structured interviews were performed with clinic staff to map the processes for immunization and create cause-and-effect diagrams. Interventions consisted of staff and provider education, a standardized process for obtaining immunization histories and a standing order permitting clinical support staff to order and administer immunizations via a protocol.

Results: At baseline, there was no standardized process for assessing immunization histories or providing immunizations in the clinic. Barriers included provider knowledge gaps, uncertainty regarding whether specialists or primary care providers should immunize, missing immunization records, lack of reminders and lack of time. The interventions resulted in statistically significant increases in the PCV-13 immunization rate from 3.0% to 33.3% (p-value < 0.001) and the PPSV-23 immunization rate from 36.1% to 64.9% (p-value < 0.001).

Conclusion: Rheumatologists place many patients on immunosuppressant medications rendering them high risk for infection yet many clinics have not incorporated immunizations into their standard processes. Standing orders combined with education should be considered as a potential intervention.

Figure 1. Up-to-date immunization rate for the 13-valent pneumococcal conjugate vaccine (PCV-13) at Dartmouth-Hitchcock Medical Center Adult Rheumatology Clinic.

Background/Purpose: Vaccination rates among patients with rheumatoid arthritis (RA) remain low. Improving these rates is important, as RA patients are inherently immunocompromised and frequently treated with immunosuppressives. To address this, we implemented a multifaceted, system-level intervention to improve pneumococcal (PVX) and zoster (ZVX) vaccination rates among patients with RA that was designed to make clinicians aware of their low vaccination rates, improve processes at the point of care (i.e., during a visit), and use panel-management strategies to contact patients between visits.

Methods: This study was conducted at an academic medical center in Chicago, IL. The study cohort included all adults seen in the faculty practice plan’s rheumatology clinic with a diagnosis of RA. Our intervention had 3 main components: (1) clinicians received quarterly performance reports of the PVX and ZVX rates for their RA patients, generated from EHR data; (2) EHR clinical decision support best practice alerts (BPAs), designed to alert clinicians and facilitate PVX and ZVX administration at the point of care; and (3) outreach to patients needing vaccination via mail or secure electronic messaging through the EHR patient portal, regardless of whether they had in-person clinic visits. Study BPAs allowed clinicians to either link to a standing order set for vaccination at the time of the visit, document why vaccination was inappropriate, or write a prescription for the patient to receive ZVX elsewhere. We assessed vaccination rates monthly from baseline in October 2013 through May 2014 using EHR data. For this interim analysis we assessed the statistical significance of differences in vaccination rates pre- and post-intervention.

Results: The study cohort included 1255 eligible patients. At baseline 293 (23.3%) had received PVX, and this increased to 524 (41.8%) at follow-up (p<0.001). An additional 11 (0.9%) patients had a documented medical exemption for why PVX was not administered, and 53 (4.2%) had a documented refusal. At baseline, 35 (2.8%) patients had received ZVX, and at follow-up 63 (5.0%) patients had received ZVX at clinic or received a prescription to receive ZVX elsewhere (p<0.01). During follow-up, 99 (7.9%) patients had a documented medical exemption and 44 (3.5%) had a documented patient exception (refusal or financial barrier) for ZVX.

Conclusion: Vaccination rates increased substantially following implementation of this multifaceted intervention. However, the rate of PVX remained much lower than rates we have achieved for PVX using similar interventions in a primary care clinic, and ZVX rates remained quite low. The reasons for these suboptimal vaccination rates are unclear, but could be due to rheumatologists’ limited time to discuss prevention with patients or beliefs that vaccination is the responsibility of primary care providers. Alternatively, our results could be due to clinical confusion following the recent publication of new PVX recommendations, and uncertainty regarding ZVX administration in immunocompromised patients under age 60. Future research should seek to identify and overcome barriers to vaccination in this patient population.

Disclosure: D. W. Baker, None; T. Brown, None; J. Y. Lee, None; D. S. Sandler, None; D. T. Liss, None; A. Ozanich, None; E. Harsha Strong, None; A. Patel, None; E. M. Ruderman, Pfizer Inc. S.
equivalent of prednisone >3 months. Clinical staff and physicians were educated in vaccine guidelines and planned intervention. Intervention was an electronic medical record (EMR)-based best practice alert (BPA), which is a user-friendly system for ancillary staff and physician with integrated vaccine eligibility verification, documentation and vaccine order capability at the time of patient visit. The BPA appeared for eligible patients upon opening the EMR, prompting the medical assistant or nurse to document vaccination status and order HZ vaccine if the patient agreed. The physician subsequently reviewed and confirmed the order. BPA was passed to physician if a patient was unsure. The pre-intervention phase included all eligible RA patients who were seen at the Rheumatology Clinics between 7/1/2012 – 6/30/2013. The intervention phase data was collected for 3 months after implementation of BPA system. Reasons like patient refusal or physician deferral were also documented. The proportion of patients vaccinating and documented among all eligible patients pre- and post-intervention was compared using chi-square tests.

Results: 1846 RA patients were analyzed for pre-intervention (baseline) data (76% female, 90% white, mean age of 72 years) and 1267 patients for the post-intervention data (76% female, 82% white, mean age of 71 years). Overall vaccination rate increased from 9.9 to 15.7% \( p=0.001 \), and documentation rate increased from 30.1 to 44.8% \( p<0.0001 \). Academic clinic vaccination rate improved from 12.4 to 24.3% \( p=0.003 \), documentation rate from 32 to 44% \( p<0.04 \). Community clinic vaccination rate improved from 8.6 to 14.5% \( p=0.0008 \); and documentation rate increased from average 25.2 to 35.6% \( p=0.014 \) (Figure 1). There was 4.4% patient refusal while 15.7% patients had documented physician deferral. The process was automated using EMR and user-friendly interface for ordering and documentation of vaccination without much increase in physician burden.

Conclusion: EMR-based BPA at the time of patient encounter and physician education intervention resulted in significant increase in HZ vaccination and documentation rates in RA patients.

Figure 1. Rates of HZ vaccination and documentation in 2 academic and 10 community clinics before and after use of EMR-based BPA and education intervention.

Disclosure: H. Sheth, None; S. Moghadam-Kiai, None; R. J. June, None; H. J. Peterson, None; D. Sa Leitao, None; L. W. Moreland, Pfizer Inc, 9; R. Aggarwal, Questcor, 2, Pfizer Inc, 2, NIEHS-NIH, 2, Questcor, 5, aTyr Pharma, 5.

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A Decision Support Tool to Improve Herpes Zoster Vaccination Rates Among Patients Starting Biologic Medications. Sara Schoenfeld, Eli Miloslavsky, Weihong Yang, Naina Rastalsky, Mollie Carruthers, Zachary Wallace, Traci Powers, Marcy Bolster and Deborah Collier. Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital/ Harvard Medical School, Boston, MA.

Background/Purpose: Herpes zoster infection causes serious morbidity and mortality in immunocompromised patients. Vaccination reduces the risk of zoster infection by up to 40% among patients with autoimmune disease and is recommended for patients aged 60 or above before starting immunosuppressive treatment. We implemented an electronic medical record-based zoster vaccine decision support tool to improve vaccination rates among patients prescribed but not yet started on biologic medications.

Methods: We incorporated a zoster vaccine screening tool into the mandatory prior authorization (PA) process required for prescribing biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) across a multicenter rheumatology practice at a tertiary care academic medical center. The revised electronic PA form included a zoster section with decision support prompts to screen each patient’s appropriateness for the vaccine and to facilitate referral for the vaccine.

Process and outcome measures were analyzed during a 9 month period. The process measure assessed whether physicians accurately completed the zoster section of the PA form. The outcome measure assessed whether patients actually received the zoster vaccine. As a comparison group we used zoster immunization data derived from chart reviews of 133 patients over age 60 prescribed biologic medications in the same rheumatology unit during the 12 month period before implementation of the zoster screening decision support tool.

Results: During the 9 month period following the intervention, 119 PA forms with the zoster section were filled out for patients starting a biologic medication. The form was filled out correctly in 114/119 cases (Figure 1a). Prior to implementation of the zoster section on the PA form, 86/123 patients over age 60 who were prescribed a biologic were eligible for the vaccine without a contraindication. Of these 86 patients, 25% received the vaccine (Figure 1b). After the intervention, 41 of 119 patients prescribed a biologic were age-appropriate for the zoster vaccine, of whom 29 had one of the pre-defined contraindications to receiving the vaccine. Of the 12 age-eligible patients without contraindications, 42% received the vaccine (Figure 1c).

Conclusion: Incorporating a zoster immunization decision support tool in an electronic PA form for biologic medications was a successful method of prompting physicians to screen patients requiring biologic DMARD therapy for the zoster vaccine. After the support tool was implemented, a greater percentage of age-appropriate patients without a contraindication received the vaccine. Vaccination rates could be further improved by addressing a number of barriers including cost and logistical vaccine administration hurdles as well as by considering zoster screening prior to initiating a nonbiologic DMARD or prednisone.

Figure 1. Zoster Screening Tool - Process and Outcome Measures

Disclosure: S. Schoenfeld, None; E. Miloslavsky, None; W. Yang, None; N. Rastalsky, None; M. Carruthers, None; Z. Wallace, None; T. Powers, None; M. Bolster, Johnson and Johnson, 1, Eli Lilly and Company, 2, ABIM Rheumatology Specialty Board, Chair, 6, ABIM Rheumatology Test Writing Committee, Chair, 6, ACR COTW, Chair, 6, ACR Board of Directors, 6, RRF Board of Directors, 6; D. Collier, None.
Practice What You Preach? Suboptimal Guideline Adherence By Rheumatologists in Patients with Rheumatoid Arthritis. Nienke Lesuis, Ronald van Vollenhoven, Marlies Hulscher and Alfons den Broeder. Sint Maartenskliniek, Nijmegen, Netherlands; The Karolinska Institute, Stockholm, Sweden; Radboud University Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Tight control based treatment principles of rheumatoid arthritis (RA) are superior to usual care and therefore recommended in many (inter)national guidelines. Unfortunately guideline adherence to these guidelines has often been shown to be suboptimal in clinical practice. As this is mainly described in clinical trials and pre-defined cohorts, we aim to assess RA guideline adherence in daily practice. In addition, we will also explore potential determinants of guideline adherence.

Methods: In this retrospective, single-center observational study, all adult RA patients with a first outpatient clinic visit at the Sint Maartenskliniek (SMK) between September 2009 and March 2011 were included, either new RA patients or second opinions. Data from all visits in the first year of treatment were collected by manual chart revision. Afterwards, for every single visit guideline adherence to 7 indicators was assessed. The indicators were based on evidence-based national and local RA guideline recommendations (issued in 2009) and concerned diagnostic, therapeutic and follow-up decisions. To assess potential determinants of guideline adherence, all rheumatologists working at the SMK in March 2011 received a set of questionnaires about personality traits, propensity towards cognitive bias, thinking styles and knowledge about guideline content. Furthermore, demographic and disease characteristics of the patients were collected during the chart revision.

Results: A total of 994 patient visits for 137 RA patients were reviewed (mean age 59 years ± 14.1; 67% female; disease duration 4.9 years ± 8.5; 85% rheumatoid factor and/or anti-CCP positive). Guideline adherence varied between 21 and 72%, with referral to the physician assistant as worst scoring indicator and referral to a specialized nurse as best scoring one (see table 1). Both are routine measures implemented at our centre in order to facilitate frequent systematic follow-up. Patients and physician characteristics were analysed for relations with guideline adherence, preliminary analyses found two associations. In patients never seen by a rheumatologist before intervals between visits were more often correct and X-rays were more frequently taken. None of the patients had documentation of disease prognosis. Documentation of a glucocorticoid management plan was done in 60% (N=5) of the patients who required it. 48.9% (N=174) of patients either did not take glucocorticoids or received glucocorticoids but did not meet the criteria to require a management plan, 98.8% (N=328) of eligible patients were treated with a DMARD. 63.1% (N=215) of patients on a DMARD required intervention for increased disease activity, of which 100% received it.

Conclusion: The majority of patients had documentation of TB screening. Our assessment of disease activity and functional status improved significantly over time, likely due to increasing provider awareness of quality metrics. Although most patients were stratified and treated as per disease severity, their prognosis was not documented. Only a small percentage of our patients met the criteria requiring a glucocorticoid management plan, thus limiting our assessment of this quality indicator. Our clinic had excellent adherence to treatment with DMARDs, as well as managing worsening disease.

Better adherence to guidelines and documentation is required, especially with regards to assessment and classification of disease prognosis, which could be achieved through provider education. In addition, an automated EMR reminder to obtain TB screening upon ordering a biologic treatment may further improve documentation of this QI.

Disclosure: N. Lesuis, None; R. van Vollenhoven, None; M. Hulscher, None; A. den Broeder, None.

Table 1: Guideline adherence percentages

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Adherence percentages (lowest - highest score rheumatologists)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) X-rays of hands, feet and thorax within the first three visits</td>
<td>54.7 [29.0–100.0]</td>
</tr>
<tr>
<td>2) Therapy change in case of moderate to high disease activity</td>
<td>65.6 [46.7–84.4]</td>
</tr>
<tr>
<td>3) Prescription of conventional and biological DMARDs in agreement with the local preferential sequence</td>
<td>23 [0–50.0]</td>
</tr>
<tr>
<td>Follow-up and shared care</td>
<td></td>
</tr>
<tr>
<td>4) Referral to a specialized nurse within the first three visits</td>
<td>71.5 [43.0–100.0]</td>
</tr>
<tr>
<td>5) Referral to a physician assistant (PA) or nurse practitioner (NP) within the first year of treatment</td>
<td>21.2 [0–50.0]</td>
</tr>
<tr>
<td>6) Regular outpatient clinic visits combined with a nurse visit for DAS28 assessment (clinimetric center)</td>
<td>35.5 [9.3–70.5]</td>
</tr>
<tr>
<td>7) Correct intervals between regular outpatient clinic visits</td>
<td>23.1 [11.1–44.3]</td>
</tr>
</tbody>
</table>

Conclusion: Guideline adherence to the seven recommendations varied between 21 and 72%. This indicates that there is still room for improvement with regard to guideline adherence. Guideline adherence seems only marginally related to factors on patient- or clinician level. Therefore, adherence is more likely to be guided by a complex interplay of facilitators and barriers.

References:

Disclosure: N. Lesuis, None; R. van Vollenhoven, None; M. Hulscher, None; A. den Broeder, None.

Assessment of ACR Endorsed Quality Indicators in Rheumatoid Arthritis Patients – A Quality Improvement Initiative. Puneet Bajaj, Erik Anderson, Siddharth Raghavan, Asha Patnaik and Heidi Roppelt. Stony Brook University Medical Center, East Setauket, NY.

Background/Purpose: Quality assessments are being increasingly used for quality improvement, accountability, and performance based incentives. The current research regarding quality of care provided to rheumatoid arthritis (RA) patients, although limited, does identify gaps and variations in several domains of care.

The Amarian College of Rheumatology (ACR) has endorsed seven RA quality indicators (QI), which are used to access the quality of care provided to RA patients at our institution.

Methods: A retrospective chart review was performed on patients identified by the ICD9 code for RA (714.0) entered by a Rheumatologist between 1/1/09 to 8/31/13. We excluded patients whose records were not available and those without a definitive diagnosis of RA.

Our clinic began consistently applying the Multi-Dimensional Health Assessment Questionnaire for assessment of disease activity and functional status in June 2009; therefore, we only included patients seen in our clinic between 1/1/2010 and 12/31/2012. We adhered to specifications for inclusion and exclusion criteria endorsed by the ACR regarding the seven RA QI. In addition, we excluded patients being considered for initial DMARD therapy or undergoing management for worsening disease, who were lost to follow-up. P-values were calculated using Chi-Squared Test.

Results: A total of 356 patients were included. 87.9% (N=308) of eligible patients had documentation of TB screening. Measurement of disease activity and functional status rose significantly each year from 2010 to 2012 (72.8 to 94%, p < 0.0001 and 70.8% to 93.3%, p < 0.0001 respectively). None of the patients had documentation of disease prognosis. Documentation of a glucocorticoid management plan was done in 60% (N=5) of the patients who required it. 48.9% (N=174) of patients either did not take glucocorticoids or received glucocorticoids but did not meet the criteria to require a management plan, 98.8% (N=328) of eligible patients were treated with a DMARD. 63.1% (N=215) of patients on a DMARD required intervention for increased disease activity, of which 100% received it.

Conclusion: The majority of patients had documentation of TB screening. Our assessment of disease activity and functional status improved significantly over time, likely due to increasing provider awareness of quality metrics. Although most patients were stratified and treated as per disease severity, their prognosis was not documented. Only a small percentage of our patients met the criteria requiring a glucocorticoid management plan, thus limiting our assessment of this quality indicator. Our clinic had excellent adherence to treatment with DMARDs, as well as managing worsening disease.

A limitation of our study was a lack of electronic medical records (EMR), which may have negatively impacted data collection. As a result, actual rates of adherence may have been higher than those measured.

Better adherence to guidelines and documentation is required, especially with regards to assessment and classification of disease prognosis, which could be achieved through provider education. In addition, an automated EMR reminder to obtain TB screening upon ordering a biologic treatment may further improve documentation of this QI.

Disclosure: P. Bajaj, None; E. Anderson, None; S. Raghavan, None; A. Patnaik, None; H. Roppelt, None.


Background/Purpose: Timely disease activity assessment (DAA) and population management (PM) are known to reduce the burdens of chronic diseases, including RA. Currently, the measures and processes being used by clinician rheumatologists for managing RA are poorly documented. Our purpose is to survey DAA and PM processes across a cohort of clinician rheumatologists as a starting point for improving RA management and outcomes in these practices.

Disclosures: None.
Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a voluntary collaboration of US clinician rheumatologists whose goal is to improve RA management, and to document our performance. Most invited to participate are multi-biomarker disease activity test users. To date, 97 physicians from 91 practices have attended quality improvement project kick-off meetings, and each has completed a baseline survey regarding their DAA and PM processes. Their aggregated responses are reported here.

Results: Participants represent all regions of the United States and differing practice environments: solo (33%), single-specialty (35%), and multispecialty group/integrated systems practices (32%). RA patients managed per rheumatologist derived from practice billing systems vary from 112 to 1800, self-reported patient visits/day from 12 to 80, and new patients/week from 0 to 32. Forty-six % have mid-level providers sharing in RA management, 91% have an electronic medical record (38 different brands), and 35% have any RA disease registry capability. DAA use varies from none (25%), to RAPID3 (39%), DAS28 (18%), CDAI (20%) and SDAI (2%). Disease activity documentation in medical records includes a non-numeric impression (active/controlled) (63%), 0–10 Physician Global (23%), composite score (11%), or other (3%).

Conclusion: 1. Practices vary in RA population size, office work flows, staffing, and DAA utilized. 2. Use of composite disease activity measures is limited, with the majority documenting a binary, active/controlled clinical impression. 3. PM processes (analytic disease registries and team management) are used infrequently. 4. These results indicate opportunities to improve practice performance and RA disease outcomes in rheumatology practices.
days passed between the assessments. The mean total RAPID3 scores for the paper and EHR versions were 9.57 (SD = 6.45) and 9.75 (SD = 6.46) respectively. There were no statistically significant differences between the mean total RAPID3 of the paper and electronic versions (p = 0.46), or each component score (table 1).

Table 1. Comparison of paper and EHR versions of RAPID3.

<table>
<thead>
<tr>
<th>Physical Function</th>
<th>Paper Mean (± Standard Deviation)</th>
<th>EHR Mean (± Standard Deviation)</th>
<th>t-test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dress yourself</td>
<td>1.87 (1.91)</td>
<td>1.85 (1.83)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Get in and out of bed</td>
<td>0.46 (0.61)</td>
<td>0.34 (0.59)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Lift full cup or glass to mouth</td>
<td>0.20 (0.53)</td>
<td>0.18 (0.56)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Walking outdoors on flat ground</td>
<td>0.40 (0.67)</td>
<td>0.40 (0.67)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Wash and dry your entire body</td>
<td>0.42 (0.64)</td>
<td>0.48 (0.68)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Bend down to pick up clothing from floor</td>
<td>0.48 (0.68)</td>
<td>0.50 (0.68)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Turn regular faucet on and off</td>
<td>0.20 (0.53)</td>
<td>0.20 (0.53)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Get in and out of a car, bus, train or airplane</td>
<td>0.54 (0.65)</td>
<td>0.50 (0.58)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Walk two miles or three kilometers, if you wish</td>
<td>1.20 (1.18)</td>
<td>1.20 (1.20)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Participate in recreational activities and sports</td>
<td>1.28 (1.03)</td>
<td>1.34 (1.08)</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** There was no significant difference in responses between the electronic and paper versions. The electronic RAPID3 built in an Epic system v2010 can and should be included in the care of all RA patients without interrupting clinic flow, and will facilitate research and systems-based practice improvement.

Disclosure: R. M. Chua, None; J. Machelela, None; A. Zbehlik, None.

1355

Population Management of Rheumatoid Arthritis (RA) in Rheumatology Practices: A Quality Improvement Project. David Sikes1, Gary Crump2, Kathleen Thomas3, Alex Bangs4 and J. Timothy Harrington5. 1Florida Medical Clinic PA, Zephyrhills, FL, 2Rheumatology Associates - Louisville, Louisville, KY, 3Community Rheumatology, Noblesville, IN, 4Crescendo Bioscience, Inc, South San Francisco, CA, 5Joiner Associates LLC, Madison, WI.

**Background/Purpose:** Population management (PM) is required for reducing the burden of chronic diseases, including RA. PM depends on standardizing disease activity assessment (DAA) and coordinating care for the entire disease population, as well as for individuals within this context. Our purpose is to implement PM for RA within rheumatology practices by optimizing DAA to define controlled, low, moderate, and high disease activity cohorts; to focus resources on those patients with the highest needs; and to document our delivery of care and outcomes.

**Methods:** The Rheumatoid Arthritis Practice Performance (RAPPP) Project is a rapidly growing voluntary collaboration of U.S. clinician rheumatologists (current N = 94) who manage more than 50,000 RA patients in total, based on ICD-9 diagnoses. Patients are being enrolled in an analytic RA disease population registry from practice billing records, and RAPP physicians are reporting their preferred disease activity measures, including CDAI, RAPID3, DAS28, SDAI, Physician Global Assessment, and/or a multi-biomarker disease activity score. Monthly Population Reports are provided that include 1) patients registered (N) and % ever assessed, 2) % with controlled-low DAA within 7 months, 3) % with moderate-high DAA within 4 months, and 4) %’s with controlled, low, moderate, and high disease activity. Working lists are also provided of patients lacking timely DAA and implementing these population management processes through clinical practice improvement projects.

**Results:** A aggregated data from the baseline Population Reports for the first 26 fully enrolled registries are included in this abstract using multi-biomarker assay results. Other encounter-based disease activity measures are being added currently. The total patients enrolled = 16,979 (Median = 954/physician). At least one DAA is documented for 58% of the total (Median/physician = 69%). Forty-seven % of the controlled-low disease activity cohort has been assessed within 7 months, as has 29% of the moderate-high disease activity cohort within 4 months. The population disease activity distribution includes 21% with controlled-low, 39% with moderate, and 40% with high RA disease activity.

**Conclusion:** 1. These PM capabilities identify care gaps in DAA and disease control that were not identified previously. 2. Timely DAA and tracking of population measures are known to support improved care and disease activity outcomes.

Disclosure: D. Sikes, Crescendo Bioscience, 5, Abbvie, 8; G. Crump, Crescendo Bioscience, 5, Abbvie, 8; A. Bangs, Crescendo Bioscience, 5, Abbvie, 8; A. Sikes, Crescendo Bioscience, 5, Abbvie, 8; A. Thomas, Crescendo Bioscience, 5, Abbvie, 8; A. Bangs, Crescendo Bioscience, Inc, 1, Crescendo Bioscience, Inc, 3; J. T. Harrington, Joiner Associates LLC, Crescendo Bioscience, 5, Pfizer Inc, 5.

1356

Collaboration Between a Third Party Payer and Community Rheumatologists to Create a Clinical Pathway for the Treatment of Rheumatoid Arthritis to Assure Proper Use of Biologics and Quality of Care. Alan K. Matsumoto1, Herbert S. B. Baraf2, Bruce Feinberg3, Phil Miller4 and Daniel Winn2. 1Arthritis & Rheumatism Associates, PC, Wheaton, MD, 2Cardinal Health, Dublin, OH, 3CareFirst BlueCross, Baltimore, MD.

**Background/Purpose:** Use of biologic agents for the treatment of rheumatoid arthritis continues to grow rapidly, with the cost of these agents putting a significant strain on health care budgets. Although rheumatologists and third party payers share the goal of ensuring quality of care for RA patients, rheumatologists fear potential limitation of access to biologics due to cost while third party payers are concerned about the rising expenses associated with the use of these agents. New models of healthcare delivery stress the relationship of cost to quality and improved outcomes. This results in adversarial and inefficient procedures between physician and insurer. Treatment pathways have been suggested as a means to address these issues.

**Methods:** At the request of CareFirst Blue Cross and Cardinal Health, we organized a committee of 12 community based rheumatologists to create a treatment pathway for RA patients based on published evidence and community standard of care. CareFirst did not participate in the specific details of the pathway in accordance of the belief that structure should be driven by community standards. Practices that reached 80 % compliance with the program were offered increased reimbursements to offset the cost of data collection and program compliance. Compliance was judged as follows. All patients insured by CareFirst with the RA ICD-9 code of 714.0 were required to be entered into the pathway. Patient visits were required at a minimum of every 3–6 month intervals with a Clinical Disease Activity Index (CDAI) measure recorded at each visit. The use of a non -biologic DMARD (methotrexate unless contraindicated) was mandated for 3 months prior to initiation of first biologic therapy. Indication and dosing of biologics were to be within the package insert guidelines but no specific biologic agent was preferred on the pathway. Site of infusion was required to be non-hospital based. Patients were not required to change biologics for ongoing disease activity, but biologics could not be initiated, switched or increased if the patient was in CDAI remission. Data was captured using a real time iPad based tool.

**Results:** Over the first 12 months, 80 physicians from 37 practices in the mid Atlantic were recruited and 1800 patients were entered into the pathway. Over 90% of patients were on compliant pathways and 74 % of practices reached compliance. Over 70% of patients were in remission or low disease activity by CDAI measurement. Biologic switches were infrequent. Within the program, site of infusion was more likely non-hospital based.

**Conclusion:** To our knowledge this is the first collaboration between rheumatologists and a third party payer to create a Rheumatoid Arthritis treatment pathway to assure proper biologic use and assess outcomes. We believe this is a powerful model to assess and improve cost and effectiveness of treatment strategies for rheumatoid arthritis.

Disclosure: A. K. Matsumoto1, Cardinal Health, 5; H. S. B. Baraf2, Cardinal Health, 5; B. Feinberg3, Cardinal Health, 5; P. Miller4, CareFirst BlueCross, 3; B. Winn, CareFirst BlueCross, 3.

1357

Improving Compliance for Tuberculosis Screening for Patients on Biologics in Rheumatology Clinics. Shraddha Jatwani, Rajani Rudrangi, Karan Jayawari, Vijaya M urthy, Rashmi Maganti, Rex M Calium and Emilio Gonzalez. University of Texas Medical Branch, Galveston, TX.
Background/Purpose: Biologics are used commonly for patient with autoimmune diseases. These agents have ensured important efficacy advantages in the treatment of inflammatory rheumatic diseases. All biologics have been associated with risk of infections. The risk of serious infections has been reported to increase 1-2-1.8 times for patients on tumor necrosis factor inhibitors (TNFi) compared to patients on conventional agents. The risk of tuberculosis (TB) has been reported to increase manifold, up to 12 to 35 times. American College of Rheumatology (ACR) recommends that all patients on biologics should be screened for risk of latent TB infection (LTBI) either with tuberculin skin test (TST) or interferon-release assays (IGRAs), regardless of risk factors for LTBI.

With this Quality improvement exercise, we aim to improve compliance with TB screening in patients receiving biologics to a target of 90% over 3 months.

Methods: We generated an EMR query to review pre-intervention screening rates of patients on biologics from 3 university clinics over 6 months (July-December 2013). A list of 104 such patients was created. Chart review for these 104 patients was performed to determine adequacy of TB screening defined by presence of a documented TB screening, either PPD or Quantiferon gold TB test, within 1 year of last clinic visit. At baseline, TB screening had been performed in 78% of patients. To improve compliance, as an intervention, we conducted conferences with providers to educate them on the guidelines and our current performance. Nurses were educated through emails. Monthly email follow-up reminders were also sent to the providers and nurses. At 3 months a follow up chart review was conducted for 152 patients in the same three clinics, who had received prescriptions of biologics between March-June 2014 to determine effect of provider education on compliance with TB screening.

Results: Educational conferences and emails were well received by providers and nurses. At follow up after 3 months, the target was achieved in all clinics, with compliance rates for TB screening at 94.7% across board.

Conclusion: Developing methods to improve quality will become even more relevant in future. In this study, we demonstrated provider education makes a difference in implementation of guidelines for TB screening in patients receiving biologics. This was achieved in relatively short period of time. A similar strategy can be implemented in other subspecialties like dermatology and gastroenterology where biologics are also being used.

Disclosure: S. Jatwani, None; R. Rudrangi, None; K. J. Jawani, None; V. Murthy, None; R. Maganti, None; R. M. Callum, None; E. Gonzalez, None.

1358
A Systematic Analysis of the Safety of Prescribing Anti-Rheumatic Immunosuppressive and Biologic Drugs in Pregnant Women. Sonia Panchal1, Julia Flinn2, Maud van de Venne3, Madeline Piper4, Alice Hurrel2, Joel Cunningham5, Mary Gayed5, Karen Schreiber6, Subha Ananthanar7, M ohamed Nisar7, David Williams7, Munther Khamash7, Caroline Gordon8 and Ian Giles9. 1University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, 2University College London, London, United Kingdom, 3North Bristol NHS Trust, Bristol, United Kingdom, 4University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, 5North Bristol NHS Trust, Bristol, United Kingdom, 6Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom, 7Burton Hospitals NHS Foundation Trust, Burton-upon-Trent, United Kingdom, 8Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom.

Background/Purpose: The use of anti-rheumatic drugs in pregnancy is often complicated by concerns over their potential for adverse effects. Given that rheumatic diseases often affect women of childbearing age and may flare during pregnancy, the safety (or otherwise) of anti-rheumatic drugs and immunosuppressant’s are of particular importance. Practice has relied on information based mainly on experimental and animal studies. Human data is limited to inadvertent exposure described in case reports/series and population registries. Previous systematic reviews have identified risks with various anti-rheumatic drugs and biologics. This systematic review is an update on the consensus papers on anti-rheumatic drugs, biological agents and reproduction published in 2006/8.

Methods: A systematic search from 2006–2013 of PubMed, Embase, Cochrane, Lactmed and the UK Tetratology Information Services was carried out using MESH and free terms for drug, rheumatic disease and pregnancy. Review articles and non-English language papers were excluded.

Results: The search strategy identified 352 papers with original pregnancy outcome data.

Table 1. illustrates pregnancy outcomes for the immunosuppressant and biologic therapies.

Conclusion: Evidence from this systematic review supports the compatibility of hydroxychloroquine, azathioprine, sulphasalazine and steroids in pregnancy. Increasing evidence of compatibility was found from pregnancies exposed (mostly at conception or during the first trimester) to anti-TNF alpha drugs that do not show an appreciable increase in the number of spontaneous

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of pregnancies exposed to drug</th>
<th>Live births related to exposure</th>
<th>Spontaneous 1st trimester loss (min)</th>
<th>Spontaneous 2nd/3rd trimester loss (min)</th>
<th>Major &amp; minor malformations in control (min)</th>
<th>Molar pregnancies (min)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>771</td>
<td>565</td>
<td>23</td>
<td>35</td>
<td>19</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>77</td>
<td>78</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>D</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>320</td>
<td>269</td>
<td>32</td>
<td>7</td>
<td>12</td>
<td>5</td>
<td>C</td>
</tr>
<tr>
<td>HCQ</td>
<td>213</td>
<td>213</td>
<td>15</td>
<td>0</td>
<td>29</td>
<td>7</td>
<td>B</td>
</tr>
<tr>
<td>MMF</td>
<td>17</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>136</td>
<td>135</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>D</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>D</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>122</td>
<td>120</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Etanercept</td>
<td>19</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>D</td>
</tr>
<tr>
<td>Infliximab</td>
<td>130</td>
<td>120</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>D</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>215</td>
<td>160</td>
<td>39</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Abatacept</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>D</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>10</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>D</td>
</tr>
</tbody>
</table>

3Combination antiTNFi (infliximab, etanercept, adalimumab, certolizumab) #Includes twin pregnancies. @No increased risk of minor malformations compared to control group. §Major & minor malformations meet the EUROCAT criteria for congenital anomalies

Conclusion: Evidence from this systematic review supports the compatibility of hydroxychloroquine, azathioprine, sulphasalazine and steroids in pregnancy. Increasing evidence of compatibility was found from pregnancies exposed (mostly at conception or during the first trimester) to anti-TNF alpha drugs that do not show an appreciable increase in the number of spontaneous
miscarriages and congenital malformations. Further registry data is required for biologic drugs, before the safe use of these drugs can be advocated throughout pregnancy.

Disclosure: S. Panchal, None; J. Flint, None; M. van de Venne, None; M. Piper, None; A. Hurrel, None; J. Cunningham, None; M. Gayed, None; K. Schrauber, None; S. Anthanari, None; M. Nisar, None; D. Williams, None; M. Kamasha, None; C. Gordon, None; I. Giles, None.

1359
Care of Women with Rheumatological Conditions during Family Planning and Pregnancy
Megan E. B. Clowse1, Munther Khamashta2, Daphne S. Pushparajah3 and Eliza Chakravartty4. 1Duke University Medical Center, Durham, NC; 2The Rayne Institute, London, United Kingdom; 3UCB Pharma, Brussels, Belgium; 4OMRF, Oklahoma City, OK.

Background/Purpose: Rheumatological diseases often affect women of reproductive age and can impact pregnancy outcomes. There is a need to understand how women with RDs are managed by their rheumatologists. We investigate the treatment pathway and care of women with rheumatological conditions who become pregnant.

Methods: Two online surveys, one in rheumatologists and one in pts, were undertaken. Surveys were conducted in the US, UK, Germany and Mexico. Rheumatologists were questioned on the last three pts who they have consulted whilst being pregnant or considering becoming pregnant. Rheumatologists were questioned on pts with rheumatoid arthritis (RA) and lupus. Pts survey included women with RA who had been pregnant in the past 2 years. Pts were questioned on their interactions with rheumatologists and obstetrician/gynaecology physicians (OB/GYN).

Results: 30 rheumatologists completed the physician survey. 57 RA pts completed the pt survey. Rheumatologists were aware of the pt’s intention to become pregnant in 76% of pts. When planning their pregnancy 44% of pts consulted with a rheumatologist and 51% with their OB/GYN. One quarter of pts consulted with their rheumatologist and 61% with their OB/GYN. For rheumatologists the majority of initial visits occurred prior to pregnancy (70%). During pregnancy rheumatologists saw 43% of pts once a month or more, 42% every trimester and 14% only once during pregnancy. 83% of pts reported that rheumatologists were very influential on how they managed their pregnancy. For OB/GYN, this figure was 87%. The majority of pts rated the level of information reliability on managing disease from both the rheumatologist and OB/GYN high. A treatment plan related to management of RA or pregnancy was initiated by rheumatologists for 56% of pts. 51% of pts reported they had a treatment plan in place prior to pregnancy. 60% of rheumatologists made treatment changes in anticipation of or during pregnancy. When considering treatment switches during pregnancy, rheumatologists increased steroid use and decreased biologic use (Table). For rheumatologists, the most common reason for switch was the pt request to pregnancy medication concerns (43%).

Conclusion: The involvement of rheumatologists in the management of women with rheumatological conditions who are planning to become or are pregnant is high, and they have substantial influence on how pts manage their pregnancy. The patients had a high level of interaction with both rheumatologists and OB/GYN throughout the journey. This emphasizes the importance of cross-collaborative care and the sharing of information between specialists involved in the management of women with rheumatological conditions during family planning and pregnancy.

Table: Treatment switches in pregnant women

<table>
<thead>
<tr>
<th>Rheumatologists (N = 30)</th>
<th>Before Switch</th>
<th>After Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>35%</td>
<td>43%</td>
</tr>
<tr>
<td>DMARDs</td>
<td>76%</td>
<td>35%</td>
</tr>
<tr>
<td>No treatment</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Other treatment</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Anti-TNF biologic</td>
<td>28%</td>
<td>0%</td>
</tr>
<tr>
<td>Non-anti-TNF biologic</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Response to question: Thinking about your last three patients who have consulted you whilst being pregnant or considering becoming pregnant, what treatment change did you make during pregnancy? Please indicate the product before and after the switch. If you stopped the treatment without switching the patient to another product, you don’t need to indicate a product in the “after switch” column.

Disclosure: M. E. B. Clowse, UCB Pharma; S. Kamasha, INOVA diagnostics; A. strawberries, Medimmune; UCB, GSK; D. S. Pushparajah, UCB Pharma; J. Ashwini, UCB, 5.

1360
Monitoring Methotrexate and Leflunomide Treatment for Liver Toxicity: the Kaiser Permanente Experience.
Robert Goldfien1 and Lisa Herrinton2. 1Kaiser Permanente, Richmond, CA; 2Kaiser Permanente, Oakland, CA.

Background/Purpose: Methotrexate (MTX) and Leflunomide (LEF) are widely prescribed to treat rheumatologic and other diseases. Each has the potential to cause liver injury in some patients. Current guidelines recommend regular monitoring of either ALT or AST every 2–3 months even in patients on a stable, long-term dose. Adherence to monitoring guidelines has not been reported for a large, community-based population. As part of a quality improvement project, we assessed adherence to monitoring guidelines as well as practices used by rheumatologists to assure monitoring.

Methods: First, we queried the clinical databases of Kaiser Permanente Northern California to identify all patients who had received 2 or more prescriptions of MTX or LEF, with at least 1 prescription dispensed in the previous 6 months. A adherence to guidelines was defined as having a result for ALT or AST in the 90 days prior to data collection. Second, to assess knowledge of guidelines, as well as clinical prescribing and monitoring practices, we surveyed 40 rheumatologists.

Results: We identified 8,276 Internal Medicine patients on MTX/LEF. Among the rheumatologists, the rate of adherence ranged from 62.3 to 94.6% (weighted mean, 82.3%) (Figure). Survey of the rheumatologists (87.5% response) revealed that all were knowledgeable of guidelines, all prescribed an ALT or AST in the 90 days prior to data collection. 71% did not refill prescriptions in patients without an ALT or AST in the prior 3 months.

Conclusion: Despite use of an electronic health record, knowledge of monitoring guidelines, and efforts to assure adherence, we observed significant variation in monitoring liver toxicity in a community rheumatology practice. Our results underscore the need for more effective tools and workflows that integrate prescribing with monitoring. Such solutions, implemented at the system level, would have wide applicability for drugs used across a range of diseases and specialty areas.

Disclosure: R. Goldfien, None; L. Herrinton, Medimmune, 2.

1361
Rheumatologists’ Attitudes on Cardiovascular Risk and Lipid Screening in Patients with Rheumatoid Arthritis at an Academic Medical Center.

Background/Purpose: Cardiovascular (CV) disease is a major cause of morbidity and mortality in the rheumatoid arthritis (RA) population. Thus, the recognition and management of cardiovascular risk factors in patients with RA is especially important. Despite increased awareness of this risk, recent data suggests that adherence to both primary and secondary prevention strategies is low in the RA population compared to other high risk groups (e.g. diabetics). The objective of this study was to assess rheumatologists’ perceptions of screening for and treating hyperlipidemia (HLD) and CV risk in patients with RA to inform the development of quality improvement initiatives.

Methods: In this qualitative study, all University of Pennsylvania rheumatologists were contacted with an email link to an online survey. The survey, administered via REDCap, included 15 questions assessing attitudes towards lipid screening and CV risk in RA. Answers were deidentified. The
chi-squared test was used to examine the association between respondent characteristics and attitudes.

**Results:** Of 28 survey invitations, 24 (85.7%) were returned. All respondents felt there was either a high (N = 14) or moderate (N = 10) risk of CV disease in RA. Rheumatologists’ perceptions of their practice are given in the Table. Seventeen (70.8%) respondents did not believe that primary care physicians (PCPs) are aware of the increased CV risk in RA. Eighteen (75%) believed that both rheumatologists and PCPs should screen for HLD in patients with RA; the remainder felt that PCPs are responsible. Female physicians were more likely to report that both rheumatologists and PCPs should be responsible for screening for HLD (p = 0.03). Nearly all respondents (87.5%) felt that PCPs should be responsible for treating HLD. When asked to rank the clinically most useful approach to estimating CV risk in RA among 3 options, 17 of 21 respondents ranked “CAD equivalent like diabetes mellitus” as their first choice. The most commonly mentioned barriers to screening were time (N = 11), patient complexity (N = 6), and forgetting or needing a prompt (N = 4). An electronic health record (EHR) reminder was the most commonly mentioned idea for increasing HLD screening in rheumatology and primary care practices (N = 11).

**Conclusion:** All respondents believed that there is at least a moderately increased risk of CV disease in RA. Most believed that PCPs are not aware of the increased risk, but the majority also believed that PCPs should be responsible for treating HLD. Quality improvement strategies to bridge this disconnect are needed. Several barriers to screening were identified. Respondents recommended using an EHR prompt to increase screening for HLD and improve recognition of CV risk.

**Table.** Rheumatologists’ Perceptions of Their Own Practice

<table>
<thead>
<tr>
<th>Question</th>
<th>Total Respondents - n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you routinely check lipids in your patients with RA?</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Almost Never</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Most of the Time</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Always</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Do you routinely initiate treatment of hyperlipidemia in your patients with RA?</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Almost Never</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Most of the Time</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Always</td>
<td>0</td>
</tr>
<tr>
<td>How comfortable do you feel in counseling about diet and exercise in your patients with RA and hyperlipidemia?</td>
<td></td>
</tr>
<tr>
<td>Not at all comfortable</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Somewhat comfortable</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Very comfortable</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>Always</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>How comfortable do you feel initiating medication therapy for hyperlipidemia?</td>
<td></td>
</tr>
<tr>
<td>Not at all comfortable</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Somewhat comfortable</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>Very comfortable</td>
<td>10 (41.7)</td>
</tr>
</tbody>
</table>

**Disclosure:** A. Komarla, None; A. Ogdie, None.

**ACR/ARHP Poster Session B**

**Rheumatoid Arthritis - Clinical Aspects: Comorbidities, Treatment Outcomes and Mortality**

**Monday, November 17, 2014, 8:30 am - 4:00 pm**

**1362**

**Impact of Rapid Attainment of Stringent Measures of Efficacy in Rheumatoid Arthritis on Patient-Reported Outcomes.** EA Alemao, S Joo, S Banerjee, P Emery, M Weinblatt. *Bristol-Myers Squibb, Princeton, NJ, BMS, 1, BMS, 3; 1, BMS, 3; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1; 1, BMS, 3; 1, BMS, 1.*

**Background/Purpose:** Treatment guidelines in RA recommend that therapies aim to reach a target of remission or low disease activity (LDA) and that these targets should be reached in 3–6 months (mths). This timeframe is based on “expert opinion” rather than empirical data. Our objective was to evaluate the benefits of rapid (within 3 mths) vs later attainment of stringent measures of efficacy (SME) such as ACR/EULAR remission criteria (SDAI <3.3, CDAI <2.8), LDA (DAS <2.6), and ACR70 on pt-reported outcomes (PROs) in pts with RA in a randomized controlled trial.

**Methods:** Data were analyzed from a Phase IIb study evaluating SC anti-IL-6 monoclonal antibody clazakizumab (CLZ) with or without MTX in pts with moderate-to-severe RA and inadequate response to MTX. Pts were randomized equally to CLZ 25, 100 or 200 mg with MTX every 4 wks; CLZ 100 or 200 mg monotherapy every 4 wks; MTX alone; or adalimumab with MTX every 2 wks. ‘Rapid’ attainment of SME (DAS28 (CRP) <2.6, ACR70, SDAI <3.3 and CDAI <2.8) was based on attaining SME within 3 mths. Pts attaining SME between 3 to 6 mths and after 6 mths were considered ‘intermediate’ and ‘late’, respectively. PROs evaluated during the 12-mth follow-up period included physical functioning using HAQ-DI, quality of life (QoL) using the Short Form-36 Health Survey (SF-36) (physical component summary [PCS] and mental component summary [MCS]), and pain and fatigue using visual analog scales. Mixed models were used to estimate both fixed and random effects of independent variables on the outcome measures.

**Results:** A total of 418 pts were included in the analysis; average age was 50.4 yrs and 83.5% were females. At 12 wks (‘rapid’ group), 33.3%, 22.7%, 19.6% and 18.9%, respectively. Pts who attained SME within 3 mths had attained ACR70, SDAI <3.3 and CDAI <2.8 rapidly vs ‘late’; the mean differences (delta) between the ‘rapid’ vs ‘late’ group were higher than the thresholds for minimum clinically important differences for these outcomes. Directionally similar results were observed for those attaining SME at 6 mths and CDAI <2.8 rapidly vs late, although the results did not meet statistical significance due to small numbers of pts. There was no consistent pattern in PROs between the ‘rapid’ vs ‘intermediate’ group (Table).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>D[ DAS28 (CRP) &lt;2.6]</th>
<th>p-value</th>
<th>D[ ACR70 ‘rapid’ vs ‘late’]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>-0.37</td>
<td>0.0085</td>
<td>-0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>3.5</td>
<td>0.0007</td>
<td>3.4</td>
<td>0.0011</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>-2.2</td>
<td>0.1073</td>
<td>2.2</td>
<td>0.1261</td>
</tr>
<tr>
<td>Pain</td>
<td>-16.4</td>
<td>&lt;0.0001</td>
<td>-14.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-15.5</td>
<td>&lt;0.0001</td>
<td>-13.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusion:** Pts with rapid attainment of SME (including treatment guideline targets) tend to benefit more in the longer term in physical functioning, QoL, pain and fatigue than those attaining these measures much later; the findings are mixed for those attaining SME in the intermediate 3–6 mths time period.

**Disclosure:** E. Alemao, BMS, 1, BMS, 3; S. Joo, BMS, 1, BMS, 3; S. Banerjee, BMS, 1, BMS, 1, BMS, 1, P. Emery, A. Ogdie, None; K. Davidson, None; J. Bathon, None; J. Giles, None.

**1363**

**Psychosocial Comorbidities Are Independently Associated with Subclinical Atherosclerosis in Rheumatoid Arthritis.** Ying Liu, M. Szklarz, K. Davidson, J. Bathon, J. Giles. *Columbia University Medical Center, New York, NY, J. Hopkins Bloomberg School of Public Health, Baltimore, MD, Columbia University, New York, NY.*

**S599**
Background/Purpose: Rheumatoid arthritis (RA) is associated with higher rates of cardiovascular disease (CVD) and subclinical atherosclerosis as well as psychosocial comorbidities, which themselves are associated with CVD. We explored if psychosocial comorbidities differentially contribute to CVD risk in individuals with RA compared with non-RA controls.

Methods: Data were derived from a longitudinal cohort study of subclinical cardiovascular disease in RA and non-RA controls. Using validated scales, psychosocial comorbidities (depression, chronic life stressors, anxiety/anger, social support, discrimination/hassles) were assessed. Differences in the associations of psychosocial measures with measures of subclinical atherosclerosis (coronary artery calcium [CAC] assessed using computed tomography and carotid intima-media thickness [IMT]/plaque assessed using ultrasound) were explored using multivariable regression models incorporating RA × psychosocial variable interaction terms. Models were adjusted for relevant unbalanced demographic variables, CVD risk factors, and markers of RA activity/inflammation.

Results: 195 RA patients [mean age = 59 ± 9 years, 61% female; 87% Caucasian; median RA = 9 years; mean DMAS8 = 3.65 ± 1.1] were compared with 1073 controls. RA participants had a higher prevalence of psychosocial comorbidities (depression and personal health, job, and total stress) compared with controls. In RA, per-unit higher Spielberger trait anxiety scores and the presence of caregiver stress were associated with an increased adjusted odds of CAC > 100 units (Table). Per-unit higher Spielberger trait anger scores and Center for Epidemiologic Studies Depression scores were also associated with an increased odds of CAC > 100 after adjustment (Table), although these effects were diminished with adjustment for anxiety. All associations were preserved after adjusting for markers of inflammation (IL-6 and CRP) and were only observed in RA patients, but not controls (adjusted interaction term p-values 0.001–0.077). Having job stress was associated with an increased frequency of carotid plaque (adjusted OR = 3.21 (p = 0.019)), and increasing social support was associated with lower internal carotid IMT (adjusted p = 0.024) in RA participants, but not in controls.

Conclusion: Depression, stress, anger/anxiety and social support may affect CVD risk, specifically in RA patients, by promoting atherosclerosis. Because the impact of these factors on atherogenesis may be accentuated in RA compared with the non-RA population, screening and treatment of psychosocial comorbidities may help reduce the known increased burden of CVD in RA.

Disclosure: Y. Liu None; M. Szklo None; K. Davidson None; J. Bathon None; J. Giles None.

1364 Accelerated Diastolic Dysfunction in Premenopausal Women with Rheumatoid Arthritis. Yune-Jung Park1, JiHee Kim 2, Ki-Jo Kim 3, Wan-Uk Kim 3

Background/Purpose: Disturbances of diastolic function precede systolic heart failure and, although clinically silent, represent the earliest sign of cardiac involvement. Diastolic dysfunction is associated with age, female, and hypertension. However, little is known about the age-specific incidence rates and risk factors for diastolic dysfunction in patients with rheumatoid arthritis (RA).

Methods: We used standard two-dimensional/Doppler echocardiography to screen for the presence of diastolic dysfunction in 61 patients with RA (mean ± SD age, 48.1 ± 7.9 years) and 107 healthy subjects (47.3 ± 9.4 years). All participants were premenopausal women with no history of hypertension. Diastolic dysfunction was defined as impaired relaxation with or without increased filling pressures.

Results: The two groups were similar with respect to age (P = 0.269). Patients with RA had significantly higher LV mass index, LV filling pressure, and lower E/A velocity than controls. All patients had preserved ejection fraction (EF ≥ 50%). Diastolic dysfunction was more common in patients with RA at 47% compared with 26% in the controls (P = 0.004). Women with RA in the 30- to 49- year age group were over 3.5 times more likely to have diastolic dysfunction than those of similar age in the control group (OR = 3.54; 95% CI 1.27 to 9.85). A mong patients with RA, high CRP levels were independently associated with diastolic dysfunction even after adjustment for cardiovascular risk factors (P = 0.009).

Conclusion: Premenopausal women with RA, diastolic dysfunction is much more common and the age at onset is reduced. Early screening of myocardial function may provide an opportunity for preventing future cardiovascular disease.

Disclosure: Y. J. Park None; J. Kim None; K. J. Kim None; W. U. Kim None; C. S. Cho None; K. S. Park None; K. D. Yoo None.

1365 ARE Erosions a Disappearing Feature in Rheumatoid Arthritis (RA)? Joint Damage in Patients with EARLY RA at 10 YEARS after Diagnosis. Juha Asikainen1, Kalevi Kaarela 2, Heidi Mäkinen 3, Hannu Kautiainen 4, Pekka Tarkkanen 5, T忤is Dohanich6, and Tuuliikki Sokka2

Background/Purpose: Treatment of rheumatoid arthritis (RA) has improved during the last decade. Also importance of regular monitoring has been emphasized. Our objective was to study the extent of radiographic joint damage in an early RA cohort at 10 years after diagnosis.

Methods: Our early RA cohort includes 990 patients from a single clinic with a clinical diagnosis of early RA in 1997 – 2004. Radiographs of hands and feet were taken at a 10 year follow-up visit and were analyzed according to the Larsen score (0–100) including M CP I-V, wrists, and M TP II-V. Patients were treated with the T2T strategy by a multidisciplinary care for 2 years with follow-up visits at 5 and 10 years.

Results: Baseline characteristics of 990 patients were the mean (SD) age 57 (16) years, 67% female, 61% seropositive (RF/CCP + any time over 10 years) and median (IQR) duration of symptoms before diagnosis 6 (3, 12) months; 657(66%) patients were available for a 10 year follow up. Reasons for non-attendance among 333 patients included death (52%), high age, multi-comorbidity or institutionalization (10%), moving from the area (12%); 8% declined, 4% were lost to follow-up and 14% miscellaneous reasons. Thus, radiographs were available in 657 patients (66% seropositive); serology of one patient was missing.

At 10 years, erosions were present in 48% (314/656) patients including 61%(266/435) seropositive and 22% (48/221) seronegative patients. Among seropositive patients, Larsen score was >=10% of theoretical maximum in 28% (121/435) patients, <10% of max in 33% (145/435) patients, and 39% (169/435) remained non/erosive; for seronegative patients the corresponding figures were 5%(11/221), 17%(37/221) and 78%(173/221), respectively. The mean (SD) and median (IQR) Larsen score in seropositive patients was 7.8 (11) and 4.0 (1.0, 10), and in seronegative patients 2.0 (4.0) and 0 (0.3).

In seropositive patients, the 10-years Larsen score declined over time while in seronegative patients erosiveness remained low and stable (figure). Over 10 years, all patients had been taking csDMARDs, 83% had been taking systemic glucocorticoids, and 20% bDMARDs.

Conclusion: Larsen score remained low over 10 years and erosion rates decreased over time.
Outcomes of Interstitial Lung Disease Associated with Rheumatoid Arthritis in High Volume Referral Centers. Megan Krause1, Amish Dave2, Cynthia S. Crowson1, Arun K. Chandran1, C. John Michet1, Paul F. Dellaria3, and Eric L. Matteson4. 1Mayo Clinic, Rochester, MN; 2Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: To describe the characteristics and morbidity and mortality impact of interstitial lung disease in rheumatoid arthritis (RA).

Methods: A retrospective review was performed at 2 high volume tertiary care centers identifying patients with clinician determined RA associated interstitial lung disease (RA-ILD) in 1997-2012. Data regarding demographic and disease characteristics of RA, including serologic status and erosions, were collected. Features of pulmonary disease, including successive radiographic findings and pulmonary function test (PFT) results, were abstracted. Kaplan-Meier methods and Cox models were used to estimate survival rates and examine risk factors for mortality.

Results: A total of 119 patients were identified with RA-ILD (55% women; mean age at RA diagnosis 56.6 [range: 13.1–84.8] years; 63% former/current smokers; 75% rheumatoid factor positive). Cyclic citrullinated antibodies were tested in 92 (79%) and present in 71/92 (77%). Erosive arthritis was present in 62 patients (52%). The mean time from RA diagnosis to ILD diagnosis was 9.4 [10.9–43.0] years. The mean follow-up time after ILD diagnosis was 3.5 [0.0–15.0] years. Over follow-up, 61 patients (51%) required supplemental oxygen. On repeat PFT, the mean percent predicted were 76.1% [40–148] for total lung capacity (TLC), 70.5% [32–141] for forced vital capacity (FVC), 70.0% [25–135] for forced vital capacity in one second (FEV1), both absolute volume and percent predicted, were associated with mortality (p = 0.027 and p = 0.007, respectively, adjusted for age and sex).

Conclusion: In this large cohort, ILD is an important complication of RA with a very high mortality rate in the first 5 years following diagnosis. The most common RA-ILD diagnoses were UIP and NSIP, and contrary to previously published data, there was no survival difference between these two groups. Earlier in disease, a lower diffusion capacity may identify UIP RA-ILD compared to non UIP RA-ILD. Further research is required to identify risk factors and biomarkers for this extracutaneous manifestation of RA.

Disclosures: M. Krause, None; A. Dave, None; C. S. Crowson, None; A. K. Chandran, None; C. J. Michet, None; P. F. Dellaria, None; E. L. Matteson, None.
positive trend for CVD in RA (OR = 1.58; 95% CI = 0.90–2.76; p = 0.10) and AS (OR = 1.77; 95% CI = 0.96–3.27; p = 0.07). Disease duration in all CIRD groups and functional capacity (HAQ) in RA were associated with an increased risk of CVD (OR = 2.15; 95% CI = 1.29–3.56; p = 0.003). Most patients had a moderate CV risk according to the SCORE charts.

**Conclusion:** Despite recent advances in the management of CIRD, incidence of CVD remains increased in Spanish subjects with CIRD attending outpatient rheumatology clinics. It is of particular relevance that almost half of them were receiving biological therapy and most patients had low disease activity at the time of assessment.

![Graph](Image)

**Disclosure:** S. Castaneda, None; M. A. Martin, None; C. González-Juanatey, None; J. Llorca, None; M. J. García Yébenes, None; S. Pérez-Vicente, None; J. Sánchez Costa, None; F. Díaz-González, None; M. A. González-Gay, None; C. P. Collaborative Group, None.

### 1368

**Are Tender Joints Better Than Synovitis to Predict Structural Damage in Rheumatoid Arthritis?**


**Yang Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.**

**Background/Purpose:** Longitudinal studies indicate that synovitis can predict subsequent structural damage in rheumatoid arthritis (RA) but the clinical relevance of tenderness is unclear. The aim is to evaluate the predictive validity of tenderness for subsequent structural damage in RA, with synovitis as the comparator.

**Methods:** Study design: 2-year prospective study. Patients: Active RA (1987 ACR criteria) requiring anti-TNF. Data collected: For each patient, 32 joints (16 hands and 16 feet) were examined by clinical and Power Doppler (PDUS), at baseline and after 4 months of anti-TNF. For each joint, PDUS was performed at baseline and after 4 months of anti-TNF. For each joint, PDUS was performed at baseline and after 4 months of anti-TNF.

**Patients:** A total of 1888 joints were examined at baseline and after 4 months of anti-TNF.

**Results:** Fifty-nine out of 77 recruited patients completed the 4 months of the study with radiographic evaluation at 2 years (female: 81%, age 56 ± 12 years, rheumatoid factor positive: 73%). Radiographic progression was observed in 9% of the 1888 evaluated joints (16% of the 118 wrists, 7% of the 590 MCP, 8% of the 590 PIP, and 11% of the 590 MTP). Baseline tender joints were the least predictive for radiographic progression at 2 years (OR = 1.53 [1.02; 2.29] p = 0.04) when compared to synovitis (clinical OR = 2.08 [1.39; 3.11] p < 0.001 or PDUS OR = 1.80 [1.20; 2.71] p = 0.005 respectively). Tender joints with presence of synovitis was predictive of radiographic progression (OR = 1.89 [1.25, 2.85] p = 0.002) while non-tender joints with no synovitis was negatively predictive (OR = 0.57 [0.39, 0.82] p = 0.003) (Figure 2).

**Conclusion:** Clinical or US synovitis is more predictive than tenderness to predict subsequent structural progression. Co-existence of tenderness and synovitis at the level of an individual joint would suggest the need for either local/systemic treatment to prevent subsequent structural damage.

![Graph](Image)

**Disclosure:** P. Cheung, None; K. Mari, None; V. Devauchelle, None; J. Bentin, None; S. Jousse-Joulin, None; M. A. d’Agostino, None; G. Chales, None; I. Chary-Valckenaere, None; F. Etchepare, None; P. Gaudin, None; X. Mariette, None; A. Sarau, None; M. Dougdos, None.
cognitive complaints among patients with RA. Less is known about the relative contribution of how a change in these risk factors may affect an RA patient’s perceived cognitive function.

**Methods:** We analyzed data from BRASS, a longitudinal RA cohort study. The data collection includes joint exams, serological analyses, and patient reported outcome measures collected annually from 2003-2014. Patients were asked to report the degree of their cognitive complaints concerning their memory, concentration, and word-finding difficulties (Table 1). In univariate analyses, we assessed known predictors for cognitive complaints (age, gender, ethnicity, education, CV Risk (Desai et al, 2012)) and computed variables that measured the past year’s change (MDHAQ depression, MDHAQ fatigue, MDHAQ sleep, exercise level (METS), DAS28-CRP3, corticosteroid use) in relation to a worsening of cognitive complaints. Univariate factors (p<0.10), sociodemographic variables and the CV risk score were then entered into a multivariable backwards elimination mixed model to assess their impact on the degree of cognitive complaints.

**Results:** There were a total of 1126 subjects with at least two annual visits used in this analysis. Univariate analyses revealed that an increase in MDHAQ depression, fatigue, and corticosteroid use as well as a decrease in sleep quality and exercise level were associated with worsened cognitive complaints at follow-up. The multivariable mixed model that adjusted for sociodemographic variables and the CV risk score showed only that worsening MDHAQ depression, fatigue and increased corticosteroid use were associated with an increase in cognitive complaints one year later (Table). Neither a change in DAS28-CRP3 score nor exercise level impacted the degree of reported cognitive complaints.

**Conclusion:** Cognitive difficulties in RA are sensitive to a worsening of psychological factors such as depression but also to a change in corticosteroid use and fatigue. In this analysis disease activity measures did not appear to influence subjective cognitive complaints over time. Future studies of cognition difficulties in RA patients should focus on whether corticosteroid use and fatigue levels may be markers of subclinical disease activity that may drive patients to more likely reflect upon cognitive difficulties.

Clinical and Psychological factors predicting an increase is subjective cognitive complaints:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Sex (Female or not)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>CV Risk Score (0–9)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Ethnicity (White or not)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Education (college and above or not)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Poor Concentration (Not at all, Sometimes, Often)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Poor Memory (Not at all, Sometimes, Often)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Word-finding Difficulty (Not at all, Sometimes, Often)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (underweight vs. Obese)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (Normal vs. Obese)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (Overweight vs. Obese)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Worsened MDHAQ Depression (−3, 3)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>Worsened MDHAQ Fatigue (−100, 100)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Dependent variable (Δ Cognitive complaint -6, 6) higher equals increased cognitive complaints.

Do you have any of the following symptoms NOW?

- 1371 Background/Purpose: The purpose of the study was to describe prevalence and components (c) of MetS in a cohort of early RA, to compare it with data from matched controls and to investigate MetS impact on disease activity. **Methods:** The study population was a prospective cohort of early RA (95% satisfying 2010 ACR/EULAR criteria) initiated in 2004. At baseline, 2 months-apart for the first 2 years and thereafter at least six-months-apart, patients had complete medical evaluations that included height, weight and blood pressure, standardized rheumatic evaluations and assessments of...
comorbidity and treatment: at 6 months fixed intervals, fasting serum glucose (GLU), triglycerides (TRG), HDL-Cholesterol (HDL) and acute reactant-phase were performed. Data from a local database of health controls randomly selected and matched were used.

M eTs was defined according to 3 sets of criteria (ATP-III, AHA/NHLBI, IDF) and body mass index (BMI) ≥30 was used as a surrogate of the waist circumference criteria-c. Sustained remission (SR) was defined according to ACR/EULAR 2012 criteria and lasting ≥ 6 months.

The study was approved by the internal review board. Written informed consent was obtained.

Appropriate statistics was used. All statistical tests were 2-sided and evaluated at the 0.05 significance level.

Results: Up to March 2014, 162 patients were included in the cohort, of whom 160 had complete baseline data, they were more frequently middle-aged females [42 (55%); mean (SD) years of age: 51.2 ± 12.6]; RF (+) (81.3%), ACP + (83.8%) had high disease activity; comorbid conditions were present in 82 patients (51.3%). Patients were treated with conventional DMARDs.

Prevalence of MetS at the baseline evaluation varied (depending on the criteria applied) from 11.3% to 17.5% in RA patients and was similar to that in controls (vs. 13.8% to 18.8%). Distribution of MetS criteria applied) from 11.3% to 17.5% in RA patients and was similar to that from matched controls and varied from 11 to 18%.

Up to last follow-up, 39 patients (34.5%) developed incidental MetS (out of 113 baseline MetS-free patients). A usual incident rate decreased after the third year of follow-up. Patients who developed incidental MetS were older, more frequently menopause females, had higher BMI, had more cumulative disease activity and disability previous incidental MetS and developed more frequently erosive disease than their counterparts. In the Cox regression analysis, cumulative DAS28 (OR: 1.81, 95% CI: 1.346–2.433, p = 0.05) was less prevalent in the HCV-positive RA group [24 (25%) vs. 729 (39%)]. There was no difference noted in the prevalence of other comorbidities (type 2 diabetes, chronic kidney disease, or hypertension). LDL, HDL, and triglyceride levels were similar between groups (Table 1). After adjusting for age, sex, race, smoking, BMI, comorbidities, disease duration, and RA therapies, the prevalence of CVD was lower in the HCV-positive RA group [OR 0.58 (0.33–0.99) p = 0.05]. In multivariate regression logistic models performed in a subset of 942 subjects with available data and adjusting for DAS28 scores, these associations were no longer significant [OR 0.55 (0.28–1.09), p = 0.09 (Table 2)], although the point estimate remained similar.

Conclusion: Patients with concomitant RA and chronic HCV appear to have a lower odds of prevalent CVD at enrollment compared to those with RA alone. It might be hypothesized that comorbid HCV infection modulates chronic systemic inflammation by altering known atherogenic pathways.

Table 1: Baseline Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCV + RA N = 97</th>
<th>HCV-RAN = 1853</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.2 ± 7</td>
<td>63.9 ± 11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>94 (96.9)</td>
<td>1640 (90.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>5 (5.3)</td>
<td>198 (10.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current smoker, N (%)</td>
<td>46/97 (47.4)</td>
<td>461/1814 (25.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (0.56)</td>
<td>28.5 (0.14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Disease Duration (yrs)</td>
<td>8.4 (9.4)</td>
<td>10.9 (11.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>RA disease Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSAS28 (N = 986)</td>
<td>4.7 (1.6)</td>
<td>4.02 (1.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>DAS28 (N = 1561)</td>
<td>74/93 (80.0)</td>
<td>1260/1632 (77.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>CCP</td>
<td>73/91 (80.2)</td>
<td>1241/1625 (76.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Erosions</td>
<td>44/79 (55.7)</td>
<td>72/1403 (51.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate, N (%)</td>
<td>21 (23.3)</td>
<td>852 (51.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prednisone, N (%)</td>
<td>42 (46.7)</td>
<td>625 (37.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Anti-TNFα, N (%)</td>
<td>23 (25.6)</td>
<td>321 (19.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lipid panel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (N = 1128)</td>
<td>102.5 ± 4.2</td>
<td>101.2 ± 1.05</td>
<td>0.93</td>
</tr>
<tr>
<td>HDL (N = 1357)</td>
<td>46.5 ± 2.5</td>
<td>44.7 ± 0.47</td>
<td>0.39</td>
</tr>
<tr>
<td>Triglycerides (N = 1133)</td>
<td>129.7 ± 9.6</td>
<td>141.3 ± 2.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD, N (%)</td>
<td>3 (3.1)</td>
<td>127 (6.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>DM, N (%)</td>
<td>25 (25.8)</td>
<td>530 (28.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>COPD, N (%)</td>
<td>12 (12.4)</td>
<td>144 (7.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>HTN, N (%)</td>
<td>68 (70.1)</td>
<td>1212 (65.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>CAD, N (%)</td>
<td>17 (17.5)</td>
<td>564 (30.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>CVD, N (%)</td>
<td>24 (24.7)</td>
<td>729 (39.3)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = Body Mass Index; CVD = Coronary Artery Disease; CVD = Cardiovascular Disease; DM = Diabetes Mellitus; COPD = Chronic Obstructive Pulmonary Disease; HTN = Hypertension; CAD = Coronary Artery Disease; CVD = Cardiovascular Disease.

Table 2: Prevalence of cardiovascular disease in Hepatitis C positive RA patients compared to RA controls

<table>
<thead>
<tr>
<th>Model</th>
<th>Observations</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1 observations (1905)</td>
<td>0.70 (0.43-1.14)</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 2</td>
<td>2 observations (1561)</td>
<td>0.58 (0.33-0.99)</td>
<td>0.05</td>
</tr>
<tr>
<td>Model 3</td>
<td>3 observations (942)</td>
<td>0.55 (0.28-1.09)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, race

Model 2: Model 1 + DM, HTN, BMI, current smoking, metotrexate use, prednesone use, anti-TNF therapy use, disease duration

Model 3: Model 2 + DSAS28

Abbreviations: DM = Diabetes Mellitus; HTN = Hypertension; BMI = Body Mass Index; CRP = c-reactive protein; DSAS28 = disease activity score

Background/Purpose: Chronic hepatitis C (HCV) and rheumatoid arthritis (RA) have both been associated with higher cardiovascular disease (CVD) in US veterans. Whether the presence of both conditions compounds the risk of CVD remains unknown. We compared the prevalence of CVD in RA patients with and without HCV.

Methods: In this cross-sectional study, 97 out of 1952 (5%) RA subjects were identified with HCV within the Veterans Affairs Rheumatoid Arthritis (VARA) registry by the presence of at least one diagnosis (ICD9) code for chronic HCV. This was validated by chart review in a subset of 28 RA patients, of which 25 (89%) were identified as HCV-antibody positive. At enrollment, the presence of cardiovascular disease (composite of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, heart failure, and peripheral vascular disease) was determined using previously validated algorithms based on ICD9 codes and Current Procedural Terminology codes. Step-wise multivariable logistic regression models assessed differences in the prevalence of CVD, adjusting for factors known to be associated with CVD in RA.

Results: At enrollment, HCV-positive RA patients were more likely to be African-American, were more likely to smoke, had a lower body mass index (BMI), and had shorter disease duration (Table 1). RA disease characteristics between the two groups were similar, though HCV-positive patients were less likely to be prescribed methotrexate and had higher disease activity scores. CVD was less prevalent in the HCV-positive RA patients [24 (25%) vs. 729 (39%)]. There was no difference noted in the prevalence of other comorbidities (type 2 diabetes, chronic kidney disease, or hypertension). LDL, HDL, and triglyceride levels were similar between groups (Table 1). After adjusting for age, sex, race, smoking, BMI, comorbidities, disease duration, and RA therapies, the prevalence of CVD was lower in the HCV-positive RA group [OR 0.58 (0.33–0.99) p = 0.05]. In multivariate regression logistic models performed in a subset of 942 subjects with available data and adjusting for DAS28 scores, these associations were no longer significant [OR 0.55 (0.28–1.09), p = 0.09 (Table 2)], although the point estimate remained similar.

Conclusion: Patients with concomitant RA and chronic HCV appear to have a lower odds of prevalent CVD at enrollment compared to those with RA alone. It might be hypothesized that comorbid HCV injection modulates chronic systemic inflammation by altering known atherogenic pathways.
Disclosures: R. Patel, None; T. R. Mikuls, None; J. S. Richards, None; G. W. Cannon, None; G. S. Kerr, None; L. A. Davis, None; L. Caplan, None; J. F. Baker, None.

1373

Physical Function of Patients with RA Varies Importantly Across Countries, and These Differences Are Not Attributed to GDP: Results from Multi-National Study with 17 Countries. Polina Putrik1, Sofia Ramiro2, Andras Keszi3, Ihane Hmamouchi4, Maxime Dougdas5, Till Uhlig6, Tore K. Vien6 and Annelles Boonen1. 1Maastricht University Medical Center, Maastricht, Netherlands, 2Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, University of Amsterdam, 3Uniklinik RWTH Aachen University, Aachen, Germany, 4Mohamed V. Souissi University, Rabat, Morocco, 5Paris Descartes University, Paris, France, 6Diakoniejejmet Hospital, Oslo, Norway.

Background/Purpose: Physical function is an important outcome in RA and is essential for patients’ quality of life. Is has not yet been sufficiently explored whether country level differences in reported function exist, and whether they interact with individual level factors. The objective of this study was to understand which individual or country level socio-economic factors contribute to functional status of RA patients.

Methods: Data from a cross-sectional multinational (17 countries) study (COMORA) was used. Contribution of age, gender, education, employment to function (as measured by the HAQ) were explored, adjusting for potential confounders. Adjusted differences (Bonferroni correction) between countries were tested. Taiwan was chosen as the reference (country with lowest mean HAQ). Further, country was replaced by gross domestic product (GDP) (low vs high GDP), and contribution of socio-economic welfare was investigated. Improvement in R-square of the two models that included either country or GDP was compared. Interactions between (1) education (2) age and (3) gender with country and GDP were tested.

Results: A total of 3920 RA patients from 17 countries (range 30 to 411) were included in COMORA. Mean age was 56 y.o. (SD13), 82% females, 35% and 39% had primary and secondary education, respectively. Mean HAQ was 1.0 (range 0.7 (Taiwan) - 1.5 (Morocco)). Gradients in HAQ across individual socio-economic factors were seen for education and gender but not age, after adjusting for individual disease characteristics and disfavoring low educated (β=0.16 vs high educated) and females (β=0.11 vs males). Final model was adjusted for comorbidities (Wolfe-Michaud index), total joint count, swollen joint count, erythrocyte sedimentation rate, and marital status. Country differences in HAQ varied from 0.11 (Venezuela) to 0.74 (Netherlands) compared to Taiwan, after adjustment for individual factors (Figure 1). Low GDP countries had 0.11 higher score on HAQ compared to high GDP countries. Contribution of country to R-square (model fit) was 0.05 and of GDP 0.01 (negligible). Interactions were either not statistically significant or not clinically relevant after stratification.

Conclusion: Among socio-economics factors, female gender and low education were independently associated with worse physical function after adjusting for individual disease characteristics. While substantial differences in HAQ exist between countries, socio-economic welfare did not explain these differences. Other cultural factors should be examined. Awareness of existing inequalities is a first step towards clinical and policy actions to reduce them.

Figure 1. Difference in HAQ score between countries, adjusted for confounders.

Disclosure: P. Putrik, None; S. Ramiro, None; A. Keszi, None; I. Hmamouchi, None; M. Dougdas, None; T. Uhlig, None; T. K. Vien, None; A. Boonen, None.

1374

A Comparison of the Risk for Cardiovascular Event in Patients with Rheumatoid Arthritis Treated with Biologic Disease Modifiers and Patients Treated with Methotrexate Only. Majed Khraishi2 and Rana Aslanov3. 2Nexus Clinical Research, St John’s, NF, 3M’emorial University of Newfoundland, St John’s, NF.

Background/Purpose: We aimed to investigate whether the 10-year cardiovascular risk (CV) differs between patients with RA treated with Biologic Disease Modifiers (BDMARDs) and Methotrexate (MTX) and with MTX only.

Methods: Patients with RA receiving MTX and BDMARDs were prospectively followed up from January 2011 to March 2014. Cardiovascular risk was assessed using the Framingham Risk Score (CCS 2009 Guidelines) and compared between cohorts. The presence of traditional CV risk factors was ascertained at the baseline and at every six months of observation up to 24 months.

Results: From 515 patients enrolled at the baseline, 15 patients dropped out of the study. Total 500 patients (75.2% females) with median age 57 years (Q1-Q3=50–65) were prospectively followed for at least 24 months. The mean (SD) age at RA diagnosis was 46.7 (13.5) years with the mean (SD) duration of RA symptoms 10.0 (8.6) years. Overall, females were significantly younger (p (95% CI)=0.016 (0.6-5.7)) while more males were obese (61.3% vs 49.5%, p=0.023). Forty (8.0%) patients with documented MI and 32 (2.4%) patients with TIA were excluded from the analysis. Twelve patients (2.4%) experienced MI during the observation period with median age for males 68 years and for females 75 years. Significant differences in age, disease duration and activity indices were detected between cohorts. However, no significant changes were found in gender distribution, smoking status, and mean Atherogenic Index (AI) values. RA patients treated with MTX were older at the time of RA diagnosis and enrollment into the study but with significantly shorter duration of disease. 50.2% of patients were treated by Prednisone; 95.8% by MTX. 10-year CV risk was strongly correlated with Prednisone (r=0.122, p=0.006) and MTX only (r=0.178, p<0.001) therapy, and with total number of comorbidities in RA patients (r=0.569, p<0.001). Men had a significantly higher risk for CV event than women at the baseline and 24 months later.

Conclusion: Our findings demonstrated significant difference in the 10-year cardiovascular risk at 24 months between the two treatment modalities. The combination of BDMARDs and MTX treatment modality seems to be more beneficial in the reducing patients’ risk for CV events. Intensive treatment of chronic inflammation positively affects both patients’ arthritis symptoms. The combination of BDMARDs and MTX treatment modality seems to be more beneficial in the reducing patients’ risk for CV events. Intensive treatment of chronic inflammation positively affects both patients’ arthritis symptoms and their RA-dependent CV risk.

Disclosure: M. Khraishi, Research grants, 2; R. Aslanov, None.

1375

Educational Level and Not Ethnicity an Important Determinant of Disease Progression in Patients with Rheumatoid Arthritis. Sharon Dowell1,2, Gail S. Kerr2, Yusuf Yazici3, Christopher Swearingen4, Mercedes Quinones3, Luis R. Espinoza2, Edward L. Treadwell5, Theresa Lawrence-Ford1, Yvonne Sherrer1, Angelica M. Foreman6, Ignacio Garcia-Valladares1, Rodolfo Perez Alamo1, Chunqiao Luo7, Akgun Ince8, Adrian Godoy9 and John Amatruda10. 1Howard University, Washington, DC; 2Washington DC VAMC, Georgetown and Howard University, Washington, DC; 3New York University School of Medicine, New York, NY; 4University of Arkansas, Little Rock, AR; 5Howard University Hospital, Washington, DC; 6VA Medical Center, Newark, Delaware; 7VA Medical Center, Middletown, DE; 8VA Medical Center, Greenville, NC; 9North Georgia Rheumatology Group, PC, Lawrenceville, GA; 10Center Rheum Immunol Arthritis, Fort Lauderdale, FL; 11Detroit VAMC, Detroit, MI; 12Hospital General de Occidente, Zapopan, Jal., Mexico; 13LSUHSC, New Orleans, LA; 14University of Arkansas for Medical Sciences, Little Rock, AR; 15St Louis University, St. Louis, MO.

Disclosure: M. Dougados, None; CDAI 11.9 (8.4) 18.1 (10.0) 0.001 (<3.2–2.0); 6HCQ 0.7 (0.9) 1.1 (0.8) 0.001 (0.5–0.9); 7Lumbar TC 4.1 (1.9) 3.2 (2.0) 0.001 (0.5–0.9); 8MTX 50–65) were prospectively followed for at least 24 months. The mean (SD) age at RA diagnosis was 46.7 (13.5) years with the mean (SD) duration of RA symptoms 10.0 (8.6) years. Overall, females were significantly younger (p (95% CI)=0.016 (0.6-5.7)) while more males were obese (61.3% vs 49.5%, p=0.023). Forty (8.0%) patients with documented MI and 32 (2.4%) patients with TIA were excluded from the analysis. Twelve patients (2.4%) experienced MI during the observation period with median age for males 68 years and for females 75 years. Significant differences in age, disease duration and activity indices were detected between cohorts. However, no significant changes were found in gender distribution, smoking status, and mean Atherogenic Index (AI) values. RA patients treated with MTX were older at the time of RA diagnosis and enrollment into the study but with significantly shorter duration of disease. 50.2% of patients were treated by Prednisone; 95.8% by MTX. 10-year CV risk was strongly correlated with Prednisone (r=0.122, p=0.006) and MTX only (r=0.178, p<0.001) therapy, and with total number of comorbidities in RA patients (r=0.569, p<0.001). Men had a significantly higher risk for CV event than women at the baseline and 24 months later.

Conclusion: Our findings demonstrated significant difference in the 10-year cardiovascular risk at 24 months between the two treatment modalities. The combination of BDMARDs and MTX treatment modality seems to be more beneficial in the reducing patients’ risk for CV events. Intensive treatment of chronic inflammation positively affects both patients’ arthritis and their RA-dependent CV risk.

Disclosure: M. Khraishi, Research grants, 2; R. Aslanov, None.
Background/Purpose: Formal educational level is often used as a surrogate for socioeconomic status and in patients with rheumatoid arthritis (RA), low levels have been associated with greater morbidity and worse disease outcomes. Yet, the role of formal educational level and its impact on meaningful clinical response (MCR) in ethnic minorities with RA is unknown. We evaluated the correlation of educational level with meaningful clinical response in ethnic minorities with RA.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with at least one follow up visit were assigned to three educational level categories: high school only (HS), high school with some college, and college graduates. Comparisons between educational categories of demographic (age, gender, race, tobacco use), RA disease status (RF, ACPA, nodules/erosions), and RA treatment (prednisone, MARD, biologics) and RA were performed between these groups. The frequency of MCR (RAPID3 ≥0.6) at 3, 6, and 12 months was also evaluated between educational groups.

Results: EMRAC patients (n=723) with approximately 10 months of follow-up were evaluated (Table 1). HS patients were significantly older, with longer disease duration and follow-up than those with advanced educational levels. HS patients also had higher baseline RAPID3 scores (p<0.001). Overall, fewer patients achieved MCR and there was no difference in the frequencies of MCR between educational categories at 3, 6 and 12 months. However, in multivariate analyses adjusted for age, ethnicity, disease duration, and baseline RAPID3 scores, of those who did not achieve MCR, there were more HS patients with significant disease progression (RAPID3 D+0.2) versus college (RAPID3 D-0.5) and college graduates (RAPID3D-0.6) (p=0.02).

Conclusion: Regardless of race or ethnicity, RA patients with low formal educational levels are at risk of clinical progression. In dis ease progression, this category of patient needs to be identified early, and focused interventions such as self-efficacy and health literacy instituted in order to improve disease outcomes.

Table 1

<table>
<thead>
<tr>
<th>Clinical Characteristics of Educational Categories in EMRAC cohort</th>
<th>High School</th>
<th>Some College</th>
<th>College Graduate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
<td>320</td>
<td>306</td>
<td></td>
</tr>
<tr>
<td># of Follow-ups</td>
<td>2.9 (2.5)</td>
<td>3.0 (2.6)</td>
<td>2.9 (2.6)</td>
<td>0.681</td>
</tr>
<tr>
<td>Follow-up Length (months)</td>
<td>11.6 (13.1)</td>
<td>9.1 (7.4)</td>
<td>6.8 (6.3)</td>
<td>0.033</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.1 (12.5)</td>
<td>56.4 (14.3)</td>
<td>49.5 (15.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (%), N</td>
<td>72 (75.6%)</td>
<td>258 (81.9%)</td>
<td>249 (81.6%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>12.0 (11.8)</td>
<td>9.7 (9.1)</td>
<td>8.4 (9.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>36 (47%)</td>
<td>118 (42%)</td>
<td>56 (24%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11 (14%)</td>
<td>99 (35%)</td>
<td>151 (63%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>29 (39%)</td>
<td>65 (23%)</td>
<td>31 (13%)</td>
<td></td>
</tr>
<tr>
<td>RAPID3</td>
<td>13.7 (7.3)</td>
<td>12.8 (7.2)</td>
<td>9.6 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Hx Smoking (N, %)</td>
<td>25 (33.8%)</td>
<td>91 (39.1%)</td>
<td>45 (21.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF + (N, %)</td>
<td>57 (70.4%)</td>
<td>152 (57.6%)</td>
<td>94 (43.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACPA + (N, %)</td>
<td>41 (50.6%)</td>
<td>99 (39.9%)</td>
<td>50 (21.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hx Nodules (N, %)</td>
<td>5 (8.1%)</td>
<td>24 (11.9%)</td>
<td>10 (5.8%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hx Erosions (N, %)</td>
<td>22 (33.3%)</td>
<td>54 (25.2%)</td>
<td>36 (19.7%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Prednisone (N, %)</td>
<td>38 (39.2%)</td>
<td>119 (37.2%)</td>
<td>79 (25.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>MARD (N, %)</td>
<td>73 (75.3%)</td>
<td>234 (73.1%)</td>
<td>215 (70.3%)</td>
<td>0.560</td>
</tr>
<tr>
<td>Biologic (N, %)</td>
<td>28 (28.9%)</td>
<td>96 (30.0%)</td>
<td>119 (38.9%)</td>
<td>0.036</td>
</tr>
<tr>
<td>RAPID3 -3.6 (N, %)</td>
<td>27 (27.8%)</td>
<td>94 (29.4%)</td>
<td>84 (27.5%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Response in 3M (N, %)</td>
<td>9 (9.3%)</td>
<td>34 (10.6%)</td>
<td>32 (10.5%)</td>
<td>0.928</td>
</tr>
<tr>
<td>Response in 6M (N, %)</td>
<td>14 (14.4%)</td>
<td>66 (20.6%)</td>
<td>56 (18.3%)</td>
<td>0.375</td>
</tr>
<tr>
<td>Response in 12M (N, %)</td>
<td>19 (19.6%)</td>
<td>81 (25.3%)</td>
<td>76 (24.6%)</td>
<td>0.498</td>
</tr>
<tr>
<td>Average RA RAPID3</td>
<td>0.2 (0.33)</td>
<td>0.5 (0.34)</td>
<td>0.6 (0.32)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

*Analysis of variance, adjusted for baseline RAPID3, age, race, disease duration

1376

Angiographic Pattern Among Rheumatoid Arthritis Patients Who Are Hospitalized Due to Acute Coronary Syndrome. Marie Holmqvist1, Angela Mantel1, Tomas Jernberg1, Stefan James1, Solveig Wålberg-Jonsson1 and Johan Askling2. 1Clinical Epidemiology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, 2Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden. Background/Purpose: We aimed at investigating and to compare the angiographic pattern of stenoses in patients with rheumatoid arthritis (RA) and general population comparators hospitalized due to acute coronary syndrome (ACS). This was done in a population which we have previously shown to be at increased risk for ACS, at increased risk of death following first event of ACS, and with more severe ACS events than the general population [1]. Our purpose was to investigate whether differences in angiographic findings could explain the more severe ACS phenotype.

Methods: Using nationwide Swedish registries, a cohort of individuals with established RA and general population individuals matched on sex, year of birth, area of residency and educational level were identified between 2006 and 2009. They were followed for a year to identify all cases hospitalized with a first time ACS and admitted to a coronary intensive care unit (CICU). For those with ACS who underwent angiography, the occurrence and extent of coronary stenoses were compared using logistic regression models. Analyses were stratified by diagnosis resulting in coronary angiography (non-ST-elevation myocardial infarction [NSTEMI], ST-elevation myocardial infarction [STEMI]), and adjusted for age and sex. The overall analyses were adjusted for age, sex, and diagnosis.

Results: 1135 RA patients and 3184 general population individuals were hospitalized with ACS during follow-up. Of those, 743 (65%) RA patients and 2203 (69%) general population comparators were admitted to a CICU within ±10 days of the event. 531 (71%) of those RA patients and 1683 (76%) of those general population comparators underwent angiography in conjunction with the ACS event. After adjusting for diagnosis resulting in angiography the adjusted OR for undergoing angiography was 0.84 (95% confidence interval [CI] 0.69, 1.02). Men age at angiography was 70 years and 60 years for RA patients and 58 % of the general population and 53 % of the general population were women. STEM I was a more common indication for investigation in RA (45%) than in the general population (36%). RA patients were more likely to have three-vessel disease than the general population, even after adjusting for diagnosis, age, and sex, OR 1.53 (95% CI 1.04, 2.26). When stratified by indication, we noted an increased risk of having any stenosis, and for three-vessel disease with STEMI and for those with NSTEMI. All ORs are found in the table below.

Conclusion: RA patients with ACS seem to have more stenoses and a more unfavourable angiographic pattern than the general population with ACS. This, however, is seen regardless of indication for investigation and therefore does not seem to offer a ready explanation for the more severe presentation of ACS seen in RA.

Table. Odds ratios (OR) and 95% Confidence Intervals (CI) comparing findings on angiography in RA patients and general population comparators. Normal findings are used as reference group in all models.

<table>
<thead>
<tr>
<th></th>
<th>Overall OR (95% CI)</th>
<th>NSTEMI OR (95% CI)</th>
<th>STEMI OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stenosis</td>
<td>1.18 (0.88-1.59)</td>
<td>1.12 (0.80-1.56)</td>
<td>1.50 (0.79-2.85)</td>
</tr>
<tr>
<td>Any main stem</td>
<td>1.22 (0.76-1.96)</td>
<td>1.10 (0.63-1.93)</td>
<td>1.76 (0.67-4.61)</td>
</tr>
<tr>
<td>One vessel, not main stem</td>
<td>1.12 (0.81-1.55)</td>
<td>1.02 (0.70-1.49)</td>
<td>1.40 (0.72-2.72)</td>
</tr>
<tr>
<td>Two vessels, not main stem</td>
<td>1.12 (0.78-1.60)</td>
<td>0.99 (0.64-1.52)</td>
<td>1.65 (0.81-3.38)</td>
</tr>
<tr>
<td>Three vessels, not main stem</td>
<td>1.53 (1.04-2.26)</td>
<td>1.44 (0.91-2.38)</td>
<td>1.97 (0.92-4.24)</td>
</tr>
</tbody>
</table>
Anti-Citrullinated Peptide Antibody Titers and the Prevalence of Interstitial Lung Disease in Patients with and without Rheumatoid Arthritis.

Chase Correia, Melissa R. Bussey, Brittany Panico, Rong Guo and Rochella A. Ostrowski. Loyola University Medical Center, Chicago, IL.

Background/Purpose: Rheumatoid arthritis (RA) is a multisystem inflammatory disease characterized by a symmetric, destructive polyarthritis. Interstitial lung disease (ILD) is an extra-articular manifestation that occurs in inflammatory disease characterized by a symmetric, destructive polyarthritis.

Methods: A chart review was performed of all adult patients with anti-CCP testing between January 1, 2007 and December 31, 2012 at a single academic hospital. Patients were excluded if they had any of 12 other exposures or conditions known to cause ILD. Patients meeting inclusion criteria were divided into four groups based on anti-CCP tertiles: 0–4 U/mL (negative titer), 5–149 U/mL (low titer), 150–299 U/mL (moderate titer), and 300 U/mL or greater (high titer). Charts were reviewed to determine a diagnosis of RA by a rheumatologist or American College of Rheumatology (ACR) 2010 criteria, a diagnosis of ILD by imaging, relevant laboratory analysis, and treatment of RA. Fisher’s exact test and logistic regression were used to compare the prevalence of ILD in the anti-CCP tertile groups and to adjust for potential confounders.

Results: 2,030 patients met inclusion criteria, and 334 of these patients were diagnosed with RA by a rheumatologist or 2010 ACR criteria. Among all patients tested for anti-CCP, a progressively higher prevalence of ILD was associated with each anti-CCP tertile group (p<0.0001) (Figure 1). However, the association was diminished when adjusting for age, C-reactive protein (CRP), tobacco use, and a diagnosis of RA (odds ratio: 1.18, 95% confidence interval: 0.78–1.78). Charts were reviewed to determine a diagnosis of ILD by an imaging, relevant laboratory analysis, and treatment of RA. Fisher’s exact test and logistic regression were used to compare the prevalence of ILD in the anti-CCP tertile groups and to adjust for potential confounders.

Conclusion: An increasing prevalence of ILD was observed in patients with higher levels of anti-CCP titers, regardless of a diagnosis of RA. However, additional factors, particularly age and disease activity represented by CRP, may influence these findings. To our knowledge, this is the first study to evaluate the relationship of increasing anti-CCP titers and ILD prevalence. Larger investigations are essential to better define the role of anti-CCP in the development of ILD and to determine whether higher anti-CCP titers further augment the risk of developing ILD.

Disclosure: C. Correia; None. M. R. Bussey; None. B. Panico; None. R. Guo; None. R. A. Ostrowski; None.

Studies on Ageing and the Severity of Radiographic Joint Damage in Rheumatoid Arthritis.


Background/Purpose: While rheumatoid arthritis (RA) has historically improved in pregnancy, recent studies suggest the improvement may not be dramatic now that we are able to control the disease better outside of pregnancy. TNF inhibitors are now routinely continued during pregnancy for women with inflammatory bowel disease (IBD) because active IBD is associated with pregnancy morbidity. The link between RA activity and pregnancy outcomes, however, is less clear. We sought to explore the role that RA activity and medications play in pregnancy outcomes.

Methods: Pregnancies in women with RA from a prospective registry were reviewed to determine the extent that RA activity and medications in the 1st and 2nd trimesters impacted pregnancy outcomes. Disease activity was divided into 2 levels based on the worst DAS-CRP3 and/or physician’s global assessment in the first 24 weeks of pregnancy. Chi-square and non-parametric tests were used for univariate analysis. A general estimating equation was used for multivariate analysis to account for multiple pregnancies in some women.

Results: A total of 31 pregnancies in 25 women with RA or JIA were enrolled in the registry before 24 weeks gestation. Seven pregnancies were in women with JIA and 24 with adult-onset RA. Two women had first trimester miscarriages; both in women with low RA activity without prednisone or TNF inhibitor exposure, but one took methotrexate in pregnancy. Of the remaining 29 pregnancies, 15 (51.7%) had RA that was either mild or in remission throughout the 1st and 2nd trimesters and 14 (48.3%) had RA that was moderately to severely active during this period. 6 of 29 (20.7%) live births had poor outcomes: 4 with preterm delivery, 1 with preeclampsia, and 1 with preterm prelCLAmsia.

The rate of Sulfasalazine (SSZ), hydroxychloroquine (HCO), and TNF inhibitor exposure was not statistically different for women with low vs high RA activity. Women with high RA activity, however, were more likely to take prednisone (57.1% vs 13.3%, p=0.02).

Significantly more women with preterm birth and/or prelCLAmsia had moderate/severe RA in early pregnancy (see table). While not statistically significant, more pregnancies with poor outcomes were exposed to prednisone and fewer to TNF inhibitors early in pregnancy. SSZ and HCO were not associated with pregnancy outcomes. Methotrexate was associated with preterm birth.

A logistic regression model demonstrated that lower RA activity and use of a TNF inhibitor in the 1st and 2nd trimesters were associated with term birth without preeclampsia. Taking prednisone in the first half of pregnancy did not appear to impact pregnancy outcomes.

Conclusion: In this era of treat-to-target management of RA, our paradigm for RA pregnancy management may need adjusting. By controlling RA activity with medications considered relatively safe in pregnancy, we may be able to improve both the pregnancy experience and pregnancy outcomes.

Table: RA activity and medications in the 1st and 2nd trimesters of pregnancy for live births:

<table>
<thead>
<tr>
<th>Medication</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>7 (24.1%)</td>
<td>6 (26.1%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Any prednisone</td>
<td>10 (34.5%)</td>
<td>6 (26.1%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Prednisone dose</td>
<td>9.5mg (3.7%)</td>
<td>10mg (SD 6.89)</td>
<td>8.75mg (SD 2.5)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2 (6.9%)</td>
<td>0</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>TNF inhibitor use</td>
<td>9 (31.0%)</td>
<td>8 (34.8%)</td>
<td>1 (16.7%)</td>
</tr>
</tbody>
</table>

Disclosure: M. E. B. Clowse, UCB Pharma, 5.
Background/Purpose: The Western population is getting older; consequently the proportion of elderly persons presenting with Rheumatoid Arthritis (RA) is increasing. We studied whether age is associated to the severity of RA at presentation and during the disease course, measured using radiographic joint damage.

Methods: Relationship between age and structural damage was studied in 7,232 radiographs of hands and feet of 1,879 RA-patients included in five European and North-American cohorts (Leiden EAC, Groningen, Lund, Umeå, Wilhelmina). Within 702 early RA-patients included in the Leiden EAC between 1993–2006 associations between age and joint space narrowing (JSN) and erosions were evaluated separately; secondly mediation analyses were performed to explore whether the association of age with joint damage was mediated by symptom duration at diagnosis, swollen joint count (SJ/C), tender joint count (TJC), CRP or ACPA. Finally, 56 RA-patients included in the Leiden EAC between 2010–2012 underwent 1.5 Tesla MRI of the most symptomatic hand and foot at baseline and radiographs at baseline and after 1 year. The MRI-inflammation score (RAMRIS-synovitis plus bone marrow edema) was evaluated.

Results: In all cohorts, age at diagnosis was positively associated with more severe joint damage at baseline and during follow-up. A meta-analysis of these cohorts revealed that per year increase in age, patients had 2.6% (β=0.026 p<0.001) more joint damage. Both JSN and erosion-scores correlated with age; Pearson correlation coefficients were significantly stronger for erosion-scores than for JSN-scores (r 0.38 versus 0.29, p=0.006). Structural damage in PIP, CMC-1 and MTP-1 joints increased with age, however a similar increase was observed in wrist, MCP and MTP(2-5)-joints. Together this suggests that the association of joint damage with age cannot be totally explained by osteoarthritis. Age at diagnosis was associated with a shorter symptom duration (β=0.09, p=0.011), a lower odds on ACPA-positivity (OR 0.98 p=0.011) and was not associated with SJ/C or TJC. Older age was positively associated with CRP (β=0.016, p=0.001) but in a multivariate analysis including age and CRP, CRP was not associated with radiographic damage (β=0.10, p=0.14). Therefore, symptom duration, ACPA and regular measures of inflammation did not mediate the association between age and joint damage. Finally, we questioned whether subclinical inflammation was a mediator. A ge was significantly associated with the severity of MRI-detected inflammation when adjusted for CRP and SJ/C (β=0.27). The effect size of the association between age and joint damage reduced after including MRI-inflammation in the analysis (from β0.012, p=0.004 to β0.021, adjusted for CRP and SJ/C), suggesting partial mediation.

Conclusion: RA-patients with a higher age at diagnosis had more severe joint damage at the time of diagnosis and during the disease course. This effect was partially explained by more severe subclinical joint inflammation at higher age. To what extend the remaining part of the effect is caused by disease-specific processes or is related to ‘normal ageing’ needs to be explored in further studies.

Disclosure: L. Mangnus: None; H. W. van Steenbergen: None; E. Brouver: None; E. Lindqvist: None; M. Reijnierse: None; P. K. Gregersen: None; S. M. Rantapää-Dahlqvist: None; D. M. van der Heijde: None; A. H. M. van der Helm-van Mil: None.

1381

Subaxial Cervical Spine Involvement in Symptomatic Rheumatoid Arthritis Patients: Comparison with Cervical Spondylodiscitis

Background/Purpose: To investigate the frequency, location, nature, and clinical significance of subaxial involvement (below C1-C2) in a series of patients with rheumatoid arthritis (RA) and symptomatic involvement of the cervical spine.

Methods: Forty-one patients with RA were studied with cervical spine MRI. A comparative study of the incidence of the different types of lesions was also performed with respect to 41 age- and sex-matched patients with symptomatic cervical spondylodiscitis.

Results: Stenosis of the spinal canal was found at the subaxial level in 85% of RA patients, and at the atlantoaxial level in 44%. The comparative study with cervical spondylodiscitis revealed significant differences in the type and frequency of subaxial lesions (Table 1). In RA patients, subaxial stenosis seems to be the consequence of both the inflammatory activity of the disease (multilevel vertebral subluxations, inflammatory involvement of cervical spine ligaments, interapophyseal synovitis, bone marrow edema involving the vertebral bodies and the interapophyseal joints, spinous process damage, and acquired vertebral blocks) and mechanical-degenerative changes (discopathy and ligamentum flavum hypertrophy).

Unconditional logistic regression analysis was used to identify MRI parameters of subaxial spine involvement associated with the development of pain, patient’s global assessment (PTGL) by 21-point Numeric Rating Scale: RAPID3; and comorbidities were extracted in standardized manner from medical records. Comorbidity burden was quantified by a composite comorbidity score (range 0–9) categorized as low (0–1), moderate (2–3) and high (≥3). Random effects analysis of variance models were used to assess the association between change in disease characteristics and PGIC classification. Since each subject may have multiple observations in the data, a random effects term was included to account for the correlation among observations from the same subject.

Results: Data on 155 patients [125 (80.6%) females; 112 (72.3%) white; median (interquartile range, IQR) age of 58 (50–66) years; RA duration 6 (1.9–8.5) years; seropositive 76.5%] were available for analysis. 46 (29.7%), 64 (41.3%), and 45 (29%) patients had low, moderate and high comorbidity burden respectively. Table shows the estimated mean of the study measures. Negative values means improvement in scores compared to prior Rheumatology clinic visit. For each PRO and RAPID3 there was strong interaction with comorbidity burden. In general patients with low comorbidity burden have higher threshold for change for MCID than those with moderate to high comorbidity burden (Table).

Conclusion: Comorbidities have strong influence on RA patient’s assessment of change of their health status. Comorbidities need to be considered when interpreting MCID.
neurological dysfunction (Ranawat class II or III). Evidence of alterations in the signal intensity of the spinal cord was the only independent risk factor found for the development of neurological dysfunction ($p=0.01; OR=11.43$), increasing the risk 11-fold. There was a trend toward statistical significance for spinal cord compression ($p=0.06; OR=3.95$). The presence of stenosis of the subaxial spinal canal without evidence of cord compression did not achieve statistical significance ($p=0.17$). These data suggest that neurological manifestations correlate poorly with MRI findings at this level.

Table 1. Frequency of subaxial lesions in patients with RA and Spondylosis.

<table>
<thead>
<tr>
<th></th>
<th>RA patients</th>
<th>Spondylosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis of the subaxial canal</td>
<td>85% (N=41)</td>
<td>27% (N=41)</td>
<td>0.0000003</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>34% (0%)</td>
<td>0% (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Alteration in signal intensity of the spinal cord</td>
<td>27% (0%)</td>
<td>0% (0%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Bone marrow edema involving the vertebral plates and the interapophyseal joints</td>
<td>27% (2%)</td>
<td>2% (0.0002)</td>
<td>0.03</td>
</tr>
<tr>
<td>Inflammatory involvement of cervical spine ligaments (interspinous ligaments and/or ligamentum nuchae)</td>
<td>32% (0%)</td>
<td>0% (0.0002)</td>
<td></td>
</tr>
<tr>
<td>Interapophyseal or facet joint synovitis</td>
<td>17% (0%)</td>
<td>0% (0.12)</td>
<td></td>
</tr>
<tr>
<td>Synovitis of the uncovertebral joints</td>
<td>0% (0%)</td>
<td>0% (0)</td>
<td></td>
</tr>
<tr>
<td>Spinalis process damage (sharpening, erosion, sclerosis or fusion)</td>
<td>7% (0%)</td>
<td>0% (0.02)</td>
<td></td>
</tr>
<tr>
<td>Pannus formation</td>
<td>0% (0%)</td>
<td>0% (0)</td>
<td></td>
</tr>
<tr>
<td>DISCOPHYSEAL OR DISC RUPTURE OR DISC HERNIATION</td>
<td>90% (98%)</td>
<td>0% (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Ligamentum flavum hypertrophy</td>
<td>66% (22%)</td>
<td>0% (0.0001)</td>
<td></td>
</tr>
<tr>
<td>Degenerative spinal osteophytosis</td>
<td>71% (78%)</td>
<td>0% (NS)</td>
<td></td>
</tr>
<tr>
<td>Vertebral subluxation</td>
<td>24% (5%)</td>
<td>0% (0.026)</td>
<td></td>
</tr>
<tr>
<td>Vertebral ankylosis</td>
<td>24% (2%)</td>
<td>0% (0.007)</td>
<td></td>
</tr>
<tr>
<td>Sclerosis and/or hypertrophy of the interapophyseal joints</td>
<td>0% (0%)</td>
<td>0% (0.000001)</td>
<td></td>
</tr>
<tr>
<td>Sclerosis and/or hypertrophy of the uncovertebral joints</td>
<td>0% (17%)</td>
<td>0% (0.0012)</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant.

**Conclusion:** Subaxial stenosis seems to be the consequence of both the inflammatory process and mechanical-degenerative changes. Despite its frequency, it was not usually related to the occurrence of myelopathy symptoms, not even in cases with MRI evidence of spinal cord compression. These data seem to indicate a notable behavioral adaptation of this segment.

**Disclosure:** H. Borrell, None; J. Narvaez, None; J. A. Narvaez, None; M. Serralonga, None; C. Gomez Vaquero, None; E. de Lama, None; J. Hernandez Galian, None; J. M. Nolla, None.

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**The Longitudinal Course of Fatigue in Rheumatoid Arthritis - Results from the Norwegian Arthritis Register.** Kable L Druce1, Gareth T Jones1, Gary J. M. Macfarlane2, Suzanne M. Verslappen3 and Neil Basu1. 1University of Aberdeen, Aberdeen, United Kingdom, 2Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

**Background/Purpose:** Fatigue is common and burdensome in Rheumatoid Arthritis (RA). Though RA fatigue progression varies significantly between individuals, to date, published analyses only had considered average changes in fatigue. The aim of the current study was to determine if it is possible to distinguish participants who follow distinct trajectories of fatigue reporting over time and thus potentially inform to whom specific management should be targeted.

**Methods:** Participants from the Norwegian Arthritis Register (NOAR), a large, longitudinal study (1987-2012, 323,790 RA patients, 650,391 patient-years) were included. Fatigue was measured in 16 weeks duration. The current study included 3,782 patients as of December 2012. Patient trajectories were identified using a group-based trajectory modelling approach. The model was estimated using the TTMGA program. The number of trajectories were chosen based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The number of trajectories was compared between RA patients and non-RA arthritis patients using a chi-square test.

**Results:** The current study included 3,782 patients as of December 2012. Patient trajectories were identified using a group-based trajectory modelling approach. The model was estimated using the TTMGA program. The number of trajectories was chosen based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The number of trajectories was compared between RA patients and non-RA arthritis patients using a chi-square test.

**Conclusion:** Among a group of patients who, on average, show only small improvements in fatigue, significant variation in fatigue progression exists. At presentation, it is possible to identify and characterise sub-groups of patients who do not improve. Such patients are most likely to require early and targeted interventions, to alleviate fatigue.

**Disclosure:** K. L. Druce, None; G. T. Jones, None; J. A. Macfarlane, None; M. S. Verstappen, None; N. Basu, None.

1383

**Disease Characteristics and RA Development in Undifferentiated Arthritis: A 2-Year Follow-up Study of 413 Patients with Arthritis of Less Than 16 Weeks Duration.** Gina Hetland Brinkmann1, Ellen Sauer Norti1, Tore K. Kvien1, Anne Jilsrud Haugen2, Lars Gravel3, Halvor Nygaard4, Cathrine Thunem5, Maria Dahl Mjaavatten6 and Elisabeth Lie1. 1Diakonhjemmet Hospital, Oslo, Norway, 2Østfold Hospital Trust, Fredrikstad, Norway, 3Righospitalet, Oslo, Norway, 4Tellemark Hospital, Skien, Norway.

**Background/Purpose:** Correct identification of the subset of patients with undifferentiated arthritis (UA) who will develop rheumatoid arthritis (RA) is important to enable initiation of appropriate treatment. Our objectives were to compare baseline characteristics and treatment of UA patients developing vs. not developing RA according to the 2010 ACR/EULAR RA classification criteria (UA-RA vs. UA-non RA) over a 2-year follow-up period, and to investigate the relationship between clinical RA diagnosis and fulfilment of the RA criteria in these patients.

**Methods:** Patients (18-75 years old) with ≥1 swollen joint of ≤16 weeks duration were from 2004 included in a multi-center longitudinal observational study and followed for 2 years with examinations at 0, 3, 6, 12 and 24 months. Patients with arthritis due to trauma, septic arthritis, crystal arthritis and osteoarthritis were excluded. Mann-Whitney U test, independent samples T test and chi-square test were used to compare baseline characteristics between UA-non RA and UA-RA patients.

**Results:** 1119 patients were included during the period 2004-2010 (mean (SD) age 46(15) years, 55% females, median (25, 75) percent duration of joint swelling 34(13, 66) days). Patients with a clinical diagnosis of a rheumatic disease other than RA, and those without available anti-CCP/RF or follow-up data were excluded. Consequently, 663 patients were eligible for the current analyses, and 250 (37%) of these patients fulfilled the 2010 ACR/EULAR RA classification criteria at baseline. Among the remaining 413 patients, who were denoted UA, 27 patients (7%) were classified as RA during follow-up, 21/27 (78%) of these UA-RA patients fulfilled the criteria within the first 6 months. 58/386 patients (15%) of patients started DMARDs (3 patients started biologics for diagnosis of AS, RA and UA, respectively) vs. 16/27
(59%) in the UA-RA group (3 patients on biologics, all with clinical RA diagnosis) (p<0.001). In both groups approx. 2/3 of those started on DMARDs did so within the first 3 months and were mostly started on methotrexate. 22/386 (6%) of all the UA-non-RA were given a clinical diagnosis of RA during follow-up (19 of these patients were anti-CCP and RF negative).

Comparison of baseline characteristics between the UA-non-RA and UA-RA patients

<table>
<thead>
<tr>
<th></th>
<th>UA-non-RA (n=386)</th>
<th>UA-RA (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>46.6 (14.8)</td>
<td>51.3 (13.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>207 (53.6)</td>
<td>20 (74.1)</td>
<td>0.039</td>
</tr>
<tr>
<td>Duration of joint swelling, days, median (25, 75 perc.)</td>
<td>31 (10,66)</td>
<td>30 (14,60)</td>
<td>0.75</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>25.9 (4.4)</td>
<td>26.2 (4.4)</td>
<td>0.707</td>
</tr>
<tr>
<td>Shoulder involvement, n (%)</td>
<td>15 (3.9)</td>
<td>10 (37.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker ever, n (%)</td>
<td>214 (55.7)</td>
<td>21 (77.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>CRP, mg/L median (25, 75 perc)</td>
<td>10 (8,38)</td>
<td>8 (3,21)</td>
<td>0.96</td>
</tr>
<tr>
<td>CRP, mg/L median (25, 75 perc)</td>
<td>10 (8,38)</td>
<td>8 (3,21)</td>
<td>0.96</td>
</tr>
<tr>
<td>Shoulder involvement, n (%)</td>
<td>5 (1.3)</td>
<td>5 (18.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Assessor global VAS, mean (SD)</td>
<td>29.2 (16.7)</td>
<td>37.6 (18.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>HAQ, mean (SD)</td>
<td>0.69 (0.58)</td>
<td>1.17 (0.80)</td>
<td>0.049</td>
</tr>
<tr>
<td>Criteria points, median (25, 75 perc.)</td>
<td>1 (1,4)</td>
<td>3 (3,5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Standard 66-swollen joint count plus hips

**Conclusion:** Among 431 patients with UA of ≤16 weeks duration only 7% fulfilled the 2010 RA classification criteria during 2 years of follow-up. Female gender, positive RF and/or ACPA, shoulder arthritis and number of involved joints were among the factors associated with RA development while ankle arthritis was more common in UA-non-RA patients. Some patients (mostly RF and/or ACPA negative) were given a clinical diagnosis of RA despite not fulfilling the criteria, but the proportion was low (6%).

**Disclosure:** G. H. Brinkmann; None; E. S. Norli; None; T. K. Kvien; None; A. J. Haugen; None; L. Grave; None; H. Nygaard; None; C. Thuem; None; M. D. Mjaavatten; None; E. Lie; AbbVie, 5; UCB, 5; Hospira, 5; Pfizer Inc, 5.

1384

**Fibromyalgia and Its Effect on Treatment Response in Early Rheumatoid Arthritis Patients.** Josefa Durán Santa Cruz1, Bernard Combe2, Jingbo Niu3, Nathalie Rincheval, Cécile Gaujoux-Viala4 and David T. Felson1. 1Boston University School of Medicine, Boston, MA, 2Hôpital Lapeyronie, Montpellier, France, 3Institut Universitaire de Recherche Clinique, Montpellier, France, 4EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France.

**Background/Purpose:** Fibromyalgia (FM) occurs commonly in patients with rheumatoid arthritis (RA) and it affects on treatment response is unknown. In this study we aimed to evaluate if patients with RA and concomitant FM have an impaired response to treatment measured by a decrease in indexes of disease activity but may miss the target of remission or low disease activity.

**Results:** At baseline, patients with FM (n=120) had a higher DAS28, SDAI, CDAI and HAQ than patients with isolated RA (n=548). While they started out higher, DAS28 and other disease activity scores improved to a similar extent as in the isolated RA group. However, scores remained consistently higher among FM patients. (see figure). Achievement of LDA and of remission was significantly less likely in subjects with FM and few would have met criteria to target goal.

**Conclusion:** Patients with FM and RA have a similar response to treatment according to a decrease in indexes of disease activity but may miss the target of remission or low disease activity.

**Disclosure:** J. Durán Santa Cruz, None; B. Combe, None; J. Niu, None; N. Rincheval, None; C. Gaujoux-Viala, None; D. T. Felson, None.

1385

**What Discriminates Best Flares in Rheumatoid Arthritis (RA)? a Subanalysis of the Strass Treatment Tapering in RA Study.** Agnès Danre1, Bruno Fautrel2, Thierry Alfafate2, Thao Pham1, Jacques Mor2, Emmanuel Dennis Labous3, Philippe Gaudin4, Olivier Broca5, Elisabeth Solau-Gervais6, Jean-Marie Berthelot7, Jean Charles Balblanc1, Xavier Marietti2, Florence Tubach8 and Laure Gossec9. 1EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France.

**Activity Index (CDAI) and the Health Assessment Questionnaire. In addition attainment of low disease activity (LDA) (DAS28<3.2) and remission (DAS28<2.6, SDAI<3.3, CDAI<2.8) at these timepoints were analyzed using a log binomial regression.

**Results:** At baseline, patients with RA (n=120) had a higher DAS28, SDAI, CDAI and HAQ than patients with isolated RA (n=548). While they started out higher, DAS28 and other disease activity scores improved to a similar extent as in the isolated RA group. However, scores remained consistently higher among FM patients. (see figure). Achievement of LDA and of remission was significantly less likely in subjects with FM and few would have met criteria to target goal.

**Conclusion:** Patients with FM and RA have a similar response to treatment according to a decrease in indexes of disease activity but may miss the target of remission or low disease activity.

**Table 1.** Comparison of rheumatoid arthritis activity scores and radiologic scores over follow up according to the presence of fibromyalgia

<table>
<thead>
<tr>
<th></th>
<th>FM</th>
<th>No FM</th>
<th>Difference in scores</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS 28</td>
<td>3.50</td>
<td>3.05</td>
<td>0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDAI</td>
<td>16.09</td>
<td>11.54</td>
<td>4.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDAI</td>
<td>14.98</td>
<td>10.75</td>
<td>4.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.63</td>
<td>0.45</td>
<td>0.18</td>
<td>0.5476</td>
</tr>
<tr>
<td>SJC</td>
<td>2.32</td>
<td>2.18</td>
<td>0.14</td>
<td>0.4366</td>
</tr>
<tr>
<td>TJC</td>
<td>5.64</td>
<td>3.27</td>
<td>2.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PthG VAS</td>
<td>3.82</td>
<td>3.01</td>
<td>0.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PthG VAS</td>
<td>2.88</td>
<td>2.36</td>
<td>0.51</td>
<td>0.0044</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0.75</td>
<td>0.84</td>
<td>0.09</td>
<td>0.4147</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>13.99</td>
<td>15.05</td>
<td>1.06</td>
<td>0.3602</td>
</tr>
<tr>
<td>SHARP</td>
<td>7.33</td>
<td>7.68</td>
<td>0.34</td>
<td>0.3125</td>
</tr>
</tbody>
</table>

*P values denote the overall significance of a linear regression adjusting for baseline score, gender, age and smoking status. HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PthG: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

**Figure 1.** DAS28 score at different time points grouped by fibromyalgia presence

**Disclosure:** J. Danre, None; B. Fautrel, None; T. Alfafate, None; T. Pham, None; J. Mor, None; E. Dennis Labous, None; P. Gaudin, None; O. Broca, None; E. Solau-Gervais, None; J. M. Berthelot, None; J. C. Balblanc, None; X. Marietti, None; F. Tubach, None; L. Gossec, None.
Background/Purpose: Flares in rheumatoid arthritis (RA) are a patient-perceived increase of disease activity which might be particularly important to assess in the context of treatment tapering. However, there is little data on what patient-perceived flares really encompass. In a treatment tapering study, STRASS, patients were asked about flares, and many validated outcomes were collected.

The objective was to explore the discrimination properties of different validated outcomes for flares, by comparing these outcomes between visits where patients self-reported flares, and visits without flares, in the STRASS tapering study.

Methods: The STRASS study was a step-down randomized trial (ref). Patients had RA, were treated with adalimumab or etanercept for ≥12 months, and were in DAS 28 remission (DAS < 2.6) for ≥6 months. Patients were randomized to either the “sparking” (S) arm (where the TNF blocker was tapered gradually) or the “maintaining” (M) arm, over 18 months. Flares were evaluated through a patient-reported questionnaire every 3 months, asking: “Concerning the last 3 months, did you experience symptoms of a relapse of RA?” RA outcomes, including HAQ, patient global assessment, SF36, pain, tender joint count, swollen joint count, ESR and CRP were compared between visits with flares and visits without. Cohen’s effect size was calculated for indicative purposes, without adjustment on these repeated measures. Effect size is considered high when above 0.8.

Results: In all, 137 patients were included in STRASS, 64 and 73 in the S and M arms respectively: age (mean±SD) 55±11 yrs, females 78%, RA duration 9±8 years. Over the 18 months of the study, the mean number of visits where the patient reported at least one flare (out of a possible total number of visits of 6 visits) was 1.87±1.74, with 2.44±1.68 visits with flares in the S arm, and 1.37±1.65 visits with flares in the M arm (p=0.0001). Overall, 55 patients (88.7%) in the S arm and 40 patients (55.6%) in the M arm reported flares at least once. Comparisons between visits at which patients reported flares, and visits without, showed statistically significant differences concerning all the outcomes, with effect sizes comprised between 0.27 (0.12-0.42) and 1.09 (0.94-1.25) (table). The highest effect sizes were observed for patient global assessment and SF36 PCS, and the lowest for ESR.

Conclusion: Patient-perceived flares are frequent during treatment tapering. Patient-reported outcomes discriminated better between visits with versus without flares, than physician measures or biology. More work is needed on the concept of flares.

Table: Visits with patient-reported flares, N=256 Visits without patient-reported flares, N=684 Indicative effect size [95% CI]

Patient global assessment
S 2.92 ± 2.41 1.11 ± 1.07 1.09 [0.94-1.25]
M 2.00 ± 1.56 0.67 ± 0.66 0.09 [-0.18-0.75]

SF36 PCS
S 42.28 ± 8.66 40.67 ± 7.66 -0.69 [-1.28-0.00]
M 41.34 ± 7.53 40.31 ± 7.01 0.76 [0.30-1.24]

Tender joint count
S 4.31 ± 7.53 3.72 ± 2.91 0.95 [0.40-1.51]
M 3.57 ± 5.67 2.78 ± 2.59 1.37 [0.89-1.86]

Swollen joint count
S 2.00 ± 3.12 1.91 ± 0.63 0.37 [-0.03-0.80]
M 2.42 ± 3.40 1.85 ± 0.83 0.77 [0.47-1.08]

HAQ
S 0.67 ± 0.66 0.37 ± 0.53 0.56 [0.35-0.77]
M 0.57 ± 0.46 0.37 ± 0.30 0.55 [0.29-0.80]

SF36 M CS
S 43.77 ± 9.96 48.43 ± 10.05 -0.35 [-1.70-0.00]
M 47.33 ± 8.96 46.01 ± 8.00 1.09 [0.56-1.62]

CRP, mg/l
S 5.73 ± 8.96 3.00 ± 3.68 0.44 [0.09-0.79]
M 6.07 ± 10.57 3.79 ± 2.34 0.65 [0.28-1.05]

ESR, mm
S 16.54 ± 15.40 12.31 ± 9.72 0.27 [0.12-0.42]
M 10.49 ± 11.04 7.01 ± 8.81 0.41 [0.06-0.75]

Disclosure: I. M. Markuse, None; L. Dirven, None; Y. P. Goekoop-Ruiterman, None; P. A. van der Lubbe, None; A. J. Peeters, None; J. S. M. Karstens, None; W. F. Lems, None; W. J. H. Huizinga, None; C. F. Allaart, None.

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Radiographic Progression Differs Between Trajectory Clusters Defined By DAS28 Scores in Early Rheumatoid Arthritis

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Background/Purpose: Group-based trajectory modeling defines clusters of individuals in observed data with similar disease trajectories. We have previously defined five distinct trajectories in early rheumatoid arthritis based on DAS 28 scores. Our objective was to examine radiographic progression in these defined clusters.

Methods: Patients were assigned to mutually exclusive trajectories by their DAS 28 scores over 24 months. Patients with baseline and follow-up radiographs (n=601) were included in this analysis and baseline demographics did not differ from the larger cohort (n=1,568). Radiographs were scored with the van der Heijde modification of the Sharp score (vdHSS). ANOVA with the Bonferroni correction was applied to test for mean differences in baseline and follow-up vdhSS between clusters. Paired t-tests were applied to assess the difference between visits with and without a flare.
test differences in mean total vdHSS between baseline and last follow-up by cluster group. Pearson’s chi-squared test was used to identify differences between clusters in the proportion of patients with vdHSS progression (>3.5 units/year) and rapid progression (>5 units/year).

**Results:** Clusters (CI) were characterized as: CI-1 (n = 163, 27%) began in high disease activity and achieved remission; CI-2 (n = 121, 20%) began in moderate or low disease activity and achieved remission; CI-3 (n = 158, 26%) began in moderate disease activity and achieved low disease activity; CI-4 (n = 237, 40%) began in low disease activity and achieved moderate disease activity; and CI-5 (n = 27, 5%) began and remained in high disease activity. At 24 months, patients in CI-5 were more frequently on biologics (35%) and steroids (38%) but were less frequently on methotrexate monotherapy (18%), despite earlier use of DMARD combination therapy (43% at 3 months) relative to other clusters. The overall mean baseline vdHSS score was 5.3 units (SD 8.4) with progression of 2.8 units annually (95%CI 2.4–3.2, p < 0.001); 45% of the cohort had no change in radiographic scores in follow-up. Clusters differed in baseline and follow-up scores for joint space and total vdHSS but not erosions, with CI-4 and CI-5 experiencing the worst radiographic progression by 3.6 units annually (95%CI 2.5–4.6) and 4.4 units annually (95%CI 1.1–7.7) respectively (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline and Mean Change in van der Heijde Sharp Scores over 24 months in Early Rheumatoid Arthritis, Overall and by Trajectory Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erosion Score</strong></td>
</tr>
<tr>
<td>OVERALL n=601</td>
</tr>
<tr>
<td>Cluster LHOA b REM n=163</td>
</tr>
<tr>
<td>Cluster UHOA b REM n=121</td>
</tr>
<tr>
<td>Cluster Cl-3 n=132</td>
</tr>
<tr>
<td>Cluster Cl-4 n=158</td>
</tr>
<tr>
<td>Cluster Cl-5 n=163</td>
</tr>
<tr>
<td>Cluster UHOA b LDA n=26</td>
</tr>
</tbody>
</table>

Legend: HDA high disease activity; REM remission; LDA low disease activity

CI-4 and CI-5 had the highest proportion of patients (24 and 26% respectively) compared to the other clusters (range 14–19%) although not statistically significant (p<0.204) and CI-5 was characterized by all patients being rapid progressors.

**Conclusion:** We have defined five clinical disease trajectories in early rheumatoid arthritis. The cluster defined by patients beginning and remaining in high disease activity have the lowest baseline radiographic scores but the highest propensity for radiographic progression despite aggressive therapy. This highlights the importance of defining patient prognosis at baseline and immediately optimizing therapy to prevent functional decline.

**Disclosure:** C. Barnabe, None; Y. Sun, None; G. Boire, None; C. Hitchon, None; E. C. Keystone, Abbott Laboratories, 2, A mcugen Canada, 2, AstraZeneca Pharmaceuticals LP, 2, B. riso-Myers Squibb, 2, F. Hoffman La-Roche Inc., 2, Janssen Pharmaceutica Product LP, 2, E. Lilly and Company, 2, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2, Abbott Laboratories, 2, AstraZeneca, 2, Biotest, 5, Bristol-Myers Squibb, 5, F. Hoffman-La Roche Inc., 5, Genentech and Biogen IDEC Inc, 5, Janssen Pharmaceutica Product LP, 5, E. Lilly and Company, 5, M. eck Pharmaceuticals, 5, Pfizer Inc, 5, Abbott Laboratories, 8, AstraZeneca, 8, Bristol-Myers Squibb, 8, F. Hoffman-La Roche Inc., 8, Janssen Pharmaceutica Product LP, 8, Pfizer Inc, 8, UCB, 8, A mcugen, 8, J. C. Thorne, None; B. Harouli, AbbVie, 2, AbbVie, 2, A mcugen, 2, A mcugen, 2, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 2, Janssen Pharmaceutica Product LP, 2, Janssen Pharmaceutica Product LP, 2, Pfizer Inc, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 2, UCB, 2, UCB, 2, J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A mcugen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A mcugen, Pfizer, BMS, Crescendo, AbbVie, 5, D. van der Heijde, Director Imaging Rheumatology BV, 4, P. Din, None; J. E. F. Poe, A mcugen, 2, A mcugen, 5, V. P. Bykerk, Bristol-Myers Squibb, 5, Pfizer Inc, 5, UCB, 5.

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Prevalence and Predictive Factors of Drug-Free and Sustained Remission in Patients with Early Arthritis.

**Background/Purpose:** Early and sustained remission has become the ultimate goal in early arthritis patients. The aim of our study was to estimate the prevalence of clinical, sustained and drug free remission in patients with early arthritis, and to explore possible predictive factors of remission.

**Methods:** We included a cohort of DMARDs naïve patients with diagnosis of early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) of less than 2 years of disease duration. Data was collected every 3 months, including sociodemographic characteristics, functional status, disease activity and medication. Remission was defined according to 2010 ACR/EULAR criteria. We selected four outcomes: Clinical Remission, Drug-Free Remis- sion, steroids-Free Remission (Patients receiving DMARDS but not cortico- steroids) and Sustained remission (patients who in the last follow up visit were still in remission). Time to outcome was assessed from date of baseline visit to the date of remission or last follow-up. Kaplan-Meier product limit method was used to estimate probability of each outcome. Patients were stratified according to initial and final diagnosis: UA-UA, UA-RA and RA-RA, respectively. Groups were compared with the log-rank statistic. Cox proportional hazards (PH) models were fit to determine possible predictors of remission including gender, age, disease duration, HAQ, DA28, rheumatoid factor and baseline diagnosis.

**Results:** A total of 684 patients were included: UA-UA = 125 (18%), UA-RA = 127 (19%) and RA-RA = 432 (63%). Mean follow-up was 21 ± 16 months (1228 patients-year). Baseline DA28 and HAQ were 5.2 ± 1.3 and 1.2 ± 0.8, respectively. Mean age was 51 ± 15 years, 81% were female and 62% had positive rheumatoid factor. The mean disease duration was 7 ± 6 months. At baseline, 625 (96%) of patients were not in remission. During follow-up 36% achieved clinical remission at a median time of 12 months. Only 54% of these patients continued in sustained remission (median follow-up after first remission = 17 months). Steroids-free remission and Drug-free remission were achieved in 21% and 13%, respectively. The overall probability of remission per patients-year of follow-up were 0.29, 0.13, 0.07, for clinical, steroids-free and drug-free, respectively. There were significant differences in rate of remission between different diagnosis groups. On multivariate analysis, male gender and baseline diagnosis of RA were associated with higher probability of remission (HR=1.70, p=0.001 and HR=1.43, p=0.03, respectively), while higher HAQ-score and longer disease duration were associated with lower probability of remission (HR=0.77, p=0.01 and HR=0.95, p=0.01; respectively).

**Conclusion:** In our cohort 36% of patients with early arthritis achieved clinical remission; however half of them relapse during follow-up. Only one in every ten patients reached drug free remission. A short disease duration, lower disability, male gender and initial diagnosis of RA were associated with higher probability of remission.

**Disclosure:** M. Landi, None; C. A. Waimann, None; G. Citera, None; O. Cerda, None; F. Ceccato, None; S. Paire, None; F. Caiero, None; L. Marino, None; M. Maman, None; A. Secco, None; G. Crespo, None; A. Alvarez, None; M. Haye Salinas, None; A. Alvaralos, None; J. Rosa, None; V. Scaglioni, None; E. R.
Osteophytes Increase the Ambiguity of Clinical Evaluation of Joint Swelling in Rheumatoid Arthritis. Peter Mandl, Paul Studenic, Gabriela Supp, Tanja A. Stamm, Martina Sadlonova, Michæla Ernst, Stefanie Haider, Daniel Aletaha and Josef Smolen. M edical University of Vienna, Vienna, Austria.

Background/Purpose: It is recommended that a joint be classified as clinically swollen if this swelling is beyond doubt. However in clinical practice the evaluation of joint swelling in patients with rheumatoid arthritis (RA) is often hindered by joint deformity, secondary osteoarthritis (OA) or adiposity. The aim of this study was to evaluate the ambiguity and reliability of clinical swollen joint assessment in patients with RA.

Methods: Clinical joint swelling was evaluated in 2 cohorts of consecutive RA patients with at least 1 swollen joint. In Cohort A (n = 20) a conventional 28 swollen joint count (SJC) was performed on the same day by 2 independent, blinded examiners. In Cohort B (n = 28) the same examiners performed a modified 28 SJC in which joints were graded as either definitely swollen, non-swollen or doubtfully swollen (defined as a joint where swelling can not be excluded or confirmed due to limited evaluation attributed to the physical characteristics of the joint). In addition a standard grey-scale (GS) and Power Doppler (PD) ultrasonographic evaluation (US) was performed by a sonographer blinded to clinical data in Cohort B patients. Presence/absence of GS synovitis, PD signal, erosion and osteophytes were recorded.

Results: A total of 1316 joints were clinically evaluated in 48 RA patients (89% women; median ± age: 59.4 (12.1) years, disease duration: 12.5 (8.1) years, SDAI: 10.74 (8.9)) in 2 cohorts. Eighty-five percent (24 out of 28) of patients in Cohort B had at least 1 doubtfully swollen joint, with a maximum number of 4 doubtful joints/patient. The top joints with doubtful swelling were the wrist, knee, MCP3 and MCP1 joint. Interobserver reliability, evaluated by intraclass correlation coefficient in Cohort A for the conventional SJC and in Cohort B for the modified SJC was 0.80 (95% confidence interval (95%CI) 0.77–0.83) and 0.83 (95%CI: 0.81–0.85) respectively. Agreement between the 2 examiners for definitely swollen and doubtfully swollen joints was 65% and 16% respectively. Doubtfully swollen joints were more often GS (p = 0.001) and PD positive (p < 0.001) as compared to non-swollen joints (80% vs. 54% and 26% vs. 12% respectively) and had more frequently osteophytes on US than either swollen (p = 0.021) or non-swollen joints (p = 0.003) (11% vs. 4.5%/4.5% respectively). Erosions were more commonly detected in swollen joints than in doubtfully swollen or non-swollen joints (4.8% vs. 1.8%/2.2%) (Table 1). No association was found between body mass index and the number of doubtfully swollen joints.

Conclusion: A modified SJC including doubtfully swollen joint is characterized by similar interobserver reliability as the conventional SJC. Background of joint swelling in patients with secondary OA was common. Doubtfully swollen joints were more commonly GS synovitis, PD signal, and osteophytes were recorded.


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Weight Loss and Risk of Death in Rheumatoid Arthritis. Joshua Baker1, Eric Billig2, Grant W. Cannon3, Liron Caplan4, Vilas Majithia5 and Ted R. Mikuls6. 1University of Pennsylvania, Philadelphia, PA, 2Salt Lake City VA and University of Utah, Salt Lake City, UT, 3Denver VA and Univ of Colorado School of Medicine, Aurora, CO, 4University of Mississippi Medical Center, Jackson, MS, 5Ohio VA Medical Center and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Low body mass index (BMI) has been linked to greater mortality among patients with Rheumatoid Arthritis (RA). Weight loss has also been associated with a greater risk of death among the elderly. The purpose of this study was to determine if weight loss is a predictor of death in RA.

Methods: Our sample consists of 1634 subjects from the Veterans Affairs Rheumatoid Arthritis (VARA) Registry. Dates of death were identified through review of the VA Computerized Patient Record System. BMI was
extracted within 14 days of each visit and the change in BMI from the previous visit was determined. BMI category and weight change were considered time-varying. Weight loss at each visit was defined as a decrease in BMI of 1 kg/m² from the preceding visit. Rate of loss (per 1 year) was defined as the change BMI from the preceding visit divided by the preceding interval length. Potential confounding co-variables associated with mortality in this cohort were identified. Cox proportional hazard models were used to assess associations between time-variant and time-invariant predictors of survival including the change in BMI and the rate of decline in BMI from the preceding visit adjusting for age, gender, race, BMI, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, smoking, and current use of methotrexate, prednisone, and anti-Tumor Necrosis Factor (TNF-α) medications.

**Results:** Among 1634 subjects (280 deaths, 8102 patient-years, 17,057 unique observations), weight loss of 1 kg/m² of BMI occurred in 2,308 (13.5%). Weight loss over the preceding interval was associated with an increased risk of subsequent death [HR: 2.00 (1.54, 2.60) p < 0.001] (Table 1). In a subset of 1520 subjects with available data (223 deaths, 6650 patient-years), weight loss remained associated with an increased risk of death after further adjusting for CRP [HR 1.78 (1.33, 2.38) p < 0.001] (full model not shown). In similar models, a rate of weight loss of >1 kg/m² of BMI over a 6-month period was associated with a greater risk of death [HR: 1.74 (1.31, 2.32) p < 0.001] while a slower rate of weight loss was not associated with an increased risk compared to those who did not lose weight [HR: 0.94 (0.70, 1.27) P = 0.7].

**Conclusion:** Recent weight loss, particularly a loss of more than 1 kg/m² of BMI (approximately 3.1 kg on average) over a 6-month period, is an independent predictor of death in RA. Changing weight may be a marker of poor functional status, poor nutrition, ongoing inflammation, and/or underlying malignancy and may help risk-stratify patients for more aggressive interventions.

**Table 1:** Multivariable-adjusted risk of death among subjects with rheumatoid arthritis. (N = 1634, Deaths = 280, Person-Years = 8102)

<table>
<thead>
<tr>
<th>Risk of Death</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Age</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.06 (1.04, 1.07)</td>
</tr>
<tr>
<td>White</td>
<td>1.10 (0.82, 1.49)</td>
</tr>
<tr>
<td>BMI Category</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;20 kg/m²</td>
<td>2.89 (1.99, 4.21)</td>
</tr>
<tr>
<td>BMI 20-25 kg/m²</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>BMI 25-30 kg/m²</td>
<td>0.91 (0.67, 1.23)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>0.88 (0.61, 1.25)</td>
</tr>
<tr>
<td>Interval Weight Change</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 kg/m² loss</td>
<td>1.00 (1.54, 2.60)</td>
</tr>
<tr>
<td>&gt; 1 kg/m² loss</td>
<td></td>
</tr>
<tr>
<td>Current Therapies</td>
<td></td>
</tr>
<tr>
<td>Methotrexate Use</td>
<td>0.59 (0.45, 0.76)</td>
</tr>
<tr>
<td>Prednisone Use</td>
<td>1.40 (1.10-1.80)</td>
</tr>
<tr>
<td>TNF Use</td>
<td>0.73 (0.53, 1.01)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>1.42 (1.09, 1.84)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>1.35 (1.05, 1.72)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.73 (1.26, 2.36)</td>
</tr>
<tr>
<td>Active Smoking</td>
<td>1.57 (1.16, 2.13)</td>
</tr>
</tbody>
</table>

**Table 1:** GEE in linear and logistic regression models evaluating independent predictors of the change in BMI and the risk of weight loss over the subsequent observation period.

<table>
<thead>
<tr>
<th>Change in BMI (kg/m²)</th>
<th>Risk of Weight Loss (HR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs (N=1296)</td>
<td>Obs (N=1296)</td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>Age (per 1 year)</td>
</tr>
<tr>
<td>0-0.070</td>
<td>0.001</td>
</tr>
<tr>
<td>0.070-0.090</td>
<td>0.001</td>
</tr>
<tr>
<td>0.090-0.113</td>
<td>0.9</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.9</td>
</tr>
<tr>
<td>0.113-0.133</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline BMI (per 1 kg/m²)</td>
<td>0.1</td>
</tr>
<tr>
<td>Low CRP (lnCRP)</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.3</td>
</tr>
<tr>
<td>Anti-TNF Therapy</td>
<td>0.3</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline Erosive Disease</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline Smoker</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Background/Purpose:** Low body mass index (BMI) is a risk factor for poor long-term outcomes in rheumatoid arthritis (RA). Low BMI in RA has been speculated to reflect weight loss due to the greater resting energy expenditure among subjects with more active and severe RA. We determined predictors of change in BMI in RA, and specifically examined whether greater disease activity was associated with weight loss over time.

**Methods:** Subjects from the Veterans Affairs RA Registry (VARA) (n = 1396) were studied. Information on inflammatory markers, presence of erosions, and smoking status were extracted from the VARA database. VARA participants without longitudinal data were excluded (n = 349) but were similar in age, gender, race, and enrollment. BMI was extracted from the vital signs package from VA electronic medical records within 14 days of each visit date. VA pharmacy records were queried to identify prescriptions for specific RA therapies within 1 month of each visit. Robust Generalized Estimating Equations (GEE) regression models determined independent associations between pre-hypothesized clinical variables and change in BMI (or odds of weight loss > 1 kg/m²) over the subsequent observation period. Variables were either time-varying (log-transformed C-Reactive Protein [lnCRP] and medication use) or time-invariant (baseline CCP seropositivity, erosive disease, and smoking status).

**Results:** Significant age, current smoking, and the presence of erosions at baseline were associated with lower BMI (all p < 0.001). On average, weight decreased over time (β = −0.017 (−0.029, −0.0052) p < 0.001). Higher lnCRP, current smoking at baseline, greater baseline BMI, and older age were associated with greater reductions in BMI over the subsequent observation period (Table 1) (all p < 0.01). Higher lnCRP, current smoking, greater baseline BMI, and older age were also associated with a greater risk of weight loss over the subsequent observation period (Table 1) (all p < 0.01). The use of prednisone and the use of anti-TNF therapies were not associated with change in BMI or the risk of weight loss.

**Conclusion:** Greater age, greater inflammatory activity, and current smoking are associated with weight loss in RA. The weight loss (and lack of weight gain) among subjects with inflammation may be due to the greater resting energy expenditure and catabolism seen with the active inflammatory process. While methotrexate was associated with a decreased risk of weight loss, there were no consistent associations between other RA medications and changes in weight.

**Table 1:** GEE in linear and logistic regression models evaluating independent predictors of the change in BMI and the risk of weight loss over the subsequent observation period.

**Disclosures:** J. Baker, None; G. W. Cannon, None; S. Ibrahim, None; C. Haraldsen, None; L. Caplan, None; T. R. Mikuls, None.

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**Background/Purpose:** Periodontal disease (PD) or periodontitis is currently considered an epigenetic determinant of both occurrence and severity of Rheumatoid Arthritis (RA). Common pathophysiological mechanisms like the migration of osteoclasts and secretion of pro-inflammatory cytokines, would occur in RA and PD but it has not been determined if the severity of
PD influence on joint damage (JD). The aim of the study was to demonstrate that a more severe PD is independently associated with a greater JD in RA patients.

Methods: A cross sectional study. RA was defined using the 1987 ACR criteria. Patients should not have other autoimmune disease and they were older than 18 years at time of diagnosis. We excluded patients with less than 4 teeth, serious or local ongoing infections, oral cancer or precurserous lesions; patients, pregnant, Diabetic patients, severe SJögren syndrome and local antibiotic or gingival hyperplasia associated drug users were also excluded. We applied a personal interview, physical examination, laboratory analysis and review of medical records to assess factors associated with JD. An assessment of periodontal attachment loss and panoramic dental X ray were done. To determine diagnosis and severity of PD the American Academy of Periodontology criteria were applied. Two categories were defined mild PD and moderate/severe PD. All dental assessments and radiographs were interpreted by a periodontologist blinded to JD. A blinded investigator to clinical RA and PD status determined JD scoring hands/foot radiographs according to Sharp VDH method. The association of PD severity and JD was determined using student’s T test, after that a multivariable linear regression model adjusted for age, tobacco, gender, rheumatoid factor (RF), anticitrullinate protein antibody (ACPA), disease duration, socioeconomic status (SES) using Graffar scale, disease activity (DAS28CRP), functional status (MDHAQ) and quality of life (SF36) was performed to determined persistence of the associations. SPSSv21.0 statistical package was used.

Results: 213 patients were evaluated, 192 (90.1%) were women, mean (SD) age was 59.59 (12.59) years, disease duration was 15.14 (11.74) years, SES were more frequently medium / medium low (31.5% and 36.6% respectively); 79.3% were ACPA positive, mean ACPA title was 679.23 U/mL, mean DAS28CRP was 3.85 (1.24), 2.3% and 14.6% were current or past smokers respectively. Erosion, joint space narrowing and total Sharp VDH scores were 41.25 (49.02), 64.65 (42.30) and 105.81 (88.44) respectively; 94 (44.1%) patients had mild PD and 119 (55.9%) patients had moderate/severe PD. In multivariable analysis PD severity (adjusted for age, SES, tobacco, gender, RF, ACPA, disease duration, DAS28CRP, MDHAQ and SF36) was independently associated with a higher score join narrowing space (p=21.47, p = 0.008) and total Sharp VDH scores (p=17.78, p = 0.029); Erosions and PD severity did not remain associated (p=18.17, p = 0.085).

Conclusion: A more severe PD impacts on structural joint damage independently of other known associated factors. A routine periodontal evaluation and monitoring could be useful for better outcomes in RA patients.

Disclosure: R. V. Gamboa-Cardenas, None; F. Ugartegui, None; J. Quinones, None; Z. Zavala-Miranda, None; L. F. Lazo, None; M. C. Cucho-Venegas, None; L. A. Perich Campos, None; J. L. Alfaro-Lozano, None; M. Medina-Chinchon, None; R. A. Rodriguez-Bellido, None; H. Torrealva, None; C. A. Pastor-Asurza, None.

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Low Vitamin D Level Is Not Associated with Increased Risk of Cardiovascular Disease in Rheumatoid Arthritis Patients. Tarun S. Sharma1, Xiaojun Teng1, Deepak Vedanthamy2, Jonida Cote1 and Androniki Bili3.

Methods: A retrospective cohort of adult patients with RA (defined as ICD-9 714.0 twice by a rheumatologist) within a tertiary health system and with primary care physician within the health system from 1/1/2001 to 10/31/2013 was constructed (n=1459). Patients with prevalent diagnosis of CVD at the time of RA diagnosis (n=127) or those without available vitamin D levels (n=410) were excluded. Vitamin D level was analyzed as both a continuous and dichotomous variable with level <20 ng/ml defined as "deficient" and =20 ng/ml "sufficient" vitamin D level groups. Primary outcome was independent physician adjudicated incident CVD defined as a composite of CAD, stroke, transient ischaemic attack or peripheral artery disease. Data was censored for death or end of the study period and vitamin D levels closest to the censoring point were captured. Poisson regression models were used to calculate the relative risk (RR) for CVD between the deficient and sufficient vitamin D level groups. Cox regression models were used to calculate the hazard ratios (HR) for CVD between the two vitamin D groups. The models were adjusted for age, gender, BMI, smoking, RF and ACPA positivity, LDL, NSAID, corticosteroid, DMARD, statin and TNF inhibitor use. The study was designed to have an 80% power to detect a minimum HR for incident CVD of 2.5 between the two groups.

Results: 921 RA patients were included. Patients were 80.5% women, 96.9% Caucasian, with mean age of 58 years and BMI 30.4 kg/m². Median time from vitamin D level measurement to CVD events was 2.7 years. There were 138 CVD events in the deficient and 793 patients in the sufficient vitamin D level groups with mean vitamin D levels of 14.3 ng/ml and 36.8 ng/ml respectively. There were 88 incident CVD events with an Incidence Rate (IR) of 14.8/1000 patient years; of these events, 19 were in the deficient and 69 in the sufficient vitamin D groups with Incidence Rate Ratio (IRR) of 1.43 (0.84–2.43, p = 0.19) for CVD between the groups. In the multivariable fully adjusted Cox model, the HR for incident CVD events was 1.30 (95% CI 0.78–2.35, p = 0.32) between the two groups. When treating vitamin D as a continuous variable, the HR for incident CVD was 0.99 (95% CI 0.97–1.004, p = 0.14) between the deficient and sufficient vitamin D level groups.

Conclusion: In this study, vitamin D level <20 vs. =20 ng/ml was not associated with increased risk of incident CVD in patients with RA. However, the study was powered to detect a minimum of double the risk between the vitamin D groups and may have missed an association of smaller magnitude.

Disclosure: T. S. Sharma, None; X. Tang, None; D. Vedanthamy, None; J. Cote, None; A. Bill, None.

1395
Disease Activity Is Associated with Insulin Resistance in Early Rheumatoid Arthritis. Androniki Bili1, Debra Webb2, Cynthia Matzkow2, Andrea Berger3, Eric D. Newman4, Thomas P. Olenengski5, David M. Pugliese6, Maria Butterwick6, Lisa L. Schroeder7, Thomas M. Harrington, Jonida Cote1, Lyudmila Kiriillova, Susan Mathew1, Tarun Sharma1, H. Lester Kirchmer8, Jon Giles9 and Mary Chester M. Wasko9.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic disease that manifests mainly with articular symptoms, but the main cause of death is cardiovascular disease (CVD). Chronic inflammation is thought to contribute both directly to CVD as well as indirectly to cardiometabolic risk factors such as insulin resistance, atherogenic lipid profile and sarcopenic obesity, all features of chronic active RA. Data on the presence of these risk factors in newly diagnosed RA are scarce but need to be defined so that they can be addressed if present in early disease. The aim of the present study was to examine the association of disease activity with cardiometabolic risk factors in newly diagnosed RA.

Methods: Patients are participants in an ongoing study that compares the effects of a novel target in RA on cardiometabolic comorbidities in RA. For the present study, baseline patient data were analyzed in a cross-sectional fashion. Participants had RA based on 2010 ACR classification criteria with symptoms < 2 years; were DMARD and biologic-naïve (except hydroxychloroquine); took corticosteroid equivalent of prednisone ≤10 mg daily; had clinical disease activity index >10, and did not have known diabetes. Disease activity was assessed by the disease activity score (DAS28) and disability by the Modified Health Assessment Questionnaire (MHAQ). The primary outcome was insulin resistance as assessed by the 2 hour glucose tolerance test (GTT). Secondary outcomes were high density lipoprotein cholesterol (HDL-c) and body composition measurements by DXA (Hologic), including android/gynecoic ratio, appendicular lean mass (kg/m²) and appendicular lean mass/height². The associations between DAS28 and MHAQ with the outcome variables were evaluated using linear regression analysis, both unadjusted and adjusted for age, gender and BMI. All outcome variables were analyzed as continuous. Pearson’s partial correlation coefficient was used to estimate the strength of the associations.

Results: Of the 33 participants, 64% were female, with mean age 50 years, 70% RF positive, 53% ACPA positive, with median BMI 30.3 kg/m² and median DAS28 4.5. In the unadjusted model, DAS28 was positively associated with insulin resistance (p = 0.01). In the adjusted model, the Pearson partial correlation was 0.3777 (p = 0.05). There was no association of the DAS28 with HDL or body composition measures. MHAQ was inversely associated with HDL (p = 0.05) in the unadjusted analysis but this
The high prevalence of pulmonary function abnormalities may precede symptoms of rheumatoid arthritis. Observations detected by pulmonary function tests may precede the diagnosis of rheumatoid arthritis. The presence of pulmonary function abnormalities is directly responsible for 10–20% of all mortality in rheumatoid arthritis patients. Spirometry is becoming increasingly available and could be used in peripheral areas to screen and monitor pulmonary function abnormalities in well-characterized patient populations such as those with rheumatoid arthritis. Abnormalities detected by pulmonary function testing may precede symptoms of rheumatoid arthritis by years and may lead to early diagnosis of pulmonary fibrosis in rheumatoid arthritis and hence intervention.

Objective: To determine the prevalence of pulmonary function abnormalities in rheumatoid arthritis patients attending rheumatology clinics in Nairobi.

Methods: Rheumatoid arthritis patients who fulfilled the study inclusion criteria were recruited. Sociodemographic characteristics and respiratory symptoms were assessed using Lung Tissue Research Consorium questionnaire (LTRC) and RA disease activity was established by Disease Activity Score (DAS28). Pulmonary function tests were then done using SpiroLab 111 according to the American thoracic society recommendations.

Results: One hundred and sixty six RA patients were recruited; the male to female ratio was 1.9:3, with a median age of 47 years. The overall 6 month prevalence of pulmonary function abnormalities was 38.5% as measured by Spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was obstructive pattern at 20.4%, followed by restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. Factors that were shown to be independently associated with all mortality in RA patients. Spirometry is becoming increasingly available and could be used in peripheral areas to screen and monitor for pulmonary function abnormalities in well-characterized patient populations such as those with RA. Abnormalities detected by pulmonary function tests may precede symptoms of rheumatoid arthritis by years and may lead to early diagnosis of pulmonary fibrosis in rheumatoid arthritis and hence intervention.

Conclusion: Treatment with systemic CS was associated with an increased hazard ratio for acquiring an infection upon adjusting for possible confounders. Despite the achievement of remission, steroid use was continued in 15% of cases without having an impact on sustainability of remission. We show that treatment with systemic CS is an independent predictor of infection in patients treated with anti-TNF agents and suggest that the use of concomitant medications should be considered in the interpretation of safety data.
female. 82%, duration of MTX administration, 7.5 years, RA duration, 11.9 years. In these patients, MTX was withdrawn without any additional treatment, and LPD was assessed during the follow up (median 5 weeks, range: 3–12 weeks). Seventeen patients were pathologically diagnosed as LPD and 10 were highly suspected of LPD with imaging tests. Spontaneous regression was observed in 19 patients with 3 achieving complete remission (CR) and 16 partial remission (PR). Three patients were stable disease (SD) and 5 were progressive disease (PD).

We focused on the time course changes in absolute number of lymphocytes at the MTX withdrawal and at the time of follow-up assessment. In CR/PR group, the number of lymphocytes were decreased at the MTX withdrawal (median 510/\mu L, range:87-1045), but restored at the time of follow-up assessment (median 1409/\mu L, 900–2969). In SD/PD group, the patients could be classified into 2 groups; 3 of low lymphocytes (median 426/\mu L, 235-578) and 5 of high lymphocytes (median 1725/\mu L, 1165-2438). However, in both groups the lymphocytes ratios did not change after follow up duration. Therefore, the ratio between the number of lymphocytes at the MTX withdrawal and at the time of follow-up assessment was significantly higher in PR/CR group than SD/PD group (3.73 vs 0.96, p=0.02). There was no significant difference of follow up duration between 2 groups (median 4 vs 5.5 weeks, p=0.46).

Same tendency were observed in histologically diagnosed 17 patients. The outcomes were 2 CR, 11 PR, and 4 PD, and lymphocytes ratios were 4.07 in CR/PR group and 0.65 in SD/PD group (p=0.261). Of 17 histologically defined LPDs, 15 had information on Epstein Barr virus encoded small RNA (EBER). EBER positivity was relatively higher in CR/PR group and 0.65 in SD/PD group (p=0.04). In the univariate analysis, RA patients tended to have lower levels of total cholesterol (p=0.08), LDL (p=0.18) and apolipoprotein A1 (p=0.15), although statistical significance was not reached. PCSK9 levels were not different between patients and controls even adjusting for comorbidity or disease activity. PCSK9 tended to be correlated with LDL cholesterol in patients and controls, but statistical significance was not reached. Nevertheless PCSK9 was positively correlated with apolipoprotein B in RA patients (beta coef. 0.06 [0.02–0.09] x10 ng/ml, p=0.00). In a small study, not in controls, we showed that the higher values of FMD was associated with increasing levels of LDL(p=0.03) and apolipoprotein A1(p=0.03) was correlated with PCSK9 levels. Therefore, whether the higher values of FMD we observed in RA patients as FMD increased we observed that the risk of having PCSK9 values included in the third tertile compared to that of being in the first tertile was statistically significant multiplied by OR 0.98 ([0.82–0.99], p=0.04), this association was not found in controls.

Conclusion: PCSK9 concentrations are associated with disease activity scores and endothelial dysfunction in RA patients. The role of PCSK9 in RA related dyslipidemia and cardiovascular risk needs further investigation.

Disclosure: E. Delgado-Frias, None; I. Ferraz-Amaro, None; V. Hernandez-Hernandez, None; A. M. de Vera-Gonzalez, None; A. F. Gonzalez-Rivero, None; M. A. Gonzalez-Gay, None; F. Diaz-Gonzalez, None.

1400 Risk of Venous Thromboembolic Events in Patients with Rheumatoid Arthritis: A Meta-Analysis of Observational Studies. Michelle Avina1, None; Sharan Rai, None; A. M. de Vera-Gonzalez, None; A. F. Gonzalez-Rivero, None; M. A. Gonzalez-Gay, None; F. Diaz-Gonzalez, None.

Background/Purpose: Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular event after myocardial infarction and stroke. Several studies have investigated the risk of VTE among patients with rheumatoid arthritis (RA), a chronic and disabling disease associated with systemic inflammation. Our objective was to perform a meta-analysis of studies evaluating the risk of DVT and PE in patients with RA.

Methods: We systematically searched MEDLINE (1946–2013) and EMBASE (1974–2013) databases for studies that reported the risk of VTE in patients with RA. Our search strategy employed Med Cal Subject Headings (MeSH terms) together with keywords for unindexed concepts relating to the themes of RA and VTE. Eligibility criteria were: 1) original data from cohort or case-control studies; 2) pre-specified RA; 3) clearly defined VTE outcomes; 4) relative risk (RR), odds ratio (OR), or hazard ratio (HR), and corresponding 95% confidence intervals (CI); 5) sex- and age-matched comparison group; and 6) English language. We calculated weight-pooled summary estimates of RRs for VTE outcomes using the random effects model. The robustness of the results was evaluated using a jackknife sensitivity analysis (i.e., removal of a single study from the baseline group of studies). All analyses were done using HEPIMA software.

Results: Our search strategy yielded 86 articles, and we identified an additional 2 citations through a hand-search of relevant bibliographies. After applying the eligibility criteria, we identified 8 studies with a total of 479,452 RA patients for inclusion in the meta-analysis. We identified 7 cohort studies (of which one reported results for three separate cohorts) and 1 case-control study, which provided 738 VTE events. The summary RR of VTE in RA patients compared to the general population was 2.57 (95% CI 2.07–3.19). Pooled estimates of HR for fatal and non-fatal DVT (7 studies, 2,556 events) were 1.76 (95% CI 1.12–2.75) and 2.07 (95% CI 1.19–3.58) respectively. The HRs for PE (6 studies, 724 events) were 2.30 (95% CI 1.01–5.18) and 2.31 (95% CI 1.10–4.82) for fatal and non-fatal PE, respectively. The summary RR of having a VTE among RA patients was 2.26 (95% CI 1.78–2.88). The summary RR of having a PE among RA patients was 1.79 (95% CI 1.27–2.53). The summary RR of having a DVT among RA patients was 2.27 (95% CI 1.76–2.94).

Conclusion: Patients with RA have an increased risk of VTE compared to the general population. The risk of PE was significantly higher than the risk of DVT in RA patients. Further studies are needed to understand the risk factors for VTE in RA patients.
study. Overall, pooled estimates for VTE, DVT and PE were significantly increased (Table 1 and Figure 1). The estimates remained statistically significant in the jack-knife sensitivity analysis with the point estimates ranging from 1.58 to 1.72 and the corresponding 95% CIs >1 in all cases except for DVT.

Conclusion: The risk of new VTE events is increased in RA patients compared to age- and sex-matched controls. However, there exist a paucity of data on the risk of PE and DVT. These findings support increased vigilance of VTE complications and potential risk-factor intervention among RA patients.

Table 1. Pooled estimates on the risk of VTE events in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Events</th>
<th>No. of Studies</th>
<th>Pooled RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>8</td>
<td>1.64 (1.42, 1.89)</td>
</tr>
<tr>
<td>DVT</td>
<td>3</td>
<td>2.06 (1.14, 3.74)</td>
</tr>
<tr>
<td>PE</td>
<td>4</td>
<td>1.92 (1.85, 1.99)</td>
</tr>
</tbody>
</table>

Disclosure: M. Avina, None; S. Choi, None; S. Rai, None; H. K. Cho, None; M. De Vera, None.

1402

Parameters of Periodontitis Correlate with Anti-Citrullinated Protein Antibodies and P. Gingivalis Antibody Titters in Patients with Early or Chronic Rheumatoid Arthritis. Shelia L. Avirkine1, Hatice Hasturk2, Maryc B. Bolster3, Deborah S. Collier1, Alpdogan Kantarc1 and Allen C. Steere, 1Massachusetts General Hospital, Boston, MA, Forsyth Institute, Cambridge, MA, 2Massachusetts General Hospital, Boston, MA, Health Medical School, Boston, MA.

Background/Purpose: Emerging evidence suggests that periodontitis and periodontal pathogens, such as Porphyromonas gingivalis (Pg), may be an environmental trigger for rheumatoid arthritis (RA). We found that antibodies to Pg are increased in a subset of untreated early RA patients and correlate with anti-citrullinated protein antibodies (ACPA). As a next step, we are evaluating periodontal disease in our RA patients. We report here findings of periodontitis in the first 23 patients who have completed formal dental examinations.

Methods: 23 RA patients, 15 with new-onset disease and 8 with chronic RA, completed standardized dental examination performed by a single periodontist. All patients met the 2010 ACR/EULAR criteria for RA. Age and gender-matched healthy subjects without periodontitis or RA were also enrolled. Dental parameters for assessment of periodontitis per the Centers for Disease Control criteria included pocket depth (PD), gingival margin, bleeding on probing (BOP) measured at 6 sites per tooth, and clinical attachment loss (CAL). Serum Pg IgG antibodies were measured by ELISA. The dental examiner was blinded to joint and laboratory findings.

Results: Typical of RA cohorts, the patients were predominantly female (87%) with median age of 46 (IQR 31-63) years. Thirty-nine percent were positive for rheumatoid factor (RF), and they had a range of disease activity. None were current smokers, but 10 previously smoked. All but one patient received routine dental care with cleanings every 6 months.

Of the 23 patients, 10 (43%) had gingivitis, a precursor of periodontitis, and only 4 patients (17%) had healthy periodontal tissue. Compared with the 20 healthy subjects, the 23 RA patients had significantly increased pocket depth (P<0.000001), CAL (P<0.001), and BOP (P=0.001). There were no differences in dental parameters between former vs. never smokers.

In the 23 patients, ACPA levels correlated directly with CAL (P=0.03), the most significant determinant of periodontal disease, and with BOP (P=0.05). In addition, dental parameters correlated with ESR values (P=0.04) and tended to correlate with RF (P=0.09) and disease activity (P=0.08). Six of the 23 patients (26%) had elevated serum Pg IgG antibodies. A 6 patients with positive Pg antibodies had periodontitis, while no patient with gingivitis or normal periodontal tissue had elevated Pg antibodies (P<0.001). Finally, Pg antibodies strongly correlated with all dental parameters including pocket depth (P<0.0001), BOP (P<0.003), and CAL (P=0.02).

Conclusion: Most of our patients with early and chronic RA had gingivitis or periodontits on formal examination, although they received regular dental care. Parameters of periodontitis correlated significantly with ACPA, supporting a role for periodontal disease in RA pathogenesis. As Pg antibodies correlate strongly with periodontitis, these may be useful biomarkers in screening for periodontal disease in RA patients. Finally, periodontitis

1401

Higher-Order Neuropsychological Deficits Are Frequent and Occur Early in RA and SLE: The Impact of Basic Processing Abilities on Psychological Well-Being. Giorgia Dimitraki1, Georgia Katsikai2, Emmanuel Papafotianakis3, Antonios Fanourakis4, Irini Gergiannaki5, George Bertsias6, Nikolaos Kougkas7, Avgiro Repa8, Evangelos Karademas9, Prodromos Sidiropoulos10 and Panagiotis Simos11. 1University of Crete, Rethymnon, Greece. 2University of Crete, Heraklion, Greece.

Background/Purpose: Deficits in higher-order cognitive abilities (episodic memory, executive functions) have been reported in patients with chronic inflammatory disorders, albeit inconsistently. We investigated whether such deficits are associated with impairments in basic cognitive processes (short-term memory, visuomotor speed) and premorbid verbal intelligence, and their potential impact on psychological well-being in newly diagnosed rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Methods: Patients with RA (N=84, age: 54.1 ± 9.1 years, education: 12.1 ± 2.7 years), SLE (N=60, age: 43.8 ± 9.7 years, education: 12.1 ± 3.7 years) and controls (N=60, age: 49.6 ± 9.9 years, education: 12.1 ± 3.7 years) were included. A battery of standardized tests of short-term memory (Digits Forward and Digits Reverse tasks), episodic memory (Auditory Verbal Learning Test [AVLT]), executive functions (Stroop Color-Word Naming, General Ability Measure for Adults [GAMA], Controlled Oral Word Association Test [COWAT], Trail Making Test [TMT A, B]), visuomotor processing speed (TMT A), premorbid verbal capacity was estimated using the Peabody Picture Vocabulary Test (PPVT-R). Scores were evaluated against age- and education-adjusted Greek population norms. The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of impaired mood.

Results: Compared to population norms, RA patients had significantly lower average scores on short term memory, immediate and delayed episodic recall, phonemic fluency, problem solving ability, visuomotor speed and set-shifting ability (p<0.002). SLE patients had significantly reduced performance on short-term memory, immediate and delayed episodic recall, visuomotor speed and set-shifting ability (p<0.003). Cognitive impairment (defined as performance ≤1.5 SD below the population mean on ≥3 indices) was found in 15.5% and 23.9% of RA and SLE patients respectively, and was not significantly affected by medical comorbidities or disease activity. Notably, impairments on higher-order cognitive abilities in patients were explained by deficits in verbal IQ, short-term memory and visuomotor speed. Both clinical variables (number of physical symptoms experienced, age, sex) contributed independently to the intensity of depression symptoms experienced by patients.

Conclusion: A wide range of cognitive domains was affected in a significant proportion of patients with newly diagnosed RA and SLE. Deficits in higher-order complex memory and executive tasks were largely due to impaired basic cognitive abilities and had an adverse impact on patients' psychological well-being. Emergence of cognitive defects early in the course of RA and SLE suggests common etiopathogenesis possibly linked to underlying disease processes (including inflammation) and/or administered treatments.

Disclosure: G. Dimitraki, None; G Katsiaki, None; E. Papafotianakis, None; A. Fanourakis, None; I. Gergiannaki, None; G. Bertsias, None; N. Kougkas, None; A. Repa, None; E. Karademas, None; P. Sidiropoulos, None; P. Simos, None.

1402

Parameters of Periodontitis Correlate with Anti-Citrullinated Protein Antibodies and P. Gingivalis Antibody Titters in Patients with Early or Chronic Rheumatoid Arthritis. Shelia L. Avirkine1, Hatice Hasturk2, Maryc B. Bolster3, Deborah S. Collier1, Alpdogan Kantarc1 and Allen C. Steere, 1Massachusetts General Hospital, Boston, MA, Forsyth Institute, Cambridge, MA, 2Massachusetts General Hospital, Boston, MA, 3Massachusetts General Hospital, Harvard Medical School, Boston, MA.

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Conclusion: Most of our patients with early and chronic RA had gingivitis or periodontitis on formal examination, although they received regular dental care. Parameters of periodontitis correlated significantly with ACPA, supporting a role for periodontal disease in RA pathogenesis. As Pg antibodies correlate strongly with periodontitis, these may be useful biomarkers in screening for periodontal disease in RA patients. Finally, periodontitis
Psychosocial Impact of Rheumatoid Arthritis Patients on Their Family Members. Sang Wan Chung, Ji Ae Y Yang, Eun Ha K Yang, Yun Jong L Lee and You Jung H Ha. 1Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, 2Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that can cause pain and functional disability, and RA patients have a higher risk of psychiatric disorders, especially depression. However, disability and socioeconomic burden of RA patients can also contribute to psychosocial wellbeing of their family members. To date, several studies have been conducted for evaluation of the burden of caregivers in chronic disease such as stroke and dementia, however, the burden of family members of RA patients has not been evaluated. In this study, we conducted a population-based analysis to examine the psychosocial characteristics of family members of RA patients in comparison with the general population and to evaluate the psychosocial impact of RA patients on their family members.

Methods: From the Fifth Korea National Health and Nutrition Examination Surveys (KNHANES V) (2010–2012) dataset, we identified 452 RA patients and then selected family members of these patients who were aged 20 years or older (n=515). The control group was sampled from members of families without RA patient with matching for sex and age (n=1,545).

We compared the psychosocial characteristics between family members of RA patients and control group. Also, serial conditional logistic regression models were performed to evaluate the association of psychosocial impact with the presence of RA patient after adjustment of covariants.

Results: The mean age was 51.9 ± 18.8 years and sixty percent were male in our study population. Family members of RA patients were more employed (63.6% vs. 60.2%, p = 0.037), and had higher household income (p = 0.037) compared with sex and age-matched control subjects. No significant differences were observed in comorbidities between two groups.

Family members of RA patients had a significantly higher level of stress (29.2% vs. 24.3%, p = 0.046), history of depression (17.3% vs. 11.9%, p = 0.004). The presence of a RA patient in the family showed significant association with history of depression (odds ratio, 1.60; 95% confidence interval, 1.19 to 2.16; p = 0.002), after adjustment for household income, education level, and employment status.

Conclusion: Family members of RA patients have higher level of stress and they are more susceptible to depression. Our findings suggest that physicians or rheumatologists who treat RA patients should pay more attention to psychosocial burden of their family members.

Table 3. Multivariate (adjusted) analyses of factors influencing psychosocial status of the study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Level of stress OR 95% CI p-value</th>
<th>History of depression OR 95% CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of RA patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.27 (0.10-1.61) 0.055 1.60 1.19-2.16 0.002</td>
<td></td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Higher intermediate</td>
<td>0.96 (0.72-1.29) 0.803 1.02 0.68-1.53 0.919</td>
<td></td>
</tr>
<tr>
<td>Lower Intermediate</td>
<td>1.07 (0.79-1.44) 0.673 1.30 0.87-1.95 0.196</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>1.15 (0.82-1.62) 0.418 1.64 1.04-2.50 0.022</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>High</td>
<td>0.90 (0.69-1.18) 0.453 1.46 0.97-2.19 0.068</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>0.69 (0.48-1.01) 0.055 1.25 0.77-2.04 0.368</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>0.70 (0.51-0.96) 0.026 1.46 0.97-2.19 0.068</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Employed</td>
<td>0.81 (0.64-1.03) 0.813 1.34 1.00-1.78 0.048</td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
Comorbidity in Rheumatoid Arthritis. It is Feasible to Record Concomitant Medical Conditions and Multi-Morbidity in Observational Research Studies. Can This Be Extended to Routine Clinical Settings? Elena Nikiphorou¹, Sam Norton² and Adam Young³. ¹University of Hertfordshire, Hatfield, United Kingdom, ²King’s College London, London, United Kingdom, ³ERAS, St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Comorbidity in RA can delay diagnosis and influence treatment decisions. It is known to affect RA outcomes, and can confound data analysis. Most RA observational cohort studies have used either the generic and weighted Charlson Comorbidity Index (CCI), one of the most widely used multi-morbidity tools, or modified versions of it. Clinical trials and large registries used different tools to collect comorbidity data. This study aims to compare the feasibility of collecting comorbidity data which is relevant to contemporary and routine care in RA, and the impact of comorbidity on survival and function.

Methods: A prospective longitudinal study of patients with RA from our prospective longitudinal study of patients with RA from our clinic. The purpose of the study is to evaluate the feasibility of collecting comorbidity data which is relevant to contemporary and routine care in RA. The study will recruit patients with early RA (≤ 18 months duration) from our clinic, and assess their comorbidity status at baseline and 5 years using the Charlson Comorbidity Index (CCI) and the Measure of Disease Activity (MDA).

Results: More than 90% of all comorbidities reported covered 10 systems in order of frequency - Non Cardiac Vascular (to comply with WHO classification), Cardiovascular, Endocrine, Gastro Intestinal & Hepatic, Respiratory, Psychiatric, Malignancies, Renal, Dermatology, Ophthalmology. A musculoskeletal and extra articular RA conditions would be managed within the specialty, these were identified and remained as a separate group and not part of this analysis. 75% of all individual comorbidities were identified and included in the Charlson Comorbidity Index (CCI), one of the most widely used multi-morbidity tools, and the most common 2-3 specific conditions in each CCI system made up most of the comorbidities. The results with respect to the risk of future heart failure.

Conclusion: This study has shown the feasibility of collecting comorbidity data in a relatively simple way using standard definitions, and its value in identifying multi-morbidity. It is this latter group with complex disease that requires prompt identification, multiple specialty input and coordination of patient care routine clinical settings.

Disclosure: E. Nikiphorou, None; S. Norton, None; A. Young, None.

1407
Low HAQ and Pain Predict Patient Perceived Remission in Rheumatoid Arthritis Patients Receiving MTX or Anti-TNF-Alpha Treatment. Paul Studenic¹, Josef S. Smolen² and Daniel Alehaha³. ¹Medical University of Vienna, Vienna, Austria, ²Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: The induction of remission is the primary target of RA therapy. Failing to achieve the patient global estimate of disease activity criterion (PGA ≤1cm) has been shown to be the primary cause of disease activity criteria. PGA ≤1cm has been shown to be the primary cause of disease activity criteria that require prompt identification, multiple specialty input and coordination. Remission requires prompt identification, multiple specialty input and coordination.

Methods: We selected patients from a longitudinal RA database, who started MTX monotherapy or TNFi treatment in combination with MTX or leflunomide and had at least 6 months of follow-up. In univariate analysis, we tested core-set variables to identify candidate predictors of patient perceived remission (PGA ≤1cm), which we then subjected to multivariate logistic regression analysis for the outcome: PGA ≤1cm.

Results: Data of 172 patients receiving MTX (82% female, 65% rheumatoid factor positive, mean SDAI: 18.5 ± 12.3) and of 112 patients on TNFi (82% female, 62% rheumatoid factor positive, mean SDAI: 19.7 ± 13.3) were used for analysis. After 6 months of treatment, 70% of those receiving MTX and 55% of the TNFi group were in a state of remission or low disease activity, based on the SDAI. Forty-seven percent of MTX and 34% of TNFi patients evaluated their PGA as being ≤1cm. Seventy-four percent of MTX and 58% of TNFi treated patients who had PGA ≤1cm had also an evaluator global assessment of ≤1cm. The overlap of patient perceived remission and remission by SDAI was 49% in the MTX group and 46% in the TNFi group.

Conclusion: This study shows that PGA ≤1cm has been shown to be the primary cause of disease activity criteria that require prompt identification, multiple specialty input and coordination. Remission requires prompt identification, multiple specialty input and coordination.

Disclosure: E. Nikiphorou, None; S. Norton, None; A. Young, None.
1.25 or a pain score of 50mm has a 20% probability of achieving PGA remission, whereas a baseline HAQ of 0.5 or a pain score of 20mm coincides with a 40% probability.

Table. Summary of the multivariate logistic regression model for the outcome PGA ≤1cm

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>β coefficient</th>
<th>Standard error</th>
<th>p</th>
<th>95% Confidence Interval for OR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite score</td>
<td>0.01</td>
<td>0.42</td>
<td>-0.04</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In CRP</td>
<td>-0.05</td>
<td>0.48</td>
<td>-0.55</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In TNF-α</td>
<td>0.13</td>
<td>0.72</td>
<td>0.52</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In IL-6</td>
<td>0.15</td>
<td>0.13</td>
<td>-0.87</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In EGF</td>
<td>-0.25</td>
<td>0.16</td>
<td>1.33</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In VEGF-A</td>
<td>-0.31</td>
<td>0.07</td>
<td>3.14</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Leptin</td>
<td>-0.13</td>
<td>0.18</td>
<td>2.54</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In SAA</td>
<td>0.05</td>
<td>0.57</td>
<td>-0.83</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In VCA M1</td>
<td>0.05</td>
<td>0.70</td>
<td>-0.69</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In MMP-1</td>
<td>-0.18</td>
<td>0.20</td>
<td>3.83</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In MMP-3</td>
<td>-0.02</td>
<td>0.91</td>
<td>-1.62</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In YKL-40</td>
<td>0.09</td>
<td>0.56</td>
<td>0.87</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Resistin</td>
<td>-0.18</td>
<td>0.46</td>
<td>6.28</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All results are from multivariable linear regression models adjusted for age, sex, RA disease duration and seropositivity.

Conclusion: We demonstrated here that patients with poor function or high pain levels are likely to fail patient reported remission, as shown here for the patient global variable, which is part of the established remission criteria. These findings were independent of the treatment regimen. Improvement in function enhances the chances for achieving patient perceived remission after 6 months of DMARD treatment.

Disclosure: P. Studenic, None; J. S. Smolen, None; D. Aletaha, None.

### 1408

Inflammatory Biomarkers, Sleep Quantity and Sleep Quality in Rheumatoid Arthritis. Alexander Fine1, Michelle A. Frits2, Jing Cui3, Christine K. Iannaccone3, Jonathan S. Coblyn4, Michael E. Weinblatt5, Nancy A. Shadick6. 1Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA, 3Insel, Bern, Switzerland, 4Duke University Medical Center, Durham, NC, 5Brigham and Women’s Hospital, Boston, MA, 6Brigham and Women’s Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Sleep problems affect over 60% of rheumatoid arthritis (RA) patients. However, little is known about the association between sleep problems and inflammatory pathways in RA. In the general population, studies have shown that sleep problems are associated with elevations in inflammatory biomarkers, notably CRP and the inflammatory cytokines, TNF-α and IL-6. The goal of this study was to examine the cross-sectional association between biomarkers associated with RA disease activity and sleep quantity and quality in patients with RA.

Methods: 208 patients in a RA registry were enrolled in a substudy on sleep and psychosocial distress. All subjects completed the Medical Outcomes Study (MOS) Sleep Scale. Of these 208 patients, 189 also had 12 biomarkers of disease activity (EGF, VEGF-A, leptin, IL-6, SAA, CRP, VCA M1, M MP-1, M MP-3, TNF-α, YKL-40 and resistin) measured using a quantitative multiplex immunoassay. Biomarkers with non-normal distributions were transformed. The primary independent variables were the individual biomarkers and a composite disease activity score, calculated according to a validated algorithm. The primary dependent variables were sleep quantity (in hours) and sleep quality, measured by the MOS Sleep Problems Index II (0-100 scale with 100 indicating greater sleep problems). Linear regression models were used to examine the association between biomarkers and sleep quantity and quality, adjusted for age, sex, RA disease duration and RF or anti-CCP seropositivity. To elucidate the impact of TNF inhibitors on this association, secondary analyses were performed including an indicator variable for TNF inhibitor use. Using the Bonferroni correction for multiple comparisons, the threshold for significance was set at p < 0.002.

Results: The study population (N = 189) included 85.2% women. The average age was 58.2 ± 11.2 years. The average DAS28-CRP was 2.95 ± 1.29. 17.5% were taking corticosteroids. 59.8% were taking non-biologic disease-modifying anti rheumatic drugs, and 54.0% were taking TNF inhibitors. 61.9% were either RF or anti-CCP positive.

After adjustment for multiple comparisons, neither the composite disease activity score nor the individual biomarkers of disease activity were significantly associated with sleep quantity or the MOS Sleep Problems Index II (Table). Similarly, neither the composite disease activity score nor the individual biomarkers were significantly associated with sleep quantity or the MOS Sleep Problems Index II in secondary analyses including TNF inhibitor use as an indicator variable.

Conclusion: Contrary to previous studies in the general population, no associations were observed between inflammatory biomarkers and measures of sleep quantity and quality in this cross-sectional study of established RA patients. These findings suggest that RA disease activity may not be the primary driver of sleep problems in RA.

Table. Adjusted associations between biomarkers of RA disease activity and sleep quantity and sleep quality, measured using the Medical Outcomes Study Sleep Scale.*

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Sleep Quantity (n = 174)</th>
<th>Sleep Quality (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β coefficient</td>
<td>β</td>
<td>p</td>
</tr>
<tr>
<td>Composite score</td>
<td>0.01</td>
<td>0.42</td>
</tr>
<tr>
<td>In CRP</td>
<td>-0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>In TNF-α</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>In IL-6</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>In EGF</td>
<td>-0.25</td>
<td>0.16</td>
</tr>
<tr>
<td>In VEGF-A</td>
<td>-0.31</td>
<td>0.07</td>
</tr>
<tr>
<td>In Leptin</td>
<td>-0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>In SAA</td>
<td>0.05</td>
<td>0.57</td>
</tr>
<tr>
<td>In VCA M1</td>
<td>0.05</td>
<td>0.70</td>
</tr>
<tr>
<td>In MMP-1</td>
<td>-0.18</td>
<td>0.20</td>
</tr>
<tr>
<td>In MMP-3</td>
<td>-0.02</td>
<td>0.91</td>
</tr>
<tr>
<td>In YKL-40</td>
<td>0.09</td>
<td>0.56</td>
</tr>
<tr>
<td>In Resistin</td>
<td>-0.18</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* All results are from multivariable linear regression models adjusted for age, sex, RA disease duration and seropositivity.

Disclosure: A. Fine, None; M. A. Frits, None; J. Cui, None; C. K. Iannaccone, None; J. S. Coblyn, CVS caremark; M. E. Weinblatt, UCB, 2, Bristol-Myers Squibb, 2, Crescendo, 2, UCB, 5, Bristol-Myers Squibb, 5, Crescendo, 5, N. A. Shadick, Crescendo Bioscience, 2, Agena, 2, UCB, 2, Abbvie, 2, Bristol Myers Squibb, 2, Genentech, 2, Y. C. Lee, Forest Research Institute, 2, Merck Pharmaceuticals, 1, Cubist Pharmaceuticals, 1, Pfizer, 1, Express Scripts, 1.

### 1409

Pregnancy Outcomes after Exposure to Certolizumab Pegol: Updated Results from Safety Surveillance. Megan E. B. Clowse1, Douglas C. Cow2, Frauke Förger3, John J. Cush4, Amanda Golembesky5, Laura Shaughnessy6, Dirk De Cuyper6, Kristel Luijtens6, Sarah Abbas7 and Uma Mahadevan8. 1Duke University Medical Center, Durham, NC, 2Atlanta Gastroenterology Associates, Atlanta, GA, 3Inselspital, University of Bern, Bern, Switzerland, 4Duke University Medical Center, Dallas, TX, 5UCB Pharma, Raleigh, NC, 6UCB Pharma, Brussels, Belgium, 7UCB Pharma, Paris, France, 8UCSF Medical Center, San Francisco, CA.

Background/Purpose: Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF approved for the treatment of RA, CD, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The objective was to provide an updated analysis of pregnancy outcomes in rheumatic patients (pts) after CZP exposure, with a focus on RA pregnancies, from clinical trial and spontaneous post-marketing reports. Concomitant medications and disease activity are also reported from clinical trials.

Methods: The UCB Pharma global safety database was searched for all medically confirmed cases of pregnancy through 28 March 2013. The number of live births, spontaneous miscarriages and elective terminations for neonates exposed to CZP (maternal/paternal exposure) was examined. Congenital abnormalities, neonatal deaths, maternal demographics, disease activity and concomitant medications were also investigated.

Results: 309 CZP-exposed pregnancies were reported: 285 maternal exposure, 24 paternal. For maternal exposure pregnancies, the most common underlying maternal conditions were CD (190/285) and RA (52/285), with the remaining 43/285 for other indications (including AS and PsA). Pregnancy outcomes were available for 190 of 285 pregnancies: 42 in women with RA, 124 in CD and 24 in other rheumatic indications. Pregnancy outcomes, where reported, are shown in Table 1. Maternal disease activity in women with RA are shown in
Table 2. Common concomitant medications in all pregnancies are shown in Table 3. 5 congenital anomalies were reported, in 4 neonates, among all maternal exposure live births (n = 132); vesicoureteric reflux; congenital morbus hirschprung disease and club foot; right aortic arch with aberrant left subclavian artery; mild unilateral hydro-nephrosis on antenatal ultrasound (healthy at birth). None were aortic arch with aberrant left subclavian artery; mild unilateral hydro-reflux; congenital morbus hirschprung disease and club foot; right

Table 1: Pregnancy outcomes and characteristics for all maternal exposure pregnancies with known outcomes, with focus on the subgroup of women with RA

<table>
<thead>
<tr>
<th>RA Subgroup (n = 42)</th>
<th>All Pregnancies [a] (N = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome, n (%)</td>
<td></td>
</tr>
<tr>
<td>Number with available data</td>
<td>42</td>
</tr>
<tr>
<td>Live birth</td>
<td>26 (61.9%)</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>9 (21.4%)</td>
</tr>
<tr>
<td>Elective termination</td>
<td>7 (16.7%)</td>
</tr>
</tbody>
</table>

| Maternal age at delivery [b] (years) |                                  |
| Number with available data | 21 |
| M age (SD) | 31.2 (5.74) | 30.5 (5.10) |
| M edian | 30.7 | 29.8 |
| M in, max | 21.5, 40.5 | 21.5, 42.5 |

| Gestational age at outcome [c] (weeks) |                                  |
| Number with available data | 22 |
| M age (SD) | 37.9 (1.99) | 38.3 (1.97) |
| M edian | 38.1 | 39.0 |
| M in, max | 33.7, 41.0 | 32.0, 41.7 |

| Prematurity [c] |                                  |
| Number with available data | 24 |
| <32 weeks | 4 (0.0%) | 1 (1.2%) |
| 32–36 weeks | 4 (16.7%) | 10 (11.6%) |
| ≥37 weeks | 20 (83.3%) | 75 (87.2%) |

| Birth weight [d] (grams) |                                  |
| Number with available data | 16 |
| ≤2500 grams | 3168.7 (523.89) | 3194.3 (447.84) |
| M edian | 3080.0 | 3215.0 |
| M in, max | 2500.0, 4535.9 | 2100.0, 4535.9 |

| Low birth weight [d] |                                  |
| Number with available data | 16 |
| 1500–2499 grams | 62 |
| ≥2500 grams | 16 (100.0%) | 60 (96.8%) |

[a] Pts with all indications, including CD, RA, axial spondylarthritis (asSpA) and PsA. [b] Analyses restricted to live births; [c] Analyses restricted to singleton live births; [d] Analyses restricted to singleton, term, live births.

Table 2: Maternal disease activity for pregnancies from clinical trial reports (RA subgroup only)

<table>
<thead>
<tr>
<th>Live Birth (n = 7)</th>
<th>Spontaneous Abortion (n = 4)</th>
<th>Elective Termination (n = 3)</th>
<th>Total (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA528 (ESR) at baseline (RA study entry)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M age (SD)</td>
<td>6.39 (0.79)</td>
<td>6.14 (0.68)</td>
<td>6.64 (0.92)</td>
</tr>
<tr>
<td>M edian</td>
<td>6.18</td>
<td>6.09</td>
<td>6.56</td>
</tr>
<tr>
<td>M in, max</td>
<td>5.1, 7.3</td>
<td>5.4, 7.0</td>
<td>5.8, 7.6</td>
</tr>
</tbody>
</table>

| DA528 (ESR) at visit prior to pregnancy report |                                 |                               |               |
| M age (SD) | 3.51 (1.65) | 2.43 (1.44) | 4.41 (1.05) | 3.39 (1.56) |       |
| M edian | 2.67 | 1.93 | 4.18 | 2.86 |       |
| M in, max | 2.2, 6.3 | 1.3, 4.5 | 3.5, 5.6 | 1.3, 6.3 |       |

| DA528 (ESR) change from baseline |                                 |                               |               |
| M age (SD) | 2.88 (1.59) | 3.71 (1.62) | 2.23 (0.76) | 2.98 (1.47) |       |
| M edian | -2.99 | -4.02 | -2.05 | -3.03 |       |
| M in, max | -4.7, -0.6 | -5.2, -1.6 | -3.1, -1.6 | -5.2, -0.6 |       |

Table 3: Concomitant medications at time of pregnancy report for all pregnancies from clinical trials

<table>
<thead>
<tr>
<th>Concomitant Medication, n (%)</th>
<th>Live Birth (n = 42)</th>
<th>Spontaneous Abortion (n = 13)</th>
<th>Elective Termination (n = 10)</th>
<th>Outcome Unknown (n = 8)</th>
<th>Total (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any concomitant medications</td>
<td>29 (69.5%)</td>
<td>11 (84.6%)</td>
<td>15 (75.0%)</td>
<td>7 (87.5%)</td>
<td>62 (94.5%)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>2 (6.5%)</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td>Anti-inflammatories or antirheumatics</td>
<td>9 (29.0%)</td>
<td>4 (30.8%)</td>
<td>7 (46.7%)</td>
<td>1 (12.5%)</td>
<td>21 (32.3%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7 (22.6%)</td>
<td>3 (23.1%)</td>
<td>4 (30.0%)</td>
<td>2 (25.0%)</td>
<td>16 (24.6%)</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>12 (38.7%)</td>
<td>8 (61.5%)</td>
<td>4 (40.0%)</td>
<td>1 (12.5%)</td>
<td>37 (56.9%)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>11 (35.5%)</td>
<td>3 (23.1%)</td>
<td>1 (16.7%)</td>
<td>1 (12.5%)</td>
<td>25 (38.5%)</td>
</tr>
<tr>
<td>Mesalamine/Sulfasalazine</td>
<td>12 (38.7%)</td>
<td>3 (23.1%)</td>
<td>5 (33.3%)</td>
<td>2 (25.0%)</td>
<td>29 (44.6%)</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>5 (15.6%)</td>
<td>3 (23.1%)</td>
<td>2 (25.0%)</td>
<td>0</td>
<td>10 (15.4%)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>6 (19.4%)</td>
<td>4 (30.8%)</td>
<td>4 (30.0%)</td>
<td>0</td>
<td>14 (21.2%)</td>
</tr>
</tbody>
</table>

[a] Concomitant medications are defined as any medication taken at the time of the pregnancy report study visit.
Conclusion: Among RA patients with available EMR data for traditional CV risk factors, a majority had modifiable obesity, HL and HTN (including uncontrolled). Yet, only a minority were treated with statins, ACE-I, or ARB. These data suggest that CV risk factor management is suboptimal in RA patients, even in the subgroup of RA patients with “high-risk” disease features. The low rates of CV risk factor modification are potential barriers to optimizing CV preventive strategies in RA. Future studies are needed to improve workflows using EMR for CV risk factor documentation and to help modify them in this high-risk population.

Table 1: Prevalence of CV Risk Factors Reported in EMR in RACER Cohort. Analysis of 934 active RACER patients (out of 1039 patients) from enrollment up to October 2013

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Present</th>
<th>Absent</th>
<th>Data Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN*</td>
<td>505</td>
<td>428</td>
<td>95</td>
</tr>
<tr>
<td>Uncontrolled HTN</td>
<td>705</td>
<td>216</td>
<td>13</td>
</tr>
<tr>
<td>HL</td>
<td>480</td>
<td>453</td>
<td>18</td>
</tr>
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ICD codes: *401.0-401.9; 272.0-272.9; **250.00-250.83; V17.49; V12.50, 429.0-429.9, 410.0-410.9, 414.00-414.19, 414.2-414.9; **250.00-250.83, V17.49, V12.50, 429.0-429.9.

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1412
Sarcopenia and Its Impact on Disability in Rheumatoid Arthritis, a Pilot Study. Meltem Alkan Melikoglu1 and Kazim Senel2. 1Ataturk University Faculty of Medicine, Erzurum, Turkey, 2Ataturk University Medical School, Erzurum, Turkey.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased morbidity and mortality due to several metabolic deteriorations one of which is sarcopenia. The aim of this cross-sectional pilot study was to investigate sarcopenia in patients with RA and to evaluate its relation to the disability assessment.

Methods: Forty female patients with RA and age/gender and body mass index (BMI) matched 40 healthy controls were included. Demographic data, pain, morning stiffness duration, disease activity score (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the Health Assessment Questionnaire (HAQ) were evaluated. Body compositions were assessed with whole body dual energy X-ray absorptiometry. We compared the appendicular skeletal muscle mass (ASM) and skeletal muscle mass index (SMI) of patients to their healthy matches. Also possible correlations between SMI and the disease characteristics and HAQ score were investigated. The independent samples t test and the Pearson’s correlation test were used to evaluate the data.

Results: The mean age of the patients and controls were 48.29 ± 8.34 and 46.21 ± 6.90 years, respectively. The BMI values, percentages of obese, overweight and healthy weight subjects were similar in patient and control groups. However, ASM and SMI calculations were found to be significantly lower in patients with RA than those in controls (p < 0.05). The percentage of sarcopenia was significantly higher in patients with RA than that in their age-gender and BMI similar healthy matches (20% and 7%; respectively; p < 0.05). Although there were no significant correlations between SMI and age, disease duration, morning stiffness, pain, DAS28 levels and laboratory investigations, a significant negative correlation was determined between SMI and HAQ score in patients with RA (p < 0.05).

Conclusion: We demonstrated lower SMI values and higher sarcopenia ratios in patients with RA than their age-gender and BMI similar healthy matches. Also, independently from other disease characteristics, the inverse correlation between SMI and HAQ scores found in our study may contribute to the understanding of the impact of the process on the disability of the patients.

Disclosure: M. A. Melikoglu, None; K. Senel, None.

1413
The Prevalence of Renal Impairment in Patients with Rheumatoid Arthritis. Marion Couderc Sr.1, Martín Soubrier2, Bruno Pereira3, Aurelien Tiple4, Melanie Gilson5, Bruno Fautrel6, Sophie Pouplin7, Emmanuelme Dernis Labous5, Laure Gossec6, Cécile Gajoux-Viala8,2 and Maxime Dougados1.1. Chu G.Montpied, Clermont Ferrand, France, 2CHU G.-Montpied, Clermont Ferrand, France, 3La Colombiere Hospital, Montpellier, France, 4Hospital R Salengro CHRU, Lille CEDEX, France, 5Hospital R Salengro CHRU, Lille CEDEX, France, 6French Rheumatology Society, Clermont Ferrand, France, 7Ataturk University Medical School, Erzurum, Turkey, 8Centre Hospitalier Universitaire de Montpellier, Montpellier, France.

Conclusion: Psychological distress in very early RA is frequent and the HAQ-DI score is a predictor of depression and anxiety in these patients. Psychological evaluation in patients with early RA is important for further individual psychiatric diagnosis and management.

Disclosure: B. Combe, Lilly, Merck, Novartis, Pfizer Inc, Roche-Chugai, and UCB, 2, Lilly, Merck, Novartis, Pfizer Inc, Roche-Chugai, and UCB, 8; N. Rincheval, None; R. M. Filo, None; P. M. Goupille, None; J. P. Dauraès, None; J. Boulenger, None.
Clermont-Ferrand, France, 3Clinical research department, Clermont-Ferrand, France, 4CHU, Clermont-Ferrand, France, 5CHU Grenoble, Grenoble, France, 6Pitie Salpetriere Hospital, Paris, France, 7Rouen University Hospital, Rouen, France, 8CH Du Mans, Le Mans, France, 9UPMC GRC08, Paris 06 University, Pitie Salpetriere Hospital, Paris, France, 10EA 2415, Montpellier I University, Nimes University Hospital, Rheumatology Department, Nimes, France, 11Universite Paris René Descartes and Hôpital Cochin, Paris, France.

Background/Purpose: To assess the prevalence and associations of renal dysfunction in patients with rheumatoid arthritis (RA).

Methods: COMEDRA is a French nationwide cross-sectional multicentre study on comorbidities in RA. Renal function was assessed from the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation. RA characteristics, risk factors for renal dysfunction (cardiovascular risk factors, medications) were collected in all participants.

Results: 931 of the 970 recruited patients, were analysed (female gender: 79.6%, age: 57.8 years, disease duration: 111.1 years, DSAs-erythrocyte sedimentation rate: 3.1). About 9% of patients had an eGFR<60 ml/min/1.73m² and 9.9% of the patients had proteinuria (defined by positive dipstick testing). In the univariate analysis, age (p<0.001), the presence of hypertension (p<0.001), systolic blood pressure (p=0.03), and Framingham Risk score (p<0.001) were associated with an eGFR<60ml/min/1.73m². Renal dysfunction was not associated with gender (p=0.35), disease duration (p=0.91), disease activity (as assessed by DSAS-ESR: p=0.14), NSAID use (p=0.77), disease severity (erosions p=0.9, joint replacement p=0.6) or RA medications (p=0.14). Two multivariate analysis models were constructed: Model A, without the Framingham risk score which showed that age (OR: 1.05; 95%CI [1.03–1.09]) and hypertension (OR: 2.5, 95%CI [1.53–4.3]) were predictive of an eGFR <60 ml/min/1.73m²; Model B, which showed that the Framingham risk score was predictive of low eGFR (OR: 1.06, 95%CI [1.03–1.09]).

Conclusion: Renal impairment is relatively common in RA and is associated with cardiovascular risk factors such as age, hypertension and the Framingham risk score but not with disease activity or severity.

Disclosure: K. Ishii, None; Y. Mochida, None; Y. Ozawa, None; M. Itsugi, None; T. Saito, None.

1415


Background/Purpose: Gastroesophageal reflux disease (GERD) is caused by the abnormal reflux of the gastric contents into the esophagus. Many risk factors are considered as a cause of GERD. Nonsteroidal anti-inflammatory drugs (NSAIDs) consumption is regarded as one cause of the development of GERD; but, there are few reports regarding the relationship between NSAIDs consumption and the development of GERD. NSAIDs are commonly used to control pain, inflammation related to patients with rheumatoid arthritis (RA). Therefore, the prevalence of GERD in RA may be higher because of high rate of NSAIDs consumption. However, there are few reports regarding the development of GERD in RA. The purpose of this study was to examine the prevalence of GERD in RA. We also investigate the association between GERD and clinical factors in RA.

Methods: We investigated 378 outpatients with RA (70 males, 308 females). Three rheumatologist of orthopaedic surgery examined all patients. The presence or absence of GERD was evaluated by using GERDQ questionnaire. It is well known that GERDQ can be used to diagnose GERD with an accuracy similar to that of the gastroenterologist. When heartburn or acid regurgitation symptoms are observed more than once a week, the patients are diagnosed with GERD. The correlation between GERD and clinical factors such as age, sex, height, weight, BMI, disease duration, DSAS-ESR, DAS28, CRP, SDAI, VAS, and medication drugs (NSAIDs, steroid, bisphosphonate, and gastroprotective agents) were analyzed.

Results: The GERD symptoms were observed in 96 of these 378 patients (25.4%). SDAI and patient’s VAS were significantly higher in the GERD positive group than in the GERD negative group (p=0.05). DAS28 and DSAS-ESR, DAS28-ESR, CRP, ESR, SDAI, VAS and medications were significantly higher in the GERD positive group than in the GERD negative group (p=0.14), and the presence of osteoporosis (p=0.005), conversely women had higher prevalence of osteoporosis (18.57% vs 7.1%, p=0.02 and received more frequently anti-resorptive therapy (15.71% vs 5.71%, p=0.005). Regarding to comorbidity, men had a higher prevalence of ischemic heart disease (1.43% vs 11%, p=0.029), chronic pulmonary obstructive disease, COPD (2.86% vs 17.14%, p=0.005), and conversely women had higher prevalence of osteoporosis (18.57% vs 7.1%, p=0.02 and received more frequently anti-resorptive therapy (15.71% vs 5.71%, p=0.005). Regarding to psychological variables, women presented significantly higher scores in the Beck scale (10.78+7.52 vs 7.83+6.85, p=0.016) and numerically worse IBO scores (11.91+6.07 vs 10.55+5.86, p=0.181), not finding differences in the rest of studied psychological and disease related variables.

Conclusion: Female RA patients have lower levels of quality of life than their male counterparts. Psychological variables as a higher level of depressive symptoms and, maybe, a worse disease related behavior as well as a higher incidence of osteoporosis plays a major role in this result, rather than pure biological disease related variables. This fact should be taken into account in the management of these patients.
1416

Analysis of Cardiac Involvement in Patients with Amyloidosis Due to Rheumatoid Arthritis. Daisuke Kobayashi1, Saboshi Ito1, Satoru Kodama1, Akira Murasawa2, Ichiei Narita2 and Kiyoshi Nakazono1. 1Niigata Rheumatic Center, Shibata, Japan, 2Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is one of the major causes of amyloid A (AA) amyloidosis. The major organs affected are the kidneys and gastrointestinal (GI) tract. Although cardiac amyloidosis is the principal cause of death in patients with amyloidosis, significant cardiac involvement in AA amyloidosis is thought to be rare. On the other hand, the survival rate of hemodialysis patients with AA amyloidosis associated with RA has been shown to be low, and our previous study revealed that cardiac failure accounted for more than half of the mortality in these patients. The purpose of this analysis was to clarify the cardiac involvement and its clinical significance in patients with RA-associated AA amyloidosis.

Methods: Twenty-seven RA patients (4 males, 23 females) with AA amyloidosis who were followed up at Niigata Rheumatic Center between April 2007 and March 2014 were enrolled. Each patient fulfilled the 1987 American College of Rheumatology criteria for RA. All patients had undergone GI tract biopsies, and had been confirmed to have reactive AA amyloidosis by pathological examination. The patients’ background data and echocardiographic features were analyzed retrospectively. Differences were assessed by Mann-Whitney U test*, Fisher’s exact test*, and log rank test**, and differences at p < 0.05 were considered statistically significant.

Results: The median age was 71 (range, 49-89) yr, the period between the onset of RA and echocardiographic examination was 20 (2-41) yr, and the period between the onset of AA amyloidosis and echocardiographic examination was 1007 (20-6458) day. Echocardiography showed that the left ventricular (LV) posterior wall thickness was 11.0 (7.4-17.0) mm, with an interventricular septal thickness of 10.5 (5.5-14.2) mm, and an ejection fraction (EF) of 72.1% (32.3-85.4%). Thirteen patients with LV wall thickness exceeded 11.0 mm. An ejection fraction (EF) of 72.1% [32.3-85.4%]. Thirteen patients with LV wall thickness exceeded 11.0 mm, and an ejection fraction (EF) of 72.1% [32.3-85.4%]. Thirteen patients with LV wall thickness exceeded 11.0 mm, and an ejection fraction (EF) of 72.1%

Conclusions: It is suggested that the cardiac involvement and its clinical significance in patients with RA-associated AA amyloidosis is rare.

1417

Red Cell Distribution Width: A Measure for Cardiovascular Risk in Rheumatoid Arthritis Patients? Sobia Hassan1, Maria Antonelli2 and Stanley P Ballou3. 1Case Western Reserve University, 2MethroHealth Medical Center, Cleveland, OH, 3Case Western Reserve University School of Medicine, Cleveland, OH.

Background/Purpose: Red cell distribution width (RDW) is a measure of the variation in red blood cell size reported on the automated complete blood count. Although traditionally used to differentiate between causes of anemia, elevated RDW has recently been found to predict cardiovascular (CVS) risk and outcome in patients with and without heart disease. RDW may be a marker for the inflammation that drives CVS risk. Supporting an inflammatory link, RDW has been shown to correlate with disease activity and inflammatory markers in conditions such as Bechet’s, inflammatory bowel disease, rheumatoid arthritis (RA) and systemic lupus erythematosus.

RA is a chronic inflammatory condition with an increased risk of CVS disease. We hypothesized that RA patients with elevated RDW levels would experience greater burden of myocardial infarction (MI).

Methods: Utilizing a secure cloud-based platform, Exployrs, we searched de-identified patient data from multiple US healthcare systems between the years 1999 to 2014. Patients with a diagnosis of RA were identified by CCP and/or RF positivity. To exclude the influence of anemia only patients with Hb > 12 mg/dl were included. Patients were stratified into a high ( > 15.6 %) RDW group if they ever had an RDW > 15.6% and a low RDW group ( < 13.5%) and excluding any patient with prior episode of RDW 15.6%. The proportion of patients with a diagnosis of MI in each RDW group was collected.

For comparison, patients were divided into a high and low CRP group (> 2.5 and < 0.8 mg/dl) and a high and low ESR group (>50 and <30 mm/hr) and MI data was collected.

Statistical comparison between high and low laboratory test groups was performed with chi square and odds ratios were calculated.

Results: The proportion of RA patients with MI was significantly increased in the high compared to low RDW, ESR and CRP groups (results depicted in Table 1).

Conclusion: In keeping with previous findings in RA patients, elevated levels of ESR and CRP were associated with increased risk of MI. Elevated levels of RDW in RA patients also appear to indicate an increased risk of MI. RDW is a widely available laboratory parameter that may be useful as a measure for CVS risk in RA.

We propose that in addition to elevated ESR and CRP, elevated RDW levels in RA patients should prompt physicians to aggressively screen and treat their patients for modifiable CVS risk factors, in addition to treating RA inflammation.

Disclosure: S. Hassan, None; M. Antonelli, None; S. P. Ballou, None.
vascular (CV) risk factors with an increased prevalence in RA – are inversely correlated with VitD levels. The objectives were to determine the prevalence of VitD deficiency in RA patients versus a control population, and detect correlations between VitD levels and RA disease activity and/or characteristics, and between VitD levels and CV risk factors.

Methods: The COMEDRA study evaluated the impact of a visit with a nurse on the management of comorbidities in RA patients. VitD and lipids assays were performed in all patients. Controls were from the SU. V.I. MAX cohort and were matched for gender, age, latitude and season during which samples were taken for assay. VitD deficiency was defined as VitD < 10 ng/ml and VitD insufficiency as VitD between 10 and 29.9 ng/ml (VDI).

Results: 894 patients (79.3% women) with an average disease duration of 11.2 years [6.3 – 19.1] were analyzed. RA was erosive in 73.3% of patients and 83.9% had positive RF or anti-CCP antibodies. The DAS28-ESR was 3.0 ± 1.3. 630 patients (70.4%) were treated with biologic therapy and 341 (38.1%) received glucocorticoids (5.5 ± 5.7 mg/day). BM1 was 25.1 ± 4.8. SBP was 124.9 ± 16.5 mmHg, and DBP 75.6 ± 11.4 mmHg. Total cholesterol was 22.2 ± 5.0 g/l, LDL-c was 1.3 ± 0.4 g/l, HDL-c was 0.7 ± 0.2 g/l. 147 patients (16.4%) were smokers and 52 (5.8%) were diabetic. VitD levels were in the normal range in 362 patients (40.5%), whereas 501 patients (56.0%) had VitD insufficiency and 31 (3.5%) had VitD deficiency. Comparison of 861 RA patients with 861 matched controls revealed that the RA patients had a lower prevalence of VitD insufficiency (RA: 480 (55.6%) vs. controls: 508 (59%); p = 0.04) and of VitD deficiency (RA: 31 (3.6%) vs. controls: 45 (5.23%); p = 0.04).

Among RA patients, males had a higher frequency of VitD insufficiency (117 (63.3%) vs. 384 (54.2%); p = 0.04) and VitD deficiency (18 (4.3%) vs. 23 (3.2%); p = 0.04) in males vs females respectively. There was no difference according to latitude, but the prevalence of VitD insufficiency and VitD deficiency were higher in springtime. Univariate analysis found an inverse correlation between VitD levels and RA activity defined by DAS28-ESR-CR (ρ = 0.02), SDAI (ρ = 0.05) and CDAI (ρ = 0.05), but only a trend for DAS28-ESR (ρ = 0.08). No correlation was found with antibody status or with treatments. VitD levels were inversely correlated with BM1 (ρ = -0.001) but not with blood pressure, total-c, LDL-c, HDL-c or diabetes.

Conclusion: This study confirms that VitD is inversely correlated with RA activity and BM1 but not with other CV risk factors. The prevalence of VitD deficiency was lower than in the control population, which could be explained by the fact that RA patients more frequently received VitD supplementation.

Disclosure: S. Cecchetti, None; M. Soubrier, None; P. Galan, None; B. Pereira, None; G. Mauterle, None; M. Dougdas, None.

1419 Rituximab Use in Patients with Rhumatoid Arthritis-Associated Interstitial Lung Disease and Other Connective Tissue Disease-Associated Interstitial Lung Disease: A Single Center Experience. Sandra Charrand, Jeffrey J. Swingis, Lina Peykova and Areyh Fischer. 1Hôpital Maisonneuve-Rosemont, Montreal, QC, 2National Jewish Health, Denver, CO.

Background/Purpose: Small series have suggested that rituximab (RTX) may be effective as rescue-therapy for connective tissue disease-associated interstitial lung disease (CTD-ILD). We sought to describe our center’s experience of the outpatient use of RTX in patients with a diverse spectrum of CTD-ILD.

Methods: We identified all patients with CTD-ILD who (1) received at least one cycle of RTX as an outpatient between January 2008 and May 2014, (2) had at least one thoracic HRCT scan, and (3) pulmonary function testing pre- and post-initial RTX treatment. We extracted data from the medical record for the following: demographics, concurrent immunosuppressive medication, pulmonary function test, CT thoracic imaging, RTX-associated side effects, infection history, and discontinuation rate. We analyzed the % predicted forced vital capacity (FVC%) closest to pre- (mean 131.8 ± 204.6 days) and post-initial RTX administration (mean 121.7 ± 97.2 days). T-tests were used for continuous variables analysis and Fisher’s exact test was used for contingency table analysis.

Results: The cohort comprised 24 subjects with a diverse spectrum of CTD-ILD.

Table 1: Clinical characteristics

<table>
<thead>
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<th>All patients (n = 24)</th>
<th>RA patients (n = 15)</th>
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<tr>
<td>Age, years (mean ± SD)</td>
<td>61.3 ± 10.4</td>
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<tr>
<td>Female, n (%)</td>
<td>15 (62.5)</td>
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<td>Race, n (%)</td>
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<td>Pack-year (mean ± SD)</td>
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<td>Diagnosis, n (%)</td>
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<td>Rheumatic disease duration, years (mean ± SD)</td>
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</tr>
</tbody>
</table>

ILD duration, years (mean ± SD) 3.2 ± 2.8 2.5 ± 2.1

RTX regimen

| RA protocol | 22 | 14 |
| VDASISlator protocol | 2 | 1 |
| Concurrent corticosteroid-sparing agent, n (%) | 24 | 24 (100) |

Mycophenolate mofetil | 18 (75) | 18 (100) |
Methotrexate | 4 (16.7) | 4 (26.7) |
Leflunomide | 5 (20.8) | 5 (100) |
Azathioprine | 1 (4.2) | 1 (6.7) |
Intravenous immunoglobulin | 1 (4.2) | 1 (6.7) |
Cyclophosphamide | 1 (4.2) | 1 (6.7) |
Thoracic HRCT patterns, n (%) | 26 | 26 |
UIP | 11 (45.8) | 11 (45.8) |
NSIP | 9 (36.4) | 9 (36.4) |
NSIP + OP | 1 (4.2) | 1 (4.2) |
UIP | 1 (4.2) | 1 (4.2) |
LIP | 1 (4.2) | 1 (4.2) |
Unclassifiable diffuse lung disease | 1 (4.2) | 1 (4.2) |

There was no change in mean FVC% pre- and post-initial RTX cycle (71.3 ± 18.6 vs. 71.6 ± 17.9, p = 0.87). Post-RTX, in 92 subjects (38%) FVC% improved (4 by >10%), and in 15 subjects (63%) FVC% declined (3 by >10%). In the 15 subjects with RA, FVC% was unchanged (70.4 ± 20.2 vs. 74.5 ± 19.7, p = 0.18). Post-RTX, in 9 RA subjects (60%) FVC% improved (4 by >10%), and in 6 subjects (40%) FVC% declined (1 by >10%). In those without RA (n = 9), FVC% declined significantly (72.7 ± 15.4 vs. 66.8 ± 12.8, p = 0.015; 3 by >10%). Pre- and post-RTX change in FVC% were 4.2 ± 17.4 in RA vs. −8.6 ± 7.2 in non-RA (p = 0.025). RA subjects were also more likely to have improved FVC% (p = 0.0068).

Sixteen (67%) subjects were on a concomitant corticosteroid-sparing medication. Thirteen (54%) were on prednisone at RTX initiation (mean dosage 10.2 ± 16.2 mg) and 9 (38%) remained on prednisone at 6 months post-RTX (mean dosage 5.6 ± 11.0 mg) (p = 0.27).

Five infectious episodes (2 upper respiratory tract infections, 2 lower respiratory tract infections and 1 disseminated Herpes Zoster infection) occurred in 5 different subjects within 6 months post-initial RTX cycle. An additional 11 infectious episodes (mostly upper or lower respiratory tract infections) occurred in 5 of 12 subjects that received more than 1 RTX cycle (mean observation period of 35.6 ± 19.3 months and 66 RTX cycles).

Conclusion: Treatment of RA-ILD and other forms of CTD-ILD with RTX was associated with variable effects on pulmonary physiology and our series suggests a possible beneficial role for RTX in RA-ILD. RTX treatment was associated with modest corticosteroid sparing effects and a sizeable number of post-infusion infections. RTX warrants prospective study to better assess its role in managing RA-ILD and other CTD-ILD.

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S626
Non-Use of Glucocorticoid and Osteoarthritis Absence As Predictors of Clinical Remission in RA. Salvador Loro-Alanis1, David Vega-Mora1, Mario Garza-Elizondo2, Mario Garcia-Pompermayer3, Roberto Negrete-Lopez4, David Trevino-Montes1 and Diana Flores-Alvarado2. 1Servicio de Reumatologia, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico. 2Hospital Universitario de Bellvitge, Barcelona, Spain. 3Hospital Universitario UANL, Monterrey, Mexico. 4Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Mexico.

Background/Purpose: The clinical evaluation of Rheumatoid arthritis (RA) is accomplished with compound indexes allowing better clinical decision. Clinical remission nowadays is an attainable target in the management of RA patients. Clinical remission associated factors are under investigation.

Objective: Determine which factors are associated with clinical remission by CDAI in a RA population (ACR/EULAR 2010).

Methods: From a rheumatologic diseases cohort in a University Hospital we made an observational, descriptive, retrospective and cross-sectional study of 361 patients with RA. We analyzed variables such as demographics, rheumatoid factor, Anti-Cyclic Citrullinated Peptide antibodies, erythrocyte sedimentation rate, C-reactive protein, treatment, clinical activity, visual analog scale, comorbidities, extra-articular manifestations and temporality of RA. CDAI was calculated. Remission was defined with a CDAI score of 2.8.

Results: 361 patients were evaluated. Female sex was predominant (97.7%). Mean age was 51.4. Clinical remission was found in 40.2%. When patients with and without clinical remission were compared, we found significant differences in: non use of prednisone (p < 0.001), use of Non-steroidal anti-inflammatory drugs (NSAIDs) (p < 0.012), use of tramadol (p < 0.001), absence of osteoarthritis (p < 0.03) and BMI < 25 Kg/m2 (p < 0.017). In multivariate analysis factors associated with reach clinical remission were: Non use of oral steroids (p < 0.001, OR 3.39 IC 2.05-5.63) and absence of osteoarthritis (p < 0.025, OR 1.8, IC 1.007-3.048). It was found a negative association to reach clinical remission with use of NSAIDs (p < 0.008, OR 2.92, IC 0.117-0.73) and use of tramadol (p < 0.003, OR 0.107, IC 0.024-0.47).

Conclusion: According to our study the presence of OA in patients with RA is a factor that decreases the CDAI specificity for detecting clinical remission. This possibly related to the score given by the patient to the visual analog scale and the presence of painful joints secondary to OA, but not inflamed by RA activity. It is therefore important that clinicians consider these factors when evaluating clinical remission in RA.

Disclosure: S. Loro-Alanis, None; D. Vega-Mora, None; M. Garza-Elizondo, None; M. Garcia-Pompermayer, None; R. Negrete-Lopez, None; D. Trevino-Montes, None; D. Flores-Alvarado, None.

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Preclinical Interstitial Lung Disease in Early Rheumatoid Arthritis. Javier Narvaez1, Alejandro Robles Perez2, Maria Molina Molina2 and Joan Miquel Nolla2. 1Hospital Universitario de Bellvitge, Barcelona, Spain; 2Hospital Universitario de Bellvitge, Barcelona, Spain.

Background/Purpose: Early detection and treatment of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) may ameliorate disease progression. The objective of the present study was to: 1) study the frequency of asymptomatic preclinical ILD in early RA patients, in order to determine how early the lungs are affected in the disease and establish whether it is clinically advantageous to systematically screen asymptomatic patients for this complication; and 2) study the potential association of anti-citrullinated peptide antibody (ACPA) positivity with RA-ILD.

Methods: Observational prospective study of a cohort of early RA patients (joint symptoms < 2 years) who did not present respiratory symptoms and were included in an ILD screening program via baseline chest radiograph and complete pulmonary function tests (PFT). In patients with lung abnormalities in the chest radiograph or any restriction or impaired diffusion, defined as < 80% of predicted forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) respectively, the study was completed with a high-resolution computerized tomography scan (HRCT) of the chest.

Results: Forty patients (30 women) were included in the study, with PFR alterations detected in 18 (45%). All cases had a DLCO < 80% of predicted (mean 68%; range 43% to 78%), without significant reduction in the FVC values. The HRCT detected abnormalities in only 7 of these 18 patients: 1 radiographic pattern suggestive of non-specific interstitial pneumonia (NSIP); 1 radiographic pattern of respiratory bronchiolitis-associated interstitial lung disease (RB-ILD); the other 5 had bronchiectasis in the absence of fibrosis, emphysema or pulmonary nodules. In 11 patients with DLCO alterations, the HRCT was normal, and in none of these cases could the alteration be attributed to the presence of anemia.

A significant inverse correlation between ACPA levels and baseline DLCO was found. We also observed, a significant association between the severity of disease activity as measured by DAS28-CRP and baseline DLCO values.

Conclusion: Asymptomatic preclinical ILD, which is detectable by restrictive abnormalities in PFT (mainly, DLCO < 80% of predicted), is common (45%) among patients with early RA. PFT screening may be indicated for such patients since early detection of these alterations could change the course of the lung disease if risk factors (such as smoking or environmental exposures) are avoided, infections are prevented and drugs for RA treatment are selected that are less harmful to the lung. Our data also support a relationship between high ACPA levels and the occurrence of RA-ILD.

Disclosure: J. Narvaez, None; A. Robles Perez, None; M. Molina Molina, None; J. M. Nolla, None.

1422

Demographic Differences in Health Related Information Technology Use Among Patients with Rheumatic Diseases. David Mackey1, Aseem Bharat2, Lang Chen3, Ben Nowell3, Liana Fraenkel3, Peter J. Embi4, Kenneth G. Saag2, James Willi3, Seth Ginsberg2, Ruth M. Connell5 and Jeffrey R. Curtis4. 1University of Alabama at Birmingham, Birmingham, AL; 2Creaky Joints/Global Healthy Living Foundation, Upper Nyack, NY; 3Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT; 4The Ohio State University, Columbus, OH; 5The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Use of the Internet and mobile technologies can be a valuable resource for patients with rheumatic diseases who are seeking health-related information, allowing patients to track health longitudinally, and/or engage with similar patients or their clinicians. However, such technologies may have a limited penetration among certain demographic groups defined by older age, non-Caucasian race, and lower education and income. We evaluated use and ownership of information technologies among patients in a rheumatology clinic to assess their use of these technologies, and assess any differences based on patients’ characteristics.

Methods: Starting in 2014 (with ongoing recruitment), we approached adult patients from two rheumatology outpatient clinics at a large academic medical center to participate in a descriptive survey, administered either on paper or electronically (iPad tablet) according to patient preference. The survey included questions derived from the Pew Internet Survey regarding 1) ownership of a smartphone; 2) use of the Internet for health-related information; 3) demographic differences in health-related technology use; and lower education and income. We evaluated use and ownership of information technologies among patients in a rheumatology clinic to assess their use of these technologies, and assess any differences based on patients’ characteristics.

Results: Among 195 patients approached to take the survey, 171 (87%) completed the survey, 24 (12%) refused, and 2 (1%) failed to complete it. Among complete responders, 82% were women, 75% were white, with median age 56 years, and 77% had at least some college education. The gender and race distribution was similar between respondents and those who refused.

Aged older than 65, lower education, and lower income were associated with less smartphone ownership, less use of the Internet for health-related reasons, and a lower willingness to share electronic health information with their healthcare provider (Table). In contrast, sex and race were not strongly reasons, and a lower willingness to share electronic health information with their provider (Table). In contrast, sex and race were not strongly associated with these outcomes. However, even for patient groups with less access to or use of technologies for health reasons, more than 50% of patients reported ownership or willingness to use IT.
Conclusion: Based upon this sample of rheumatology patients, older age, lower education and lower household income were associated with less use of the Internet and information technology for health reasons. However, at least half of patients in these demographic and SES categories had access to these technologies. Given these results, it is reasonable to expect that technological solutions that address the health information needs of patients with rheumatic diseases can reach a broad patient population.

Table: Factors associated with Healthcare-related Internet use and Technology Access

<table>
<thead>
<tr>
<th>Age</th>
<th>Total respondents N=171</th>
<th>Owns a Smartphone</th>
<th>Accessed the Internet for a health-related search</th>
<th>Willing to exchange medical information electronically</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>33</td>
<td>91%*</td>
<td>79%*</td>
<td>79%*</td>
</tr>
<tr>
<td>40–55</td>
<td>49</td>
<td>92%*</td>
<td>82%*</td>
<td>82%*</td>
</tr>
<tr>
<td>55–65</td>
<td>43</td>
<td>71%*</td>
<td>86%*</td>
<td>57%*</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>36</td>
<td>53%*</td>
<td>72%*</td>
<td>53%*</td>
</tr>
</tbody>
</table>

Gender

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<tr>
<th></th>
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<tbody>
<tr>
<td>F</td>
<td>140</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>M</td>
<td>31</td>
<td>71%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Race

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Caucasian</td>
<td>129</td>
<td>78%</td>
<td>88%</td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>42</td>
<td>76%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Education Level

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>High School or less</td>
<td>39</td>
<td>59%*</td>
<td>72%*</td>
</tr>
<tr>
<td>Some college or higher</td>
<td>130</td>
<td>82%*</td>
<td>88%*</td>
</tr>
</tbody>
</table>

Annual household income:

<p>| | | | |</p>
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<tr>
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</thead>
<tbody>
<tr>
<td>&lt; $40,000</td>
<td>51</td>
<td>63%*</td>
<td>69%*</td>
</tr>
<tr>
<td>&gt; $40,000</td>
<td>101</td>
<td>86%*</td>
<td>94%*</td>
</tr>
</tbody>
</table>

* p-value < 0.05
** p-value < 0.001

Disclosure: D. Mackey, None; A. Bharat, None; L. Chen, None; B. Nowell, None; L. Franken, None; P. J. Embi, None; K. G. Saag, None; J. Willig, None; S. Ginsberg, None; R. McConnell, None; J. B. Curtis, Roche, Genentech, UCB Pharma, Janssen; CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

1423


Background/Purpose: Cardiovascular (CV) disease is one of the major causes of mortality in rheumatoid arthritis (RA). Although the CV risk in RA is well-recognized, detection of high risk patients and prevention of CV disease are still major challenges. We aimed to determine which CV risk estimation index is better in RA patients and to determine the factors that may improve CV risk estimation in RA.

Methods: Two-hundred and ten consecutive RA patients without history of CV disease or diabetes mellitus were assessed. Systematic Coronary Risk Evaluation (SCORE), 2013 American College of Cardiology/American Heart Association (ACCA/ AHA) 10-year atherosclerotic CV disease risk (ASCVD), QRisk II indices and their modified versions (mSCORE, mASCVD, mQRisk II) according to EULAR recommendations were calculated. All patients were evaluated with carotid ultrasonography (US). Carotid intima-media thickness (cIMT) > 0.90 mm and/or carotid plaques were used as the gold standard test for subclinical atherosclerosis and high CV risk (US+). Retrospectively, along with disease characteristics, DAS28 scores, ESR and CRP values of each visit during the entire follow-up of RA patients were recorded and average DAS28, ESR and CRP were calculated.

Results: The study cohort consisted of 210 RA patients (F/M = 169/41, mean age 52.5±11.4) with a mean disease duration of 11.1±7.0 years. The EULAR multiplier factor was used in 95 (45.2%) patients. The mean mSCORE was 1.6±2.5%, mASCVD risk was 5.8±7.1% and mQRisk II was 9.8±9.6%. Eleven (5.2%), 61 (29%) and 80 (38.1%) patients were defined as having high CV risk (mSCORE≥5%, mASCVD≥7.5%, mQRisk≥10%) according to mSCORE, mASCVD and mQRisk II, respectively. Concerning US results, 50 (23.8%) patients had either cIMT> 0.90 mm or carotid plaques. The mASCVD and mQRisk II indices better identified US+ patients, that 29 (58%) and 30 (60%) of the US+ patients were in high risk group according to mASCVD and mQRisk II, respectively. Whereas only 8 (16%) of the US+ patients were in high risk group according to mSCORE (P<0.0001). However mASCVD and mQRisk II still failed to identify 42% and 40% of US+ patients. When traditional risk factors and disease characteristics of US+ and US- patients were compared, it was found that US+ patients were older at diagnosis, had higher average DAS28 scores, average ESR and CRP levels. Impaired fasting glucose was also higher in US+ patients along with similar rates of biologic treatment, steroids and NSAIDs (Table 1).

Conclusion: EULAR recommendation for CV risk assessment, SCORE, seems inadequate even after modification according to RA characteristics. On the other hand QRisk II and ACC/AHA 10-year ASCVD risk indices are better in estimating CV risk in RA patients. However, still additional modifications, like age at disease onset, cumulative disease activity and inflammatory biomarkers are required to fully identify high-risk RA patients.

Table 1. Characteristics of US(+) and US(-) RA patients

<table>
<thead>
<tr>
<th>US(+)</th>
<th>US(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=50)</td>
<td>(n=160)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>35 (70)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.6±8.3</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>48.3±8.8</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10.5±7.6</td>
</tr>
<tr>
<td>RF and/or Anti-CCP positivity, n (%)</td>
<td>40 (80)</td>
</tr>
<tr>
<td>Extra-axicular involvement, n (%)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Average DAS28 score</td>
<td>4.04±1.1</td>
</tr>
<tr>
<td>HDA visits/Total visits</td>
<td>24.4±26.9</td>
</tr>
<tr>
<td>Average ESR (mm/h)</td>
<td>3.25±14.2</td>
</tr>
<tr>
<td>Average CRP (mg/L)</td>
<td>1.41±12.2</td>
</tr>
<tr>
<td>HAQ score</td>
<td>0.48±0.49</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>38 (76)</td>
</tr>
<tr>
<td>Impaired fasting glucose, n (%)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Ever-smoked, n (%)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Total cholesterol/HDL-cholesterol</td>
<td>4.0±1.64</td>
</tr>
<tr>
<td>mSCORE</td>
<td>2.8±2.5</td>
</tr>
<tr>
<td>mASCVD</td>
<td>8.9±7.7</td>
</tr>
<tr>
<td>mQRisk II</td>
<td>14.5±10.8</td>
</tr>
<tr>
<td>Current corticosteroid, n (%)</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Biologic treatment (ever), n (%)</td>
<td>23 (46)</td>
</tr>
</tbody>
</table>

Disclosure: G. Ozen, None; M. Sunbul, None; P. Atagunduz, None; H. Direskeneli, None; K. Tigen, None; N. Inanc, None.

1424


Background/Purpose: Detection of bone erosions in patients with RA is critical in clinical practice, with treatment initiation and effectiveness largely based on limiting erosive progression. While studies have compared the use of MRI and x-ray for the assessment of erosive damage, the potential influence of the anatomy of interest is not always considered. Given that the joints assessed by researchers and clinicians vary and may contribute to the half of patients in these demographic and SES categories had access to these technologies. Given these results, it is reasonable to expect that technological solutions that address the health information needs of patients with rheumatic diseases can reach a broad patient population.
Methods: This was a cross-sectional study. For each participant, MRI scans of both hands (bilateral MCP 2–5 joints) and x-ray scans of the hands, wrists, and feet were acquired. A 1.0T MRI scanner with a 100-mm diameter was used, and multiple sequences were obtained, including T1-weighted images for erosion detection. On x-ray, the conventional erosion definition was applied, and three imaging projections were used: posterior-anterior, oblique, and lateral. Four radiologists used the RA–MRI scoring system (RAMRIS) and the van der Heijde-modified Sharp scoring system (vDHSS) to semi-quantitatively evaluate the MRI and x-ray images, respectively. For statistical analysis, interval data (RAMRIS) and ordinal data (vDHSS) were classified by erosion presence (yes/no).

Results: A total of 488 joints from 122 hands of 65 RA patients were included in this analysis (median interquartile range age: 59.0 (49.0–66.0) years, sex: 83.1% female, ethnicity: 61% Caucasian, symptom duration: 4.3 (2.6–7.0) years, Rheumatoid Factor positivity: 70.8%, Disease Activity Score (DAS28) units: 4.5 (3.5–5.7), Clinical Disease Activity Index (CDAI): 62.3 (32.7–91.6)). 331 individual MCP 2–5 joints were assessed as having erosions on MRI (67.8%), while 134 erosions were detected in the same joints on x-ray (27.5%). MCP 2–5 joints of the hand were also grouped together for analysis. Overall, 2.1-fold the MCP 2–5 joint sets with erosions on x-ray had erosions on MRI.

Per common joint imaged, 2.6- to 8.0-fold the erosions detected on x-ray were detected on MRI. At the patient level of analysis, bilateral MRI of the MCP 2–5 joints resulted in the detection of erosive disease in 1.1-fold the number detected on x-rays of the hands, wrists, and feet. Limiting MRI to the dominant MCP 2–5 joints, the proportion of patients with erosive disease was 66% of the frequency detected on x-rays of the hands, wrists, and feet; the same frequency detected on x-rays of the feet alone; and 1.3-fold the frequency detected on x-rays of the hands and wrists.

Conclusion: Practically, the results suggest that the relative performance of the two imaging modalities is highly dependent on the anatomy imaged. Technologically, the findings demonstrate the enhanced capacity of MRI to detect erosions per joint imaged. The ability of a single MRI scan of the dominant hand to identify more patients with erosive disease than x-rays of both hands and wrists emphasizes the clinical value of MRI as a tool for detecting and monitoring erosive damage in patients with RA.

Disclosures: M. Tomizzana, None; I. Rodrigues, None; M. Jessome, None; J. Barbosa, None; K. Beattie, None; W. G. Benson, None; R. Bobba, None; A. Cividino, None; P. D. Emond, None; K. Finlay, None; C. Gordon, None; L. Hart, None; G. Ioannidis, None; E. Jurriaans, None; M. Kohn, None; M. Larche, None; A. Lau, None; N. Parasu, None; R. Tavares, None; S. Tytus, None; H. Wu, None; J. D. Adachi, None.

1426 Periodontal disease and Clinical Activity of Rheumatoid Arthritis Patients. Daniel Xibille-Friedmann1, Jose Ivan Martinez Rivera2, Jaqueleen Rodriguez Amado3, Carolina Bustos Rivera Bahena1,1, Marios Sandoval Rios1 and Jose Luis Montiel Hernandez1. 1Hospital General de Cuernavaca, Cuernavaca, Mexico; 2Instituto Nacional de Salud Publica, Cuernavaca, Mexico; 3Centro de Investigacion y Desarrollo en Ciencias de la Salud, Morelos, Mexico.

Objective: To evaluate the relationship between periodontal disease, infection by Porphyromona gingivalis, and rheumatoid arthritis (RA) disease activity. Its relationship with periodontal disease, oral and plasma peptidyl-arginine deiminase (PAD) activity and citrullination of soluble blood proteins still remains poorly known.

Methods: RA patients included fulfilled the ACR/EULAR 2010 criteria, signed an informed consent form and were followed at the rheumatology clinic for one year. Patients were divided into 2 groups according to clinical activity. Patients with secondary Sjögrens disease were excluded. Patients having a DAS28 of less than 3.4 were considered as having low activity and above that number they were grouped as having high activity. Periodontal evaluation and oral and peripheral blood samples were obtained on the same day as the clinical evaluation. PAD-activity was performed using a colorimetric assay employing a RA-EE (Sigma) as substrate and recombinant human PAD4 (Cayman Chem) as positive control. Citrullination was evaluated by Western Blot of immunoprecipitated saliva and blood fibrinogen, employing a polyclonal anti-citrulline antibody (Millipore). Plasma pro-inflammatory cytokines and aCCP levels were evaluated by ELISA. Descriptive statistics were employed to evaluate differences between groups and the Spearman correlation test was used to associate them with clinical parameters.

Results: 48 RA patients were divided into 2 groups: 33 presented high activity and 15 low activity; their mean age was 41.2 ± 43 years of age, respectively. BMI was 26.8 ± 27.2, and time since onset of disease 8.5 ± 10.9 vs. 5.4 ± 3.8 years, respectively. Patients groups’ demographic characteristics differed no statistically significant differences. High disease activity patients had a significantly lower index of periodontitis (1.57 ± 1.06; p < 0.02), while low disease activity patients were associated with severe periodontitis (3.0 ± 1.23). Otherwise, high disease activity patients showed a mean decrease of 1.5 DAS28 units after one year of follow-up and treatment, while low disease activity patients showed no statistically significant difference.

Conclusion: RA patients with severe periodontitis, although the same patients showed a higher therapeutic response after one year of follow up, in comparison to low disease activity RA patients.
Low Prevalence of Sarcopenic Obesity in Rheumatoid Arthritis Patients with Moderate Clinical Activity. Nina Tello-Winniczuk, David Vega-Morales, Mario Garza-Elizondo, Dionicio Galarza-Delgado, Jorge Esquivel-Valerio, Octavio Ilizaliturri-Guerra and Jorge Rodríguez-Olivo.

Service de Reumatología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, México. 2Hospital Universitario UANL, Monterrey, México. 3Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, México.

Background/Purpose: Rheumatoid arthritis is an inflammatory systemic disease that leads to body composition alterations. Objective: The aim of our study was to identify the prevalence of sarcopenia, obesity and sarcopenic obesity in our population.

Methods: We performed an observational, analytical study with 101 rheumatoid arthritis patients. Demographic, clinical and biochemical variables were recorded. Studies of body composition by dual X-ray absorciometry were performed. We took into account different definitions to determine body composition alterations (Table 1).

Results: Ninety-seven (96%) patients were female, the rest of baseline characteristics are shown in Table 2. The mean age of our patients was 50.5 years (SD 12.3). The mean body mass index was 29.29 kg/m² (5.4 SD). According to the World Health Organization classification of body mass index (BMI), 24 (23.8%) patients had normal weight, 38 (37.6%) were overweight and 39 (38.6%) some degree of obesity. According to the BMI adjusted for rheumatoid arthritis, 13 patients (12.9%) were normal, 34 (33.7%) overweight and 54 (53.5%) obese. Ten patients had sarcopenia (9.9%). Six patients (5.9%) had sarcopenic obesity. Patients with obesity by dual X-ray absorciometry were 83 (82.2%). Among clinical and paraclinical variables, the only significant association with sarcopenia was assessed with the use of the Framingham risk calculator. American recommendations (ACC/AHA) have recently changed and a new equation to assess overall CVR has been validated.

Conclusion: The most prevalent body composition alteration in RA patients were obesity. Sarcopenic obesity had a low prevalence, contrary to previous reports.

**TABLE 1.** Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, SD</td>
<td>50.4 ± 12.3</td>
</tr>
<tr>
<td>Gender Female/Male, n (%)</td>
<td>97 (96)/4 (4)</td>
</tr>
<tr>
<td>Time elapsed since diagnosis, Mean, SD</td>
<td>9.8 ± 8.6</td>
</tr>
<tr>
<td>Rheumatoid factor +, n (%)</td>
<td>61 (71.8)</td>
</tr>
<tr>
<td>Anti-CCP +, n (%)</td>
<td>31 (57.4)</td>
</tr>
<tr>
<td>DAS28, mean, SD</td>
<td>3.26 ± 1.29</td>
</tr>
<tr>
<td>HAQ, mean, SD</td>
<td>0.62 ± 0.68</td>
</tr>
<tr>
<td>DMARD, n (%)</td>
<td>97 (98)</td>
</tr>
<tr>
<td>Methotrexate, n (%)</td>
<td>85 (85.9)</td>
</tr>
<tr>
<td>Prednisone, n (%)</td>
<td>47 (47%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>17 (18.2)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Type 2 Diabetes mellitus, n (%)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Hipothyroidism, n (%)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

**TABLE 2.** Sarcopenia and Sarcopenic Obesity Prevalence according to different definitions.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Sarcopenia, n (%)</th>
<th>Sarcopenic obesity, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lean mass index &lt;50% (LM1 &lt; 13.3 kg/m²)</td>
<td>10 (9.9)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>2 Elkan et al (9) (LM1 &lt; 13.7 kg/m²)</td>
<td>21 (21.6)</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>3 Cruz-Jentoft et al (14) (LM1 a &lt; 5.67 kg/m²)**</td>
<td>21 (21.6)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

*Sarcopenia + Fat mass index >25%, **women, LM1 = lean mass index, LMMA = appendicular lean mass index.

**Disclosure:** D. Xibille-Friedmann, Pfizer Inc, 5 CONACYT, 2; J. I. Martínez Rivera, None; J. Rodriguez Amado, None; C. Bustos Rivera Bahena, None; M. Sandoval Rios, Beckton Dickinson, 3; J. L. Montiel Hernandez, None.
Systemic Inflammation in Alzheimer’s Disease: Relevance to Patients with Rheumatoid Arthritis. M. Elaine Husni1, Colin O’Rourke2, Travis Moore6 and Jagan Pillai3.

1Cleveland Clinic Foundation, Cleveland, OH, 2Cleveland Clinic, Cleveland, OH.

Background/Purpose: Alzheimer’s disease (AD) dementia is the most common form of dementia affecting ≈ 25 million people worldwide without known cure. Research regarding involvement of inflammatory component of Alzheimer’s Disease (AD) has been well documented. A recent study via whole genome and exome DNA sequencing have provided evidence that coding mutations in the TREM2 gene are associated with a 2-5-4 fold increased risk in developing AD. Notably TREM2 is only expressed within macrophages and dendritic cells in the periphery and within microglia within the brain and is involved in innate immunity, suggesting that alterations in neuroinflammation are directly linked to the development and progression of AD. Autoimmune diseases such as rheumatoid arthritis (RA) known to be a chronic systemic inflammatory disorder may thereby be important to see if the prevalence of these diseases makes a subsequent neurodegenerative diagnosis like AD more likely.

Our objective was to investigate whether the risk of Alzheimer’s disease is increased in patient with rheumatoid arthritis in a large population cohort.

Methods: Our study consists of a large retrospective hospital based cohort from a network of north east Ohio health providers through Epic database. Population was defined by a) subjects using medications in RA and AD, b) ICD9 codes (714.0, 294.1, 331.0, 331.11, 331.82, 331.83, 290.0, 290.43, 294.20 and 294.21) was used to understand the specific subtypes of dementia. Descriptive analysis was performed on individual cohorts. Statistical Analysis: Relative risk of use of AD medications among subjects using RA medications will be compared with a control cohort without these medications use, to determine the risk of AD medication use in each cohort.

Results: Overall number of subjects from our database was 2,592,280 (77% females). Number of subjects with RA medication + AD medications was 430. Subjects with either RA and/or FDA approved AD medications were 52,330. Subjects with RA but no AD medications was 37,650. In this cohort, 60% of treated RA subjects had an RA diagnosis based on ICD9 codes, but only 2.2% subjects using AD medications had an AD or AD dementia diagnosis and 1.25% had a diagnosis of mild cognitive impairment based on ICD9 codes.

Relative risk of AD medication use among subjects using RA medications was 2.02 [1.83-2.22], P<0.001. This effect was noted to be most prominent in subjects less than 65 years old.

Conclusion: Our study supports that patients with RA could be associated with an increased risk of Alzheimer’s Dementia and raises the possibility of shared risk factors that may not have been appreciated previously. Further study into this association would help develop guidelines to screen for cognitive impairment and elucidate novel therapeutic options in AD.

Disclosure: M. E. Husni, national psoriasis foundation, 2, UCB, 5, Bristol Myers Squibb, 5, Lilly, 5, Celgene, 5, Abbvie, 5, Novartis Pharmaceutical Corporation, 5, Arthritis National Research Foundation, 2; C. O’Rourke, None; T. Moore, None; J. Pillai, None.


1Hospital Universitari de Bellvitge, Barcelona, Spain, 2Hospital Universitari de Bellvitge, Barcelona, Spain, 3Hospital Universitari de Bellvitge, Barcelona, Spain, 4Hospital Universitari de Bellvitge, Barcelona, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased mortality and reduced life expectancy compared with the general population. This mortality gap has increased in the last years since mortality rates for RA have remained constant through time while mortality rates for the general population have decline. Excess mortality has been associated with disease activity. Radiographic joint destruction reflects the cumulative burden of inflammation and it is conceived as an objective measure of RA severity. The aim of our study was to analyze the influence of radiological joint damage in the mortality rate in a cohort of RA patients.

Methods: We included 783 RA patients in a retrospective longitudinal study, from May 1993 to November 2013, attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain). Subjects were included at the moment of their first X-ray of the hand between October 2012, and followed until patients’ death, loss of follow up or November 2013. Clinical records were examined and demographic and clinical data was collected. Radiographic joint damage of hands and wrists was assessed with the Sharp-vander-Heijde score (total (SHS), erosion (ES) and narrowing) and carpal tunnel syndrome was assessed through the Carpal tunnel syndrome index. RA activity was measured with the DAS28 criteria (DAS28<3.2: low activity, DAS28 3.2-5.1: moderate activity, DAS28>5.1: high activity). The observed mortality rate was compared to that of the general population matched for age, gender and area of residence.

Results: The observed mortality rate was 3.27 per 1000 person-years, with 118 deaths (14.9%). This mortality rate was similar to that of the general population matched for age, gender and area of residence.

Conclusion: The observed mortality rate was similar to that of the general population matched for age, gender and area of residence, suggesting the presence of a RA specific mortality gap.

Disclosure: A. Zacarias Crovato, None; J. Narvaez, None; J. M. Nolla, None; J. Rodriguez-Moreno, None; M. Jordana, None; C. Gomez Vaquero, None.


1Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, 2University Hospital la Fe, Valencia, Spain, 3Hospital Clínico San Carlos, Madrid, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased mortality and reduced life expectancy compared to the general population. The mortality gap has increased in the last years since mortality rates for RA have remained constant through time while mortality rates for the general population have decline. Excess mortality has been associated with disease activity. Radiographic joint destruction reflects the cumulative burden of inflammation and it is conceived as an objective measure of RA severity. The aim of our study was to analyze the influence of radiological joint damage in the mortality rate in a cohort of RA patients.

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Disclosure: A. Zacarias Crovato, None; J. Narvaez, None; J. M. Nolla, None; J. Rodriguez-Moreno, None; M. Jordana, None; C. Gomez Vaquero, None.
(NSLS) components. Survival techniques were applied to estimate the mortality rate (MR; expressed per 1000 person-years with a 95% of Confidence Interval [95% CI]). Cox bivariate and multivariate regression models were conducted to examine risk factors for death. Interaction terms between radiological damage and rheumatoid factor (RF) positivity, and the elapsed time from RA onset to X-ray, were introduced in the models. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. Results: were expressed as hazard ratio (HR) and 95% CI.

Results: Most of the patients included were women (74%), with a median age of 61 years old (interquartile range [IQR]: 47–71), 67% were RF positive, and the median (IQR) elapsed time between RA symptoms onset and the X-ray was 2 (0–7) years. The median (range) followed up time per patient was 5 [0.4–20] years. 92 patients died during follow up time of 4758 person-years. Mortality rate (MR) was 19 per 1000 patient-year [95% CI 16–24]. We observed in the bivariate analysis that older age, male sex, higher elapsed time from RA onset to X-ray, SHS, ES, NSLS, number of hospital admissions (used as a surrogate measure of comorbidity), basal Health Assessment Questionnaire, RF positivity, earlier RA onset (in calendar time), and no treatment with biological therapy, were associated with a higher MR. 3 multivariate models were constructed, using SHS, ES or NSLS as measures for joint destruction, and adjusted by the previous variables. In none of the models radiographic damage was associated with MR. However, we observed that the interaction between ES and RF positivity was significant (p = 0.001). ES was associated with MR only in RF negative patients.

Conclusion: Erosive joint damage seems to be a risk factor for all cause mortality only among RF negative RA patients.

Disclosure: L. Rodriguez-Rodriguez, None; J. Izcorna-Cortes, None; L. Abasolo, None; L. Leon, None; O. Fontesare, None; B. Fernandez-Gutierrez, None; J. A. Jover, None.

1432
Mortality Ratio of Rheumatoid Arthritis Under Biological Treatment.
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, which, in many patients, leads to a substantial disability and has a major effect on the quality of life. Patients with RA also have an increased mortality compared with the general population. Main causes of mortality in RA are cardiovascular events and serious infections. The objective of this study was to evaluate mortality ratio in patients with RA during biological treatment.

Methods: HUR-BIO (Hacettepe University Rheumatology Biologic Registry) is a single center biological registry since 2005 that include 815 RA patients under biological treatments. Data collected includes demographic data, co-morbidities, smoking, switch ratio, baseline and follow-up disease activity parameters (such as DAS28, CRP, ESR, global VAS, swollen joint count ad tender joint count). For all individuals in the study population, follow up time began at the first known use of etanercept, infliximab, or adalimumab. The outcome of interest was death from any cause, which was identified through linkage of the study population to the Turkish Cause of Death Register through May 31, 2014. Overall and anti-TNF biologic stratified mortality only among RF negative RA patients.

Results: HUR-BIO includes 815 RA patients (77,9% female). Mean age was 51 ± 13 years and mean disease duration was 11 ± 8 years. TNFı drug duration was 2.7 ± 2.6 years and 176 (21.5%) patients were used TNFı drugs more than 5 years. Positive ACPA and RF were 297/465 (63,9%) and 454/740 (61,3%), respectively. First biological drugs were etanercept 321 (39.4%), adalimumab 223 (27,4%) and infliximab 115 (14,1%), rituximab 92 (11,3%), abatecept 43 (5,3%), golimumab 20 (2,5) and tocilizumab 1 (0,1%). TNFı switch was found in 262 (32,1%) patients. Among the 815 patients in our entire study population and during a total of 2,235 person-years of follow-up (mean 2.7 years; median 1.8 years), 21 patients died. The all-cause mortality rate was 9.4 per 1000 person-years. Five of 21 patients died in our hospital (3 patients were lung infection, 1 tuberculosis and 1 acute coronary syndrome). Mortality ratio was slightly, not significantly, higher in male patients (%38,1 vs %21,4 p = 0.071). There were certain difference in age (60.1 ± 10.9 vs 51.1 ± 13.1, p = 0.004), biological drug duration (2.7 ± 2.7 vs 0.6 ± 0.9 years, p < 0.001), baseline erythrocyte sedimentation rate (53 ± 18 vs 40 ± 25 mm/hour, p = 0.018), positive RF [%89,5 vs %60,6, p = 0.039] and level of RF (median 103 (0–2500) vs 44 (0–2710), p = 0.032).

Conclusion: Crude mortality ratio in our biological database was comparable with literature, that between 5.3 to 16.8 (1–2). Crude mortality ratio of our patients is slightly higher than general population [93/1000 person-year vs 89/1000 person-year (3)]. Biological treatments seem like relatively safe drug in our database, however, we need biological naive RA cohort for certain conclusion.

References:

Disclosure: U. Kalaycun, None; A. Erden, None; H. Babaoglu, None; M. Torgutalp, None; S. Kilickap, None; O. K. Karadag, None; S. Aras Bilgen, None; I. Ertener, None; A. Akdogan, None; S. Kiraz, None.

1433

Background/Purpose: Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a common manifestation of rheumatoid lung disease. Subclinical RA-ILD is most commonly identified on HRCT imaging. In this study, we aimed to define the clinical characteristics of subclinical RA-ILD on HRCT, and to analyze long-term prognosis of subclinical RA-ILD.

Methods: 340 patients with RA were treated at our hospital and followed them up for three years or until development of symptomatic ILD. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity (2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7) pleural irregularity, and (8) pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which included the extension score, ACPA and the clinical features at the initial presentation were retrospectively analyzed.

Results: 76 (22.3%) out of 340 RA patients had abnormal chest radiological findings which consist with ILD. 5 out of 76 patients had shortness of breath and showed a rapidly progressive ILD (6.6%). The rest of 71 (48 women, 23 men) had subclinical RA-ILD who were either asymptomatic or have symptoms and physiologic abnormalities that are, as yet unrecognized as being due to RA-ILD. There was no difference in the positive rates of anti-CCP2 between subclinical RA-ILD and clinical evident RA-ILD. However there were no difference in the HRCT findings which included nonseptal linear attenuation, ground-glass attenuation and air space consolidation between subclinical RA-ILD group and clinical RA-ILD group, subclinical RA-ILD group showed less degree in honeycombing (p = 0.0003) and focal ILD (p = 0.0061). There have only two cases lead to clinically evident RA-ILD within 6 months. These two cases were treated with azathioprine and with MMF showed stable ILD on HRCT.

Conclusion: HRCT finding focused on honeycombing and the extension score at the initial presentation is a sensitive technique for detection of subclinical RA-ILD. This study suggest the progression of asymptomatic radiologic changes could lead to the development of clinical RA-ILD.

Disclosure: M. Yamasaki, None.

1434
The Longitudinal Association Between Inflammation and Blood Pressure in Rheumatoid Arthritis. Chih-Chin Liu1, Daniel H. Solomon2, Rishi Desai3, Seyoung C. Kim2 and KP Liao2. 1Rheumatology & Immunology, Brigham & Women’s Hospital, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA.
Background/Purpose: Inflammation is hypothesized to have direct effects on arterial endothelial and vasomotor function, functions which regulate blood pressure (BP). While inflammation has been implicated in the development of elevated BP, few studies have examined BP longitudinally after diagnosis of an inflammatory disease. The objective of this study is to examine the longitudinal association between changes in levels of inflammation and changes in BP in patients with rheumatoid arthritis (RA).

Methods: We studied RA subjects classified using a validated electronic medical record (EMR) algorithm (positive predictive value 94%) linked with Medicare Claims Data (patients age >65 years) between 2006-2010. We extracted EMR data on age, gender, systolic BP (SBP), diastolic BP (DBP), erythrocyte sedimentation rates (ESR), smoking status (ever/never), and calendar year of measurements. We extracted RA treatment data from Medicare prescription data including non-steroidal anti-inflammatory drugs (NSAIDs), anti-hypertensive drugs and dates of claims. We studied all subjects with ≥2 concurrent BP and ESR measurements at separate visits at least one week apart. The baseline was defined as the 1st concurrent ESR and BP measurement 6 months after the 1st Medicare claims date. We examined the association between the change in ESR and change in SBP between baseline and follow-up using multiple linear regression models adjusted by age, gender and smoking status. We performed sensitivity analyses by including potential treatments received +/- 15 days of ESR measurements that may affect blood pressure individually into the models; the treatments included anti-TNF, NSAIDs, anti-hypertensive medications, and steroids.

Results: We identified 313 subjects with ≥2 instances with ESR and BP measured on the same date. The mean age was 69.2 years (SD 10.3), 63.7% female, and 57.6% ACAs positive. The mean SBP was 134.4 (SD 18.8) mm/Hg, mean DBP was 75.7 (SD 12) mm/Hg, and the mean ESR was 32 (SD 27.1) mm/hour. We observed an inverse association between change in ESR and SBP, where every 10mm/hour increase in ESR was associated with a 1.22mm/hg lower in SBP, adjusted by age, gender and smoking status (Table). A similar relationship was found with DBP: each 10mm/hour increase in ESR was associated with a 0.75 mm/Hg lower DBP (95% CI: 0.75 to 0.01, p = 0.009). The effect size of the association between change in ESR and change in BP was similar with the addition of indicator variables for anti-hypertensive treatments, anti-TNF, and NSAIDs into the model.

Conclusion: In a linked dataset containing clinical data from the EMR and detailed prescription data from Medicare, we observed that increases in ESR were associated with a modest reduction in blood pressure. These findings have potential implications for CV risk assessment in RA patients who commonly experience large fluctuations in inflammation.

Table. The association between change in ESR (per 10mm/hour) increase with change in systolic blood pressure (SBP), N = 313.

<table>
<thead>
<tr>
<th>Linear regression models for ΔESR and ΔSBP, adjusted by:</th>
<th>ΔSBP (mm/Hg) per 10mm/h ΔESR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Age, gender, race, smoking Sensitivity analyses</td>
<td>–1.22</td>
<td>–1.74, –0.71</td>
</tr>
<tr>
<td>Model 2: Model 1 + anti-hypertensive</td>
<td>–1.21</td>
<td>–1.72, –0.70</td>
</tr>
<tr>
<td>Model 2 + anti-TNF</td>
<td>–1.19</td>
<td>–1.70, –0.70</td>
</tr>
<tr>
<td>Model 2 + NSAIDs</td>
<td>–1.21</td>
<td>–1.72, –0.70</td>
</tr>
<tr>
<td>Model 2 + Steroids</td>
<td>–1.21</td>
<td>–1.72, –0.70</td>
</tr>
<tr>
<td>Model 3: Model 1 + anti-hypertensive + anti-TNF + NSAIDs</td>
<td>–1.16</td>
<td>–1.67, –0.65</td>
</tr>
</tbody>
</table>

All p-values <0.0001

Disclosure: C. C. Liu, None; H. D. Solomon, None; R. Desai, Biogen Idec, 1; S. C. Kim, Pfizer Inc, 2; K. Liao, None.

1436

Impact of Depression on Clinical and Social Outcomes in Patients with Rheumatoid Arthritis: Comparative Study in Germany and Brazil.

Harriet Morfo, Olga Myalycheva, G da Rocha, Anna Beatrix Vargas and Christoph G. Baerwald. University Hospital, Leipzig, Germany, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.

Background/Purpose: Rheumatoid Arthritis (RA) can be associated with psychological disorders and especially depression. A bout 13 - 20 % of patients have clinical significant depression. It was shown (Doughas, 2014 COMORAD Study) that depression in this group of patients has a high variability between countries (2 % Morocco - 33 % USA). However, it is still incompletely understood how RA could influence on perception of depression and its impact on quality of life in RA patients from different countries. The purpose of study was to characterise distribution of depression and its impact on pain and social status of patients with RA in different countries.

Methods: 100 RA patients from Germany (age 62.4 ± 12.3 years) and 91 RA patients from Brazil (age 56.3 ± 12.6 years), mean duration of disease in Germany was 14.3 ± 10.4 years and in Brazil 15.9 ± 10.2 years, could be included in this study. RA was diagnosed according to the ACR/EULAR Criteria 2010 and the following questionnaires were utilised: Beck depression inventory (BDI), painDETECT test (Freyn-
significant gender and age differences in the impact of depression on outcomes of RA management program. Future research should attempt to obtain a clearer understanding of these differences.

Results: There were significant differences between the activity of disease (DAS 28) and pain (HAQ and pain: r = 0.628, p < 0.001) in both groups of patients. Only 5% of Brazilian patients had biologics compared to 30% of RA patients in Germany. There are correlation between the functional status of patients and depression (HAQ and BDI: r = 0.392, p < 0.001). Furthermore, a significant difference was detected in psychological scales of quality of life between both groups of patients (46.6 ± 12.3 Brazil compared to 51.4 ± 11.4 Germany; p = 0.002). Interestingly, there was no difference between the activity of disease (DAS 28) between two groups of patients (3.4 ± 1.5, Brazil vs 3.3 ± 1.3, Germany). However, Brazilian patients had more erosions (X-ray) compared to Germans group of patients (p = 0.011). Moreover, it was significant difference between methods of therapy in both groups of patients. Only 5% of Brazilian patients had biologics compared to about 30% of RA patients in Germany. There are correlation between the functional status of patients and depression (HAQ and BDI: r = 0.552, p < 0.01). Concerning family status, more Brazilian patients were single compared to Germans patients (p = 0.001). In Brazil there was found an higher number of patients with children compared with German group (74.2%; p = 0.015).

Conclusion: The study indicates that RA-related depression could contribute to diminished psychological well-being in RA patients and suggests the need for educational and management strategies that specifically target depression as part of RA management program. Future research should attempt to obtain a larger sample of male and younger RA patients to determine if there are significant gender and age differences in the impact of depression on outcomes of RA in different countries.

Disclosures: None.


Background/Purpose: Cardiovascular (CV) risk is increased in patients with rheumatoid arthritis (RA), but not fully explained by traditional risk factors such as LDL and HDL cholesterol concentrations. The cholesterol efflux capacity of HDL may be a better CV risk predictor than HDL concentrations. We hypothesized that HDL’s cholesterol efflux capacity is impaired and inversely associated with coronary atherosclerosis in patients with RA.

Methods: We measured the cholesterol efflux capacity of apolipoprotein B-depleted serum and coronary artery calcium score in 134 patients with RA and 76 control subjects, frequency-matched for age, race and sex. The relationship between cholesterol efflux capacity and coronary artery calcium score and other clinical variables of interest was assessed in patients with RA.

Results: Cholesterol efflux capacity was similar among RA (median [IQR]: 34% removal [28%, 41%] and control subjects (35% removal [27%, 39%]) (P=0.73). In RA, increasing cholesterol efflux capacity was not significantly associated with decreased coronary calcium score (OR=0.78 [95% CI 0.51–1.19], P=0.24), adjusted for age, race and sex. Framingham risk score also was not significantly associated with cholesterol efflux capacity. None of other clinical variables of interest was significantly associated with RA disease activity score, C-reactive protein, uric acid, F$_2$-isoprostanes, or degree of insulin resistance in RA.

Conclusion: Cholesterol efflux capacity is not significantly altered in patients with relatively well-controlled RA nor is it significantly associated with coronary artery calcium score.

Disclosures: None.

1438 Association Between Chronic Inflammatory Conditions and Anti Cyclic Citrullinated Peptide Antibodies in Patients with Early Rheumatoid Arthritis. Lucia Mariona, Marta Mamiana, Antonio Catalán Pelletc, Fernando Dal Pra2, Gustavo Citera3, Margarita Landi2, O Cerda2, Alejandro MacRae1, Rafael Chaparro del Moral2, Oscar Rillod, Francisco Colombreb, Alberto Berman6, Horacio Bermanc, Josefina Marcosc, Mercedes García6, A Salas6, Francisco Cañero6, A C Alvarez6, Maria Haye Salinas7, N Benzaquen1, Enrique Soriano1, Javier Rosa8, Emanuel Berti10, Federico Ceccato11, Sergio O. Paíra12, Gabriela Salvatierain, C. Ledesman, Aña Quinteros, M. Leal13, Maria Elena Crespo14, V. Juez14, Edson Veloso15, Monica P. Sacnun15, R. Quintana16, Marcelo Abdala1 and Anastasia Secco.

Background/Purpose: Increased citrullination process and anti-CCP production are not restricted to rheumatoid arthritis (RA). Other inflammatory processes could develop citrullinated proteins which may contribute to the production of such antibodies. The aim of our study was to analyze whether patients with anti-CCP positive early rheumatoid arthritis have higher frequency of previous history of chronic inflammatory conditions than anti-CCP negative patients at the time of diagnosis.

Methods: We included patients with early RA according to ACR/EULAR classification criteria, belonging to a prospective cohort of patients with early arthritis (<2 years of disease duration). Data from the first visit were collected. We studied the relationship between anti-CCP antibodies with the previous history of chronic inflammatory conditions (ischemic heart disease, peripheral vascular disease, ischemic or hemorrhagic stroke, hypertension, dyslipidemia, asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypothyroidism, tuberculosis, alcohol and smoking). Multivariable logistic regression analysis with anti-CCP as dependent variable, showed that dyslipidemia [OR = 0.39 (0.17–0.89); p = 0.03] and alcoholism [OR = 0.29 (0.15–0.55); p < 0.01] were independently associated with negative anti-CCP antibodies.

Conclusion: In this cohort with early rheumatoid arthritis, we did not found higher frequency of previous chronic inflammatory conditions in patients with positive anti-CCP antibodies. Nevertheless, negative anti-CCP antibodies were significantly and independently associated with previous history of dyslipidemia and alcoholism.

Disclosures: None.
Miscarriage in Rheumatoid Arthritis - Association with Disease Characteristics and Medication Use. Jenny Brouwer, Joop SE Laven, Johanna MW Hazes and Radboud EM Dolhain. Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands.

Background/Purpose: The chance of miscarriage is increased after the diagnosis of rheumatoid arthritis (RA). The association of miscarriage with RA disease activity or anti-rheumatic medication is unclear, mainly due to lack of prospective studies. Our aim was to study the associations of miscarriage with RA serology, disease activity and periconceptional medication use in women with RA.

Methods: In a large prospective cohort on pregnancy in RA (PARA study, 2002–2010) women with RA according to the 1987 American College of Rheumatology (ACR) criteria were visited preconceptionally, during pregnancy and after delivery or miscarriage. General characteristics and medication use were recorded and disease activity (DA S28) was measured. We analyzed the data retrospectively by logistic regression with purposeful selection of covariates, with inclusion at a significance level of p=0.20.

Results: A total of 239 preconceptional visits resulted in 181 pregnancies in 164 women. We analyzed only the first pregnancy included for each woman. Thirty (18%) of 164 pregnancies resulted in a miscarriage.

There were significant differences between women with a miscarriage and women with an ongoing pregnancy in age (33.8 (3.9) vs 32.0 (3.8) years, p=0.022) and presence of ACPA (83% vs 60%, p=0.032). The preconceptional DAS28 was higher in women who had a miscarriage (4.0 (1.0) vs 3.6 (1.2), p=0.087) and more women who miscarried had used MTX in the past (83% vs 68%, p=0.121), though these differences were not significant. There were no significant differences in RF positivity (80% vs 69%, p=0.121), though these differences were not significant. There were no significant differences in RF positivity (80% vs 69%, p=0.121), though these differences were not significant. There were no significant differences in RF positivity (80% vs 69%, p=0.121), though these differences were not significant.

Conclusion: The miscarriage rate in the PARA study is comparable to that in the general population. However, this might be biased by a healthy cohort effect found earlier in this study. Despite having miscarried, the majority of patients were pregnant again within one year. RA patients who had a miscarriage tended to be older, to have higher disease activity, to be ACPA positive and to have a past of MTX use. This indicates that miscarriages are more likely to occur in a subgroup of RA patients with more severe disease. Although the PARA study is a large prospective cohort on pregnancy in RA, the associations found did not reach statistical significance due to the relative low frequency of miscarriages in the study.

Table 1. Logistic regression for the occurrence of miscarriage in women with rheumatoid arthritis in the PARA study

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% Confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - per year</td>
<td>1.11</td>
<td>0.99–1.24</td>
<td>0.081</td>
</tr>
<tr>
<td>Presence of ACPA</td>
<td>2.71</td>
<td>0.94–7.78</td>
<td>0.065</td>
</tr>
<tr>
<td>DAS28 - per point</td>
<td>1.35</td>
<td>0.92–1.97</td>
<td>0.124</td>
</tr>
<tr>
<td>MTX use in past</td>
<td>2.78</td>
<td>0.95–0.89</td>
<td>0.061</td>
</tr>
</tbody>
</table>

PARA = pregnancy induced amelioration of rheumatoid arthritis; ACPA = anti-citrullinated peptide antibody; DAS28 = disease activity score with a 28-joint count; MTX = methotrexate.

Disclosure: J. Brouwer, None; J. S. Laven, None; J. M. Hazes, None; R. J. Dolhain, None.

1440

Asymptomatic Carotid Plaques in RA Patients Are Associated with Increased HDL Function. Silvia Rollesfad, Bente Halvorsen, Tonje Skarpengland, Sella Provan, Tore K. Kven and Anne Grette Semb. Diakonhjemmet Hospital, Oslo, Norway, #Oslo University Hospital Rikshospitalet, Oslo, Norway, #PsAID taskforce, EULAR, Zurich, Switzerland.

Background/Purpose: Reverse cholesterol transport (RCT) is a major antiatherogenic function of high density lipoprotein cholesterol (HDL) and has been shown to be related to disease activity in patients with rheumatoid arthritis (RA). Our aim was to evaluate if atherosclerosis affects HDL function differently in RA patients compared to controls.

Methods: RA patients from the ORA register and the EURIDISS cohorts without cardiovascular (CV) disease and not using statins or biologic DMARDs were included. Healthy community controls were selected by Statistics Norway. RCT was measured as plasma induced 14C-cholesterol efflux from 14C-cholesterol loaded human THP1 macrophages as previously described. Apo-polipoprotein (Apo) A1 and paraoxonase-1 (PON-1) activity were measured.

Results: RA patients; 10 with and 10 without carotid plaques (CP), and 10 controls were age and gender matched (Table 1). Traditional CV risk factors were comparable in RA patients with and without CP and controls; smoking: p=0.55, systolic blood pressure: p=0.77, total cholesterol: p=0.48, LDL-c: p=0.31, HDL-c: p=0.89, triglycerides: p=0.85. None had diabetes. Untraditional biomarkers of CV disease such as CRP and ESR were also comparable across the 3 groups; p=0.53, p=0.86 and p=0.45, respectively.

A disease factors as disease duration, rheumatoid factor, anti-CP and DA S28 were comparable between RA patients with and without CP (p=0.81, p=0.34, p=0.34 and p=0.94). Efflux capacity was significantly increased in RA patients with CP compared both to controls without CP (p=0.03) and controls with CP (p=0.01) (Table 2). Likewise, both ApoA1 and PON-1 activity were increased in RA patients with CP compared to controls (p=0.02 and p=0.05, respectively). Further, ApoA1 and PON-1 activity were comparable between RA patients without CP and controls (p=0.52 and p=0.08, respectively).

Conclusion: The cholesterol efflux capacity was increased in RA patients with early atherosclerosis compared to controls, independent of HDL level and CRP. Our findings indicate an association between atherosclerosis and increased HDL function in patients with RA having low disease activity, possibly as a compensatory mechanism to the atherosclerotic process. This study is hypothesis generating and larger studies are warranted to verify these findings.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>RA with Carotid Plaque</th>
<th>RA without Carotid Plaque</th>
<th>Controls n=10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (IQR)</td>
<td>65.2 (53.7, 68.1)</td>
<td>59.1 (54.1, 62.2)</td>
<td>56.6 (51.1, 61.4)</td>
<td>0.09*</td>
</tr>
<tr>
<td>RA with Carotid Plaque</td>
<td>n=20</td>
<td>n=20</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>RA without Carotid Plaque</td>
<td>n=20</td>
<td>n=20</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>Controls n=10</td>
<td>n=10</td>
<td>n=10</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>Disease duration median (IQR)</td>
<td>16.0 (2.1)</td>
<td>16.2 (1.5)</td>
<td>-</td>
<td>0.81</td>
</tr>
<tr>
<td>CV risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoke n (%)</td>
<td>3 (30)</td>
<td>1 (11)</td>
<td>3 (30)</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (3.5)</td>
<td>26.3 (4.0)</td>
<td>27.3 (5.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>TC (mmol/L) median ± SD</td>
<td>6.0 (0.67)</td>
<td>5.7 (0.97)</td>
<td>6.0 (0.84)</td>
<td>0.48</td>
</tr>
<tr>
<td>HDL-c (mmol/L) median ± SD</td>
<td>1.44 ± 0.48</td>
<td>1.57 ± 0.55</td>
<td>1.5 ± 0.47</td>
<td>0.89</td>
</tr>
<tr>
<td>TG (mmol/L) median ± SD</td>
<td>1.08 (0.64, 1.43)</td>
<td>1.12 (0.82, 1.40)</td>
<td>0.98 (0.72, 1.49)</td>
<td>0.85**</td>
</tr>
<tr>
<td>HDL-c (mmol/L) median ± SD</td>
<td>4.04 ± 0.91</td>
<td>3.6 (0.90)</td>
<td>3.54 (0.91)</td>
<td>0.31</td>
</tr>
<tr>
<td>BP systolic (mmHg)</td>
<td>131.1 ± 11.1</td>
<td>131.6 ± 14.8</td>
<td>136 (21.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>BP diastolic (mmHg)</td>
<td>81.2 ± 8.4</td>
<td>79.8 ± 8.3</td>
<td>82.4 ± 12.9</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Table 2. HDL function

<table>
<thead>
<tr>
<th></th>
<th>RA with CP</th>
<th>RA without CP</th>
<th>Controls</th>
<th>RA with CP vs. CTR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL mean ± SD</td>
<td>1.44 ± 0.48</td>
<td>1.57 ± 0.55</td>
<td>1.5 ± 0.47</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>RA with CP</td>
<td>n=20</td>
<td>n=20</td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA without CP</td>
<td>n=20</td>
<td>n=20</td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls n=10</td>
<td>n=10</td>
<td>n=10</td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efflux, % (g/L)</td>
<td>32.2 ± 4.70</td>
<td>28.05 ± 6.04</td>
<td>23.24 ± 4.13</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>ApoA1, % (g/L)</td>
<td>8.74 ± 1.39</td>
<td>7.86 ± 1.70</td>
<td>7.30 ± 0.96</td>
<td>0.02</td>
<td>0.58</td>
</tr>
<tr>
<td>PON-1, U/mL</td>
<td>0.19 ± 0.05</td>
<td>0.14 ± 0.06</td>
<td>0.15 ± 0.04</td>
<td>0.05</td>
<td>0.69</td>
</tr>
</tbody>
</table>

RA patients had HDL with sign. higher ApoA1 and PON-1 compared to control subjects.
Echocardiography 2, coronary calcium score (Agaston score) by coronary computer tomography (CT COR), diffusing capacity of the lungs for carbon monoxide (DLCO), C-reactive protein (CRP), fasting insulin (fIns) levels and whole body fat percent by whole body DXA-scan. The assay was performed on serum from 30 treatment-naive RA patients (mean age 56 yr; range 27–73) and 24 healthy controls (age 44 yr; range 24–64). RA patients and controls were free of medication at the time of serum sampling (the RA patients received methotrexate treatment at year one). Disease activity was scored by the 2010 Disease Activity Score 28 (DAS28) after treatment was initiated. We found “accelerated aging” measured as decreased wound healing in vitro to be associated with increased LDL levels (p < 0.0001). One year of national guideline DMARD treatment improved the “in vitro decreased wound healing” to mean 60% although not significant (p = 0.068). We found “decreased wound healing in vitro” to be associated with increased LDL levels (p = 0.02; r = 0.43) in univariate analysis (no association to GLS, Agaston calcium score, DLCO (mmol/min/kPa/l), total fat %, fIns and CRP (p-values in the range 0.31-0.79). We also found a significant difference in GLS in patients with high values of anti-CCP titers (≥ 340) compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≥ 340 compared to patients with normal titers and anti-CCP titers ≤ 340). We observed a significant decreased “wound healing” in vitro using hTERT-MSC assay in early RA. The “decreased in vitro wound healing” was significantly associated with increased LDL. Further we found a significant association between increased anti-CCP titers and initial increased cardiac function and decreased pulmonary function.

References:

Disclosure: T. Ellingsen, None; H. Jørgensen, None; D. Demirovic, None; L. Deiberg, None; F. Andersen, None; A. Hedemann-Andersen, None; B. B. Legstrup, None, S. Rattan, None.

1442

The 2013 ACC/AHA Cardiovascular Risk Prediction Model and Coronary Atherosclerosis in Patients with Rheumatoid Arthritis. Vivian K. Kawai1, Cecilia P. Chung1, Joseph F. Solus1, Annette Oeser1, Paolo Raggi1 and C. Michael Stein1. 1Vanderbilt University, Nashville, TN, 2University of Alberta, Edmonton, AB.

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased risk of atherosclerotic cardiovascular (CV) disease that is underestimated by the Framingham risk score (FRS). We hypothesized that the new 2013 ACC/AHA 10-year risk score could better identify patients with RA with high coronary artery calcification (CAC) scores, and consequently elevated CV risk, compared to the FRS and the Reynolds risk score (RRS).

Methods: We calculated the 10-year FRS, RRS and ACC/AHA risk score in 98 RA patients aged between 40 and 75 years who would be eligible for risk stratification using the ACC/AHA score and assigned them to either elevated or low risk categories. We identified patients categorized as having elevated CV risk based on the presence of high CAC scores using the thresholds defined by Goff et al. (≥ 300 Agatston units or ≥ 75th percentile) and compared the ability of the three risk scores to correctly categorize these patients with high CAC as having elevated cardiovascular risk. We used receiver operator characteristic (ROC) curves (or c-statistics) to compare the ability of the three risk scores to identify patients with high CAC.

Results: All three risk scores were higher in patients with high CAC than those without (all P values < 0.05). The FRS (32% vs. 16%, P = 0.055) and RRS (32% vs. 13%, P = 0.018) both assigned more patients with high CAC than low CAC into the elevated risk category. The ACC/AHA risk score assigned more patients with high CAC into the elevated risk category (41%) and also assigned 28% of patients without high CAC into the elevated risk category so that the proportion patients with and without high CAC assigned to the elevated CV risk category was not significantly different (P = 0.190). The c-statistics (95% CI) for the FRS, RRS and ACC/AHA risk score predicting the presence of high CAC were 0.65 (0.53–0.76), 0.66 (0.55–0.77), and 0.65 (0.53–0.76), respectively.

Table: Cardiovascular risk estimates in patients with rheumatoid arthritis with and without high coronary artery calcium

<table>
<thead>
<tr>
<th>10-year cardiovascular risk scores</th>
<th>CAC &lt; 300 agatston units or CAC &lt; 75th percentile (n = 64)</th>
<th>CAC ≥ 300 Agatston units or CAC ≥ 75th percentile (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham risk score</td>
<td>Low risk category, 54 (84) vs. 23 (68), P = 0.055</td>
<td>Low risk category, 55 (87) vs. 23 (68), 0.018</td>
</tr>
<tr>
<td>Reynolds risk score</td>
<td>Low risk category, 56 (87) vs. 23 (68), 0.018</td>
<td>Low risk category, 56 (87) vs. 23 (68), 0.018</td>
</tr>
<tr>
<td>ACC/AHA risk score</td>
<td>Low risk category, 8 (13) vs. 11 (32), 0.190</td>
<td>Low risk category, 8 (13) vs. 11 (32), 0.190</td>
</tr>
</tbody>
</table>

Conclusion: The new ACC/AHA 10-year risk score, despite classifying more patients with high CAC into the elevated risk category than the FRS and RRS, assigned almost 60% of patients with elevated risk as determined by a high CAC score into the low CV risk category. Modifications of standard CV risk prediction models used in the general population may not improve risk prediction in patients with RA.

Background/Purpose: Several lines of evidence indicate that classical cardiovascular disease (CVD) risk factors, such as arterial hypertension, diabetes mellitus, smoking and dyslipidemia, are significantly increased in rheumatoid arthritis (RA), which, in turn, is associated with 1.5- to 2-fold increased prevalence of CVD. The exact contribution of the RA disease per se in this association, in terms of systemic inflammation, drugs, disease-related genetics and/or other factors, remains under study. We aimed to test the hypothesis that RA per se in patients free of classical CVD risk factors is associated with accelerated subclinical arterial disease.

Methods: Consecutive patients with RA (n = 267) were comprehensively studied by ultrasound for a) subclinical atheromatosis, assessed by the presence of carotid artery and/or femoral artery plaques, b) stiffness of common carotid artery and aortic stiffness by pulse wave velocity, and, c) hypertrophy of common carotid artery assessed by intimal-medial thickness and cross sectional area (calculated adjacent to plaques, when plaques were present). Of all patients, we identified those who were CVD-free, non-smoking, without hypertension, diabetes and dyslipidemia (only 18%). Of them, 41 (aged 49-13 years, 36 women, median disease duration of 7 years, range 3-19 years) were compared to 41 healthy non-smokers, without hypertension, diabetes and dyslipidemia who were effectively matched 1:1 for age and gender and studied in parallel.

Results: Patients had more than 2-fold higher prevalence of carotid and/or femoral atheromatous plaques than healthy controls (29% vs. 12%, p = 0.05). All patients with plaques had an acceptable functional status of class I or II. Moreover, body mass index, as well as family history of CVD, was similar between patients with plaques and their matched controls. Multi-arterial subclinical atheromatosis, defined as plaque presence at more than 1 of 8 arterial sites evaluated, was by far more prevalent in RA patients than controls (22% vs. 2%; p = 0.007). Notably, plaque burden in the subgroup of RA patients with less than 5 years of disease duration was comparable to their matched controls. Either arterial stiffness or hypertrophy, however, was not significantly increased compared to controls, even in patients with long-standing RA.

Conclusion: These data directly show, independently of the classical CVD risk factors, an acceleration of atheromatosis in RA, but not of arterial stiffness or hypertrophy. This phenomenon is not evidenced during the first 5 years after disease onset and seems to be chronic inflammation-dependent. Also, the dissociation between atheromatosis and arterial stiffness in this selected population suggests a minimal, if any, effect of chronic inflammation in arterial remodeling and arterial stiffness. Studies testing whether early and effective RA clinical disease control prevents the development of arterial damage in the long-term are ongoing.


ACR/ARHP Poster Session B
Clinical Practice/Patient Care (ARHP)
Monday, November 17, 2014, 8:30 AM–4:00 PM

1443

The Vocational Experiences of Young People with Juvenile Idiopathic Arthritis and the Role of the Multidisciplinary Team Supporting Positive Employment Outcomes. Helen Hanson, Ruth Hart, Alison Jordan, Rachel Tattersall, Ben Thompson and Helen E. Foster. Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; 2Newcastle University, Newcastle upon Tyne, United Kingdom; 3University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; 4Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom.

Background/Purpose: Recent decades have seen marked changes in the management of juvenile idiopathic arthritis (JIA), with improved clinical outcomes for many patients. However, unemployment rates for adults with JIA remain high compared to peers, highlighting the need to address vocational issues as an integral part of transitional care.

The aims of this study were to explore: i) experiences and expectations of employment amongst young people with JIA; ii) the actual and potential role of the multidisciplinary team in promoting positive employment outcomes.

Methods: We interviewed 13 young people with JIA (median age 22y, range 16–31y) and nine health professionals from three tertiary rheumatology services. A focus group for young people with JIA was held in each of the three centres. Qualitative techniques were used to analyse the transcripts.

Results: Three related themes associated with vocational experience emerged from our data analysis; i) JIA has made education and employment more challenging for all the young people in our sample, ii) young people often disclose only minimal information about their condition to educators or employers, iii) all the young people have experienced emotional challenges associated with having JIA and learning to manage these emotions would appear to contribute to vocational success. Young people from one recruiting centre have met peers with JIA at social events and many associate this with gains in both practical coping skills and emotional wellbeing.

Data relating to vocational expectations suggests two important issues. Firstly, many young people have low expectations of employers’ willingness to support employees with health conditions and secondly, few are well informed about their legal rights.

Each tertiary rheumatology service includes nurses, doctors and occupational therapists, while access to other professionals varies. We identified three themes concerning perceived barriers to maintaining and improving vocational support, namely i) staff need appropriate knowledge and skills to address vocational issues (currently training or team discussions about vocational issues (currently training or team discussions about vocational issues), ii) all staff find it challenging to provide holistic care within short appointments, with some describing a lack of attention to vocational issues, iii) dialogue with educators or employers can improve support for struggling individuals but happens less for young people compared to under 16s.

Conclusion: Young people with JIA have a significant need for vocational support from health professionals. Specifically, our work suggests that these young people would benefit from accessible information on: taking about arthritis; anti-discrimination legislation; and local support services. Many would value emotional support, which may include opportunities to meet peers.

The generic nature of vocational challenge lends itself to cross-specialty approaches to addressing training needs and facilitating dialogue with educators and employers. Further work is indicated to improve information resources, explore the needs of educators and employers and develop appropriate and cost-effective interventions.

Disclosure: H. Hanson, Pfizer Inc, 2; R. Hart, None; A. Jordan, None; R. Tattersall, Pfizer Inc, 3; B. Thompson, None; H. E. Foster, None.

1445

Improving Osteoarthritis Outcomes Utilising a Multidisciplinary Model of Care: Experience in a Diverse Multicultural Urban Teaching Hospital. Caroline Jones, Laurence A. Rubin, Angela Papachristos, Elaine Hamman and Jann Fabrick Ong. 1St. Michael’s Hospital, Aurora, ON, 2St. Michael’s Hospital, Toronto, ON, 3St. Michael’s Hospital, Toronto, ON, 4University of Toronto, Toronto, ON.

Background/Purpose: In 2008, a multidisciplinary osteoarthritis (MOA) clinic was established at St. Michael’s Hospital (SMH), a tertiary care academic teaching facility, serving a diverse social, economic and cultural urban population in Toronto. The team (Rheumatologist, Advanced Practice Physiotherapists) designs a comprehensive treatment plan which consists of one or more of the following:

- patient education
- weight loss strategies which may include a referral to a dietitian and possible bariatric surgery
- an exercise program
- prescription for an unloader brace, orthotics or wedges
- intrarticular corticosteroid or hyaluronic acid injection
- discussion about referral for joint replacement surgery

All patients complete two questionnaires at each visit:

1. Multidimensional Health Assessment Questionnaire (MDHAQ).

 Monday, November 17
The purpose of this continuous qualitative improvement project is to evaluate the outcomes of patients who attend the OA clinic. The research question is: How much change occurs in a patient’s functional scores from the initial assessment to the three month follow up visit after a treatment intervention has occurred?

Methods: This study is a retrospective observational cohort. Patients with knee, hip, or other joint OA visiting the OA clinic from January 2009 to December 2011 were included in the study. Patients visiting for other reasons such as rheumatoid arthritis or bursitis were not included in the analysis. A chart review of patients with baseline information and 3-month follow-up (+/- 3 weeks) was performed. Results were analyzed using WOMAC and MDHAQ questionnaires.

Results: Approximately 1/3 of the patients were recommended for surgery consult. Most patients attended the clinic for symptomatic knee OA. Approximately 1/3 of the patients were recommended for surgery consult.

Discussion: The importance of integrating MSUS in the rheumatology clinic, specifically highlighting multiple benefits in daily practice of reduced visits, discharge at first encounter, immediate management decisions. Our survey shows the importance of integrating MSUS service in a one-stop clinic.

Disclosure: K. Bhamra, None; C. Swales, None; M. Seymour, None; C. McClinton, None; P. C. Taylor, None.
adherence to ACR quality guidelines but this will need to be studied in larger cohorts in the region.

Disclosure: H. Beerann, None; J. Daoud, None; H. Badsha, None.

1448

A Questionnaire Assessment of Knowledge about Methotrexate of Patients with Rheumatoid Arthritis. Francianne Fayet1, Carine Savel1, Malory Rodere2, Bruno Pereira3, Dihya Abdal, Marion Couderc Sr.4, Sylvain Mathieu5, Anne Tournadre6, Sandrine Maloche-Guimand7, Martin Soubrier1 and Jean Jacques Dubost8.1CHU Gabriel-Montpied, Clermont-Ferrand, France, 2CHU Gabriel-Montpied, Clermont-Ferrand, France, 3Clinical research department, Clermont-Ferrand, France, 4CHU G.Montpied, Clermont-Ferrand, France, 5Rheumatology CHU Gabriel Montpied, Clermont-Ferrand, France, 6COMEDRA trial group, Paris, France, 7CHU G.-Montpied, Clermont-Ferrand, France.

Background/Purpose: Methotrexate is the reference treatment for rheumatoid arthritis (RA). It has potentially serious side effects which can be prevented by an improvement in patient’s information.

The aim is to assess the knowledge of patients suffering from RA about their methotrexate treatment with a questionnaire.

Methods: A questionnaire containing 21 closed questions and 2 situation studies about the medication (mechanism of action, method of administration, therapeutic interactions, side effects, monitoring and implications on lifestyle) was given to all RA patients treated with methotrexate who consulted between March and September 2013 in the rheumatology department of Clermont-Ferrand Hospital.

Results: 183 patients were recruited, including 143 women (79%), with a mean age of 60 years +/-13.5 and a median RA duration of 12 years (IQR: 7–20). Methotrexate has been initiated for a mean of 8 years (IQR: 5–13). Methotrexate was identified as a DMARD by 78% of participants. The weekly administration method was well-known (97%) and 67% said that alcohol consumption should be reduced. In multivariate analysis, a comparison to 90% of women of child-bearing age (n/H11005) was given to all RA patients treated with methotrexate who consulted between March and September 2013 in the rheumatology department of Clermont-Ferrand Hospital.

Conclusion: These results show comparable efficacy of intra-articular corticosteroid and placebo when combined with exercise for pain relief in knee OA.

Disclosure: M. Henriksen, None; R. Christensen, None; L. Klokker, None; C. Bartholdy, None; K. Elleegaard, None; M. Boesen, None; R. Riis, None; E. Barrels, None; H. Bliddal, None.

1450

Spironolactone As a Novel DMARD in Rheumatoid Arthritis. Inderjeet Verma1, Pawan Krishan2, Aashit Syngle3, 1Punjabi University Patiala, India, Chandigarh, India, 2Punjabi University Patiala, India, Patiala, India, 3Healing Touch City Clinic, Fortis Multispeciality Hospital, Chandigarh, India.

Background/Purpose: Synthetic disease-modifying antirheumatic drugs (DMARDs) though effective have limitations often requiring use of expensive biologic DMARDs which have their own drawbacks. Spironolactone is effective but has limitations. Given the TNF inhibiting potential of spironolactone (SPIR)1-4, We therefore investigated the anti-inflammatory effects of SPIR in RA patients in a randomized, placebo-controlled, open label study.

Methods: We organized a 24-week study on 70 patients (36 in SPIR and 34 in placebo arm) with active RA. They were randomized to oral SPIR (2 mg/kg/day) or placebo for 24 weeks as an adjunct to existing stable DMARD regimen. Therapy results were evaluated by ESR, CRP, Disease Activity Score in 28 joints (DAS28), simple disease activity index (SDAI), ACR response criteria and pro-inflammatory cytokines (TNF-α, IL-6 and IL-1). Flow mediated dilatation (FMD) was assessed by AngioPower® and carotid intima media thickness (CIMT) of brachial artery. Endothelial progenitor cells (EPCs) (CD34+/CD133+) were quantified by flow cytometry. Quality of life was assessed using HAQ-DI.

Results: A total of 263 patients were screened and 100 patients were randomized to receive either Steroid (n=50) or Placebo (n=50). Of these, 93 completed the week 14 assessment and 89 completed the 26 weeks trial. At 24 weeks, no group differences in the proportions completing. Mean age was 63.4 (SD 9.3) years, 61% were women. The mean exercise attendance rate was 79% (SD 15); no group difference. The mean (SD) KOOS pain score at randomization was 53.3 (11.4) and 55.2 (16.0) in the Steroid and Placebo groups, respectively. The mean (SEM) change in pain at week 14 was 13.6 (1.8) and 14.8 (1.8) in the Steroid and Placebo Groups, respectively, corresponding to a mean difference of 1.2 units (95% CI -3.8 to 6.2; P = 0.64). These results were robust. ACR20 response to RA treatment was 47.5% (n/H11005) in SPIR group and 34% in placebo arm (p=0.03) compared with placebo (p=0.008) for SPIR versus placebo. The rate was 79% (SD 15); no group difference. The mean (SD) KOOS pain score at randomization was 53.3 (11.4) and 55.2 (16.0) in the Steroid and Placebo groups, respectively. The mean (SEM) change in pain at week 14 was 13.6 (1.8) and 14.8 (1.8) in the Steroid and Placebo Groups, respectively, corresponding to a mean difference of 1.2 units (95% CI -3.8 to 6.2; P = 0.64). These results were robust. ACR20 response to RA treatment was 47.5% (n/H11005) in SPIR group and 34% in placebo arm (p=0.03) compared with placebo (p=0.008) for SPIR versus placebo.

Conclusion: These results show comparable efficacy of intra-articular corticosteroid and placebo when combined with exercise for pain relief in knee OA.

Disclosure: H. Beermann, None; J. Daoud, None; H. Badsha, None.

1449

Combined Intra-Articular Corticosteroid and Exercise in Patients with Knee Osteoarthritis: A Randomised Trial. Marius Henriksen1, Robin Christensen2, Louise Klokker2, Cecile Bartholdy3, Karen Elleegaard4, Mikael Boesen5, Robert Riis6, Else Bartels7 and Henning Bliddal8.1The Parker Institute, Copenhagen, Denmark, 2Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, 3Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark.

Background/Purpose: Combined non-pharmacological and pharmacological treatment is recommended as optimal management of knee osteoarthritis (OA). However, the two treatment approaches have mostly been investigated separately. We aimed to assess the efficacy of combined intra-articular corticosteroid injection and exercise compared to placebo injection and exercise in patients with knee OA.

Methods: This randomized, double blinded, placebo-controlled trial running over 26 weeks was designed as a superiority trial comparing the efficacy of a single intra-articular corticosteroid injection (1 mL of 40 mg/mL methylprednisolone dissolved in 4 mL 10 mg/mL Lidocaine) plus exercise, with a single placebo injection (1 mL isotonc saline mixed with 4 mL 10 mg/mL Lidocaine) plus exercise. Participants with clinical and radiographic knee OA were randomly allocated (1:1) to either corticosteroid (Steroid Group) or saline (Placebo Group) injection. Two weeks after injections, all participants started a 12 week supervised exercise program with 3 weekly sessions. Outcomes were assessed at baseline, week 2 (exercise start), week 4 (end of exercise), and week 26 (follow-up). The primary outcome was the mean change in KOOS pain subscale at week 14. Analyses were done on the intention-to-treat basis (ITT) population (all randomised participants). Pain data were replaced using multiple imputation. A repeated measures mixed model was used to analyze the primary outcome; week, treatment, and week x treatment were included as fixed effects, adjusting for the baseline value.

Results: A total of 263 patients were screened and 100 patients were randomized to receive either Steroid (n=50) or Placebo (n=50). Of these, 93 completed the week 14 assessment and 89 completed the 26 weeks trial. At 24 weeks, no group differences in the proportions completing. Mean age was 63.4 (SD 9.3) years, 61% were women. The mean exercise attendance rate was 79% (SD 15); no group difference. The mean (SD) KOOS pain score at randomization was 53.3 (11.4) and 55.2 (16.0) in the Steroid and Placebo groups, respectively. The mean (SEM) change in pain at week 14 was 13.6 (1.8) and 14.8 (1.8) in the Steroid and Placebo Groups, respectively, corresponding to a mean difference of 1.2 units (95% CI -3.8 to 6.2; P = 0.64). These results were robust. ACR20 response to RA treatment was 47.5% (n/H11005) in SPIR group and 34% in placebo arm (p=0.03) compared with placebo (p=0.008) for SPIR versus placebo.

Conclusion: These results show comparable efficacy of intra-articular corticosteroid and placebo when combined with exercise for pain relief in knee OA.
patient experienced adverse events or discontinued treatment because of adverse events.

Conclusion: These results suggest that SPIR is a powerful anti-inflammatory agent that significantly reduces inflammatory biomarkers and disease severity and improves physical function in RA. It also improves endothelial dysfunction, EPC population and CIMT indicating its beneficial effects on the enhanced cardiovascular risk of RA. SPIR could therefore possibly be used as an adjunct therapy with DMARDs in patients with RA.

Disclosure: I. Verma, None; P. K. Rishan, None; A. Syngle, None.

1451

Use of Analgesics in Patients with Knee and/or Hip Osteoarthritis: Results from the Amsterdam Osteoarthritis Cohort. Joyce van Tunen1, Marike van der Leeden1, Martin van der Esch1, Leo D. Roorda2, Willem F. Lems3 and Joost Dekker4. 1Amsterdam Rehabilitation Research Center | Reade, Amsterdam, the Netherlands, 2University of Amsterdam, Amsterdam, Netherlands, 3Jan van Breemen Research Institute | Reade, Amsterdam, the Netherlands, 4VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Use of analgesics is recommended by international guidelines to reduce pain complaints related to knee and/or hip osteoarthritis. Underuse of analgesics might be substantial in patients with knee and/or hip osteoarthritis due to poor implementation of guidelines. Factors associated with analgesic use are not assessed systematically, although knowledge of the use of analgesics will improve the prescription of analgesics. Therefore, the first aim of this study was to describe the use of analgesics in patients with knee and/or hip osteoarthritis, referred to an outpatient center for rehabilitation and rheumatology in the Netherlands.

The second aim was to determine factors that are associated with analgesic use in this population.

Methods: Data from 497 patients with knee and/or hip osteoarthritis according to clinical ACR criteria from the Amsterdam Osteoarthritis cohort were used. Self-reported analgesic use was measured. Independent factors included predisposing (e.g. demographic and social characteristics), enabling (the ability to use care resources, e.g. referring physician) and disease-related (the most immediate cause for analgesic use) factors. Logistic regression analysis was performed to analyze the association between analgesic use and the independent factors.

Results: The mean±SD age of patients was 61.6±9.0 year and 72% were woman. Total scores on pain, stiffness and activity limitations on the Western Ontario and McM Master Universities Arthritis Index (WOMAC) were 43.5±18.1. Analgesic use was reported in 53% of the patients; 37% used acetaminophen, 21% used non-selective non-steroidal anti-inflammatory drugs (NSAIDs), 3% used codeine and 8% used opioids. Both monotherapy or combinations of analgesics were used. Univariate logistic regression analysis showed that high scores on pain, stiffness and activity limitations on the WOMAC were associated with analgesic use. In addition, gender (women), being overweight or obese, having bilateral knee symptoms, higher levels of psychological distress and a higher amount of comorbidities were associated with analgesic use. Higher levels of psychological distress were associated with the use of acetaminophen. Preliminary results of multivariate logistic regression analysis showed that a higher score on the subscale pain of the WOMAC was associated with analgesic use.

Conclusion: Half of patients with knee and/or hip osteoarthritis referred to an outpatient center for rehabilitation and rheumatology used analgesics. More pain was associated with use of analgesics, suggesting that the analgesics used are not sufficiently effective in reducing symptoms. This may indicate that more effective strategies of pain management need to be implemented.

Disclosure: J. van Tunen, None; M. van der Leeden, None; M. van der Esch, None; L. D. Roorda, None; W. F. Lems, None; J. Dekker, None.

1452

Timing of Decisions to Adjust Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy for Rheumatoid Arthritis (RA) Patients with Active Disease in a Realistic Practice Setting. Yomié Shaw1, Chung-Chou H. Chang2, Marc C. Levesque2, Julie M. Donohue2, Kaleb M. Michaud3 and Mark S. Roberts4. 1University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, 2University of Pittsburgh Department of Medicine, Pittsburgh, PA, 3National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: Current guidelines recommend that rheumatoid arthritis (RA) patients with poor response to their current regimen of disease modifying anti-rheumatic drugs (DMARDs) have therapy adjusted until reaching low disease activity or remission. We examined factors associated with timing of decisions to adjust DMARD therapy for RA patients with active disease and how the timing of decisions impacts resolution of active disease.

Methods: Data came from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry, which captures subjects’ disease activity status (DA$28$-CRP) and medications at clinic visits.

We conducted survival analyses on time to DMARD therapy adjustment and time to resolution of active disease for RA patients with active disease. A Cox proportional hazards model was used to assess the impact of covariates on the survival times. For both analyses, followup begins when the subject is first known to have active disease (DA$28$-CRP$\geq3.2$) and ends with the event of interest (DMARD therapy adjustment or resolution of active disease). For the analysis of time to therapy adjustment, we excluded patients who adjusted therapy at t=0 and those who exited active disease before adjusting therapy, and the model included covariates at baseline, gender, African-American race, comorbidities, duration of RA, and current use of a biologic therapy. For the analysis of time to resolution of active disease, the model included the same covariates plus an indicator for time to therapy adjustment.

Results: We identified 562 subjects with active disease at a first timepoint and a followup DA$28$-CRP measurement. The analysis for time to therapy adjustment included 177 subjects (117 therapy augmentations observed). 364 subjects were excluded because they adjusted DMARD therapy at t=0 (n=196) or because they exited active disease status before adjusting therapy (n=162). The median time to therapy adjustment was 203 days. Age over 75 and longer duration of RA were significantly associated with longer times to therapy adjustment. The analysis for time to resolution of active disease included 530 subjects (383 achieved DA$28$-CRP$\leq3.2$). The median time to resolution of active disease was 257 days. African-American race and duration of RA $>$1 year were associated with longer times to resolution of active disease. (See Table 1)

Conclusion: Among those with persistent active disease (n=394), 60% adjusted DMARD therapy within 90 days; however 50% of subjects took longer than 275 days to achieve DA$28$-CRP$\leq3.2$. We found that age $>$75 and longer duration of RA were associated with longer times to DMARD therapy adjustment, while African-American race and duration of RA $>$1 year were associated with poorer disease outcomes. Future studies should further examine how these factors affect treatment choices as well as long term health outcomes.

Table 1. Rheumatoid arthritis patient characteristics associated with time to therapy adjustment/resolution of active disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cox regression 1 Outcome: Time to DMARD therapy adjustment*</th>
<th>Cox regression 2 Outcome: Time to resolution of active disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p-value</td>
</tr>
<tr>
<td>Age at baseline $\geq75$</td>
<td>0.800</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>0.950</td>
<td>0.785</td>
</tr>
<tr>
<td>Charlson group 2*</td>
<td>1.200</td>
<td>0.408</td>
</tr>
<tr>
<td>Charlson group 3*</td>
<td>0.788</td>
<td>0.447</td>
</tr>
<tr>
<td>African-American</td>
<td>1.000</td>
<td>0.999</td>
</tr>
<tr>
<td>Using biological at baseline</td>
<td>0.830</td>
<td>0.301</td>
</tr>
<tr>
<td>Disease duration at baseline</td>
<td>0.961</td>
<td>0.014</td>
</tr>
<tr>
<td>Disease duration &lt;1 yr at baseline</td>
<td>-</td>
<td>1.574</td>
</tr>
<tr>
<td>Adjusted therapy in &lt;90 days</td>
<td>0.844</td>
<td>1.057</td>
</tr>
</tbody>
</table>

*DMARD therapy adjustment is defined as adding, switching or increasing dose of biologic or nonbiologic DMARD therapies.

Disclosure: Y. Shaw, None; C. C. H. Chang, None; M. C. Levesque, None; J. M. Donohue, None; K. Michaud, None; M. S. Roberts, None.

1453

Gastrointestinal Risk Factors and Treatment Patterns of Rheumatoid Arthritis Versus Osteoarthritis Patients in Korea. Eun Yung Lee1, Sang Heon Lee2, Hyo-Jin Kim2 and Korea RA/OA OR Group. 1Seoul National University College of Medicine, Seoul, South Korea, 2Konkuk University Hospital, Seoul, South Korea, 3Pfizer Tower, 1–11, Hoebyeong-Dong 3-Ga, Jung-Gu, Seoul, South Korea.
**Background/Purpose:** Little is known about local data of the gastrointestinal risk factors (GI) and treatment patterns in rheumatoid arthritis (RA) and osteoarthritis (OA) patients. This study aimed to investigate and compare the GI risk factors and treatment patterns of RA and OA patients in real clinical practice of Korea.

**Methods:** This was a nationwide, cross-sectional and observational study of patients taking non-steroidal anti-inflammatory drugs (NSAID, either non-selective or selective COX-2 inhibitor (COX2i)) from 20 hospitals between April 2012 and September 2013. Total 1,896 patients who were ≥20 years old (RA:981 OA:915) and were taking NSAID at least 1 month were enrolled. Data were collected through medical chart review and patients survey. The GI risk factors included NSAID duration (>3 months), high-dose of NSAID use, drinking, smoking, comorbid disease, aspirin use, anticoagulant-warfarin use, steroid use, Helicobacter pylori infection, experience of GI event (i.e. GI bleeding or ulcer). The treatment patterns were identified as non-selective NSAID (ns-NSAID) or COX2i with/without gastroprotective agents respectively.

**Results:** In RA, proportion of patients taking NSAID ≥3 months, smoker and steroid users were higher in than OA patients (p<0.001). In OA, proportion of patients who have comorbid disease and take aspirin were higher than in RA patients (p<0.0001). The rest of the GI risk factors were present as a similar proportion in both groups. The percentage of treatment with COX2i (RA:54.3% vs OA:44.2%, p=0.001) and gastroprotective agents (RA:83.0% vs OA:78.3%, p=0.009) in RA patients was higher than in OA patients. In older aged patients (age=≥60) in both groups, there was tendency to get more treatment with COX2i (RA: 60.9%, OA:50.2%) compared to ns-NSAID. Interestingly, as patients get more numbers of GI risk factors, there seemed to get more proportions of ns-NSAIDs users in both RA and OA patients.

**Conclusion:** The proportion of GI risk factors found in OA patients was comparable to that in RA patients. There was a tendency to show preferential ns-NSAID treatment pattern rather than COX2i especially in the presence of multiple GI risk factors in arthritis patients.

**Disclosure:** E. Y. Lee; None. S. H. Lee; None. H. J. Kim; None.

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**ACR/ARHP Poster Session B Rheumatoid Arthritis - Human Etiology and Pathogenesis Monday, November 17, 2014, 8:30 AM–4:00 PM**

### 1454

**Quantitative and Qualitative Tracking of Expanded CD4 T Cells in Rheumatoid Arthritis Patients.** Kazarugyo Ishigaki1, Hirofumi Shoda2, Yuta Kochi2, Tetsuro Yasui1, Yuho Kadono1, Sakae Tanaka1, Keishi Fujio1 and Kazuhiro Yamamoto1. 1The University of Tokyo, Tokyo, Japan; 2RIKEN, Yokohama, Japan.

**Background/Purpose:** The purpose of this study is to elucidate the characteristics of expanded CD4+ T cell clones (ECs) in peripheral blood and synovium of rheumatoid arthritis (RA) patients by T cell receptor (TCR) repertoire and single cell transcriptome analysis.

**Methods:** We obtained peripheral blood from 5 RA patients and 5 control subjects. We performed TCR repertoire analysis by combination of single cell and next-generation sequencer (NGS) in CD4+ T cells. We also performed single cell RNA-Seq and real time PCR analysis of ECs and non-expanded clones (NECs). Similarly, CD4+ T cells from synovium were analyzed in 1 patient.

**Results:** We detected significantly higher frequency of ECs in peripheral blood of 4 RA patients compared with controls both in naive and memory subset of CD4+ T cells. Within memory CD4+ T cells of peripheral blood, non-Th1/Th17/Th17/f Th subset (negative for CXCR3, CCR6 and CXCR5) contained majority of expanded clones in PBM of 3 RA patients and synovium-infiltrating clones in 1 RA patient. Gene expression analysis of the mostly expanded CD4+ T cell clones in synovium of 1 RA patient and peripheral blood of 2 RA patients revealed up-regulation of GZMB, TBX21 and CD5 and down-regulation of CD28 compared with NECs. The tracking of gene expression profile of one unique EC in peripheral blood showed down-regulation of CXCR4 and CCR5 compared with that of the identical clone in synovium of the same patient.

**Conclusion:** ECs were more frequently observed in non-Th1/Th17/Th17/f subset in peripheral blood and had gene expression profiles consistent with senescent CD4+ T cells in both of peripheral blood and synovium. Given that there are no reliable markers of clonal expansion, single cell transcriptome analysis is the only method to investigate gene expression profiles of expanded clones. Combined with the robustness of NGS TCR repertoire analysis, our approach should be a rational strategy to characterize ECs and might be able to identify pathogenic clones in RA.

**Disclosure:** K. Ishigaki; None. H. Shoda; None. Y. Kochi; None. Y. Yasui; None. Y. Kadono; None. S. Tanaka; None. K. Fujio; None. K. Yamamoto; None.

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**1455**

**Ex Vivo-Expanded, but Not In Vitro-Induced, Human Regulatory T Cells Are Suitable for Cell Therapy in Rheumatological Autimmune Diseases Thanks to Stable FOXP3 Demethylation.** Maura Rossetti1, Roberto Spreafico2, Meryam Moshe2, Jorg van Loosdregt3 and Salvatore Albanì1. 1Singapore Health Services Pte Ltd, Duke-NUS Graduate Medical School, Translational Research Unit, Sanford-Burnham Medical Research Institute, Singapore, Singapore; 2Translational Research Unit, Sanford-Burnham Medical Research Institute, La Jolla, CA; 3Translational Research Unit, Sanford-Burnham Medical Research Institute, San Diego, CA.

**Background/Purpose:** Treg cell therapy is a promising approach for transplant rejection and severe autoimmunity. Unfortunately, sufficient Treg numbers can be obtained only upon in vitro culture. Functional stability of human expanded (e)Treg and induced (i)Tregs has not been thoroughly addressed for all proposed protocols, hindering clinical translation. We undertook a systematic comparison of eTreg and iTregs to recommend the most suitable protocol for clinical implementation, and then tested its effectiveness and feasibility in autoimmune rheumatological settings with cells from rheumatoid arthritis (RA) patients.

**Methods:** eTregs were expanded with rapamycin (rapi), while iTregs were induced from naïve T cells in the presence of TGF-β with either all-trans retinoic acid (ATRA) or rapi. FOXP3 expression and demethylation, regulatory molecular signature and suppressive function were evaluated after first round of differentiation and a secondary restimulation deprived of differentiation factors.

**Results:** Regardless of the protocol, iTregs acquired suppressive functions and FOXP3 expression, but lost them upon withdrawal of differentiation factors. In contrast, rapi eTregs maintained their regulatory properties and retained FOXP3 upon restimulation. Demethylation, but not expression, of FOXP3 predicted Treg functional stability upon secondary TCR engagement in the absence of stabilizing factors. Importantly, Treg expansion with rapi from RA patients produced functionally stable and suppressive iTregs with yields comparable to healthy donors.

**Conclusion:** Our data indicate ex vivo Treg expansion with rapi as the protocol of choice for clinical application in rheumatological settings, with assessment of FOXP3 demethylation as a necessary quality control step.

**Disclosure:** M. Rossetti; None. R. Spreafico; None. M. Moshe; None. J. van Loosdregt; None. S. Albanì; None.

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**1456**

**Foxp3+ Regulatory T Cells in Peripheral Blood and Synovial Fluid of Patients with RA: A Comparative Phenotypic Analysis.** Jun Saegusa1, Fumichika Matsuki2, Y asushi M iura2, Goichi Kageyama3, Seiji Kawano4, Shunichi Kumarag3 and A kio Morinobu5. 1Kobe University Graduate School of Medicine, Kobe, Japan; 2Kobe University Graduate School of Health Sciences, Kobe, Japan; 3Hokkaido University Graduate School of Medicine, Sapporo, Japan; 4Shinsho Hospital, Kobe, Japan.

**Background/Purpose:** Human regulatory T (Treg) cells play an indispensable role for the maintenance of self tolerance and immune homeostasis. Numerous studies dealt with Treg population in peripheral blood from RA patients (RAB) with various conclusions regarding the frequency of circulating Treg cells. Most studies reported decreased or normal proportions of Treg cells, whereas some other groups reported an increase. On the other hand, the frequency of Treg cells in synovial fluid from RA patients (RASF) has been reported to be significantly higher than that in RAB. In addition, Treg cells in RASF have been shown to have impaired suppressive function compared to those in RAB. However, the cause of impaired function of Treg cells in RASF is unknown. A recent study has demonstrated that human Treg cells can be separated into three functionally unique subpopulations: CD45RA+/FOXP3low naive Treg cells; CD45RA+/FOXP3mid Treg cells; CD45RA+/FOXP3high effecter Treg cells, both of which have suppressive functions, and non-suppressive cytokine-secreting CD45RA-/FOXP3high non-Treg cells. The purpose of this study is to determine the characteristics of Foxp3+ T cells in RAB and RASF.

**Disclosure:** None.
Methods: Synovial fluid and peripheral blood CD4+ T cells from RA patients were classified into different subsets based on the expression of CD45RA,CCR7,CD27, and CD28. The frequency of IFN-γ, IL-17, or TNF-α-producing cells, and of Foxp3- or RANKL-positive cells in each subset was analyzed by eight-color flow cytometry. CD4+Foxp3+ cells were further classified into three functionally distinct subsets based on the expression of CD45RA and Foxp3.

Results: The frequency of CD45RA–Foxp3high effector Treg cells was significantly decreased in the peripheral blood CD4+ T cells from RA patients, compared to those from healthy controls. As a result of the decrease of effector Treg cells, more than half of the Foxp3+ T cells (60.5 ± 9.5%) were CD45RA–Foxp3low non-Treg cells in RABP. Furthermore, the frequency of CD45RA–Foxp3low effector Treg cells in the CD27+CD28+ central memory (TEM) subset was significantly decreased in RA patients. In addition, the percentage of CD45RA+Foxp3low naïve Treg cells was negatively correlated with DAS28-CRP. In RASF, the frequency of Foxp3+ cells in the CD27+CD28+ effector memory (TEM) population was significantly increased in RASF, compared to that in RABP. Most of the Foxp3+ cells in RASF were CD45RA–Foxp3low non-Treg cells (81.7 ± 10.4%), and the frequency of non-Treg cells in RASF was significantly increased compared to that in RABP. Furthermore, the non-Treg cells in CD27+CD28+ TEM subset was significantly increased in RASF (RAF: 5.9 ± 4.0%, RABP: 0.7 ± 0.5%). Collectively, increase in Foxp3+ cells in RASF was due to increased number of non-Treg cells which exist in CD27+CD28+ TEM subset.

Conclusion: The decreased proportion of CD45RA–Foxp3low effector Treg cells and the increased proportion of CD45RA–Foxp3high non-Treg cells may have critical roles in the pathogenesis of RA.

Disclosure: J. Saegusa, None; F. Matsuki, None; Y. Miura, None; G. Kageyama, None; S. Kawano, None; S. Kumagai, None; A. Morinobu, None.

1457

Stem Cell Growth Factor Expression in Rheumatoid Arthritis. Yoon Jung Woo1, Young Ae Baik1, Yong-beom Park2, Soo-kon Lee1, William H Robinson2 and Jason Jungsik Song1. 1Yonsei University College of Medicine, Seoul, South Korea, 2Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Stem cell growth factor (SCGF) is a member of the C-type lectin superfamily, encoded by gene CLEC11A. SCGF is not related to stem cell factor (a ligand for the receptor-type protein-tyrosine kinase KIT) although the two proteins can be confused due to similarity in name. SCGF has been recently discovered as a growth factor of hematopoietic precursor cells in the bone marrow. However, the role of SCGF in inflammatory cells, we investigated SCGF expression using samples derived involved in RA pathogenesis by promoting the survival and activity of inflammatory cells, we investigated SCGF expression using samples derived from RA patients and controls.

Methods: SCGF level is measured using sandwich ELISA methods with synovial fluid and serum derived from RA patients and controls. SCGF expression in synovial tissue is evaluated by immunohistochemistry using anti-SCGF antibody. SCGF localization in synovial tissue is evaluated with confocal microscopy using anti-SCGF antibody and anti-von Willebrand factor (vWF) antibody (a marker for endothelial cells). SCGF expression in endothelial cells is evaluated using HUVEC cell and EA.hy926 cells by quantitative PCR and immunocytostaining.

Results: SCGF levels in RA synovial fluid (n=25) were significantly elevated compared to SCGF levels in osteoarthritis synovial fluid (n=25) (RA 9.4±1.6 vs OA 4.6±0.9 ng/ml, p<0.01). However there was no difference in SCGF levels in serum from RA patients and healthy controls. Immunohistochemical analyses demonstrated that SCGF is highly expressed in the endothelium of synovial tissues derived from RA patients. Confocal microscopy demonstrated SCGF positive cells are colocalized with vWF positive cells. Immunocytostaining with anti-SCGF antibody detected SCGF from various types of endothelial cells, such as HUVECs and EA.hy926 cells. LPS increased CLEC11A mRNA in EA.hy926 cells.

Conclusion: Our results suggest that SCGF expression is associated with rheumatoid arthritis. SCGF is locally produced by endothelial cells in RA synovial tissue. Inflammation promotes SCGF expression in endothelial cells. SCGF might be involved in immune cell survival and differentiation in peripheral inflammatory tissue. Studies are underway to investigate the pro-inflammatory role of SCGF in RA.

Disclosure: Y. J. Woo, None; Y. A. Baik, None; Y. B. Park, None; S. K. Lee, None; W. H. Robinson, None; J. J. Song, None.

1458

Functional Phenotype of Synovial Monocytes Modulating Inflammatory T-Cell Response in Rheumatoid Arthritis. Seong-Wook Kang1, Seung-Chul Shim2, Jinhyun Kim1, In-Seol Yoo3, Su-Jin Yoo4, Seung-Taek Song3, Bo-Ruem Yoon1 and Won-Woo Lee1. 1Chungnam National University School of Medicine, Daejeon, South Korea, 2Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Monocytes function as crucial innate effectors during inflammation. Human monocytes can be divided into three distinct subsets based on CD14 and CD16 expression. Accumulating evidences suggest that three monocyte subsets have distinct functions in inflammatory responses. Here we investigated the characteristics of monocytes in synovial fluid (SF) of rheumatoid arthritis (RA) patients.

Methods: Monocytes and T cells were separated from the peripheral blood (PB) and SF obtained from patients with RA and analyzed by using flow cytometry. For global transcriptome analysis of pathogenic monocytes in RA, we performed a microarray analysis of SF and PB monocytes from the same RA patients and PB monocytes of healthy control (HC).

Results: CD16 expression on CD14++ monocytes in the SF was significantly increased compared with that in the PB of RA patients and HC. Microarray data showed that 3,134 genes were differentially expressed in SF monocytes compared with PB monocytes from RA and HC. Among the genes, CD80 and CD276 expression were significantly elevated on SF monocytes, while PB monocytes of RA and HC did not express both of them without stimulation. CD80 and CD276 were markedly elevated by IFN-γ and GM-CSF, respectively. In vitro assay, SF monocytes were found to significantly promote Th17 and Th1 responses, compared with PB monocytes of RA patients.

Conclusion: Our findings suggest the possible role for cytokine milieu of the synovial fluid in giving unique features to SF monocytes and their cardinal roles in affecting inflammatory T-cell response in RA.

Disclosure: S. W. Kang, None; S. C. Shim, None; J. Kim, None; I. S. Yoo, None; S. J. Yoo, None; S. T. Song, None; B. R. Yoon, None; W. W. Lee, None.

1459

IL-22 Secreted By NKP44+NK Cells Promote the Proliferation of Synovium in Patients with Rheumatoid Arthritis By Activation of STAT3. Juong Zhu1, Juan Li2 and Xiaoqiang Chen2. 1Nanfang Hospital, College of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China, 2School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, China.

Background/Purpose: Although CD3+CD56+NKP44+ natural killer cells (NKP44+NK cells) have been linked to autoimmune diseases including inflammatory bowel disease,ankylosing spondylitis, and primary Sjogren’s syndrome, the expansion and role of those cells in rheumatoid arthritis (RA) remain less defined. Here, we investigate the proportion of NKP44+NK cells in RA patients and examine whether those cells play a role in the pathogenesis of RA.

Methods: The frequency of NKP44+NK cells using flow cytometric analysis in peripheral blood (PB) or synovial fluid (SF) and their association with disease activity were examined in RA patients and controls. The expansion of those cells in RA and OA synovial tissues was also detected by dual-labeling immunofluorescence. And then, the concentration of IL-22 secreted by NKP44+NK cells was examined by Enzyme-linked immunosorbent assay. Eventually, the proliferation of fibroblast-like synovioctyes (FLS) and detection of IL-22-dependent signal pathway were examined by methyl thiazolylation tetrazolium and western blot analysis respectively after the treatment of NKP44+NK cells culture supernant, IL-22 antagonist, recombiant human (rh) IL-22 or a selective signalling pathways inhibitor (AG490).

Results: When compared with controls, NKP44+NK cells significantly expanded in RA PB (3.1±2.4% vs 0.5±0.8%; p<0.001) and SF (7.1±4.2% vs 0.9±1.2%; p<0.001), which were correlated positively with disease activity score in 28 joints and clinical disease activity index (p<0.001). Those cells also highly expressed in RA synovial tissues, but were not detected in
OA synovial tissues. It provided a source of IL-22 with high concentrations (582.5±284.2pg/ml). Further, NK p44+/NK cells culture supernatant promoted the proliferation of FLS which was blocked by IL-22 antagonist. Treated with rIL-22, the proliferation and phosphorylation-STAT3 on RA-FLS increased in a dose dependent manner and time dependent manner respectively, the progress of which could be blocked by AG490.

**Conclusion:** The present study clarifies the expansion of NKp44+/NK cells in the PB and SF of RA patients, especially in the synovial tissues of RA for the first time. STAT3 is an essential pathway in mediating the effects of IL-22 secreted by NKp44+ cells on the proliferation of synovium in patients with RA.

Disclosure: J. Zhu, None; J. Li, None; X. Chen, None.

1460

*Midkine, a Growth Factor, May Play a Pathophysiological Role in Patients with Rheumatoid Arthritis.* Emiko Shindo, Tomoko Hasunuma, Shotaro Masuoka, Mai Kawazoie, Hiroshi Sato, Natsuki Fujio, Kotaro Shikano, Makoto Keburaki, Sei Murakowa, Nakoh Tanka, Kaichi K aneko, Tatsuhiro Yamamoto, Kenji Takagi, Natsuko Kusunoki and Shinichi Karwai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

**Background/Purpose:** Midkine (MK) is known as a heparin-binding growth factor. Recent studies revealed that MK has various functions such as cell proliferation, differentiation, and apoptosis in various cells. Its pathological role is noted in various diseases, especially in solid tumor, such as Wilms tumor, liver cell cancer, and neuroblastoma. High level of serum MK is reported in these cancer patients who have poor prognosis. On the other hand, we reported in the last ACR meeting that high level of serum MK is correlates with several clinical markers of RA. Moreover, expression of MK protein and mRNA was examined in RA synovial tissue and/or RA synovial fibroblasts (RSFs).

**Methods:** Serum samples were obtained from 146 RA patients (female: male = 121:25, average age ± SD: 61.0 ± 1.2 y.o.) and 85 healthy controls (female: male = 83:8, 63.2 ± 1.3 y.o.). MK concentration was measured by Human Midkine ELISA kit using a monoclonal antibody against MK (Cellmid, M erborne, Australia). Clinical parameters for RA, such as serum CRP, ESR, rheumatoid factor (RF), MMP-3, DAS28-ESR, patient and doctor scores, and Sharp score were also examined. Statistical analysis was conducted by Statflex v6.0. Immunohistochemical analysis was performed using RA synovial tissue, which was obtained at the time of knee replacement surgery. Cultured RSFs separated from RA synovial tissue were stimulated with interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α) or dexamethasone for 18 hours, then culture medium was collected for measuring MK protein and mRNA was extracted from RSFs. RT-PCR of MK was performed by standard methods.

**Results:** Serum MK level was significantly increased in RA patients compared with that of healthy controls (average value ± SD: 157.4±13.7 and 69.64±3.0 pm/ml, respectively) by Mann-Whitney U test (P < 0.0001). ESR, RF, MMP-3, DAS28-ESR, patient VAS, doctor VAS, and HAQ, Sharp score were correlated with MK values by univariate analysis. Multiple linear regression analysis showed that MK level was positively correlated with CRP and RF (P = 0.00012 and P < 0.00001, respectively), but not with MMP-3, DAS28-ESR, HAQ, and Sharp score. Immunohistochemical analysis showed that MK was stained in lining layer of RA synovial tissues. MK mRNA in RSFs and MK protein in the culture medium of RSFs were detectable, however, their expression levels were not changed by addition of IL-1β, TNF-α, or dexamethasone.

**Conclusion:** In this study, MK was significantly increased in serum of RA patients, and its level was correlated with several clinical markers of RA. In addition, MK protein and mRNA were detected in RA synovial lining layer and/or cultured RSFs. It might be possible that MK has a pathophysiological role in RA development.

Disclosure: E. Shindo, None; T. Hasunuma, None; S. Masuoka, None; M. Kawazoie, None; H. Sato, None; N. Fujio, None; K. Shikano, None; M. Keburaki, None; S. Murakowa, None; N. Tanaka, None; K. K aneko, None; T. Yamamoto, None; K. Takagi, None; N. Kusunoki, None; S. Kawai, None.

1461


**Background/Purpose:** Cadherin-11 (CDH11) is a cadherin adhesion molecule that anchors b-catenin, and is involved with various functions of synovial fibroblast cells (SFCs) during the development of rheumatoid arthritis (RA). However, the functional mechanism of CDH11 during RA-SFC proliferation is unclear. The aim of our study was to clarify the involvement of CDH11 and b-catenin signaling during human RA-SFC proliferation.

**Methods:** In order to investigate the involvement of CDH11 and b-catenin to proliferation, BrdU incorporation assay with each siRNA treatment was carried out. The effect of knockdown was determined by western blotting and immunohistochemistry. The values of Emax and EC50 in proliferation were calculated by regression analysis with GraphPad Prism.

**Results:** Using CDH11 specific siRNAs, there were a 42% reduction in IL-1b-induced human RA-SFC proliferation and a 64% reduction in b-catenin protein levels. When b-catenin specific siRNAs were applied, there was a 63% reduction in IL-1b-induced RA-SFC proliferation. The Emax values for IL-1b during RA-SFC proliferation via CDH11-mediated b-catenin-dependent, total b-catenin-dependent, and b-catenin-independent signaling were 0.0015, 0.016, and 0.18 ng/ml, respectively. Blocking homophilic CDH11 ligation with a CDH11 neutralizing antibody did not decrease IL-1b-induced RA-SFC proliferation.

**Conclusion:** CDH11-mediated b-catenin signaling was 42% involved in IL-1b-induced human RA-SFC proliferation and had the highest susceptibility to IL-1b. The mode of action for CDH11 during the cell proliferation was likely associated with a pool of b-catenin protein. In contrast to IL-1b, CDH11 and b-catenin were not involved in TNF-a-induced RA-SFC proliferation.

Disclosure: R. Yoshioka, None; Y. Kita, None; A. Nagahira, None; A. Manno, None; N. Maki ta, None; U. Tomita, None; M. Murakawa, None.

1462

**Cadherin-11 mRNA Expression in the Peripheral Blood of Rheumatoid Arthritis Patients As a Marker of Active Polyarthritis.** Petros P. Sfikakis1, Panagiotis F. Christopoulos2, Aristedis G. Vaioopoulos3, Kalliope Fragkiadaki4, Christina Katsianis5, Violeta Kapsimali2, George Laliotis2, Panagiotis Panayiotidis5, Pinelopi Korkopoulou5 and Michael Koutsilieris2.

1First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece. 2Department of Pathology, Athens University Medical School, Athens, Greece, 3School of Health Sciences, University of Thessaly, Larissa, Greece. 4Department of Microbiology, Athens University Medical School, Athens, Greece. 5Department of Pathology, Athens University Medical School, Athens, Greece.

**Background/Purpose:** Human rheumatoid arthritis synovial fibroblasts (RASF) implanted subcutaneously in immunodeficient mice trans-migrate through the vasculature and drive the progression from oligo- to poly-articular disease. On the other hand, RASFs overexpress the mesenchymal cadherin-11, an adhesion molecule involved in tumor invasion and metastasis and cadherin-11 therapeutics prevent and reduce experimental arthritis. We tested the hypothesis that aberrant expression of cadherin-11, deriving from possibly circulating RASFs with pathogenic potential, can be identified in the peripheral blood of patients with active RA.

**Methods:** Cadherin-11 mRNA was quantified by real-time reverse transcription-PCR in peripheral blood (3ml) from 100 consecutive RA patients (15 studied serially) and 70 healthy controls. Western blotting and flow cytometry were performed in synovial fluid and peripheral blood using an anti-cadherin-11 antibody that decorated RASFs in synovial tissue's immunohistochemistry.

**Results:** Cadherin-11 mRNA was detected in 69.2% of moderately or severely active disease, versus 31.8% of patients with low disease activity or clinical remission (p = 0.001), versus 17.1% of healthy controls (p = 0.0001). Repeated measurements after 2–4 months confirmed these findings. Disease duration was significantly longer in cadherin-11 positive versus negative patients, whereas rheumatoid factor, ESR, CRP levels and treatment modalities were comparable. Notably, among patients with established RA (disease duration longer than one year) cadherin-11 mRNA was detectable in 88.4% of those with active polyarthritis (5 or more tender and swollen joints at the
time of sampling) versus 48.3% in those with oligo- or monarthritids (p<0.0001). Western blotting experiments were not sensitive enough to reveal cadherin-11 expression at the protein level in either synovial fluid or peripheral blood samples. However, rare cells expressing surface cadherin-11, together or not, with the pan-hematopoietic marker CD45 were consistently present in RA-derived synovial fluid. Such rare cells were also identified in peripheral blood from 5/6 versus 1/6 patients with established or early, respectively, poly-arthritic RA.

**Conclusion:** Cadherin-11 mRNA transcripts in the peripheral blood may serve as the first biomarker of active polyarthritis in established RA. Rare circulating cells expressing surface cadherin-11 in patients with RA could possibly represent macrophages and RASFs; the latter could enter the circulation as the synovium transforms into an hyperplastic, invasive tissue with new vessel formation. Taken together, these data further identify cadherin-11 as a potential therapeutic target in RA.

Disclosure: P. P. Sfikakis None; P. F. Christopoulos None; A. G. Valiopoulo None; K. Fragiadaki None; C. Katsaris None; V. Kapsimali None; G. Lallas None; P. Panayiotidis None; P. Korkopoulou None; M. Koutibilis None.

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Dickkopf-1 Perpetuated Synovial Fibroblast Activation and Synovial Angiogenesis in Rheumatoid Arthritis. Li Zheng, Fanlei Hu, Yingli Li, Lianjie Shi, Xiaoxu Ma, Xuewu Zhang and Zhanguo Li. Peking University People’s Hospital, Beijing, China.

**Background/Purpose:** Dkk-1, a master regulator of joint remodeling, is elevated and leads to bone resorption in patients with RA. This study aimed to investigate the contribution of Dkk-1 to synovial inflammation and synovial fibroblasts-mediated angiogenesis in RA.

**Methods:** Dkk-1 concentration in synovial fluids from RA and osteoarthritids (OA) patients was evaluated by ELISA. The expression of Dkk-1 in RA synovial fibroblasts (RASF) and OA-SF was compared by real-time PCR and ELISA. RASF were stimulated with different pro-inflammatory factors and the expression of Dkk-1 was determined by real-time PCR and ELISA. The expression of angiogenic factors (MCP-1, SDF-1, VEGF, ADAM-10 and CD147), pro-inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β), and MMPs (MMP-1, MMP-3 and MMP-9) in RASF was determined by real-time PCR when Dkk-1 was silenced. Matrigel tube formation was evaluated by Western blot when it was silenced. Such rare cells were also identified in peripheral blood from 5/6 versus 1/6 patients with established or early, respectively, poly-articular RA.

**Conclusion:** Dkk-1, a master regulator of joint remodeling, is elevated and leads to bone resorption in patients with RA. This study aimed to investigate the contribution of Dkk-1 to synovial inflammation and synovial fibroblasts-mediated angiogenesis in RA. Dickkopf-1 concentration in synovial fluids from RA and osteoarthritids (OA) patients was evaluated by ELISA. The expression of Dkk-1 in RA synovial fibroblasts (RASF) and OA-SF was compared by real-time PCR and ELISA. RASF were stimulated with different pro-inflammatory factors and the expression of Dkk-1 was determined by real-time PCR and ELISA. The expression of angiogenic factors (MCP-1, SDF-1, VEGF, ADAM-10 and CD147), pro-inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β), and MMPs (MMP-1, MMP-3 and MMP-9) in RASF was determined by real-time PCR when Dkk-1 was knocked down or overexpressed. Meanwhile, the levels of MCP-1, IL-6, IL-8, and MMP-3 in the cell culture supernatants were determined by ELISA. The effects of Dkk-1 on the MAPK signaling pathway was evaluated by Western blot when it was silenced. Matriplle tube formation assay was employed to reveal the direct and indirect effect of Dkk-1 on synovial angiogenesis.

**Results:** Levels of Dkk-1 in synovial fluids and synovial fibroblasts were elevated in RA patients. The secretion of Dkk-1 was accelerated by various pro-inflammatory cytokines in RASF, including TNF-α, IL-1β, INF-y and IL-18. Dkk-1 stimulated the production of potent angiogenic factors, pro-inflammatory cytokines and MMPs in RASF, while silencing Dkk-1 expression suppressed such factor expression. Silencing Dkk-1 in RASF dampened its mediated capillary tube organization both in direct and indirect manners, accompanied with restrained ERK, JNK, and p38 signaling pathway activation.

**Conclusion:** Dkk-1 exacerbated synovial fibroblasts-mediated inflammation, cartilage erosion, and angiogenesis in RA. Targeting Dkk-1 might provide novel therapeutic strategy for overcoming the persistent disease.

Disclosure: L. Zheng None; F. Hu None; Y. Li None; L. Shi None; X. Ma None; Z. Li None.

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Numbers of Circulating CD4 Positive CD28null T Cells Are Increased in Patients with Rheumatoid Arthritis and Are Associated with Rheumatoid Factor Positivity but Not Subclinical Cardiovascular Disease. Sarah Skeoch1, John Waterton2, Y vonne Alexander3 and Ian N. Bruce.4,1Arthritis Research UK Centre for Epidemiology and NIHR M anchester M usculoskeletal Biomedical Research Unit, M anchester A cademic Health Science Centre, The University of M anchester, M anchester, United Kingdom; 2University of M anchester, M anchester, United Kingdom; 3M anchester M etropolitan Universi ty, M anchester, United Kingdom; 4Arthritis Research UK Centre for Epidemiology, Centre for M usculoskeletal Research, Institute of Inflammation and repair, M anchester A cademic Health Science Centre, The University of M anchester, M anchester, United Kingdom.

**Background/Purpose:** CD4+ T cells which lack CD28 co-expression (CD28null cells) account for less than 2.5% of CD4+ T cells in healthy individuals. These cells are pro-inflammatory, resistant to apoptosis and have cytolytic properties. Increased circulating numbers are found in some RA patients and their presence is associated with extra-articular disease. In unstable angina patients, CD28null cells are independently associated with recurrent cardiac events and are thought to promote athero-sclerotic plaque rupture. The aims of the current study were to quantify CD28null cells in RA patients and to investigate the association with RA disease characteristics and subclinical cardiovascular disease.

**Methods:** RA patients with active arthritis, who were not taking a statin, were recruited to a prospective observational study. Clinical and serological evaluation of RA disease characteristics was undertaken including extra-articular involvement, the disease activity score 28 score (DAS-28) and the health assessment questionnaire (HAQ). Presence of carotid plaque was evaluated using B-mode doppler ultrasound. Plaque was defined as 2 or more of: intima-media thickness ≥1.5mm, luminal protrusion, increased wall echogenicity.

CD28null cells were quantified using flow cytometry. In brief, fluorescently labelled CD45, CD28 and CD4 antibodies were added to whole blood. Following red cell lysis, flow cytometry was used to measure the proportion of CD45+CD28+ lymphocytes which lacked CD28 expression. Presence of an expanded CD28null cell population was defined as >2.5% of CD45+CD28+ T cells lacking CD28 expression. Descriptive and non-parametric statistics were used to analyse the data.

**Results:** 91 RA patients were included in the study and 68 (74.2%) were female. Median (IQR) age and disease duration was 56(48, 62) and 9(4, 19) years respectively. 64 patients (70.3%) were rheumatoid factor positive and 74 patients (81.3%) were ACPA positive. 1 patient had a history of clinical cardiovascular disease.

Expanded CD28null cell populations were found in 28 patients (30.8%). Presence of CD28null cells was associated with rheumatoid factor positivity (p<0.02) but not with ACPA positivity. No association was found with age, disease activity, HAQ, biologic use, extra-articular disease or with carotid plaque.

**Conclusion:** The current study confirms that this abnormal T cell subset is expanded in a significant proportion of RA patients. There was no association between CD28null cells and carotid plaque but these cells may contribute to plaque destabilisation and rupture rather than plaque development. Prospective evaluation of cardiovascular outcomes in this population is underway.

Disclosure: S. Skeoch None; J. Waterton None; Y. Alexander None; I. N. Bruce None.
via flow cytometry. Pearson correlation coefficient was determined in the analysis of correlation between IL-21R expression and clinic parameters.

**Results:** ICOS* CXCR5+ Tfh cells were identified in peripheral blood of RA patients. These circulating Tfh cells are the dominant T cell subset producing IL-21. We found that Tfh cells were significantly elevated in RA patients with moderate/high disease activity (P<0.05). IL-21R was expressed on naive B cells, germinal center B cells, and plasma cells in tonsillar lymphoid follicles. As compared to healthy donors, the level of IL-21R expression on naive B cells, pre-plasma cells, and T cells was significantly elevated in peripheral blood of RA patients and correlated with disease activity.

**Conclusion:** RA patients with moderate/high disease activity have elevated levels of IL-21 expression on Tfh cells and IL-21R expression on B cell subsets, similar to that seen in tonsillar lymphoid follicles. Our results indicate that IL-21R/IL-21 pathway is involved in RA pathogenesis. Interruption of IL-21R/IL-21R interaction may be a potential therapeutic target for RA patients.

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**Patients with Active Rheumatoid Arthritis Display an Expanded Population of GM-CSF Expressing Peripheral B Cells.** Sofia Adamidi, A nastasia M. Akris, Christos Koutsianas, Christina Tsalapaki, Emilia Hadziyannis and Dimitrios Vassilopoulos. University of Athens Medical School, Athens, Greece.

**Background/Purpose:** GM-CSF has been implicated in rheumatoid arthritis (RA) pathogenesis and is being investigated as a novel therapeutic target. B cells secreting GM-CSF have been recently reported to participate in innate immune responses in animal models. The aim of our study was to determine the expression of GM-CSF secreting peripheral B cells in RA patients.

**Methods:** 23 patients with RA (fulfilling the 2010 ACR/EULAR RA Classification Criteria), 11 disease controls (psoriatic arthritis n=4, osteoarthritis n=3, ANCA-associated vasculitides n=2, Sjogren’s syndrome n=1, giant cell arthritis n=1) and 10 healthy controls were included in the study. Peripheral blood mononuclear cells (PBMC) were stimulated overnight with Phorbol Myristate Acetate (PMA) and ionomycin in the presence of Brefeldin. Cells were then stained with specific antibodies against surface CD19 and intracellular GM-CSF (BioLegend). Positive cells were quantified by flow cytometry (Partec) and compared between the different groups.

**Results:** 23 RA patients with moderate to high disease activity not receiving anti-rheumatic drugs (females/males=19/4, DAS28-CRP=5.53 ± 0.84, median disease duration=14 months, RF and/or anti-CCP+=52%) were studied. The % of peripheral B cells (CD19+) was similar between the RA and the 2 control groups (6.9 ± 3.9% vs. 6.3 ± 3.5% vs.8.4 ± 1.9%, p=0.31). We detected an expanded population of peripheral CD19GM-CSF+ cells in RA patients (4.4 ± 2.6%) compared to healthy (1.1 ± 1.5%, p=0.0002) and healthy (0.2 ± 0.2%, p=0.0000002) controls while there was no difference between disease and healthy controls (p=0.512). Similarly, we did not observe any difference between seropositive (RF and/or anti-CCP+) and seronegative (4.8 ± 2.5%, p=0.347) patients. GM-CSF + B cell expression did not correlate with RA disease activity measured by DAS28 (r=0.926, Spearman correlation).

**Conclusion:** Our study shows for the first time an expanded population of peripheral B cells expressing GM-CSF among patients with active RA compared to patients with other inflammatory or non-inflammatory rheumatic diseases and healthy controls. The functional significance of this cell population remains to be determined.

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**Do G-CSF and Neutrophils Contribute to the Pathophysiology of Rheumatoid Arthritis?** Gabrielle Goldberg1, Simon Chatfield2, Jane Murphy1, Ee Shan Pang3, Yunnun Chen3, Gordon Smyth1, Milica Ng3, Michael Wilson1, Clare O’Neill1, Samantha Busfield3, Arna Andrews3 and Ian P. Wicks1, CSL Limited, 2; C. O’Neill, None; S. Busfield, CSL Limited, 3; A. Andrews, CSL Limited, 3; I. P. Wicks, CSL Limited, 2.

**Background/Purpose:** AA amyloidosis is a serious complication of chronic inflammatory and infectious diseases resulting from the deposition of amyloid A protein. Serum amyloid A (SAA), a precursor molecule of AA protein produced in hepatocyte, is deposited in various organs as amyloid fibril during the development of AA amyloidosis. Proinflammatory cytokines, especially IL-6, play a key role in SAA production.

**Methods:** 1. The expression of SAA mRNA in hepatoma-derived cells treated by cytokines (IL-6, IL-1, TNF-a) with or without their inhibitors was examined by quantitative real-time PCR. Luciferase assay, EMSA and Chip assay were also used for analysis of SAA transcription mechanism.

2. Clinical effects of IL-6 blockade on amyloidosis-related parameters including serum SAA, urinary protein and RA disease activity were evaluated in AA amyloidosis patients with RA. Scores of amyloid deposits in gastro-duodenal mucosal biopsy specimens were examined by histopathological staining and protein quantitative ELISA.

**Results:** 1. Our results proved that IL-6 plays a critical role in cytokine-driven SAA expression through STAT3 activation. TNF-a/IL-1 componentally contributes to the synergistic induction of the triple-cytokines-induced SAA gene through NF-kB activation. We further found that a novel STAT3 non-consensus TFBS at the immediate downstream of the NF-kB RE in the SAA1 promoter region that is required for NF-kB p65 and STAT3 to activate SAA1 transcription. In addition, the synergistic induction of SAA expression by cytokines combination was completely inhibited by tocilizumab but not by TNF-a or IL-1 inhibitor.

2. AA amyloidosis with RA patients treated with tocilizumab showed significant improvements in disease activity, and reductions in serum SAA and urinary protein levels, and these effects were more pronounced in the tocilizumab group than in the TNF-a inhibitors group at 12 months after initiation of the treatment. Meanwhile, histological scores of AA deposition observed in gastroduodenal mucosal biopsy specimens treated with tocilizumab showed significantly decreased in the area and concentration of amyloid deposits after the treatment.
Conclusion: Although activated NF-kB by IL-1 and TNF-a is also involved in hepatic production during inflammation, IL-6-activated STAT3 plays a key role in SAA regulation. Our clinical results with IL-6 blockade therapy suggest that the pathogenic cascade causing AA amyloidosis started from SAA induction by IL-6, so that IL-6 blockade constitutes a promising molecular targeting therapy for AA amyloidosis.


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Methotrexate Treatment Reduces Serum IL-6 Level By Decreasing a CD14brightCD16+ Intermediate Non-Classical Subset of Monocytes in RA Patients. Masako Tsukamoto1, Keko Yoshimoto1, Noriyuki Seta2, Katsuya Suzuki2 and Tsutomu Takeuchi2, 1, 2

Background/Purpose: It is well known that circulating monocytes are the source of inflammatory cytokines, such as IL-6 and TNFα, and newly divided into three subsets based on the expression levels of CD14 and CD16. We have previously reported that plasma IL-6 level was decreased in RA patients with clinically significant improvement after MTX treatment, but a detailed mechanism is not clearly clarified. The purpose of this study is to investigate the association between these three subsets of monocytes and change of serum IL-6 level after MTX treatment.

Methods: 33 RA patients fulfilled the 2010 ACR/EULAR RA Classification Criteria and 15 healthy donors (HD) were enrolled in this study. The patients had never been received a treatment with DMARDs or biological agents and had moderate disease activity or more (DAS28-ESR ≥ 3.2). Peripheral blood samples and clinical records of the patients were obtained at the time of 0 and 12 weeks after MTX treatment. Peripheral blood samples were also obtained HD. The expression levels of CD14 and CD16 on monocytes and serum levels of cytokines were measured by flow cytometric (FACS) analysis and multiplex electrochemiluminescence assays on the Meso Scale Discovery SECTOR Imager 2400 platform®, respectively. A decrease in DAS28-ESR of 1.2 or more was defined as a clinically significant improvement after MTX treatment.

Results: The mean DAS28-ESR score of the patients was 4.8 ± 0.8. There was no significant difference in clinical backgrounds between RA patients with and without improvement. Serum levels of IL-6, IL-8 and IL-10 at baseline were significantly higher in RA patients compared with HD. Only IL-6 significantly decreased in RA patients with improvement after MTX treatment. FACS analysis revealed that the proportion of CD14brightCD16+ monocytes was significantly decreased in RA patients at baseline (13.9 ± 6.9%) compared with HD (7.3 ± 2.1%) (p=0.01). After MTX therapy, the proportion of CD14brightCD16+ monocytes was significantly decreased (14.0 ± 6.5% vs. 9.3 ± 5.0%, p<0.01) in RA patients with improvement, but not in those without (p=0.3). Moreover, the proportion of CD14brightCD16+ monocytes were significantly correlated with serum IL-6 level and DAS28-ESR (p=0.01 and p<0.01) in RA patients.

Conclusion: These results indicate that CD14brightCD16+ intermediate non-classical monocytes possibly play an important role in the pathogenesis of RA by producing IL-6 and the curative effect of MTX may be demonstrated through the reduction of CD14brightCD16+ monocytes in peripheral blood.


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Malondialdehyde-Acetaldehyde Adducts (MAA) and Anti-Malondialdehyde-Acetaldehyde Antibody in Rheumatoid Arthritis. Geoffrey Thiele1, Michael J. Dureye2, Daniel Anderson3, Lynell W. Klassen4, Stephen M. Oettinger5, Katherine Y. Young6, Table Benissan-Messan2, Harlan Sayles2, Jeremy Sokolove2, William H. Robinson3,1, James O. Delle1, Anthony Nicholas1 and Ted R. Mikuls1, 1

OMAHA VA Medical Center, Omaha, NE, 2University of Nebraska Medical Center, Omaha, NE, 3VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, 4VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, 5University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Products of oxidative stress, MAA adducts are highly immunogenic and have been associated with tolerance loss. To examine their potential role in disease-related inflammation, we investigated the presence of MAA adducts and circulating anti-MAA antibody in RA and their relationship with citrullinated proteins and anti-citrullinated protein antibody (ACPA).

Methods: Synovial tissues from RA and OA patients were examined for the presence of MAA-modified and citrullinated proteins. An anti-MAA antibody isotypes were measured in RA cases (n=1720) and healthy controls (n=1720) by ELISA. A specific ACPA was measured in RA cases using a multiplex antigen array. Anti-MAA antibody isotype (IgG, IgM, and IgA) concentrations were compared in a subset of cases (n=80) and controls (n=80). Matched based on age, gender, race, and smoking status. Associations of anti-MAA antibody isotypes with disease characteristics, including ACPA, were examined in all RA cases.

Results: MAA-adducted and citrullinated proteins were detected and shown to co-localize in RA synovial tissues (Fig. 1). In contrast, MAA adducts were present in negligible quantity while citrullinated proteins were absent in OA synovial tissue. All anti-MAA antibody isotypes were markedly increased in RA cases vs. controls (p<0.001). Among RA cases, anti-MAA antibody isotypes were associated with anti-CCP antibody and RF positivity (p<0.001) in addition to select measures of disease activity. Higher anti-MAA antibody concentrations were associated with a higher number of antigen-specific ACPA analytes positive in high titer (p<0.001) and a higher ACPA score (p<0.001), defined as the sum of normalized fluorescence values divided by the number of analytes examined (Fig. 2). Associations of anti-MAA antibody isotypes with ACPA score and the number of analytes positive were independent of other covariates.

Conclusion: This is the first study to show that MAA adduct formation is increased in RA and appears to result in robust antibody responses that are strongly associated with ACPA. These results suggest speculation that MAA adduct formation may be a cause that drives tolerance loss resulting in the autoimmune responses characteristic of RA.

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TNFα Influences the Status of B and T Cells By Acting on BCR and TCR Pathways Via RasGRP1 and RasGRP3 Proteins. Marie-Laure Golinski1, Martine Hiron2, Céline Derambure2, Clément Guillou2,2, Manuel Frérot4, Olivier Boyer5, Olivier Vittecoq2 and Thierry Lequerre5. 1Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, 2Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, 3Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, 4Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, 5Chu De Rouen, Rouen, France.
Background/Purpose: Rheumatoid arthritis (RA) is the most common inflammatory arthritis. B and T cells play a key role in the RA pathophysiology. RasGRP is a member of the CDC25 family of Ras guanyl nucleotide exchange factors. RasGRP1 is expressed in T and B cells whereas RasGRP3 is only expressed in B cells. In previous studies, we have shown that RasGRP3 gene expression level significantly decreased in peripheral blood mononuclear cells from RA patients responders to adalimumab and etanercept (anti-TNFa drugs), leading to the question of TNFα involvement in RasGRP1 and RasGRP3 pathways. To study TNFα effects on RasGRP1 and RasGRP3 expression levels in vitro.

Methods: We measured, by qRT-PCR and western-blot, RasGRP1 and RasGRP3 expression levels in B and T cells isolated from buffy coat. In each condition, cells were cultured with or without TNFα for 24 or 48 hours. Cell proliferation was evaluated by [3H] thymidine incorporation. To investigate the TNFα implication on signaling pathways, MAPK and apoptosis protein arrays were used.

Results: In B cells, TNFα induced an increase of RasGRP1 and RasGRP3 gene expression levels without effect on B cells proliferation and BCR pathway phosphorylations, but apoptotic pathways were inhibited. In T cells, TNFα increased RasGRP1 gene expression level but RasGRP3 protein expression level decreased, inhibiting T cell proliferation and TCR pathway phosphorylations.

Conclusion: This study suggests a link, never described previously, between RasGRP1 or RasGRP3 and the TNFα effects on T and B cells. While the response to anti-TNFα treatments in RA patients modulates RasGRP3 gene expression, TNFα inhibits RasGRP1 protein expression leading to TCR pathway inhibition, in vitro, in pathophysiological condition. The better understanding of TNFα effects on RasGRP proteins could permit a better understanding of the mechanisms of action of TNFα blocking agents on T and B cells.

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Synovial Fluid from Rheumatoid Arthritis Patients Modulates the Immunophenotype and Viability of Monocytes. Maria Sole Chimenti, Alberto Bergamini, Eleonora Baffari, Eleonora Ballanti, Alessia Musto, Paola Consiglio and Roberto Perricone. Department of "Medicina dei Sistemi", University of Rome "Tor Vergata", Rome, Italy.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by infiltration of the synovium by inflammatory cells that destroys the cartilage and the bone adjacent to the joint. The thickened synovium, called pannus, causes swelling of the joint with excess of synovial fluid (SF) production. A large number of proteins involved in inflammation and immune response have been identified in SF from RA patients (SF-RA). The aim of this study was to determine the effects of synovial fluids (SF) from RA patients (SF-RA) on surface phenotype, co-stimulatory activity, viability and cytokine production of monocytes, as a model for the interaction between SF and synovial tissue macrophages in RA.

Methods: Purified monocytes from healthy donors were incubated with individual specimens of SF-RA obtained from twelve RA patients with active disease, and then analyzed by flow cytometry for ILT4 and CD86 expression, co-stimulatory ability, rate of spontaneous apoptosis and TNFα production, with or without TNFα. Comparative analysis was carried out with serum from RA patients and medium alone.

Results: Downmodulation of ILT4 and upmodulation of CD86 expression (Figure 1), together with increased ability to co-stimulate CD4+ T cells for IFNγ and TNFα production, was observed in monocytes incubated with SF-RA (SF-RA monocytes) compared with control cells, even under condition of activation by CD40L (Figure 2). A reduction of spontaneous apoptosis was observed in SF-RA monocytes compared to control cells. Adalimumab increased the rate of SF-RA monocytes apoptosis, whereas no significant influence of adalimumab was detected in control monocytes. The TNFα and IL1β response, but not that of IL-10, to LPS was greater in SF-RA monocytes compared with control cells (Figure 3).

Conclusion: Our findings suggest that soluble factors present in SF-RA could function as so-called damage-associated molecular patterns and contribute to increase the effectiveness intra-articular of the immune response and inflammation by increasing monocyte numbers and pro-inflammatory activity.

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Mancopet-Cy3 Localizes CD206 + Macrophages in Synovial Tissue and Fluid from Rheumatoid Arthritis Patients Differently Compared to Controls. Nicholas A. Young1, Larry Schlesinger2, Thomas J. Rosol1, Fred Cope1 and Wael N. Jarjour1. 1The Ohio State University Wexner Medical Center, Columbus, OH, 2The Ohio State University College of Medicine, Columbus, OH, 3The Ohio State University College of Veterinary Medicine, Columbus, OH, 4Navidea Biopharmaceuticals, Dublin, OH.

Background/Purpose: Early identification of rheumatoid arthritis (RA) would allow aggressive treatment with disease modifying rheumatic drugs and provide a system to monitor patient responses. Therefore, we developed a fluorescent agent (mancopt-Cy3) that targets C-type lectin mannose receptor (CD206) to provide a diagnostic imaging tool for RA. This receptor is expressed on macrophages, which contribute to RA pathology and are strongly implicated in autoimmunity. Mancopt-Cy3 follows work that was done in developing Technimim T1(manocept-Cy5), which is currently used in lymph node mapping of breast cancer patients. The aim of this study was to determine if this agent could detect these cells in synovial compartments of RA patients; thus providing the foundation to study its potential as an imaging biomarker in RA.

Methods: Rheumatoid arthritis and osteoarthritis (OA) patients, and healthy volunteers were recruited through approved institutional review board protocols. Synovial fluid was isolated and analyzed by flow cytometry. Synovial tissue was flash-frozen at the time of collection for immunohistochemical analysis and fluorescent imaging by microscopy. Tissue was incubated with DAPI nuclear stain, mancopt-Cy3, and/or anti-CD206 antibody. Slides were digitally scanned for image analysis to quantitate
manocyte-Cy3+ staining. To demonstrate the specificity, samples were stained with an isotype-matched control antibody for CD206 or pre-incubated with 10X unlabeled ("cold") manocyte.

**Results:** Fluorescence microscopy showed that manocyte-Cy3+/CD206+ cells were present at high levels in the synovial compartment of RA. These signals were co-localized along cellular membranes, and manocyte-Cy3+ staining was statistically significant when compared to OA patients and healthy controls, as measured by digital image analysis. Flow cytometry demonstrated similar levels of CD68, CD206, and manocyte-Cy3 in synovial fluid samples. No fluorescent signal was observed in RA synovial tissue incubated with CD206 isotype-matched antibody or with "cold" manocyte incubation prior to manocyte-Cy3 staining.

**Conclusion:** The identification of an imaging biomarker that is both sensitive and specific for the RA inflammatory process is critical in the diagnosis of patients with early joint symptoms and in monitoring therapeutic responses. Our results suggest that CD206-targeted manocyte is a viable candidate to pursue clinically as an imaging biomarker for RA.

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**Background/Purpose:** The presence of serum autoantibodies to peptidyl arginine deiminase 4 (PAD4) has been implicated as a risk factor for rheumatoid arthritis (RA). We have previously demonstrated that RA patients with PAD4 have more active and more severe disease, the latter reflected by the presence of more radiographic damage as assessed by the hands and wrists (Mikuls et al. Arthritis Rheumatol 2014). Moreover, we have shown that antigen-specific ACAP are overexpressed in those with PAD4, including ACAP implicated in osteoclastogenesis and bone damage that characterizes RA. The purpose of this study was to examine whether the presence of subgingival P. gingivalis was associated with increased bone turnover and to further explore the associations between bone turnover markers with RA-related autoantibody and joint damage.

**Methods:** RA patients (n=287) underwent a standardized full-mouth periodontal examination that included collection of subgingival plaque samples with the presence of P. gingivalis identified using PCR. Hand/wrist radiographs were scored using a modified Sharp score. Patients were tested for RF, anti-CCP, and anti-cit-vimentin antibody. Serum bone turnover biomarkers were measured by ELISA and included BAP (MicroVue), an indicator of bone formation; TRAP5b (MicroVue) and cathepsin-K (CTPK; Biomedical), the latter two biomarkers of bone resorption. The K ruskal-Wallis test was used to examine associations of bone biomarkers with the presence of P. gingivalis or PD. Spearman rank correlations were used to assess associations between these biomarkers with RA clinical measures.

**Results:** RA patients with subgingival P. gingivalis had significantly higher serum concentrations of TRAP5b (<0.001) and CTPK (p=0.003) compared to those without P. gingivalis (Table). CTPK, but not TRAP5b was higher in those with PAD4 vs. those without PAD4. There was no difference in the presence of subgingival PD or P. gingivalis status. TRAP5b demonstrated modest but statistically significant associations with modified Sharp score (r=0.16, p=0.001), anti-CCP (r=-0.26, p=0.001), and anti-cit-vimentin (r=0.14, p=0.02) while CTPK demonstrated associations with DAS-28- CRP (r=0.13, p=0.003), anti-CCP (r=0.17, p=0.005), anti-cit-vimentin (r=0.13, p=0.03), and RF (r=0.30, p<0.001).

**Conclusion:** Serum biomarkers of osteoclast mediated bone resorption, TRAP5b and CTPK, are elevated in RA patients harboring P. gingivalis infection, and are associated with disease-related autoantibody and joint damage. These results suggest that previously reported links between PD with greater RA disease severity may be related at least in part to oral infection with P. gingivalis with detrimental effects on bone that appear to be mediated by the increased osteoclast activity.

**Table:** Mean (SD) of bone turnover markers in patients with RA (n=287) based on presence/absence of subgingival P. gingivalis or PD; p-values generated using K ruskal-Wallis test

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**Disclosures:** I. Navarro-Millan, None; A. Westfall, None; E. Darrah, None; A. Rosen, None; T. R. Mikuls, Genentech/Roche; 2; R. Reynolds, NIAMS-NIH, 2; M. I. Danila, NIAMS-NIH, 2; J. R. Curtis, Roche, Genentech, UCB Pharma, Jansen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Jansen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; S. L. Bridges Jr., None.

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**1475 Porphyromonas Gingivalis and Bone Turnover Biomarkers in Rheumatoid Arthritis.** Manpreet Sethi1, Anand Dusad2, Harlan Sayles2, Geoffrey Thiele2, Jeffrey Payne3, Michael J. Duryee3, Bart Hamilton3 and Ted R. Mikuls4 University of Nebraska Medical Center, Omaha, NE, 5; Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, 4University of Nebraska Medical Center, Lincoln, NE, 3University of Nebraska Medical Center and University of Nebraska VA Medical Center, Omaha, NE, 3University of Nebraska Medical Center and University of Nebraska VA Medical Center, Omaha, NE, 2Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, 3

**Background/Purpose:** Periodontitis (PD) associated with P. gingivalis has been implicated as a risk factor for rheumatoid arthritis (RA). We have previously demonstrated that RA patients with PD have more active and more severe disease, the latter reflected by the presence of more radiographic damage as assessed by the hands and wrists (Mikuls et al. Arthritis Rheumatol 2014). Moreover, we have shown that antigen-specific ACAP are overexpressed in those with PAD4, including ACAP implicated in osteoclastogenesis and bone damage that characterizes RA. The purpose of this study was to examine whether the presence of subgingival P. gingivalis was associated with increased bone turnover and to further explore the associations between bone turnover markers with RA-related autoantibody and joint damage.

**Methods:** RA patients (n=287) underwent a standardized full-mouth periodontal examination that included collection of subgingival plaque samples with the presence of P. gingivalis identified using PCR. Hand/wrist radiographs were scored using a modified Sharp score. Patients were tested for RF, anti-CCP, and anti-cit-vimentin antibody. Serum bone turnover biomarkers were measured by ELISA and included BAP (MicroVue, an indicator of bone formation); TRAP5b (MicroVue) and cathepsin-K (CTPK; Biomedical), the latter two biomarkers of bone resorption. The K ruskal-Wallis test was used to examine associations of bone biomarkers with the presence of P. gingivalis or PD. Spearman rank correlations were used to assess associations between these biomarkers with RA clinical measures.

**Results:** RA patients with subgingival P. gingivalis had significantly higher serum concentrations of TRAP5b (<0.001) and CTPK (p=0.003) compared to those without P. gingivalis (Table). CTPK, but not TRAP5b was higher in those with PAD4 vs. those without PAD4. There was no difference in the presence of subgingival PD or P. gingivalis status. TRAP5b demonstrated modest but statistically significant associations with modified Sharp score (r=0.16, p=0.001), anti-CCP (r=-0.26, p=0.001), and anti-cit-vimentin (r=0.14, p=0.02) while CTPK demonstrated associations with DAS-28- CRP (r=0.13, p=0.003), anti-CCP (r=0.17, p=0.005), anti-cit-vimentin (r=0.13, p=0.03), and RF (r=0.30, p<0.001).

**Conclusion:** Serum biomarkers of osteoclast mediated bone resorption, TRAP5b and CTPK, are elevated in RA patients harboring P. gingivalis infection, and are associated with disease-related autoantibody and joint damage. These results suggest that previously reported links between PD with greater RA disease severity may be related at least in part to oral infection with P. gingivalis with detrimental effects on bone that appear to be mediated by the increased osteoclast activity.

**Table:** Mean (SD) of bone turnover markers in patients with RA (n=287) based on presence/absence of subgingival P. gingivalis or PD; p-values generated using K ruskal-Wallis test

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Background/Purpose: Indigenous North American populations have high prevalence of seropositive RA. The Caucasian/Iroquois population in Central Canada and the Alaskan Native population have a high prevalence of SE alleles, specifically DRB1*0404 and *1402. Presence of the SE with the non-SE allele (n = 58), a single copy of the SE (SE/X, n = 116), or two copies of the SE (SE/SE, n = 58). We similarly stratified subjects with two copies as homozygous (n = 56) or heterozygous (n = 22). Using a multiplex ACPA antigen array, we evaluated the depth of the ACPA response using an ACPA score (sum of all normalized ACPA titers divided by number of epitopes) and the breadth of the ACPA response by defining the total number of ACPA positive. We used significance analysis of microarrays to compare ACPA subtypes between different SE alleles.

Results: Those with one copy of the shared epitope had more ACPA than those with no copies of the SE and those with two copies displayed more ACPA than those with one copy. Among those with two copies of the SE, the highest levels were observed among subjects heterozygous for two different SE alleles compared to those with no copies of the SE (P < 0.01) and a trend toward higher levels in those with a single SE allele or homozygous for two copies of the same SE allele. Analysis of the predominant SE alleles within this population revealed a gradient of ACPA associations with *1402 positive patients demonstrating increased ACPA compared with all non-*1402 patients and more than the *0404 population. ACPA specificities increased among the *1402 patients included several citrullinated fibrinogen epitopes and citrullinated enolase. Subjects with the *0901 allele alone (X/0901) demonstrated no increase in ACPA and no additional contribution 0901 was noted in heterozygotes expressing a single copy of the SE and *0901.

Conclusion: We observed a stepwise increase in depth and breadth of the ACPA response with increasing dose of SE, an effect primarily seen among those heterozygous for two different SE alleles. These observations support reports suggesting that a heterozygous SE allele combination is associated with RA severity. Moreover, the prominence of the *1402 SE allele as a strong risk factor for an expanded ACPA response is intriguing considering the proposed protective effect of serine residues present in positions 11 and 13 of this allele. Exploration of the peptide binding capacity of this MHC molecule will be important in understanding how it may shape the ACPA response.

Disclosure: C. Sokolove, None; L. J. Lahey, None; C. Wagner, None; I. Smolik, None; D. B. Robinson, None; E. D. Ferucci, None; M. Newkirk, None; M. Fritzler, None; W. H. Robinson, None; H. El-Gabaly, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy: Novel therapies, Biosimilars, Strategies and Mechanisms in Rheumatoid Arthritis
Monday, November 17, 2014, 8:30 AM - 4:00 PM

1477
Overweight and Obesity Are Associated with Reduced Risk of Rheumatoid Arthritis in Men, but Not in Women.

Carol Turesson1, Ulf Bergström2, Mira Pikwer3, Jan-Åke Nilsson4 and Lennart Jacobsson5. 1Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, 2Lund University, Malmö, Sweden, 3Mälar Hospital, Eskilstuna, Sweden.

Background/Purpose: There are diverging results on the relation between body mass index (BMI) and risk of rheumatoid arthritis (RA). Several studies have reported different patterns in men and women. Our purpose was to investigate the impact of overweight and obesity on the risk of RA in a prospective study.

Methods: Between 1991 and 1996, 30447 subjects (12121 men; 18326 women) were included in a population based health survey. Height and weight were measured, and lifestyle factors were assessed using a questionnaire. From this population, we identified individuals who developed RA after inclusion by linkage to 4 different RA registers. In a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the health survey database. The impact of overweight or obesity (BMI > 25 kg/m²) compared to normal BMI (18.5–25 kg/m²) on the risk of RA was examined in conditional logistic regression models, stratified by sex.

Results: A total of 172 patients (36 men/136 women, mean age at RA diagnosis 63 years) were diagnosed with RA after inclusion in the health survey. The median time from inclusion to RA diagnosis was 5 years (range: 1–13). A total of 51% of cases and controls combined were overweight or obese. Being overweight or obese at inclusion in the health survey was associated with a reduced risk of subsequent development of RA in men [odds ratio (OR) 0.33; 95% confidence interval (CI) 0.14–0.76], but not in women (OR 1.01; 95% CI 0.65–1.54). Men who fulfilled the WHO definition for obesity (BMI >30 kg/m²) had a significantly decreased risk of RA compared to those with normal BMI (OR 0.08; 95% CI 0.01–0.67), and there was a similar trend for those with overweight (BMI 25–30 kg/m²) (OR 0.42; 95% CI 0.17–1.00). Smoking was a significant predictor of RA in both sexes, and negatively associated with overweight/obesity in men. The estimated impact of overweight/obesity on the risk of RA in men was similar in analyses adjusted for smoking (OR 0.37; 95% CI 0.16–0.87) and analyses adjusted for smoking, level of education and alcohol use (OR 0.37; 95% CI 0.13–1.04). In women, overweight/obesity had no effect on the risk of RA in multivariate analyses.

Conclusion: Being overweight or obese was associated with a reduced risk of future RA in men. This pattern did not appear to be explained by differences in smoking, education or alcohol use. There was no such association in women. Factors related to adipose tissue may contribute to mechanisms that are protective from RA in men.

Disclosure: C. Turesson, None; U. Bergström, None; M. Pikwer, None; J. Nilsson, None; L. J. Jacobsson, None.

1478
Pharmacokinetics, Bioavailability and Safety of a Modified-Release Once-Daily Formulation of Tofacitinib in Healthy Volunteers.

M. Lamm1, R. Wang2, T. Fletcher3, C. Alvey3, A. Hazra2, J. Kushner1, J. Lamann1 and T. Stock2. 1Pfizer Inc, Groton, CT, 2Pfizer Inc, Collegeville, PA.

Background/Permission: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The efficacy and safety of an immediate-release (IR) formulation of tofacitinib, dosed twice daily (BID), has been assessed in patients with active moderate to severe RA. A once daily (QD) posology of tofacitinib will enhance patient convenience, ease of use, and has the potential to optimize compliance. To facilitate QD dosing, a novel modified-release (MR) formulation of tofacitinib at a dose of 11 mg has...
been designed to achieve comparability of systemic exposure parameters vs IR 5 mg BID. The study aimed to determine equivalence for extent of exposure between the tofacitinib MR 11 mg vs IR formulation administered as two 5 mg tablets.

**Methods:** This was a randomized, open-label, 2-period, 2-sequence crossover study conducted in 26 healthy volunteers (HV). Following an overnight fast, HV were randomized to receive single doses of either MR 11 mg or IR 2 × 5 mg. Treatments were separated by a 72-hour (h) washout. Pharmacokinetic (PK) parameters were calculated using non-compartmental analyses (NCA). The primary endpoint was extent of tofacitinib exposure measured as area under the concentration-time curve from time zero extrapolated to infinite time (AUC_{\text{inf}}). A mixed-effects model was used to generate adjusted geometric mean ratios (MR/IR) and 90% confidence intervals (CIs). The steady-state profiles of tofacitinib MR and IR were predicted using single-dose data from this study.

**Results:** All 26 HV completed the study and were included in the analyses. The study population had mean age of 33.6 years, mean body weight of 77.5 kg, and was 81% male. For the MR and IR formulations, geometric mean AUC_{\text{inf}} (ng·h/mL) was 297.5 and 286.3, respectively, resulting in an MR/IR ratio of 103.91% (90% CI 100.49%, 107.45%). Maximum plasma concentration adjusted for formulation (C_{\text{max, adj}}; ng/mL) was 40.75 and 44.10 for MR and IR, respectively, resulting in an MR/IR ratio of 92.40% (90% CI 84.99%, 100.45%). For both parameters, 90% CI values were wholly contained within the 80–125% interval. Mean terminal half-life was 5.71 h and 3.41 h for MR and IR formulations, respectively. The most common AEs were nausea, abdominal pain, back pain, and headache. Incidence of AEs was similar between treatment groups and no serious or severe AEs were reported. Predictions following steady-state dosing indicate similar AUC, peak concentration and minimum concentration values, and similar time above JAK1/3 half-maximal inhibitory concentration signaling thresholds for MR and IR formulations.

**Conclusion:** This study demonstrates the single dose equivalence of AUC_{\text{inf}} and C_{\text{max, adj}} of the MR and IR formulations of tofacitinib. Single doses of both formulations were well tolerated. This novel MR formulation of tofacitinib facilitates an opportunity to enable QD dosing, while maintaining systemic drug concentrations similar to the IR formulation (administered BID). Steady-state PK parameters will be calculated using non-compartmental analysis (NCA). The primary endpoint was extent of tofacitinib exposure measured as area under the concentration-time curve from time zero extrapolated to infinite time (AUC_{\text{inf}}). A mixed-effects model was used to generate adjusted geometric mean ratios (MR/IR) and 90% confidence intervals (CIs). The steady-state profiles of tofacitinib MR and IR were predicted using single-dose data from this study.

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1481
Phase 1 and Phase 2 Data Confirm That GLPG0634, a Selective JAK1 Inhibitor, Has a Low Potential for Drug-Drug Interactions. Namour Florence1, Desrivot Julie1, Anegre Van der Aa2, Chantal Tasset1 and Gerben van t Klooster1. 1Galapagos, Romainville, France, 2Galapagos NV, Mechelen, Belgium.

Background/Purpose: GLPG0634 is an orally-available, selective Janus kinase 1 (JAK1) inhibitor. Selective inhibition of JAK1 may combine improved safety and clinical efficacy profiles with a rapid onset of action. GLPG0634 showed encouraging safety and efficacy results in early clinical studies treating RA patients for 4 weeks. As RA patients can be on multiple medications, an understanding of the potential for drug-drug interaction was of interest. The exploration of potential drug-drug interactions in vitro and in humans is presented here.

Methods: Inhibition or induction of drug-metabolizing enzymes (CYP450, uridine glucuronosyltransferases (UGT)) and key drug transporters (Pgp, BCRP, BSEP, OATs, OCTs, OATP1B1 and OATP1B3) were studied using human microsomes, cell systems or recombinant enzymes with reference substrates as suitable. An open-label study in healthy subjects was conducted to confirm the in vitro conclusion on interaction potential with CY3A4 by evaluating the effects of GLPG0634 co-administration on a sensitive CY3A4 substrate, midazolam. The oral pharmacokinetics of midazolam was assessed following a single dose of 2 mg prior to and after once daily dosing of 200 mg GLPG0634 for 7 days. Furthermore, the potential interaction with methotrexate, a drug commonly administered to RA patients and shown in vitro to be partially eliminated in urine by OCTs transporters was investigated during a clinical study in RA patients treated with up to 300 mg daily dose GLPG0634 for 4 weeks.

Results: In vitro studies showed that the GLPG0634 metabolism is not CY3A4 dependent and is mediated by carboxylesterases (CES) with 70% of the metabolite produced by CES2. In vitro, GLPG0634 and its main metabolite do not influence CY3A4, CY2B6 and CY3A4 at concentrations at least two-fold of the peak concentration (Cmax) in patients administered a 200 mg daily dose of GLPG0634. The IC50 for inhibition of each of the CY3s tested and UGT1A1 and UGT2B7 is at least 7-fold above the Cmax for GLPG0634 and its main metabolite. Drug transporters are not inhibited by GLPG0634 and its metabolite, except minor effects on OCT2. The IC50 for OCT2 inhibition are 2.6- and 6.2-fold over the Cmax values of GLPG0634 and its metabolite, respectively, after a daily dose of 200 mg, while in healthy subjects, there was no difference in the plasma midazolam pharmacokinetic profile with and without GLPG0634. Adjusted geometric ratios for midazolam plus GLPG0634 were 99.3% [87.6–112.5%] and 105.4% [94.8–117.3%] for Cmax and AUC, respectively, well within the no effect boundary (80–125%). In RA patients, neither the Cmax, nor AUC of methotrexate in plasma was influenced by the co-administration of GLPG0634, with mean values of 156–172 ng/mL and 568–680 ng/mL for Cmax and AUC, respectively. GLPG0634 was safe and well tolerated.

Conclusion: The clinical data show a lack of relevant drug interactions by GLPG0634 with CY3A4 substrates, either through inhibition or induction of CY3A4 activity in humans, as well as with OCTs transporters via methotrexate elimination. All together the in vivo data on CY3A4, UGTs and key drug transporters, support that GLPG0634 can be co-administered with drugs usually administered to RA patients without dose adjustment.

Disclosure: F. Namour, Galapagos, 3; C. Tasset, Galapagos, 3; B. Vays-si`ere, Galapagos, 3; G. van t Klooster, Galapagos, 3; P. Diderichsen, Quantitative Solutions, 3; E. Cox, Quantitative Solutions, 3.

1482
Response of Patient Reported Symptoms of Stiffness and Pain during the Day from Adding Low-Dose Delayed-Release (DR) Prednisone to Stable DMARD Therapy over 12 Weeks in Patients with Moderate Rheumatoid Arthritis (RA). Rieke Alten1, Amy Y. Grahn1, Patricia Rice1, Robert Holt2 and Frank Buttgereit3. 1Charité University Medicine, Berlin, Germany, 2Horizon Pharma, Inc, Deerfield, IL, 3Premier Research, Napeville, IL, 4University of Illinois-Chicago, Vernon Hill, IL.

Background/Purpose: RA patients experience stiffness which impacts their daily lives. Although this patient reported symptom was dropped from the RA classification criteria there is growing interest in understanding more about stiffness in RA. (1) Stiffness is described in temporal terms (morning, evening) and patients report difficulty distinguishing stiffness from pain and swelling. (1) The CAPRA-2 (C2) study previously demonstrated significant relative reductions in patient reported morning stiffness duration and severity with 5 mg daily DR prednisone as compared to placebo in RA patients receiving non-biologic DMARDs. (2) We report the 12 week relative change of reoccurrence of joint stiffness and pain during the day collected by patient diary to further characterize these symptoms. Previously a strong correlation between morning stiffness severity and morning pain was reported for C2. (3)

Methods: RA patients with moderate disease on non-biologic DMARDs previously randomized (2:1) to receive DR-prednisone or placebo were evaluated at baseline (BL). 2, 6, and 12 weeks for relative changes in patient reported outcomes listed in Table 1. Data on relative change from baseline to 12 weeks were analyzed for the modified-intent-to-treat population under observed-case and last observation carried forward (LOCF) conditions. Significance (least square means) and 95% confidence intervals were established based on the mean relative percent change from BL. Point biserial correlation of daily reoccurrence of joint stiffness (Y or N) and pain (100mm VAS) for all patients was performed.

Results: 350 moderate RA patients mean age 57, 58% female, mean duration of RA 8 years, 94% naïve to prednisone. 231 received 5 mg DR prednisone and 119 received placebo, all on stable DMARDs. There was a statistically significant reduction in reoccurrence of joint stiffness during the day over the 12 weeks; pain decreased for all patients with no difference in treatment groups (Table 1). Patient global assessment, SF-36 physical function and analgesic use showed significance between treatment groups. There was moderate correlation of reoccurrence of joint stiffness and pain (r = 0.47).

Conclusion: Adding DR prednisone to the treatment of RA patients on non-biologic DMARDs produced statistically significant reduction in reoccurrence of joint stiffness during the day, improvements in patient global assessment and SF-36 physical function and a decrease in analgesic use over 12 weeks. Correlation was shown regardless of treatment between reoccurrence of joint stiffness and pain during the day further supporting the strong patient relationship of symptoms of stiffness and pain reported previously (3).

References:

Table 1. Results of CAPRA-2 Patient Reported Outcomes Over 12 Weeks

<table>
<thead>
<tr>
<th>Patient Reported Outcome</th>
<th>DR PREDNISONE (N = 233)</th>
<th>PLACEBO (N = 119)</th>
<th>Difference % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint stiffness &amp; reoccurrence (day)</td>
<td>27.0</td>
<td>7.1</td>
<td>-19.9 (37.7, -2.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pain during the day (day)</td>
<td>25.5</td>
<td>31.7</td>
<td>6.24 (37.0, 50.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Patient Global Assessment (V10)</td>
<td>17.8</td>
<td>4.9</td>
<td>-2.9 (4.4, -5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>SF-36 Physical Functioning (V10)</td>
<td>30.9</td>
<td>12.4</td>
<td>20.5 (23.2, 38.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>SF-36 Mental Health (V10)</td>
<td>14.3</td>
<td>9.6</td>
<td>5.5 (1.7, 13.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Daily Analgesic Use (score: Y/N)</td>
<td>18.7</td>
<td>20.6</td>
<td>-1.9 (37.3, -4.0)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LOCF median, relative % change from BL (95% CI), Least Square Means (LSM), LMS are 95% confidence intervals, treatment, and geographic region as factors
*
Reference stiffness during the day is the percentage of days with stiffness reoccurrence over last 7 days
†Time to last day (including day of visit). If more than 4 assessments are missing then reoccurrence is set to missing.
‡Prior to visit day (including day of visit).

Efficacy and Safety of Baricitinib in Japanese Rheumatoid Arthritis Patients during a 52 Week Extension Phase. Yoshiya Tanaka,1,2, Kaku Emoto,3, Zhihong Cai,2, Douglas E. Schlichting,2, Terence Rooney1 and William M. Macias.1 1University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; 2Eli Lilly Japan K.K., Kobe, Japan; 3Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Baricitinib (bari), an oral JAK1/JAK2 signaling inhibitor, was evaluated in a blinded phase 2b study for 12 weeks as a treatment for rheumatoid arthritis (RA) in Japanese patients (pts) on background methotrexate therapy. Clinical efficacy (ACR20 response) was significantly greater for a combined 4- and 8-mg QD baricitinib group versus placebo (PBO) and safety signals were consistent with previous experience in non-Japanese pts. Baricitinib's safety and efficacy during an additional 52 weeks of treatment in Japanese RA pts completing the 12-week phase, PBO-controlled study is reported here.

Methods: Pts were randomized (double-blind) to receive PBO or 1-, 2-, 4-, or 8-mg baricitinib QD for 12 weeks (Part A; N=145). At 12 weeks, pts receiving PBO or 1- or 2-mg baricitinib were randomized 1:1 to 4- or 8-mg QD bari for an additional 52 weeks (Part B). Pts receiving 4- or 8-mg baricitinib QD during Part A received the same doses in Part B. However, those receiving 8 mg in Part B were dose-reduced to 4 mg bari QD in a blinded fashion, upon approval of a protocol amendment. Pts and investigators remained blinded to Part B treatment assignment following the 12-week phase. Efficacy and safety were evaluated by ACR responses at selected time points, low disease activity (LDA) and remission, adverse events (AEs), and discontinuation rates.

Results: Of 145 pts randomized in Part A, 141 entered Part B and received 4 mg (n=71) or at least one dose of 8 mg (n=70) baricitinib QD (Table). Rates of ACR20 responses at 64 weeks were 66% and 73% for the 4- and 8-mg baricitinib groups, respectively. LDA rates ranged from 48% to 65% and 53% to 70%, respectively, for 4- and 8-mg baricitinib groups. Remission rates ranged from 32% to 56% and 24% to 66% for 4- and 8-mg baricitinib groups, respectively. No deaths occurred during the study. Incidences of serious AEs (SAEs) were 11% and 17% for 4- and 8-mg baricitinib, respectively. Incidences of AEs leading to discontinuation were 21% and 14% for 4- and 8-mg groups. AE incidences leading to drug interruption occurred for 25% of 4 mg and 43% of the 8 mg baricitinib groups. Treatment-emergent AEs (TEAEs) occurred in over 95% of all pts during Part B. For those pts with TEAEs 74% and 68% were rated as mild and 9% and 12% were rated as severe for the 4- and 8-mg baricitinib groups, respectively.

Conclusion: In a single-blind 52 week extension of a phase 2b study in Japanese RA patients, efficacy rates observed at 12 weeks2 were well maintained at 64 weeks for patients on either 4- or 8-mg baricitinib QD. Consistent with prior phase 2 data, the benefit-risk profile seen during 64 weeks of treatment in this study continues to support further development of baricitinib for treatment of RA.


Disease Improvement/Activity Measure at 64 Weeks* % (n)

<table>
<thead>
<tr>
<th></th>
<th>Baricitinib 4 mg (n=71)</th>
<th>Baricitinib 8 mg (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td>66% (47)</td>
<td>73% (51)</td>
</tr>
<tr>
<td>ACR 50</td>
<td>54% (38)</td>
<td>61% (43)</td>
</tr>
<tr>
<td>ACR 70</td>
<td>37% (26)</td>
<td>34% (24)</td>
</tr>
<tr>
<td>SDAI ≤ 11.0 LDA</td>
<td>59% (42)</td>
<td>66% (46)</td>
</tr>
<tr>
<td>SDAI ≤ 3.3 Remission</td>
<td>38% (27)</td>
<td>31% (22)</td>
</tr>
<tr>
<td>DAS28 ESR ≤ 3.2 LDA</td>
<td>48% (34)</td>
<td>53% (37)</td>
</tr>
<tr>
<td>DAS28 ESR ≤ 2.6 Remission</td>
<td>32% (23)</td>
<td>33% (23)</td>
</tr>
<tr>
<td>DAS28 CRP ≤ 3.2 LDA</td>
<td>65% (46)</td>
<td>70% (49)</td>
</tr>
<tr>
<td>DAS28 CRP ≤ 2.6 Remission</td>
<td>55% (39)</td>
<td>54% (38)</td>
</tr>
<tr>
<td>HAQ-DI ≤ 0.5 Remission</td>
<td>56% (40)</td>
<td>66% (46)</td>
</tr>
<tr>
<td>Boolean Remission</td>
<td>32% (23)</td>
<td>24% (17)</td>
</tr>
</tbody>
</table>

Safety measures occurring during Weeks 12 to 64 (Part B) % (n)

<table>
<thead>
<tr>
<th></th>
<th>Serious A Event</th>
<th>Adverse Event (AE) leading to discontinuation</th>
<th>AE leading to study drug interruption</th>
<th>Treatment-emergent AEs (TEAEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety measure</td>
<td>11% (8)</td>
<td>21% (15)</td>
<td>25% (18)</td>
<td>92% (65)</td>
</tr>
</tbody>
</table>
*Non-responder imputation used to calculate all values so that all patients discontinuing study during Part B treated as non-responders.

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Discovery of ARN-4079 - A Potent, Orally Available Dual Target Inhibitor of J. anus Kinase 3 (JAK3) and Interleukin-2 Inducible T-Cell Kinase (ITK) for Rheumatoid Arthritis. Hariprasad Vankayalapatil1, Venkatakrishnaredreddy Y erramreddy2, Phillip Bendele, Alison Bendele, Rueban Jacob Anicatu Issac, Ram Sudheer Adluri, Philip LoGrasso and R. M. Kremers.1 1Arien Pharmaceuticals, Salt Lake City, UT; 2Bolder BioPATH, Inc., Boulder, CO; 3Bolder BioPATH Inc., Boulder, CO; 4GVK Biosciences Private Limited, Hyderabad, India; 5The Scripps Research Institute, Jupiter, FL; 6Albany Medical College and the Center for Rheumatology, Albany, NY.

Background/Purpose: The Non-receptor tyrosine kinases, JAK3 and ITK are key regulators of cytokine pathways and are important clinically validated targets, which offer the potential for developing targeted therapeutics in treating Rheumatoid Arthritis (RA) and other immunological, inflammatory and autoimmune diseases such as systemic lupus erythematosus, psoriasis, psoriatic arthritis, attherosclerosis, ulcerative colitis and crohn disease. Development of selective small-molecule inhibitors for both JAK3 and ITK is challenging due to the highly conserved ATP binding pocket within the Janus and TEC-kinase family members. Three variable amino acids within the ATP binding pocket of JAK3 and ITK were targeted and inhibitors were rationally designed by employing FIELDS platform. The FIELDS assisted in identifying fragments/scaffolds to a series of lead compounds, and SAR efforts lead to the discovery of the first-in-class irreversible dual JAK3 and ITK inhibitor ARN-4079 for the treatment of RA.

Methods: The JAK3 and ITK enzymatic inhibition and selectivity studies were performed at DiscoveRx. The cell-based profiling using SelectScreen was performed at LifeTechnologies. In vivo cytokine and CIA efficacy studies were conducted using BALB/c and DBA/10Iahsd mouse models.

Results: Fragment-based discovery and lead optimization of a series of highly selective JAK3 and ITK inhibitors in tandem with control of physicochemical and ADME-Tox properties culminated in selecting clinically ready ARN-4079 from ~300 new chemical entities. ARN-4079 potently inhibited JAK3 and ITK activity with an IC50 = 5 nM, and 33 nM in biochemical kinase assay. The ScanKIENTIC Kds were estimated to be 2.5 and 23 nM. ARN-4079 exhibited over 100-fold cellular selectivity within the JAK family and potently inhibited IL-4 induced STAT6 phosphorylation with an IC50 = 70 nM. Its low mW inhibition in SelectScreen IL-6, IFN-γ, and EPO supported the JAK3 selectivity and inhibition of PCL-γ-mediated calcium release from CD4+ T cells (EC50 = 630 nM) via TCR engagement supports its ITK selectivity in cells. In a set of in vivo experiments, ARN-4079 potently inhibited IL-2, IL-4 and IFN-λ production in mice which are the key characteristics supporting its dual activity. Additionally, ARN-4079 was optimized to have many drug like characteristics in terms of solubility, cell permeation, and DMPK properties. ARN-4079 is an orally available entity (%F = 23), demonstrated efficacy 84% at 60 mg/kg which was equivalent to Tofacitinib in the mouse CIA model. PK studies indicated that, after oral dosing of ARN-4079 reached plasma levels (1080 ng/mL) that are higher or comparable to the therapeutic dose of Tofacitinib (627 ng/mL). Moreover, ARN-4079 showed no toxicity up to doses of 300 mg/kg in rats. On the basis of its strong in vivo efficacity and dose tolerability, ARN-4079 was selected for IND enabling studies.

Conclusion: ARN-4079 is a novel, potent, selective small molecule irreversible dual target inhibitor of JAK3 and ITK that has demonstrated dose linear pharmacokinetic, and in vivo efficacy in CIA models on par with Tofacitinib. Safety and IND studies are ongoing to develop ARN-4079 as a therapeutic agent for RA.

Disclosure: H. Vankayalapatil, Arien Pharmaceuticals, 4; V. Y erramreddy, Arien Pharmaceuticals, 1; P. Bendele, None; A. Bendele, None; R. J. A. Issac, None; R. S. Adluri, None; P. LoGrasso, ArienPharmaceuticals, 1; J. M. Kremers, Arien Pharmaceuticals, 1.
Analysis of Patient-Reported Outcomes during Treatment with Mavrilimumab, a Human Monoclonal Antibody Targeting GM-CSFRA, in the Randomized Phase 2b Earth Explorer Study 1.

**Background/Purpose:** Active RA significantly impairs health-related quality of life (HRQOL) and physical function of patients. Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a key role in macrophage activation and RA pathogenesis, including inflammatory and arthritic pain development. A prior Phase 2a study (EARD; NCT01509998) in active RA showed that mavrilimumab produced clinically meaningful improvements across a variety of patient-reported outcomes (PROs). Here we assess the benefit experienced by patients in a 24-week Phase 2b study.

**Methods:** This randomized, placebo (PBO)-controlled, multicenter study (NCT01706926) evaluated the efficacy/safety of 3 subcutaneous mavrilimumab doses vs PBO every 2 weeks (Q2W) over 24 weeks. Patients with adult-onset RA (18–80 years; DAS28-CRP ≥ 3.2; ≥ 4 swollen joints; inadequate response to ≥ 1 DMARD; receiving methotrexate) were enrolled. Co-primary endpoints were changes in DAS28-CRP score (day 1 to week 12) and ACR20 response (week 24). PRO endpoints included changes from baseline and percent responders in patient assessments of pain, HRQOL, SF-36, physical function (HAQ-DI), and fatigue (FACIT–Fatigue). Patients could enter a long-term open-label rescue study from week 12 (not reported).

**Results:** In total, 326 patients (mean [SD] age 51.8 [11.1] years; female 86.5%) with a mean (SD) DAS28-CRP of 5.8 (0.9) and DAS28-ESR of 6.6 (0.9) were randomized to 30, 100, or 150 mg mavrilimumab, or PBO (n = 81, 85, 79, and 81, respectively). Both co-primary endpoints (DAS28-CRP at week 12; ACR20 at week 24) were met at all mavrilimumab doses. At weeks 12 and 24, mavrilimumab treatment groups showed improvements in PROs vs PBO (Table), with more than half of patients receiving mavrilimumab 150 mg having a clinically meaningful response. At this dose, significant improvements (p ≤ 0.017–0.001) were seen vs PBO across multiple PRO endpoints at weeks 12 and 24 (Table). Statistically significant improvements in pain were seen for mavrilimumab from week 1. Of mavrilimumab 30, 100, and 150 mg patients with pain at week 1, and sustained (week 24). SJC and TJC for 150 mg improved from baseline (week 1) and continued to improve (week 12); this was sustained until week 24. HAQ-DI responses at week 12 were maintained at week 24 in 75.0% (33/44), 84.0% (42/50), and 78.8% (41/52) patients (mavrilimumab 30, 100, and 150 mg, respectively). Multibiomarker disease activity (MBDA) score after week 1 (1 dose). For all PROs, mean change from baseline and mean difference vs PBO and 95% confidence intervals are presented.

**Conclusion:** Targeting activated macrophages through inhibition of the GM-CSFα pathway with mavrilimumab, especially at a dose of 150 mg Q2W, substantially and rapidly reduced RA disease activity. In turn, patients receiving mavrilimumab, vs PBO, reported significant and clinically meaningful sustained improvements in multiple PROs that reflect patients’ pain, HRQOL, physical function and fatigue. The majority of mavrilimumab patients with improvement in pain and physical function at week 12 sustained these improvements to the end of the study at week 24.

**Disclosure:** J. M. Kremer, Corona, 1, AbbVie, Amgen, Genentech, Lilly, Pfizer, 2, AbbVie, Amgen, Genentech, Lilly, Pfizer, BMS, 5, Corona, 2, G. Burmester, Medimmune, 1, M. Weinblatt, IMS, 2, Crescendo Biosciences, 2, Medimmune, 1, 5, AstraZeneca, Amgen, AbbVie, IMS, UCB, Crescendo Biosciences, Lilly, Pfizer, Roche, 3, A. Williams, Medimmune, 1, Medimmune, 3, N. Karlsson, AstraZeneca, 1, AstraZeneca, 3, A. Goddard, AstraZeneca, 1, Medimmune, 3, D. Close, Medimmune, 3.

**Table:** PRO Endpoints Data at Weeks 12 and 24

<table>
<thead>
<tr>
<th>Week 12 Mavrilimumab</th>
<th>Week 24 Mavrilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-8.16 (1.63)</td>
</tr>
<tr>
<td>Mean difference from PBO (SD)</td>
<td>-10.15 (11.5)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.016 (0.01)</td>
</tr>
<tr>
<td>Responders (MCID)%</td>
<td>32.4 (44.4)</td>
</tr>
<tr>
<td>FACIT–Fatigue</td>
<td>0.107 (0.070)</td>
</tr>
<tr>
<td>SF-36 physical component</td>
<td>2.84 (4.29)</td>
</tr>
</tbody>
</table>

**Conclusion:** Targeting activated macrophages through inhibition of the GM-CSFα pathway with mavrilimumab, especially at a dose of 150 mg Q2W, substantially and rapidly reduced RA disease activity. In turn, patients receiving mavrilimumab, vs PBO, reported significant and clinically meaningful sustained improvements in multiple PROs that reflect patients’ pain, HRQOL, physical function and fatigue. The majority of mavrilimumab patients with improvement in pain and physical function at week 12 sustained these improvements to the end of the study at week 24.
score; 100 and 150 mg showed early (week 1) and sustained (week 24) significant changes in MBDA score vs PBO (p<0.01; Figure B), with greater decreases in DAS28-CRP responders vs non-responders (week 12). Approximately ≥50% decreases in serum IL-6, CRP, and serum amyloid-A protein levels were observed at week 1 and maintained during treatment.

**Table:** Clinical Efficacy and MBDA Score Results at First Assessment (Week 1, 1 Dose)

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=81)</th>
<th>30 mg (n=81)</th>
<th>100 mg (n=85)</th>
<th>150 mg (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS28-CRP response</strong></td>
<td>3 (3.7)</td>
<td>17 (21.0)</td>
<td>17 (20.0)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>Difference from placebo, % (95% CI)</td>
<td>-17.3 (7.5, 27.1)</td>
<td>16.3 (6.9, 25.7)</td>
<td>19.1 (9.0, 29.2)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-0.001</td>
<td>0.001</td>
<td>&gt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>5.08</td>
<td>4.58</td>
<td>2.58</td>
<td>2.80</td>
</tr>
<tr>
<td>Adjusted geometric mean, mg/L</td>
<td>0.89</td>
<td>0.80</td>
<td>0.45</td>
<td>0.49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>- (0.70, 1.17)</td>
<td>- (0.39, 0.65)</td>
<td>- (0.43, 0.71)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-0.424</td>
<td>&gt;0.001</td>
<td>&gt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td>0.97</td>
<td>0.79</td>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean ratio to baseline</td>
<td>0.97</td>
<td>0.92</td>
<td>0.73</td>
<td>0.94</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>- (0.71, 0.92)</td>
<td>- (0.73, 0.94)</td>
<td>- (0.67, 0.87)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-0.002</td>
<td>0.004</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>SJC</strong></td>
<td>-1.85</td>
<td>-3.57</td>
<td>-3.18</td>
<td>-5.20</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-3.48 (0.06)</td>
<td>-12.62 (0.22)</td>
<td>-5.11 (1.58)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>-3.48 (0.06)</td>
<td>-12.62 (0.22)</td>
<td>-5.11 (1.58)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-0.058</td>
<td>0.087</td>
<td>&gt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>TJC</strong></td>
<td>-2.55</td>
<td>-5.60</td>
<td>-3.96</td>
<td>-6.37</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-5.53 (0.56)</td>
<td>-3.85 (1.05)</td>
<td>-6.30 (0.36)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>-5.53 (0.56)</td>
<td>-3.85 (1.05)</td>
<td>-6.30 (0.36)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.016</td>
<td>0.261</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>-1.58</td>
<td>-7.57</td>
<td>-6.14</td>
<td>-16.70</td>
</tr>
</tbody>
</table>

Mean change from baseline (95% CI)  
(0.70, 1.17) (0.39, 0.65) (0.43, 0.71) (0.67, 0.87)

**Conclusion:** By targeting activated macrophages via inhibition of GM-CSFR, mavrilimumab substantially reduced patients’ RA disease activity from first (week 1; 1 dose) to final assessment, evaluated by multiple clinical endpoints and biomarkers.

**Disclosures:** I. B. McInnes, Medimmune, 5; MedImmune, AstraZeneca, 5; G. Burmester, Medimmune, 5; J. M. Kremer, Corrona, 1; AbbVie, Amgen, Genentech, Lilly, Pfizer, 2; AbbVie, Amgen, Genentech, Lilly, Pfizer, BMS, 5; Corrona, 3; P. Miranda, Medimmune, 2; M. Korkosz, None; J. Vencovsky, None; A. Rubbert-Roth, None; E. Mysler, Medimmune, 2; D. Close, Medimmune, 3; M. A. Sleeman, AstraZeneca, 1; Medimmune, 3; A. Godwood, AstraZeneca, 1; Medimmune, 3; S. Sandbach, Medimmune, 3; P. C. Ryan, Medimmune, 4; Stanek, 1; M. Sini-baldi, Medimmune, 1; M. Edin, Medimmune, 3; W. White, Medimmune, 3; N. A. Defranoux, Crescendo Bioscience, 1; Crescendo Bioscience, 3; M. Weinblatt, BMS, UCB, Crescendo Bioscience, 2; Medimmune, AstraZeneca, Amgen, AbbVie, BMS, UCB, Crescendo Bioscience, Lilley, Pfizer, Roche, 5.

**Background/Purpose:** Staphylococcal protein A (SpA) binds with high affinity to the Fc region of human immunoglobulin G and also to the Fab framework region of immunoglobulin encoded from genes of the VH3 family. At intravenous doses up to 1.5 µg/kg weekly SpA was found to have an acceptable safety profile in a Phase I rheumatoid arthritis (RA) trial. The current Phase I study evaluates the safety and effect on RA disease activity of 6 months of SpA treatment.

**Methods:** This study enrolled 61 RA patients (pts) at 8 US centers. In Part 1 of the study, 41 pts received 5 weekly doses of either placebo, 1.5, 3, 6 or 12 µg/kg of SpA. Partial results from Part 1 have been reported previously [1]. In Part 2, pts received placebo or a fixed SpA dose of either 240 µg or 420 µg given as 5 weekly doses followed by maintenance doses at weeks 8, 12, 16 and 20 (6 months’ total treatment). A diverse events (AES), pharmacokinetics, anti-SpA antibodies and disease activity (ACR20/50/70, DAS28-CRP, and CDAI [Clinical Disease Activity Index]) are being evaluated over the course of this ongoing study.

**Results:** Twenty pts were randomized in Part 2: 3 pts (240 µg), 12 pts (420 µg) and 5 pts (placebo). All AEs were Grade 1 or 2 in severity with the exception of 1 pt who experienced Grade 3 influenza (unrelated to treatment) and 1 pt with Grade 3 worsening of arthritis (related to treatment). 9 pts (45%) had related AEs, the most common being transient flare of musculoskeletal symptoms usually occurring 1–3 days post-infusion. In Parts 1 and 2 of the study, there were no deaths or serious AEs considered to be related to SpA. Nine of the 12 pts in the 420 µg SpA arm met per-protocol criteria for efficacy evaluation; control group was pooled for comparative purposes, the control group was pooled from the 15 placebo pts enrolled in Parts 1 and 2; 13 placebo pts met per-protocol criteria for efficacy evaluation. Of the 9 pts in Part 2 that received 420 µg SpA, 56% achieved ACR20 at day 113 vs. 31% of pts in the control group (see table). A similar pattern was seen with the
CDAI data also indicated some reduction in disease activity, as 44% of 420 μg pts achieved a CDAI of -14 on 3 or more consecutive visits vs. 23% of pts in the control group. SpA and control pts had M DHAQ mean physical function scores of 3.57 and 3.59, respectively, at baseline. By day 85, the change from baseline was -1.17 and -0.59 for SpA and control pts, respectively. At day 113, the change from baseline was -1.38 vs. -0.6, respectively.

**Conclusion:**

- A 6-month regimen of 5 weekly infusions of SpA followed by 4 monthly ‘maintenance’ infusions had an acceptable safety profile in pts with RA. The most common AEs seemed to be associated with transient worsening of musculoskeletal symptoms.
- During a 6-month study period, SpA appeared to result in some reduction in disease activity. Some patients experienced improvements.

**Disclosure:** C. Wiesenhutter: None; R. Patel: Takeda, Exogen; J. Lavery: None; N. Tahir: None; L. Hazan: Aix Clinical Trials, South Florida Clinical Trials, New York Clinical Trials, Impact Clinica Trials; A. Kivitz: None; E. Bretton: None; J. Kaine: Pfizer Inc, Bristol-Myers-Squibb; B.

**1488**

**Clinical Efficacy of Add-on Iguratimod Therapy in Patients with Active Rheumatoid Arthritis Despite of Methotrexate—a Multicenter Registry Study**

Yasuhide Kanayama1, Toshihisa Kojima2, Atsushi Kaneko3, Yuji Hirano1, Toshihisa Kojima2, Yasuhide Kanayama3, Shinya Hirabara1, Nobunori Takahashi4, N. Ishiguro5, A. G. Todd6, B. Y. H. Lee7,8, Y. Kanamori9.

**Background/Purpose:** Iguratimod (IGU), a small-molecule antirheumatic drug that was approved in Japan in September 2012. IGU suppressed tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 via inhibition of nuclear factor-kappa B activation in cultured human synovial cells and human acute monocytic leukemia cells. IGU also reduced immunoglobulin production by acting directly on human B lymphocytes without affecting B lymphocyte proliferator. Recently, an increased release of extracellular adenosine and a decreased production of lymphotoxins such as ammonia and superoxide have been shown to be involved in the anti-inflammatory mechanisms of methotrexate. Thus, the combination of MTX and IGU may have synergic efficacy for rheumatoid arthritis (RA) treatment. To evaluate the clinical efficacy of add-on IGU in patients with Japanese active RA who had shown inadequate response to MTX therapy.

**Methods:** Patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria who had been unresponsive to MTX therapy (DAS-CR>3.2 or CDAI>10), and who had been prescribed add-on IGU from Tsuruma Biologics Communication Registry (TBCR) between November 2012 and August 2013 were enrolled. The final study cohort of 51 patients received continuous IGU therapy more than 24 weeks. We reviewed the methods about the improvement of CRP, M MP3, DAS28-ESR and CDAI which was an index of disease activity of RA using Wilcoxon signed-rank test and the rate of remission patients at Week24.

**Results:** The group of patients included 8 males and 43 females. The mean age was 63.6 ± 10.3 years old; the disease duration was 8.4 ± 9.7 years and the methotrexate dose was 9.6 ± 4.2 mg/week. Clinical findings related to RA were as follows: mean tender joint count, 4.5 ± 4.9; swollen joint count, 4.2 ± 3.9; patient’s global assessment of disease activity, 4.15 ± 22.8mm; Physician’s global assessment of disease activity, 4.00 ± 20.8mm; CRP, 2.0 ± 2.3 mg/dl; ESR, 42.9 ± 19.2 mm/h; M MP3, 249.7 ± 284.6 ng/ml; DAS28 (ESR), 4.67 ± 0.97; and CDAI, 16.9 ± 9.4. There were no patients who had received Biologics treatment. The mean CRP improved to 1.7 ± 2.2, 1.2 ± 2.0 and 1.1 ± 1.9 at Week 4, 12 and 24 (p = 0.064, p = 0.001, p < 0.001), mean M MP3 improved to 223.7 ± 266.1, 161.7 ± 242.1 and 148.3 ± 244.4 at Week 4, 12 and 24 (p < 0.045, p < 0.001, p < 0.001), the mean DAS28 improved to 4.26 ± 1.03, 3.34 ± 1.07 and 3.32 ± 1.28 at Week 4, 12 and 24 (p < 0.001, p < 0.001, p = 0.001) and the mean CDAI improved to 13.1 ± 8.2, 8.3 ± 6.5 and 7.9 ± 7.6 at Week 4, 12 and 24 (p = 0.001, p < 0.001, p < 0.001) significantly. At Week 24 the rate of patients who achieved remission were each 33.3% and 27.5% in DAS and CDAI criteria.

**Conclusion:** This study suggested that the new combination therapy of add-on IGU with MTX was effective in patients with active RA with inadequate response to MTX.

Methods: We searched Medline via PubMed, COCHRANE and EMBASE database for articles published up to April 2014 using MeSH terms ("Bone mineral density" (M eSH) OR "bone" (M eSH) OR "bone remodeling" (M eSH) AND "rheumatoid arthritis" AND ("infliximab" OR "adalimumab" OR "etanercept" OR "certolizumab" OR "golimumab" OR "anti-TNF")). To be selected a study need to be controlled trial with a group treated by TNFi and a control group without treatment of interest or to have values before and after treatment by TNFi or value of variation under treatment of at least one variable among BMD at hip or lumbar spine, CTX-1, Bone Alkaline bone Phosphatase (BAP), osteocalcin (OC) and type 1 collagen amino-terminal propeptide (P1NP). Statistical analysis of pre and post-data was performed using Comprehensive meta-analysis software. The percentage heterogeneity in the study results was determined by the Cochran’s Q-test and the I^2 values. A significant statistical threshold of 0.05 was used.

Results: The search retrieved 49 articles. 15 articles complied with inclusion criteria. Although heterogeneity was high, BMD at hip and lumbar spine stay unchanged after TNFi (6 studies for hip BMD including 386 patients and 7 studies for lumbar spine BMD including 443 patients ) with a mean difference of 0.058 (−0.220 to 0.337, IC95%) for BMD at hip and of 0.154 (−0.110 to 0.418,IC95%) for BMD at lumbar spine. In controlled trials, no difference was found for BMD at hip or at lumbar spine (6 studies; 558 patients). Concerning bone remodeling markers, CTX-1 level was statistically decreased in 2 studies and showed a trend of decrease in 4 other studies. OC level increased statistically in 4 studies and decreased no significantly in a fifth one; P1NP level was increased significantly in 1 study of 3 available whereas BAP level did not statistically change in studies available (2 studies). BMD change were influenced by therapeutic response to TNFi in 2 studies, with a trend in a third one whereas no association was found in 3 other studies.

Conclusion: TNFi in RA seem to decrease bone resorption and to increase bone remodeling at biologic levels but do not have an effect on BMD. However, only few data with mid-term assessment are available with an important heterogeneity in terms of patients included, disease duration, comediations and follow up. Several long term trials are required to evaluate the exact effect of TNFi on bone mineral density in rheumatoid arthritis.

Disclosure: A. Nutz, None; Y. Duny, None; T. Barnetche, None; J. Morel, None; B. Combe, None; C. Dalen, None.


Background/Purpose: Biologics such as TNF inhibitors have revolutionized the treatment of inflammatory diseases including rheumatoid arthritis (RA), psoriasis and psoriatic arthritis. However, recent data suggest that full and long-lasting responses to TNF inhibitors are limited because of the activation of the pro-inflammatory T17/IL-17 pathway in patients. Therefore, an attractive avenue to achieve superior efficacy levels in inflammatory diseases represents the combined inhibition of TNF and IL-17A. We present here COVA322, a bispecific TNF/IL-17A inhibitor that is currently being tested in a Phase Ib/Ia study in psoriasis patients.

Methods: Using phage display technology we have isolated Fynomers inhibiting human IL-17A. Fynomers are small binding proteins (7 kDa) derived from human T cell derived cytokines. After genetic fusion of the anti-IL-17A Fynomer to a commercially validated anti-TNF antibody the resulting bispecific molecule COVA322 was characterized for its stability, dual binding characteristics, and IL-17A and TNF inhibition properties, including the inhibition of human T cell derived cytokines.

Results: The fusion of the anti-IL-17A Fynomer to the fully human anti-TNF antibody did not alter the favorable biophysical properties of the antibody: COVA322 was monomeric and its stability was comparable to the anti-TNF antibody. Furthermore, COVA322 could be engineered to bind to essentially any target of interest with high affinity and specificity. After genetic fusion of the anti-IL-17A Fynomer to a commercially validated anti-TNF antibody the resulting bispecific molecule COVA322 was characterized for its stability, dual binding characteristics, and IL-17A and TNF inhibition properties, including the inhibition of human T cell derived cytokines.

Conclusion: COVA322 is a unique bispecific TNF/IL-17A inhibitor with excellent biophysical properties. It is currently being tested in a first-in-man, single dose escalation, tolerability, safety, PK and efficacy Phase Ib/Ia study in psoriasis.

Disclosure: D. Grabulovski, Covagen AG, 1; Covagen AG, 3; Covagen AG, 4; M. Silacci, Covagen AG, 1; Covagen AG, 3; W. Lembeke, Covagen AG, 3; Covagen AG, 4.
Background/Purpose: A phase 1, randomised, double-blind, placebo-controlled, dose-escalation trial was conducted to assess the safety and tolerability of the anti-IL-21 antibody NNC0114-0006, in patients with active moderate-to-severe rheumatoid arthritis (RA) on background methotrexate (MTX) monotherapy.

Methods: Patients (N=32; 84% female) with RA (mean duration 8.9 years; 72% RF positive; 63% anti-CCP positive; mean DAS28CRP 5.4), who were on MTX (mean duration 4.7 years; mean dose 13 mg/week) were enrolled. Patients were randomised to NNC0114-0006 or placebo (3:1) for s.c. dosing every other week for 6 weeks (a total of four doses) at 0.05, 0.25, 1 or 4 mg/kg. Dose levels of NNC0114-0006 were escalated when 6 of 8 patients in a cohort completed the third dose. The primary endpoint was incidence of adverse events (AEs) from first administration until trial completion, 26 weeks later. Secondary endpoints were changes in laboratory measurements, antibodies against NNC0114-0006, and pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

Results: There were no significant differences between the treatment groups with respect to baseline data. One patient in the 1 mg/kg NNC0114-0006 group withdrew informed consent after the second dose due to intensification of joint pain considered possibly related to the use of the trial product. Overall, 42 AEs were reported in 18 of 24 (75%) NNC0114-0006 patients, while 20 AEs were reported in 6 of 8 (75%) placebo patients. Two patients receiving 4 mg/kg NNC0114-0006 experienced serious adverse events, which were considered unlikely related to the use of the trial product. No severe or life-threatening events, or fatalities were observed. Two patients at the highest dose reported AEs related to infections, compared with only one patient in each of the other treatment groups, including placebo. No treatment-related anti-drug antibodies were detected during the course of the trial. No clinically significant changes from baseline levels were observed in laboratory safety parameters. From PK measurements, systemic exposure to NNC0114-0006 increased with increasing dose levels, as expected with a dosing regimen. IL-21 after treatment with NNC0114-0006; however, large interpatient variability was observed. No significant changes were observed in RF, CRP and ESR, IL-21R expression on selected lymphocyte subsets, B cells, or gene expression by microarray from whole blood or fractionated blood.

Conclusions: No safety or tolerability concerns were identified following multiple-dose administration of up to 4 mg/kg NNC0114-0006, and no anti-drug antibodies were detected. NNC0114-0006 has a long terminal half-life (2-3 weeks) and s.c. bioavailability similar to that of other monoclonal antibodies. An increase in circulating levels of total IL-21 after treatment with NNC0114-0006 was observed, as expected. No changes in other PD parameters were observed with increasing doses of NNC0114-0006 compared with placebo.

Disclosure: F. Wagner, Novo Nordisk, 5; B. Skrumsager, Novo Nordisk, 3; S. Fitilev, Galapagos NV, 5, M. echel, Belgium, 5; Galapagos SASU, Romainville, France.

Background/Purpose: The 4 Janus kinases (JAK1, JAK2, JAK3 and TYK2) are cytoplasmic tyrosine kinases that mediate intracellular signaling of cytokines (e.g. certain interleukins and interferons) and growth factors (e.g. erythropoietin). GLPG0634 is the first JAK inhibitor that displays a high JAK1 selectivity towards the 3 other JAK family members in functional assays. It showed a favorable safety and efficacy profile in two 4-week Phase 2a studies in rheumatoid arthritis (RA) patients. In order to further characterize GLPG0634, we compared the gene expression profile of circulating leukocytes of healthy volunteers and RA patients before and after 4 weeks of daily treatment with 200 mg GLPG0634.

Methods: RA patients participated in the Phase 2a Proof of concept, a randomized, double-blind, placebo-controlled study enrolling 36 patients with insufficient response to MTX. They were orally treated with placebo or 200 mg OD GLPG0634 for 4 weeks. Blood was sampled in PA gene tubes at pre-dose the first and the last days of treatment. Non-matched healthy
volunteers were also sampled in PAXgene tubes. mRNA was extracted, labeled and profiled using Affymetrix U219 micro-arrays. Data analysis was performed in R/BioConductor using linear regression models (limma).

**Results:** The leukocyte gene signature of 12 healthy subjects was first compared to the one obtained from 24 RA patients prior to placebo or GLPG0634 treatment. As expected, genes showing differential expression compared to healthy subjects allowed for definition of a disease signature. Four weeks of treatment with GLPG0634 (200 mg QD) impacted the signal levels for 3120 probes in RA patient samples (adjusted p-value < 0.05 and absolute log_{2}-fold change > 1 compared to the same subjects at pre-dose), while the signal levels of only 78 probes were impacted to the same extent in the placebo group. Remarkably, the highly GLPG0634-impaired genes matched with the disease-effect genes and displayed an inverse regulation (Spearman R = -0.85), showing that administration of GLPG0634 at 200 mg QD led to the restoration of a healthy-like gene expression profile (treatment-effect genes). Pathway analysis performed for the affected gene sets suggests an impact on the T-cell receptor signaling pathways.

**Conclusion:** Blood transcriptional analysis of healthy volunteers and patients recruited in the proof-of-concept study of GLPG0634 in RA identified a disease signature with many genes involved in RA-linked pathways. After 4 weeks of treatment with GLPG0634, transcriptome analysis showed that the compound was able to reverse strongly the disease effect, leading to a gene signature close to that of healthy volunteers. These data are in line with the good efficacy of the 200 mg QD administration of GLPG0634 in RA patients and further support the use of GLPG0634 in RA patients.

Disclosure: M. Ongenae, Galapagos, 3, AbbVie, 9; S. Dupont, Galapagos, 3; A. Bass, Merck Pharmaceuticals, 3; B. Vayssiere, Galapagos, 3; B. Remy, Galapagos, 3; L. Van Rompaey, Galapagos, 3; C. Menet, Galapagos, 3; R. Gellen, Galapagos, 3.

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**Preclinical and Clinical Phase I Profile of MK-8457, a Selective Spleen Tyrosine Kinase and Zeta-Chain-Associated Protein Kinase 70 Inhibitor, Developed for the Treatment of Rheumatoid Arthritis.** Gene Marcatonio,1 A. Alan Bass,2 Gretchen Baldu,2 Judd Boice,2 Hongmin Chen,3 Michael Crackower,4 Jeron Elassais-Schaap,4 Michelle Ellis,4 Tomoko Freshwater,4 Francois Guernier,5, Jane Guet,6 Sammy Kim,6 Lily Mooy,6 Alan Northrup,6 Jie Zhang-Hoover,5 Mathew Maddess,5 Richard Miller,5 Marcella Ruddy,5 Stella Vincent,5 Haoling Weng6 and Hani Houshyar6. 1Merck & Co., Whitehouse Station, NJ, 2Merck & Co., Boston, MA, 3Merck & Co., Oss, Netherlands, 4Merck & Co., Rahway, NJ.

**Background/Purpose:** Spleen tyrosine kinase (SYK) is a potential target for treatment of several diseases including rheumatoid arthritis. SYK is a member of the Zeta-chain-associated protein kinase 70 (ZAP70) family of non-receptor protein kinases, critical in signaling downstream of Fc epsilon receptor I (FcεRI) in mast cells and basophils, B-cell receptor (BCR) in B cells, and the collagen receptor in platelets. ZAP70 plays a predominant role in T-cell receptor (TCR) signaling in mature T cells. Here, we report on the in vitro, in vivo, and early clinical characterization of a highly selective and potent dual SYK/ZAP70 inhibitor, MK-8457.

**Methods:** The in vitro characteristics of MK-8457 were evaluated in a series of biochemical and cellular assays. The in vivo characteristics of MK-8457 were evaluated in the rat adjuvant- and collagen-induced arthritis models. MK-8457 preclinical PK-PD-Efficacy relationship was established in MK-8457 were evaluated in the rat adjuvant- and collagen-induced arthritis models.

**Results:** MK-8457 is a potent, reversible ATP competitive inhibitor of SYK and ZAP70, displaying comparable cellular activity for these two kinases despite 40x enzymatic selectivity for SYK vs. ZAP70. Beyond ZAP70, out of 191 off-target kinases tested, MK-8457 inhibits only 3 kinases (TRK C, SRC, BLK) with IC_{50} values less than 100-fold above the SYK IC_{50}. In vitro, MK-8457 is a potent inhibitor of (1) FcεRI-mediated anti-IgE induced degranulation in primary human mast cells (38 ± 20 nM) and human whole blood basophils (797 ± 385 nM), (2) BCR-mediated anti-IgM induced pBLNK activation in human R A M O S cells (35 ± 27 nM) and anti-CD79b induced CD69 upregulation in human whole blood B cells (1395 ± 505 nM) and (3) TCR-mediated anti-CD3 induced IL-2 production in Jurkat cells (84 ± 26 nM) and human whole blood phagocytosis glutation induced IL-2 production (1177 ± 362 nM). MK-8457 also inhibits collagen-induced platelet aggregation in human platelet rich plasma, with 20x reduced potency (19 ± 3 μM) as compared with the human whole blood basophil, B-cell, and T-cell assays. MK-8457 produces dose-dependent inhibition of adjuvant- and collagen-induced arthritis, as assessed by changes in paw thickness. Preclinical PK-PD-Efficacy modeling and simulations suggest that high level of SYK/ZAP70 inhibition (69%) is required to attain nearly full suppression of the CIA response. In healthy volunteers, MK-8457 is rapidly absorbed, shows increased exposure with dose, with a terminal half-life estimated to be 10–20 hours. MK-8457 was generally safe and well-tolerated in single dose up to 800 mg and multiple doses of 200 mg twice daily for up to 10 days. There was evidence of increased bleeding times at the T_{max} in single dose studies; however, there were no bleeding adverse events. The C_{min} for this effect in healthy volunteers is ~2x higher than observed at steady state for the highest dose (100 mg BID) tested in Phase II RA studies.

**Conclusion:** These data suggest that MK-8457 has the appropriate characteristics for assessment of the hypothesis that a selective SYK/ZAP70 inhibitor is efficacious in RA patients.

Disclosure: G. Marcatonio, Merck Pharmaceuticals, 3; A. Bass, Merck Pharmaceuticals, 3; G. Baltus, Merck Pharmaceuticals, 5; J. Boice, Merck Pharmaceuticals, 3; H. Chen, Merck Pharmaceuticals, 3; M. Crackower, Merck Pharmaceuticals, 3; J. Eliazaaisa-Schaap, Merck Pharmaceuticals, 3; M. Ellis, Merck Pharmaceuticals, 3; T. Freshwater, Merck Pharmaceuticals, 3; F. Gervais, Merck Pharmaceuticals, 3; J. Guo, Merck Pharmaceuticals, 3; S. Kim, Merck Pharmaceuticals, 3; L. Loy, Merck Pharmaceuticals, 3; A. Northrup, Merck Pharmaceuticals, 3; J. Zhang-Hoover, Merck Pharmaceuticals, 3; M. Maddess, Merck Pharmaceuticals, 3; R. Miller, Merck Pharmaceuticals, 3; M. Ruddy, Merck Pharmaceuticals, 3; S. Vincent, Merck Pharmaceuticals, 3; H. Weng, Employee of Merck Co., 3; H. Houshyar, Merck Pharmaceuticals, 3.

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**Exposure-Response Analysis for Mavrilimumab Phase2b Study in RA Patients with Informative Dropout.** Chi-Yuan Wu,1 Detong Jin2, Alex Godwood3, David Close3, Len Roskos3 and Bing Wang3. 1Medimmune, Mountain View, CA, 2Medimmune Ltd, Cambridge, United Kingdom, 3Medimmune, Gaithersburg, MD.

**Background/ Purpose:** Mavrilimumab is a recombinant human monoclonal antibody which neutralizes granulocyte-macrophage colony stimulating factor (GM-CSF) activity by selectively binding to the alpha subunit of its receptor (GM-CSFα). A Phase 2b randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of mavrilimumab in subjects with at least moderately active rheumatoid arthritis (RA). Population modeling was performed to characterize the exposure-response relationship of mavrilimumab in RA patients.

**Methods:** In a Phase2b study, subjects with RA received subcutaneously administered placebo or mavrilimumab (30, 100 or 150 mg) once every other week for 24 weeks. The pharmacokinetic data was pooled and analyzed using a population approach. The binary ACR20 and ACR50 responses were modeled by logistic regression. A dropout hazard function was introduced to describe the voluntary patient withdrawals during the study period. Stochastic simulations based on the final PK-ACR20(50)-Dropout model were subsequently conducted for model evaluations and exposure-response relationship assessment.

**Results:** A mechanistic model incorporating the subcutaneous absorption, intracellular degradation and intracellular degradation adequately described the observed PK profiles of mavrilimumab. The placebo effect and mavrilimumab treatment effect were integrated in the logit (log odds ratio) of ACR20 or ACR50. The treatment effect was described by an Emax model for ACR20, and by a linear relationship with mavrilimumab concentration for ACR50. The dropout hazard function described the volunteer patient withdrawals during the study period. Stochastic simulations based on the final PK-ACR20(50)-Dropout model were subsequently conducted for model evaluations and exposure-response relationship assessment.

Disclosure: C. Y. Wu, Medimmune, 3; D. Jin, Medimmune, 3; A. Godwood, AstraZeneca, 1; M. Edinndume, 3; L. Roskos, Medimmune, 3; B. Wang, Medimmune, 3.
Efficacy and Safety of Igaratumod for Rheumatoid Arthritis. Tsuneo Kondo, Aiko Shibata, Ryota Sakai, Kento Chino, Ayumi Okuyama, Hirofumi Takei and Koichi Amran. Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.

Background/Purpose: Igaratumod is a new small-molecular drug for rheumatoid arthritis (RA), which was approved on June, 2012 in Japan. The agent inhibits the production of immunoglobulins and various inflammatory cytokines (interleukin-1, -6 and -8 and TNF), and exerts anabolic effects on bone metabolism by stimulating osteoblastic differentiation and inhibiting osteoclastogenesis in mice through inhibiting the nuclear transcription factor NF-κB, but not a non-inhibitor, 1β-6. In addition this agent is well tolerable and may lead to clinical improvement in RA patients. In the clinical phase II study, we examined the NK cell counts in peripheral blood from 20 RA patients before and after 12 weeks of the commencement of Igaratumod by flow cytometry analysis.

Methods: 62 patients who were administered iguratimod at a dosage of 25mg qd during the first month, then 50mg qd thereafter, and followed up for 24 weeks were enrolled. Efficacy and safety were evaluated utilizing clinical and laboratory findings. We also monitored the NK cell counts in peripheral blood from 20 RA patients before and after 12 weeks of the commencement of Igaratumod by flow cytometry analysis.

Results: The mean age was 61.6 years and 75.8% of patients were female. MTX was used in 46.8%, the average dose was 8.6±2.9 mg/week. LOCQ analysis revealed that A2S28-ESR and SDAI decreased significantly from 4.49±1.33 to 3.09±1.12 and from 18.5±10.9 to 7.4±7.1 in 24 weeks respectively (P<0.01). Remission and LDA rate in SDAI were 30.4% and 47.8%. HAO-D1 score also decreased from 1.2±0.8 to 0.9±0.85. The difference between the efficacy of iraguimod with and without MTX was not significant. 29.0% of the patients discontinued iguratimod within 24 weeks. The reason for cessation consisted of adverse events (21.0%) and lack of efficacy (4.8%). Adverse events were digestive symptom (n=6), liver dysfunction (n=3), nasal hemorrhage (n=2) and so on. There’s no severe adverse event. Peripheral NK cell counts in 12 weeks had not been changed significantly.

Conclusion: Igaratumod was well tolerable and may have a good cost effectiveness. So Igaratumod may be a promising new RA agent and it’s in the market to target tofackitinib.

Disclosure T. Kondo None; A. Shibata None; R. Sakai None; K. Chino None; A. Okuyama None; H. Takei None; K. Amano None.

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Background/Purpose: Interleukin-6 (IL-6) is a pleiotropic cytokine inducing a wide range of biological activities via its receptor, which can either be soluble (sIL-6R) or membrane-bound (mIL-6R). In rheumatoid arthritis, blocking of IL-6R results in clinical benefit as demonstrated by the IL-6R inhibitor tocilizumab (TCZ). Signalling via the mIL-6R (classical pathway) is confined to selected cell types due to the restricted expression of sIL-6R. However, IL-6 can also activate cells through sIL-6R in a process known as trans-signalling. Unwanted pharmacology associated with IL-6 pathway inhibition has been linked to inhibition of mIL-6R. Preferential inhibition of sIL-6R could therefore provide higher therapeutic efficacy with a better safety profile compared to equivalent inhibition of both IL-6R forms.

Methods: ALX-0061 is a single domain antibody (sabdAb) of the Camelidae family. ALX-0061 is a nanobody® (Nb), which is the smallest antibody, which can bind target antigens with high affinity and specificity. ALX-0061 is a potent inhibitor of IL-6R signaling by targeting human serum albumin (HSA), in combination with strong pharmacokinetics.

Results: ALX-0061 specifically neutralised sIL-6R with a 0.08 pM affinity (1.5$/25 mg tablet), while the affinity of TCZ was about 50-fold lower for sIL-6R compared to sIL-6R (9.1±3.6 pM). In in vitro and in vivo assays for IL-6R, sIL-6R, mIL-6R and sIL-6R trans-signalling, ALX-0061 showed a 3-fold higher affinity for mIL-6R (462±138 pM) compared to sIL-6R (154±16 pM). In the in vivo low-dose driven cell-based assay, however, in vitro potencies were similar for ALX-0061 and TCZ, with the latter one showing avid binding due to its bivalency. In addition, TCZ showed a 3-fold higher affinity for mIL-6R (462±138 pM) compared to sIL-6R (154±16 pM). This shows that ALX-0061 was about 50-fold lower for mIL-6R compared to sIL-6R.

Conclusion: ALX-0061 demonstrates in vitro a preferential binding profile for sIL-6R with a lesser activity for mIL-6R, while TCZ has a higher preference for mIL-6R. Preferential inhibition of sIL-6R trans-signalling by ALX-0061 could provide improved therapeutic efficacy with a better safety profile compared to TCZ.


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Background/Purpose: Jak kinase blockade can effectively manage rheumatoid arthritis (RA) and in some cases achieve remission. However, first generation Jak inhibitors have not met expectations due to dose-limiting tolerability and safety issues. ABT-494 is a second generation Jak inhibitor with high Jak1 selectivity thereby minimizing the potential for jak2 and jak3 related side effects. Here we describe preclinical and early clinical data that suggest ABT-494 has potential to address some of the current unmet medical needs of RA patients.

Methods: ABT-494 was engineered for increased selectivity for Jak1 using structural predictions indicating the potential for differential binding interactions outside the ATP-binding active site of Jak1 but not Jak2 or Jak3. ABT-494 efficacy and selectivity were tested in a battery of relevant cellular and in vivo pharmacology assays including bone marrow colony formation, adjuvant induced arthritis, erythropoietin (EPO) induced reticulocyte deployment and NK/NKT cell suppression. ABT-494 potency in a variety of complementary pharmacodynamic assays was also assessed at multiple oral doses in healthy human subjects and patients with RA.

Results: ABT-494 is approximately 74 fold selective for Jak1 over mIL-6R in cellular assays dependent on specific, relevant cytokines. The ability of ABT-494 and tofacitinib to inhibit Jak2/EP0 signaling in these assays was consistent with their ability to inhibit bone marrow cell differentiation in vitro. Surprisingly, GMCSF (and IL3) signaling in TF1 cells were consistently more sensitive to inhibition than EPO signaling in UT7 cells indicating that Jak2 inhibition in some contexts may over-estimate inhibition of Jak2 via EPO signaling. Accordingly, in whole blood assays, ABT-494 was about 10X more potent against IL6 (Jak1) signaling than GMCSF (Jak2) driven signaling based on free drug concentrations. By contrast, tofacitinib under the same conditions was about 2X more potent. No changes in reticulocyte counts were observed in RA patients after 28 days of ABT-494 dosing.

Conclusion: ABT-494 and tofacitinib inhibited common gamma chain cytokine signaling (IL7, IL15 and IL21) in whole blood with similar potencies and in vivo were similarly potent in driving down NK cell counts in healthy rats. Consistent with its higher potency against IL6 signaling, ABT-494 had substantially greater potency in a rat arthritis model. Preliminary evidence suggests that compared to tofacitinib, ABT-494 may spare jak2 and jak3 dependent signaling. Taken together, these encouraging observations support further testing of ABT-494 in RA patients in Phase II randomized placebo controlled trials and indicate it may have increased potential to address patient needs over existing agents.
Preclinical and Clinical Characterization of MK-8457, a Selective Spleen Tyrosine Kinase Inase and Zeta-Chain-Associated Protein Kinase 70 Inhibitor, in Normotensive and Hypertensive Cardiovascular Models. Hani Houshyar1, Alan Bass2, Judith Boice3, Michael Ellis1, Patrick Fanelli1, Tomoko Freshwater4, Jane Guo1, Kimberly Hoagland5, Janet Kerr1, Alan Northrup1, M athew Maddess1, Richard Miller2, Marcela Ruddy3, Stella Vincent1, J ayanthi Wolf4, Haoling Weng1, Gloria Zingaro1 and Gene M arcantoni1. 1Meck & Co., Boston, MA; 2Merck & Co., Whitehouse Station, NJ; 3Merck & Co., Wakefield, NJ.

Background/ Purpose: Spleen Tyrosine Kinase (SYK) and Zeta-chain-associated protein kinase 70 (ZAP70) inhibitors are non-receptor protein kinases that bind phosphorylated receptor tyrosine-based activation motifs, critical in immune receptor signaling in multiple hematopoietic and non-hematopoietic cells, supporting potential utility of SYK/ZAP70 inhibitors in multiple indications including rheumatoid arthritis. While neither SYK nor ZAP70 are implicated in blood pressure (BP) regulation, the non-selective SYK/ZAP70 inhibitor, Fostamatinib, is associated with BP increases both preclinically and in patients. Fostamatinib’s impact on BP has been attributed to off-target activity on vascular endothelial growth factor receptor 2 (VEGFR-2). Here, we report the in vitro, in vivo, and clinical profile of MK-8457 to demonstrate that a highly selective SYK/ZAP70 inhibitor does not affect BP.

Methods: The in vitro off-target activity of MK-8457 vs. Fostamatinib on VEGFR-2 was assessed in enzymatic as well as cellular assays. In vivo, the BP effects of MK-8457 were compared with Fostamatinib in conscious telemetry instrumented rats and Beagle dogs. In the clinic, MK-8457 was studied in a multi-center, randomized, double-blind, placebo controlled 2-period crossover ambulatory BP measurement (ABPM) trial in men and women with mild to moderate hypertension. This study in 29 subjects was powered to detect a 5 mmHg increase in BP, to rule out a Fostamatinib-like BP effect.

Results: In contrast to Fostamatinib, MK-8457 is devoid of off-target VEGFR-2 activity in both enzymatic and cellular assays. Whereas Fostamatinib produces dose-dependent increases in BP in conscious telemetry instrumented rats, MK-8457 does not. Similarly, MK-8457 does not significantly affect BP in conscious telemetry instrumented dogs. In the ABPM study, MK-8457 was studied at a dose of 100 mg BID for 10 days, a dose projected to result in nearly complete 24 hour inhibition of SYK and ZAP70. At this dose, MK-8457 does not result in a statistically significant change in BP. The mean treatment difference (MK-8457-placebo) in 24 hr mean systolic and diastolic ABPM change from baseline was 2.02 and 1.57 mmHg, respectively.

Statistical Comparison of 24-Hour Change From Baseline in Ambulatory BP Parameters Following 10 Days of Multiple dosing of MK-8457 or Matching Placebo in Hypertensive Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MK-8457</th>
<th>Placebo</th>
<th>MK-8457 - Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean ± M</td>
<td>29.47 ± 2.60</td>
<td>28.60 ± 2.49</td>
<td>0.87 ± 0.52</td>
</tr>
<tr>
<td>CI 95%</td>
<td>0.31</td>
<td>0.52 - 4.56</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: These data illustrate that full SYK and ZAP70 inhibition with a selective inhibitor does not significantly impact BP preclinically or clinically in a sensitive population.

Disclosure: H. Houshyar, Merck Pharmaceuticals, 3; A. Bass, Merck Pharmaceuticals, 3; J. Boice, Merck Pharmaceuticals, 3; J. Ellis, Merck Pharmaceuticals, 3; P. Fanelli, Merck Pharmaceuticals, 3; T. Freshwater, Merck Pharmaceuticals, 3; J. Guo, Merck Pharmaceuticals, 3; K. Hoagland, Merck Pharmaceuticals, 3; J. Kerr, Merck Pharmaceuticals, 3; A. Northrup, Merck Pharmaceuticals, 3; M. Maddess, Merck Pharmaceuticals, 3; J. Miller, Merck Pharmaceuticals, 3; M. Rudy, Merck Pharmaceuticals, 3; S. Vincent, Merck Pharmaceuticals, 3; J. Wolf, Merck Pharmaceuticals, 3; H. Weng, Employee of Merck Co., 3; G. Zingaro, Merck Pharmaceuticals, 3; G. Marcatonio, Merck Pharmaceuticals, 3;
Background/Purpose: ABP 501 is being developed as a biosimilar to adalimumab, a recombinant monoclonal antibody that binds tumor necrosis factor alpha (TNF) thus inhibiting engagement of TNF receptors and initiation of consequent proinflammatory signaling. Although adalimumab and intended biosimilars share the same amino acid sequence, differences will likely exist in product quality attributes due to differences in proprietary expression systems, bioprocess and purification. Equivalence of product quality attributes, especially demonstration of comprehensive functional equivalence, is of primary importance during stepwise development of a biosimilar in order to provide confidence for similar clinical safety and efficacy in patients, including extrapolation to all indications of use.

Methods: The similarity assessment of biological activity included testing binding of ABP 501 and adalimumab to soluble TNF by surface plasmon resonance and to cell-surface expressed TNF (mbTNF) in a competitive imaging cytometry-based assay. The similarity assessment for F(ab')2-mediated activity included blocking TNF-induced caspase activation, IL-8 secretion and cytotoxicity. Inhibition of TNF activity in healthy volunteer blood samples stimulated ex vivo was also compared. To assess Fc-mediated functions, binding to the neonatal Fc receptor (FcRn) was measured in a competitive cell-based assay and to FcγRIIIa (158V) by AlphaISA™. To confirm similarity in Fc-mediated functions, antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed using cells expressing mbTNF and NK92-M1 cells expressing FcγRIIIa (158V). Complement-dependent cytotoxicity (CDC) was also tested, using complement and cells expressing mbTNF. Data from up to three lots of each antibody were assessed in the described assays as part of the initial similarity assessment.

Results: Equilibrium binding affinity to TNF was similar between ABP 501 (48-52 pM) and adalimumab (48-53 pM). Binding to mbTNF was also similar between ABP 501 (100-106% relative binding) and adalimumab (100-111%). Relative potency in the caspase activation assay was similar between ABP 501 (103-107%) and adalimumab (100-110%). Dose response profiles and resulting EC50 values in the IL-8 secretion (192-294 pM for ABP 501 and 156-253 pM for adalimumab), cytotoxicity (390-457 pM for ABP 501 and 391-544 pM for adalimumab) and whole blood assays, measuring both MCP-1 and MIP-1 beta production, were also similar between ABP 501 and adalimumab. Binding to FcRn was similar between ABP 501 (86-94%) and adalimumab (92-114%) as was binding to FcγRIIIa (158V) comparing ABP 501 (103-113%) to adalimumab (92-94%). The dose response profile for ADCC (103% relative cytotoxicity for ABP 501 and 107% for adalimumab) and CDC (97% relative cytotoxicity for ABP 501 and 93% for adalimumab) were also similar.

Conclusion: Results from an initial similarity assessment demonstrate that ABP 501 is functionally highly similar to adalimumab in multiple sensitive preclinical pharmacologic assays.

Disclosure: T. Born, Amgen, 3, Amgen, 1; J. Velayudhan, Amgen, 3, Amgen, 1; Y. F. Chen, Amgen, 3, Amgen, 1; H. Thomas, Amgen, 1, Amgen, 3; C. Pastula, Amgen, 3, G. Maher, Amgen, 3; R. Brown, Amgen, 3.


Background/Purpose: Adalimumab is a recombinant IgG1 monoclonal antibody that binds to TNFα blocking its interaction with p55 and p75 cell surface receptors. ABP 501 is being developed as a biosimilar candidate to adalimumab; it contains a fully human recombinant monoclonal antibody with the same amino acid sequence. Evidence from analytical comparisons indicates that ABP 501 is highly similar to adalimumab. This report describes the pharmacokinetics (PK) results of ABP 501 compared with adalimumab sourced from the United States (US).

Methods: This was a single-blind, single-dose, parallel-group study in healthy male and female subjects, 18 to 45 years of age with a body mass
Results: Pharmacokinetics: A total of 67 subjects received ABP 501 and 69 subjects received adalimumab. Following a single dose, the adjusted least square (LS) GM of Cmax and AUCinf for ABP 501 were 3.22 µg/mL and 2140 µg.h/mL. The adjusted LS GM of Cmax and AUCinf for adalimumab were 3.11 µg/mL and 1920 µg.h/mL. Ratios of adjusted LS GM (90% CIs) between ABP 501 and adalimumab for Cmax and AUCinf were 1.04 (0.96, 1.12) and 1.11 (1.00, 1.24). The 90% CIs of these ratios were fully contained within 0.80 to 1.25 interval, confirming PK equivalence between ABP 501 and adalimumab.

Safety: There were no deaths, treatment-related serious adverse events, or treatment-related adverse events leading to discontinuation from the study. The most frequently reported treatment-related AEs included headache, nausea, nasopharyngitis, and oropharyngeal pain.

Immunogenicity: No pre-existing anti-drug antibodies (ADA) were detected at baseline. In the ABP 501 treatment group, 36 (54%) subjects developed binding antibodies and 12 (18%) developed neutralizing antibodies. In the adalimumab treatment group, 38 (55%) subjects developed binding antibodies and 15 (22%) developed neutralizing antibodies.

Conclusion: Results of this phase 1 study demonstrated PK equivalence of ABP 501 following a single 40-mg SC injection relative to that after a 40-mg SC injection of adalimumab sourced from the US. Similar ADA rates were observed in healthy subjects.

Disclosure: P. P. Kaur, Amgen, 1, Amgen, 3; V. Chow, Amgen, 1, Amgen, 3; N. Zhang, Amgen, 3; M. Monexes, Amgen, 1; R. Markus, Amgen, 1, Amgen, 3.

1506
Incidence of Adverse Events in Patients Treated with Intended Copies of Biologic Therapeutic Agents in Colombia and Mexico. Leonor A. Barile-Fabris1, Fedra Irazoque-Palazuelos2, Ramiro Hernandez Vazquez3, Sandra Carrillo Vazquez4 and R. Guzman5. 1Hospital Especialidades CMN, Mexico City, Mexico, 2Centro Medico Nacional ‘20 de Noviembre’ ISSSTEE, Mexico City, Mexico, 3Hospital de Especialidades Dr. Bernardo Sepulveda Gutierrez, Mexico, Mexico, 4Hospital Angeles Lindavista, Mexico DF, Mexico, 5IDEARG, SaludCoop, Bogota, Colombia.

Background/Purpose: A biosimilar is a copy of an approved biologic therapeutic agent that has undergone rigorous evaluation to ensure that it is similar to the innovator in physicochemical characteristics, efficacy, and safety. In many countries, there are biologic products available that have not undergone such evaluation and thus should be labeled “intended copy”. It is critical to examine the safety profile of these intended copies to ensure that patients receive the best medical care available. The purpose was to evaluate the incidence of adverse events reported by patients treated with intended copies of etanercept (Infinitam/Enatan) and rituximab (Kikuzubam).

Methods: These data are a compilation of observations from four hospitals in Mexico and Colombia. Patients with rheumatic diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, were treated with Infinitam/Etanar or Kikuzubam. Patients were followed from initiation of treatment till first experience of an adverse event. Based on the nature and severity of the adverse event, treatment was continued, interrupted, suspended, or discontinued as determined by the treating physician.

Results: A preliminary analysis was performed of 219 patients with various diagnoses treated with Infinitam/Etanar (14) or Kikuzubam (205) in the four hospitals. Among patients receiving treatment, 10 (4.6%) in Infinitam/Etanar and 101 (46.1%) on Kikuzubam experienced at least one treatment-related adverse event (AE). Of these, 86.7% were female, and the median age was 51.9 years (range: 22 – 93 years). The median duration of disease was 14.5 years (range: 1 – 67 years). Overall, although the majority of the AEs reported (98/118, 83.1%) were Grade 2 or less, there were several reports of Grade 3 (13/118, 11.0%) and Grade 4 (7/118, 5.9%) AEs; there were no Grade 5 AEs reported for any agent. The time to the first experience of an AE from initiation of intended copy therapy was ranged from 0 – 50 months with 38 (36.2%) patients experiencing AEs on the same day as the first treatment.

Conclusion: A significant percent (14.3%) of patients receiving Infinitam/Etanar or Kikuzubam, intended copies of etanercept and rituximab, respectively, experience Grade 3/4 AEs with a very short time to onset.

Reference

Disclosure: L. A. Barile-Fabris, Abbvie, Pfizer, UCB, Roche, Janssen, 5, Abbvie, Pfizer, UCB, Roche, Janssen, 8, F. Irazoque-Palazuelos, Bristol-Myers Squibb, Janssen, Pfizer, and Roche, 2, Bristol-Myers Squibb, janssen, Pfizer, and Roche, 8, R. Hernandez Vazquez, Abbvie, Roche, UCB and BMS, 2, Abbvie, Roche, UCB and BMS, 8, S. Carrillo Vazquez, Pfizer, Roche, Bristol, 8, Janssen, Roche, Pfizer, Bristol, 5, R. Guzman, None.
Patient Perspectives on the Introduction of Subsequent Entry Biologics in Canada. Sunee Sekhon1, Raman Rai2, Debbie McClory3, Carolyn Whiskin4, Melissa Deamude4, Cynthia Mechi5, Lauri Vanstone5, Aijesh Shah6, Arthur N. Lau4 and William Bensen1. 1Division of Rheumatology, McMaster University, Hamilton, ON, 2Rheumatology Health Team, Dr. Suneet Sekhon1, Raman Rai 1, Debbie McClory 2, Carolyn Patient Perspectives on the Introduction of Subsequent Entry Biologics 1507, None; 1Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 2Inha University Hospital, Incheon, South Korea, 3Catholic University of Daegu School of Medicine, Daegu, South Korea, 4Research Medical Complex Vashe Zdorovie, Kazan, Russia, 5CELLTRION, Inc., Incheon, South Korea, 6Chungnam National University Hospital, Daejeon, South Korea, 7Ajou University Hospital, Suwon, South Korea.

Background/Purpose: Pharmacokinetic equivalence and similarity of clinical efficacy, safety and immunogenicity had been demonstrated between CT-P10 and Innovator Rituximab (RTX) in the Phase I/II clinical trial. The purpose of this analysis was to demonstrate the impact of anti-drug antibody (ADA) on efficacy and safety of CT-P10 and RTX in patients with rheumatoid arthritis (RA) over week 24.

Methods: A total of 154 RA patients were randomized 2:1 to receive 2 infusions (1000 mg, 2 week interval) of either CT-P10 (n=103) or RTX (n=51), and efficacy, safety and immunogenicity were assessed during the study. Electrochemiluminescent (ECL) assay was used to assess immunogenicity in this study since this assay is about 10 times more sensitive than the enzyme-linked immuno sorbent assay (ELISA) which was used in the historical rituximab trials.

Results: The proportion of patients who developed ADA at week 24 was exactly same (17.6% each) in both CT-P10 and RTX treatment groups. Similar proportion of patients achieved ACR20 and the European League Against Rheumatism (EULAR-20) responses after the CT-P10 and RTX treatment in both ADA (+) and (-) subgroups (Table 1). The interferon of the ADA on the clinical response was not significant in both treatment groups.

The safety profiles of CT-P10 were generally comparable to those of RTX in both ADA (+) and (-) subgroups. The proportion of patients with adverse event (AE) were 55.6% and 49.4% for CT-P10-ADA (+) and (-) subgroups and 89.9% and 76.6% for RTX-ADA (+) and (-) subgroups, respectively. Serious AE was reported in 11.1% and 15.6% in the CT-P10-ADA (+) and (-) subgroups and 22.6% and 16.2% in the RTX-ADA (+) and (-) subgroups, respectively. The proportion of patients with AE due to infections and infusion related reactions was also similar between the treatment groups in ADA (+) and (-) subgroups.

Table 1. The Impact of ADA on Efficacy in Treatment Groups (%)

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>CT-P10</th>
<th>RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (+)</td>
<td>67.5</td>
<td>62.5</td>
</tr>
<tr>
<td>ADA (-)</td>
<td>65.7</td>
<td>75.0</td>
</tr>
<tr>
<td>ADA (+)</td>
<td>85.7</td>
<td>85.7</td>
</tr>
<tr>
<td>ADA (-)</td>
<td>80.5</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Note: No statistical difference in all comparisons between ADA subgroups or treatment groups (p>0.05). EULAR (CRP/ESR): the proportion of patients with moderate or good response

Conclusion: The development of ADA did not affect clinical response or safety profiles in RA patients treated with CT-P10 or RTX, and the magnitude of impact of ADA was similar in both treatment groups. These results
confirmed the comparability of CT-P10 to those of RTX in efficacy and safety over 24 weeks regardless of the immunogenic reaction.

Reference

Disclosures

|-----------|----------------|------------------------|----------------|----------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|

| 1510 |

A Randomized, Double-Blind, Three-Arm, Parallel Group, Single-Dose Study to Compare the Pharmacokinetics, Safety, and Tolerability of Three Formulations of Infliximab (CT-P13, EU-sourced Infliximab and US-sourced Infliximab) in Healthy Volunteers

Methods:
In this double-blind, randomized, parallel group, single-dose study, a total of 213 healthy volunteers were randomized 1:1:1 to receive a single dose (5 mg/kg) of CT-P13, EU-INX or US-INX by intravenous infusion on Day 1 followed for 8 weeks. The primary endpoints were maximum serum concentration (Cmax) and area under the concentration-time curve from time zero to the last quantifiable concentration (AUCLast) and area under the concentration-time curve from time zero to infinity (AUClinf) of CT-P13, EU-INX and US-INX. A total of 31 serum blood samples were obtained for the primary PK analysis, and safety and tolerability were also evaluated up to 8 weeks. Similarity of systemic exposure (Cmax, AUCLast and AUClinf) was considered to be demonstrated if the 90% confidence interval (CI) for the ratio of geometric means was within the acceptance interval of 0.8 to 1.25 for the following comparisons: CT-P13 vs EU-INX, CT-P13 vs US-INX, and EU-INX vs US-INX.

Results: The baseline demographics for 213 subjects among 3 study groups were highly similar. The PK parameters in the study groups were highly similar (Table 1). The 90% CI for the ratios of Cmax, AUCLast and AUClinf were within the acceptance interval of 0.8 to 1.25 for the comparisons of CT-P13 to EU-INX, CT-P13 to US-INX and EU-INX to US-INX.

Adverse events (AEs) were similar between 3 study groups with AEs related to the study drug reported by 39.4%, 23.9%, and 42.3% of subjects in CT-P13, EU-INX and US-INX groups, respectively. The majority of AEs related to the study drug reported in the study groups was Grade 1, and there was only 1 AE reported as Grade 3 in US-INX group based on Common Terminology Criteria for Adverse Events. No serious AEs related to the study drug were reported, and no AEs led to the withdrawal of a subject from the study. All AEs related to study drug were resolved by the end of the study.

Table 1. Pharmacokinetic Exposure Estimates (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>CT-P13 (N=71)</th>
<th>EU-INX (N=71)</th>
<th>US-INX (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>127.6 ± 21.6</td>
<td>121.3 ± 19.7</td>
<td>119.9 ± 19.5</td>
</tr>
<tr>
<td>AUCLast (h*mg/mL)</td>
<td>31.83 mg/L</td>
<td>30.66 mg/L</td>
<td>30.20 mg/L</td>
</tr>
<tr>
<td>AUCinf (h*mg/mL)</td>
<td>32.82 mg/L</td>
<td>32.82 mg/L</td>
<td>32.82 mg/L</td>
</tr>
</tbody>
</table>

Conclusion: Equivalence of PK in terms of Cmax, AUCLast and AUClinf was demonstrated and comparable safety profiles were observed in the comparisons of CT-P13 to EU-INX, CT-P13 to US-INX and EU-INX to US-INX in healthy volunteers.

References

Disclosure: D. H. Yoo, Celltrion, Inc.; W. Park, Celltrion, Inc.; S. C. Shim, None; C. H. Suh, None; J. Y. Yun, Celltrion, Inc.; T. Pyo, Celltrion, Inc., S.

1510

Blockade of TLR5 Ligation Is a Novel Strategy for RA Therapy
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Background/Purpose: TLR5 expression is highly elevated in RA and CIA lining and sublining macrophages and endothelial cells compared to non-arthritic controls. A didactically, expression of TLR5 in RA myeloid cells closely correlates with disease activity score, indicating that ligation of TLR5+ cells intensifies disease progression. Hence studies were conducted to determine whether dysregulation of TLR5 function can be utilized as a promising strategy for RA treatment.

Methods: CIA mice were treated with IgG or anti-TLR5 antibody on days 23, 27, 30, 34, 37, 41, 44 and 48 and mice were sacrificed on day 49 post induction. CIA joint inflammation and bone erosion were assessed by measuring ankle circumference as well as H&E and TRAP staining. Joint myeloid cell recruitment and their phenotype were evaluated by F480 and iNOS immunostaining. Proinflammatory factors secreted from CIA joint were quantified by ELISA in the IgG and anti-TLR5 antibody treated mice. Remodeling of mouse bone marrow progenitor cells into M1 macrophages was examined following flagellin treatment by real-time RT-PCR and FACs analysis.

Results: To uncover whether disruption of TLR5 ligation is a potential for RA therapy, CIA mice were treated with monoclonal anti-TLR5 antibody or IgG control. Results from these experiments demonstrate that CIA mice treated with anti-TLR5 antibody have markedly lowered joint swelling starting on day 44 until day 48 post onset compared to the IgG group. Consistently, histological studies document that anti-TLR5 treatment was capable of reducing CIA synovial inflammation, joint lining thickness and bone erosion by 40% compared to the control mice. We next found that anti-TLR5 treatment impairs migration of circulating myeloid cells into the CIA joint. To better understand the mechanism by which blockade of TLR5 function relieves arthritis, joint myeloid cell phenotype was evaluated in CIA synovial tissues. Histological examination demonstrated that the frequency of INOS+ M1 macrophages is 40% higher in the IgG treated CIA mice compared to anti-TLR5 group. Corroborating with this notion, M1 macrophage producing factors, IL-6 and CCL22, are significantly suppressed in the CIA joints following anti-TLR5 treatment compared to the control group. Confirming the findings in vivo, we established that flagellin ligation to TLR5 can transform naive mouse myeloid cell into M1 macrophages. This differentiation process was assessed by transcription of TNF and IL-6 and frequency of CDB0 staining which was dysregulated by blockade of TLR5. Moreover, we show that TLR5+ bone eroding osteoclasts are 30% higher in the control group compared to CIA joints treated with anti-TLR5. These findings are in alignment with our recent data, revealing that ligation of TLR5 plays a key role in osteoclast formation through a mechanism that is predominantly comprised of myeloid cells and their production of RANK and TNF-a.

Conclusion: We conclude that TLR5 ligation promotes joint myeloid cell infiltration and can further remodel the newly recruited myeloid cells into M1 macrophages or fully mature osteoclasts suggesting that blockade of TLR5 can be employed as a promising new therapeutic target in RA.

Disclosure: S. J. Kim, None; Z. Chen, None; A. Essani, None; M. Volin, None; S. Volkov, None; W. Swedler, None; S. Arami, None; N. J. Sweiss, None; S. Shahara, None.

1511

COVA322: A Clinical Stage Bispecific TNF/IL-17A Inhibitor for the Treatment of Inflammatory Arthritis

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Background/Purpose: Biologic therapeutics such as TNF inhibitors have revolutionized the treatment of inflammatory diseases, including rheumatoid arthritis (RA), psoriasis and psoriatic arthritis. However, there is still a significant
unmet medical need in these indications. In RA for example, only about half of all patients achieve an ACR50 score and many become refractory to anti-TNF treatment after a few years. Several studies in preclinical mouse models of arthritis have demonstrated that simultaneous treatment with antibodies to TNF and IL-17 is significantly more efficacious than treatment with either antibody alone. We present here the non-clinical safety package of COVA322, a bispecific TNF/IL-17A inhibitor that is currently being tested in a Phase Ib/Ila study in psoriasis patients.

Methods: COVA322 was analyzed for its cross-reactivity in a GLP study with human and Cynomolgus tissues. In addition, a cytokine release study using human whole blood cells was performed. In Cynomolgus monkeys, COVA322 was tested in a single dose PK/dose range finding study and a GLP 4-week repeat-dose toxicity study at 5, 25 and 100mg/kg doses.

Results: COVA322 showed no unexpected tissue cross-reactivity and no indication for the potential to cause a cytokine release syndrome. COVA322 was well tolerated in single- and repeat-dose toxicity studies in Cynomolgus monkeys. In particular, no adverse effects on the cardiovascular-, respiratory- and central nervous system were observed. The toxicity package (no observed adverse effect level (NOAEL) = 100mg/kg) support the clinical starting dose as well as the anticipated clinical dose range.

Conclusion: COVA322 is a unique bispecific TNF/IL-17A inhibitor, which was well tolerated in non-clinical safety studies. The non-clinical data package supports the planned dose range for the currently ongoing first in man, single dose escalation, tolerability, safety, PK and efficacy Phase Ib/Ila study in psoriasis.

Disclosure: W. Lembke, Covagen AG, 3; Covagen AG, 1; B. Schliereth, Covagen AG, 3; Covagen AG, 1; J. Bertschinger, Covagen AG, 4; Covagen AG, 1; Covagen AG, 3; D. Grahlukogli, Covagen AG, 4; Covagen AG, 1; Covagen AG, 3; M. Locher, Covagen AG, 1; Covagen AG, 3.

1512

Therapeutic Efficacy of a Novel Oral Small Molecule Macrophage Migration Inhibitory Factor [MIF] Inhibitor: A Promising Safe & Efficacious Treatment for Rheumatoid Arthritis. Anderson Gaweco1, Samantha Palmer1, Rambon Shamilov 1, Caroline Stremnitzer 1, Michael Konrad1, Covagen AG, 1; Gregg Crichlow1, William Windsor2, Ellen M. Ginzieler2 and Jeffrey Tinley3, Innovimmune Biotherapeutics, Brooklyn, NY, SUNY- Downstate Medical Center, Brooklyn, NY.

Background/Purpose: Macrophage migration inhibitory factor [MIF] is a cytokine secreted by activated T cells and macrophages that plays an important role in RA and autoimmune disease pathogenesis. MIF exerts its proinflammatory effects through its direct biological function and downstream signaling events following receptor engagement. The therapeutic utility in targeting MIF has been established, demonstrating preclinical efficacy in several RA and autoimmune disease models. Lead development efforts of several proprietary novel chemical scaffolds of the INV-88 portfolio of small molecule MIF inhibitors led to the identification of an INV-88 clinical compound candidate demonstrating potent in vitro pharmacological effects against proinflammatory effector cells and cytokines coupled with optimal druggable properties. To establish the preclinical Proof of Concept in RA prior to advancing to IND-enabling development, the in vitro preclinical efficacy of INV-88 was assessed in the mouse CIA model.

Methods: Disease was induced in DBA1 mice according to a standard protocol. Prior mouse in vivopharmacokinetic [PK] studies determined the optimal oral bioavailability and drug exposure of INV-88 enabling p.o. dosing in this study. To assess the preclinical efficacy in a mouse CIA model, INV-88 was administered orally for 7 days as a therapeutic treatment regimen following chicken collagen CII/CFA disease induction on day 0 and CII/IFA booster immunization on day 15 in DBA1 mice. Upon disease-onset, mice with a clinical arthritis score > 1 (Scale: 0–16) were randomized to receive 7-day dosing with INV-88 at 60 mg/kg (n=12) or comparator controls: Vehicle (n=11) or Dexamethasone [Dex] (n=9).

Results: Successful disease amelioration following INV-88 and Dexamethasone treatment was observed with statistically significant reduction of cumulative arthritis score of 3.72 +/- 0.36 [mean +/- SEM] (p<0.05) and 1.51 +/- 0.58 (p<0.001), respectively, in contrast to the vehicle group of 5.92 +/- 0.68. Significant rapid improvement in clinical disease scores in the INV-88 treated group was evident as early as arthritis day 2 (p=0.041) through end of study on arthritis day 7 (p<0.036). INV-88 was well tolerated and INV-88-treated mice were unremarkable with optimal body conditions.

Conclusion: The superior safety and therapeutic efficacy data following 7-day treatment of an orally bioavailable small molecule INV-88 MIF inhibitor provides the first compelling evidence ever reported of the preclinical utility of MIF inhibition and of a small molecule-based cytokine inhibitor.

These profound findings support advancing INV-88 into further IND-enabling development and highlight the potential promise of INV-88 as a safe & efficacious novel RA DMARD treatment.

Disclosure: A. Gaweco, Innovimmune Biotherapeutics Holding, LLC, 3; S. Palmer, Innovimmune Biotherapeutics Holding, LLC, 3; R. Shamilov, Innovimmune Biotherapeutics Holding, LLC, 3; C. Stremnitzer, Innovimmune Biotherapeutics Holding, LLC, 3; M. Fisher, Innovimmune Biotherapeutics Holding, LLC, 3; G. Crichlow, Innovimmune Biotherapeutics Holding, LLC, 5; W. Windsor, Innovimmune Biotherapeutics Holding, LLC, 3; E. M. Ginzieler, Innovimmune Biotherapeutics Holding, LLC, 3; J. Tinley, Innovimmune Biotherapeutics Holding, LLC, 3.

1513

Selection of Vagus Nerve Stimulation Parameters for a First-in-Human Study in Rheumatoid Arthritis: A Unique Translational Medicine Challenge. Frieda A. Koopman1, Y.akov Levine2, Mike Falatty2, Ralph Zitnik2, and Paul P. Tak4, 1Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 2SetPoint Medical Corporation, Valencia, CA, 3GlaxoSmithKline U.K. and Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Cholinergic anti-inflammatory pathway (CAP) activation by electrical vagus nerve stimulation (VNS) is being studied in rheumatoid arthritis (RA) trials (NCT01552941). CAP signaling proceeds sequentially through vagus and splenic nerves to splenic acetylcholine-secreting T cells, which in turn signal adjacent macrophages to diminish cytokine secretion after proinflammatory stimuli(1,2). VNS devices deployorize nerves by application of charge, modulated by varying output current (OC), pulse width (PW), and pulse frequency (F). Stimulation duration (D), and daily stimulation interval (SI) can also be varied. Optimally activating this complex neural-immune pathway created unique translational medicine challenges. Herein we report preclinical data guiding stimulation parameter selection for RA trials.

Methods: VNS stimulation parameter effect on cytokine production and tissue inflammation was studied in 5 models: 1) TNF production in rat systemic endotoxemia with VNS delivered by cervical vagus hook electrodes (HE); 2) morphometric measurement of ulceration in rat indomethacin-induced inflammatory enteritis using cervical vagus cuff electrodes (CE); 3) reduction in in vitro LPS-induced whole blood TNF release using VNS delivered chronically by implanted CE in normal canines; 4) improvement in endoscopic ulceration score after dextran sulfate sodium (DSS) colitis in rats using implanted CE; and 5) improvement in ankle swelling, joint histology and systemic cytokines in rat CIA using implanted CE.

Results: Selection of PW (200–250usec) and F (10Hz) was guided by prior clinical tolerability experience with VNS in epilepsy(3), OC titration experiments in rat endotoxemia/HE showed optimal CAP activation at 0.5–1.0mA, and was confirmed in canine CE. The implanted CE used in rodent experiments surrounded the entire carotid sheath rather than only the vagus nerves by application of charge, modulated by varying output current (OC), pulse width (PW), and pulse frequency (F). Stimulation duration (D), and daily stimulation interval (SI) can also be varied. Optimally activating this complex neural-immune pathway created unique translational medicine challenges. Herein we report preclinical data guiding stimulation parameter selection for RA trials.

Conclusion: Preclinical pharmacokinetic-pharmacodynamic-efficacy relationships are typically used to understand dose-response and guide dose selection for drug trials. CAP activation involves complex interactions between neuronal cell depolarization and immune effector cell function, complicating study of analogous stimulation parameter-response relationships. These experiments show that despite these hurdles, rational optimization of therapy delivery with “bioelectronic medicines” can be achieved. 1. Science 2011; 334:98 2. Neurology 2002; 59:S31 3. Crit Care Med 2007; 35:2762

Disclosure: F. A. Koopman, None; Y. Levine, SetPoint Medical, 3; SetPoint Medical, 1; M. Falatty, SetPoint Medical, 1; SetPoint Medical, 3; R. Zitnik, SetPoint Medical, 3; SetPoint Medical, 1; P. P. Tak, SetPoint Medical, 2.
Background/Purpose: A number of JAK kinase (JAK) inhibitors are being actively investigated for treatment of rheumatoid arthritis (RA), including tocafitinib, baricitinib, filgotinib (GLPG0634), and decernotinib (VX-509). However, it is unclear how these drugs may differentiate from each other in the clinic based on their profiles of JAK-dependent cytokine inhibition. The aim of this work was to provide an integrated modeling approach using knowledge of both in-vitro and whole cell JAK inhibition potencies and plasma pharmacokinetics to better understand and predict cytokine inhibition for clinical JAK inhibitors in the context of clinically-meaningful doses.

Methods: IC50 values for IFNα, IFNγ, IL-6, IL-15, IL-21, IL-10, IL-12, IL-23 and erythropoietin (EPO) signaling of tocafitinib, baricitinib, filgotinib, and decernotinib were measured in total lymphocytes, CD34+ cells (EPO) and CD3+ cells (IL-6) in human whole blood by a flow cytometry-based assay, quantifying the phosphorylation state of various STAT proteins. Human daily average plasma concentrations (C0) were used to predict for decernotinib (5 mg SID: 68 nM), baricitinib (4 mg QD: 32 nM), and filgotinib (200 mg QD: 527 nM). Confidence in the prediction of decernotinib pharmacokinetics was considered low because high-in-vitro metabolic instability and was not assessed further. Percent levels of cytokine inhibition (IC50 = 100% C0/(C0 + C0)) were determined at clinically-meaningful doses.

Results: Each JAK inhibitor showed a relatively similar profile of cytokine inhibition versus type I and II interferons (IFNα, IFNγ), the common γ-chain cytokines IL-6 and IL-23 (Figure 1). Each also showed some decrease in potency for IL-10, IL-12 and 23, and EPO. Comparing between JAK inhibitors, tofacitinib and baricitinib were overall more potent inhibitors than decernotinib and filgotinib. Clinical pharmacokinetics of tofacitinib, baricitinib, and filgotinib were available and used to further compare predicted cytokine profiles of inhibition in patients with RA. The profile of cytokine inhibition for each JAK inhibitor was in general similar at clinically-meaningful doses (Figure 1). While the pharmacokinetics were unavailable for decernotinib, the clinical dose range being explored are consistent with filgotinib which showed similar in-vitro inhibitory potencies.

Conclusion: These analyses illustrate the importance of studying a broad range of JAK pairing potencies and clinical concentrations when comparing JAK-inhibitor compounds. Calculated profiles of cytokine inhibition for a number of JAK inhibitors in RA are in general similar when efficacious doses are considered, supporting the differentiated inhibition of these JAK inhibitors based on JAK pharmacology. Ultimately, only robust clinical testing will determine whether there are clinical differences between JAK inhibitors.
Background/Purpose: We examined Adalimumab’s effects on melanocortin receptor subtype (MC)1–5 gene expression in important leukocyte subsets in rheumatoid arthritis (RA). The melanocortin system is a neuro-immunomodulatory system with anti-inflammatory and tolerance inducing properties. It consists of MC1–5 and their ligands, the melanocortins: α-β-γ-melanocortin stimulating hormones (MSH) and ACTH. Especially CD4+ T helper (Th) lymphocytes and CD14+ monocytes express the genes of MC1, 2, 3 and 5. Binding of a melanocortin to its MC inhibits the nuclear translocation of transcription factor NFκB and thereby the synthesis of inflammatory mediators, such as TNFα, adhesionmolecules and NO. While the synthesis of the melanocortins is stimulated by TNF and IL-10, the synthesis of IL-10 is downregulated by melanocortin system. Therefore, it is not surprising, that the powerful melanocortin system is upregulated in inflammation. Adalimumab reduces circulating TNFα and MC expression. Thus the melanocortin system is upregulated in inflammation. A dalimumab reduces circulating TNF α, and is therefore supposed to down-regulate melanocortin synthesis and MC expression.

Methods: Blood was drawn at pre-start and at 4 months of Adalimumab 40 mg every other week. Leukocyte subsets were isolated by magnetic beads coated with CD4, CD8, CD14 and CD19 mAb. RNA was extracted and RT-qPCR performed with primers and probes specific to MC1–5, TNFα, TGFβ and IL-10.

Results: 6 females and 1 male with RA according to ACR criteria were examined. Mean age 48.0 ± 7.2 yrs (SD), disease duration 21 ± 31 months. 4 were treated with methotrexate 25 mg/w and 3 with leflunomide 20 mg/d. 3 patients took prednisolon, mean dose 6.67 mg/d. At start and 4 months therapy, CRP was 3.0 ± 2.21 and 2.9 ± 0.6 mg/L, (median ± SD), respectively, hemoglobin 8.4 ± 1.5 and 8.6 ± 0.4 mmol/L. DAS28 4.9 ± 1.5 and 2.0 ± 0.6. At 4 months none took prednisolon. Adalimumab significantly reduced MC2, 3 and 4 mRNA in CD8+, CD14+ and CD19+ leukocyte subsets. In CD4+ Th lymphocytes there was no uniform reaction on IL-10 was lowered in CD4+ and tended as TNFα to be so in CD14+ cells. TGFβ unchanged.

Conclusion: Here we show that Adalimumab down-regulates the MC2, 3 and 4 gene expression in the CD14+ monocytes in RA. Thus we have uncovered a new peripheral melanocortin signalling pathway through high MC4 in monocytes. Monocytes are known to have an anti-inflammatory autocrine circuit based on the melanocortins, previously thought to operate solely through MC3 as shown in experimental gouty arthritis. Interestingly, our results show that the MC1–5 gene expression of the CD4+ Th lymphocytes does not react uniformly to Adalimumab therapy. The CD4+ Th cell has a superior role in the immune reaction, as the central conductor of other cell types. Therefore, it is not surprising, that the powerful melanocortin system in just this very important cell type, seems to be controlled via several redundant mechanisms, interacting to exert fine tuning of the immune reaction.

Disclosure: M. Andersen, None; M. K. Meyer, None; I. Nagaev, None; O. Nagaeva, None; E. S. Wikberg, None; L. Mincheva-Nilsson, None; G. N. Andersen, None.

Analysis of Gene Expression Fluctuation with Abatacept Highlights the Involvement of the Proteasome Pathway As a Mechanism of Action of Abatacept in Rheumatoid Arthritis. C. Darambou, O. Vittecoq, G. Dzangue Tchoupou, M. A. d’Agostino, P. Gaudin, C. Gaillez, M. Le Bars, and T. Lequerre. Institute 105, Institute for Biomedical Research, University of Rouen, France; Rouen University Hospital, Rouen, France; AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France; University Hospital Grenoble, Grenoble, France; Formerly of Bristol-Myers Squibb, Ruei-Malmaison, France, Bristol-Myers Squibb, Rouen, France.

Background/Purpose: Abatacept (ABA) is a biologic therapy targeting T cells, which play a major role in the pathophysiology of RA. Overall, 57.1% of patients reached LDA (DAS28 [CRP] ≤ 3.2) after 6 months of treatment with Abatacept and MTX in the open-label ABA Power Doppler Ultrasoundography APPRAISE study, in patients with RA and inadequate MTX response. The objective of this study was to explore gene expression fluctuations and to identify the main molecular mechanisms that occur in a subset of ABA-treated patients according to their treatment response.

Methods: In this subset, 19 patients with active RA and inadequate MTX response were treated with approved doses of ABA and MTX. For this analysis, patients were categorized as ABA responders (R; DAS28 ≤ 3.2 [LDA]) (n = 14) or non-responders (NR; DAS28 > 3.2) (n = 5) following 6 months of treatment. Whole blood was collected in Paxgene tubes for each patient at baseline and 6 months. RNAs were hybridized to a whole human genome 4 × 44K microarray. Agilent slide to identify mRNA specifically dysregulated between baseline and 6 months in R and NR patients using GeneSpring GX software and a t-test with false discovery rate correction for multiple testing (p < 0.05). Gene ontology (GO), pathways analysis (curated WikiPathways) and text mining via Natural Language processing were performed to identify the molecular mechanisms regulated by ABA in R and NR. Correlations between gene expression fluctuation and changes in DAS28 were assessed to identify the impact of ABA treatment on disease activity.

Results: After 6 months of treatment with ABA, no genes were significantly differentially expressed in NR patients, whereas 935 genes were significantly differentially expressed in R patients (p < 0.05). Of these genes, 298 were down-regulated at 6 months and 637 were up-regulated compared with baseline. GO allowed us to identify GO terms enriched only in the list of the 637 up-regulated genes. All of these GO terms were relative to the mRNA process (p < 0.03). Pathways analysis allowed us to identify 15 curated pathways that were significantly enriched in R patients compared to NR patients (p < 0.05). The most significant pathways found to be in agreement with the GO analysis were HS mRNA processing WP41 45374 (p = 0.002) and HS-Proteasome Degradation WP183 45274 (p = 0.001). Among the 935 genes identified, 7 up-regulated genes were significantly involved in the proteasome degradation pathway, including 65 proteins in humans. Six gene expression fluctuations (among 935) between baseline and 6 months were correlated with variation of DAS28: 3 positive and 3 negative correlations (p < 0.01).

Conclusion: Comparison of gene expression fluctuations between R and NR to abatacept treatment highlighted the 935 genes differentially expressed only in R in our cohort. As the proteasome is required for essential immune functions of activated CD4(+) T cells, and can be defined as a molecular target for suppression of deregulated and unwanted T-cell-mediated immune responses, this study suggests a new mechanism of action for abatacept in patients with LDA. Small sample size may be a limitation. 1. D’Aagnosto MA, et al. Arthritis Rheum 2012;64(Suppl):S532.

Disclosure: C. Darambou, None; O. Vittecoq, None; G. Dzangue Tchoupou, None; M. A. d’Agostino, Bristol-Myers Squibb, AbbVie; B. Gaudin, None; C. Gaillez, Bristol-Myers Squibb, Novartis; A. M. Le Bars, Bristol-Myers Squibb; T. Lequerre, Bristol-Myers Squibb, 2.

1518

Disentangling the Effects of Tocilizumab on Neutrophil Survival and Function. Timo Gaber, Martin Haehne, Cindy Strehl, Paula Hof, Yvonne Dorrer, Eugen Feist, Gerd Burmester and Frank Buttgerit. Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany; Berlin-Brandenburg School of Regenerative Therapies (BSRT), Berlin, Germany; German Rheumatism Research Center (DRFZ), Berlin, Germany; Charité University Medicine, Berlin, Germany.

Background/Purpose: The synovial tissue in rheumatoid arthritis (RA) represents a hypoxic environment with up-regulated pro-inflammatory cytokines and cellular infiltrates including neutrophils. Tocilizumab, a humanized IgG1 monoclonal antibody directed against the interleukin (IL) 6 receptor, is a potent biologic treatment for RA but the inhibition of the IL6 pathway may also cause unwanted effects such as a decrease in blood neutrophil counts and occasionally high grade neumoptasia.

In order to understand both therapeutic and adverse effects of IL6 receptor inhibition, we analysed the effects of tocilizumab on survival, phagocytic capacity and energy metabolism of neutrophils under normoxic versus hypoxic conditions.

Methods: Human neutrophils were purified, pre-treated with varying doses of tocilizumab and, for comparison, dexamethasone or vehicle and finally stimulated with lipopolysaccharide (LPS) or left unstimulated. Cells...
were then incubated under normoxic (18% O₂) or hypoxic (1% O₂) condi-
tions and subsequently analysed.

**Results:** Both neutrophil survival and energy availability were signif-
ically decreased by tocilizumab in a dose-dependent manner in LPS stimu-
lated cells, but to a greater extent under normoxia as compared to hypoxia.
We also found LPS stimulated phagocytic activity of neutrophils to be
significantly higher under hypoxia versus normoxic conditions, but this difference was significantly reduced by tocilizumab.

**Conclusion:** Tocilizumab is known for both beneficial effects and a higher incidence of neutropenia (>1000 bis 1/10) when treating RA patients. Our results suggest that both effects can at least in part be explained by a
reduction in neutrophil survival and a dose-dependent inhibition of a hypoxia-
induced phagocytic activity of infiltrating hypoxic neutrophils, mimicking
conditions of the inflamed joint environment.

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**1519**

**Implementation of an Acid Dissociation Procedure for Immunogenicity
Detection in Patients Treated with Anti-TNF Drugs.** Francisco Llaneres-
Tello1, Jose Rosas2, Jose M. Senabre-Gallego3, Gregorio Santos-Soler3,
Carlos Santos-Ramirez3, Esteban Salas-Heredia2, Xavier Barber2, Juan Mo-
lina2, Catalina Cano1, Ana Pons1 and Group Aire-MB1. 1Hospital Marina
Baixa, Villajoyosa, Spain, 2Hospital Marina Salud, Denia, Spain, 4CIO, Elche, Spain.

**Background/Purpose:** To evaluate the application of an acid dissociation
procedure in monitoring patients with subtherapeutic serum concentrations
of infliximab (IFX), adalimumab (ADL) and etanercept (ETN), using an
immunoassay commercialized (Promonitor®-ETN, Progenika Biopharma,
S.A., a Grifols Company).

**Methods:** For 3 years 612 trough samples were analyzed of 247 patients
with different rheumatic pathologies treated with IFX (44 patients, 94
samples), ADL (123 patients, 289 samples) and ETN (80 patients, 229
samples). With the standard technology, ADA was detected in 27, 15 and 0%
respectively of the patients treated with IFX, ADL and ETN respectively, coinciding always with a level of undetectable drug.

92 samples quantified with detectable but subtherapeutic drug levels at the
standard treatment (31 samples of 25 patients with IFX <2 mg/L, 38 samples
of 26 patients with ADL <3 mg/L and 23 samples of 18 patients with ETN <2
mg/L), were analyzed for ADA after submitting them to an acid pre-
treatment. The protocol of acidification consisted of the incubation of the
serum during 15 minutes with acetic acid 300 mM and later neutralization
with base.

**Results:** Anti-ADL antibodies were detected in 46% of the patients with subtherapeutic levels of ADL, which
were undetectable with the standard assay (18 samples, 12 patients, middle
age: 55 years, 67% women, diagnoses: 8 ankylosing spondylitis (BASDAI:
4.8±1.5), 3 rheumatoid arthritis and 1 psoriatic arthritis (DAS28: 3.5±0.2).
In 7 cases ADA’s detection after acidification was produced already in the
first request of monitoring at 6 months of initiated the treatment. In other 3
cases, ADA’s positive after dissociation confirmed a previous positive with
the standard assay. Initially the treatment was kept with ADL in 5 patients,
which ended up by turning out to be positives with the standard technology
between 2 and 6 months after the positive with dissociation. Finally, in all the
patients a change of treatment was necessary for lack of clinical response,
being chosen by another anti-TNF before ADA’s evidence. ADL’s maximum
concentration in the samples with a positive result was of 1.8 mg/L and the
title of detected antibodies ranged between 35 and 282 UA/mL. Anti-IFX not
anti-ETN antibodies were not detected after the acidification of the samples
by subtherapeutic concentrations of these two drugs.

**Conclusion:**

1) The acid pre-treatment of the samples increases the sensibility of the
test of detection of anti-drug antibodies breaking possible drug-
antibody complexes.

2) The monitoring of immunogenicity in patients with subtherapeutic
levels of ADL, following a protocol of acid dissociation, has allowed us
to detect in a precarious way ADA’s presence in these patients
contributeing to the optimization of the treatment.

This study has received a grant from Spanish Society for Rheumatology.

**Disclosure:** S. Bandyopadhyay, Bristol-Myers Squibb, 3; M. Maldonado, Bristol-
Myers Squibb, 3, Bristol-Myers Squibb, 1; M. Schifff, Bristol-Myers Squibb, Abbvie, 5;

**1520**

**Gene Expression Analyses of Abatacept and Adalimumab-Treated Patients from the Ample Trial.** S Bandyopadhyay1, M Maldonado1, M Schifff2, ME Weinblatt3, Roy Fleischmann4 and SE Connolly1. 1Bristol-
Mayers Squibb, Princeton, NJ, 3University of Colorado, Denver, CO,
2Brigham and Women’s Hospital, Boston, MA, 4University of Texas South-
western Medical Center, Dallas, TX.

**Background/Purpose:** The distinct mechanisms of action (MoA) of
abatacept (ABA) and adalimumab (ADA) are expected to manifest in
different transcriptional profiles in RA patients (pts). This post-hoc analysis
assessed peripheral blood gene expression in RA pts from AMPLE treated
with ABA or ADA, and the pharmacodynamic (PD) changes between
baseline and month (Mth) 3 that correlate with the magnitude of clinical
response.

**Methods:** The AMPLE study has been described elsewhere. Peripheral
blood mRNA was isolated from 566 pts at baseline and 3 mths. Whole
genome transcriptional profiling used Affymetrix U219 chips, representing
18,567 genes. Differentially expressed genes from baseline to Mth 3 were identified for each treatment (fold-change >0.5, adjusted p-value <0.05)
using Bioconductor/LIMMA. PD-response analysis was done by placing pts in
non-overlapping groups on their ACR response at M th 3. From this,
consensus-stabilized k-means clustering was used to reduce the data into the
minimal number of PD clusters for ABA - and ADA-treated pts. Genes
within these clusters were analyzed by gene-set enrichment analysis (GSEA)
to estimate the over-representation of molecular pathways.

**Results:** Pt s treated with ABA had 226 genes significantly up-regulated by
Mth 3, while ADA treatment had significant up-regulation of 634 genes (Figure). There was overlap on 221 of the genes up-regulated. Treatment with
ABA resulted in the down-regulation of 179 genes, while treatment with
ADA resulted in the down-regulation of 513 genes. The therapies overlapped on 172 genes. Across therapies, many genes were significantly regulated in one group but not the other (Figure, black dots). K-means clustering based on
ACR response groups at M th 3 resulted in 6 unique patterns of PD per
treatment. GSEA identified 118 pathways enriched across the 6 ABA clusters
and 119 pathways enriched in the 6 ADA clusters. Among the pathways
showing PD response for both therapies were “NFAT in immune response,”
“inhibitory PD-1 signaling in T cells” and “T-cell subsets: cell surface
markers”.

**Conclusion:** ABA was more selective on modulating gene expression in
RA pts, although there was overlap in genes impacted by both therapies. The
treatment- and response-dependent clusters might reflect differences related to
MoA leading to similar clinical outcomes. Further delineation of the pathways
will elucidate how these two agents with unique mechanisms provide
comparable efficacy with some differences in safety and tolerability.


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1521
Sustained Improvements in Magnetic Resonance Imaging Outcomes with Abatacept Following the Withdrawal of All Treatment in Patients with Early Rheumatoid Arthritis.

Bykerk3, B G Combe 4, J C DiCarlo 1, D E Furst 5, TWJ Huizinga 6, C S Karyekar, D Wong, Philip G. Conaghan 7 and P Emery. 8

Background/Purpose: Biologic treatment can lead to improved clinical outcomes in early RA. In the Assessing Very Early Rheumatoid arthritis Treatment (AVERT) study, abatacept (ABA) + MTX achieved significantly higher rates of DAS28-defined remission (DAS28 [CRP] <2.6) vs MTX alone at 12 mths of treatment; a small but significantly higher number of patients (pts) on ABA + MTX vs MTX alone sustained remission following the rapid withdrawal of all RA drugs. 1 To assess the progression of structural joint damage in pts with early RA in AVERT, MRI changes were evaluated after 12 mths on treatment and following the withdrawal of all RA medication in pts in DAS-defined remission or LDA.

Methods: Pts with DAS28 [CRP] ≥3.2, onset of symptoms ≤2 yrs, acute synovitis in ≥2 joints, who were MTX-naive and anti-cyclic citrullinated peptide (CCP) positive were randomized to SC ABA 125 mg/wk + MTX, SC ABA 125 mg/wk monotherapy or MTX alone for 12 mths. All RA treatment was removed after 12 mths (ABA immediately and MTX and steroids tapered over 1 mth) in pts with DAS28 [CRP] ≥3.2. Gadolinium-enhanced MRI of the clinically worse hand/wrist was performed at baseline and at Mths 6, 12, 18 and 24. A adjusted mean changes from baseline in synovitis, osteitis and erosion were calculated at Mths 12 and 18 for pts with MRI assessments. In a post hoc analysis, adjusted mean changes from baseline in synovitis, osteitis and erosion MRI scores were compared in pts who had DAS28 [CRP] <2.6 at both Mths 12 and 18 (after withdrawal).

Results: Pts in the intent-to-treat population had early RA (mean symptom duration 0.56 yrs) with highly inflammatory disease (mean TJC 23.3, SJC 16.5, CRP 17.5 mg/dl), severe disease activity (mean DAS28 [CRP] 5.44 and HAQ-DI 1.42), poor prognostic factors (95.2% RF and anti-CCP2 double positive) and 31.9% were on steroids at baseline (mean dose 5 mg/day). Improvements in synovitis and osteitis were greater, and the progression of erosion was less, in the ABA + MTX arm vs MTX, both on treatment (Mth 12) and following all treatment withdrawal (Mth 18); benefits of ABA monotherapy on synovitis at Mths 12 and 18 and osteitis at Mth 12 were intermediate to those of ABA + MTX and MTX alone (Table 1). In pts with DAS28 [CRP] <2.6 at both Mths 12 and 18, MRI benefits were maintained from Mth 12 to Mth 18 (Table 2).

Table 1. Adjusted mean change from baseline in MRI scores (intent-to-treat population).

<table>
<thead>
<tr>
<th></th>
<th>Adjusted mean change from baseline (95% CI)</th>
<th>ABA + MTX (n=119)</th>
<th>ABA monotherapy (n=114)</th>
<th>MTX (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis Mth 12</td>
<td>-2.39 (-3.71, -1.08) (p=0.001)</td>
<td>-1.36 (213.9, -0.80)</td>
<td>-0.61 (212.4, 0.13)</td>
<td>-0.81</td>
</tr>
<tr>
<td>Mth 18</td>
<td>-1.34 (-2.28, -0.50) (p=0.001)</td>
<td>-1.39 (230.3, -1.13)</td>
<td>-0.49 (231.45, 0.44)</td>
<td>-0.29</td>
</tr>
<tr>
<td>Osteitis Mth 12</td>
<td>-1.46 (-2.39, -0.54) (p=0.001)</td>
<td>-1.47 (227.22, -1.46)</td>
<td>-0.76 (223.9, 0.34)</td>
<td>-1.50</td>
</tr>
<tr>
<td>Mth 18</td>
<td>-2.03 (-3.23, -0.83) (p=0.001)</td>
<td>-0.45 (231.32, 2.20)</td>
<td>-0.34 (213.22, 0.24)</td>
<td>-2.29</td>
</tr>
<tr>
<td>Erosion Mth 12</td>
<td>-0.19 (-0.38, 0.00) (p=0.05)</td>
<td>1.42 (2176.27, 2.07)</td>
<td>1.35 (215.63, 2.39)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Mth 18</td>
<td>0.013 (-0.174, 0.201) (p=0.50)</td>
<td>1.85 (2106.21, 2.74)</td>
<td>1.20 (2107.23, 0.96)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*p<0.015 for treatment difference vs MTX (95% CI): p for the estimate of treatment difference did not cross 0.

Table 2. Adjusted mean change from baseline in MRI scores; post hoc analysis in pts with DAS28 [CRP] <2.6 at both Mths 12 and 18.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted mean change from baseline (95% CI)</th>
<th>ABA + MTX (n=108)</th>
<th>ABA monotherapy (n=148)</th>
<th>MTX (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis Mth 12</td>
<td>-1.98 (-2.62, -1.34) (p=0.001)</td>
<td>-2.43 (213.38, 1.43)</td>
<td>-1.12 (213.26, 0.23)</td>
<td>-2.05</td>
</tr>
<tr>
<td>Mth 18</td>
<td>-2.14 (-3.34, -1.10) (p=0.01)</td>
<td>-2.64 (214.39, 1.42)</td>
<td>-1.17 (213.26, 0.10)</td>
<td>-2.95</td>
</tr>
</tbody>
</table>

Conclusion: A batacept reduced MRI-detected joint inflammation and joint damage in pts with early RA; these benefits may be maintained for at least 6 mths after treatment withdrawal in pts in remission or low disease activity, suggesting an alteration in the autoimmune process.


References:


1522
Impact of Sarilumab on Health Related Quality of Life (HRQoL), Fatigue, and Sleep in Rheumatoid Arthritis Patients at Week 24 - Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-center Study. Vibeke Strand 1,2, George Joseph 3, Hubert van Hoogstraten 4, Chiehi Chen 4, Chunpeng Fang 5, Paolo Carlia 5, Neil Graham 5, Tanya Momtahen 5 and Mark C Genovese 5.

Background/Purpose: Sarilumab, a fully human monoclonal antibody directed against the IL-6 receptor, demonstrated efficacy in the phase 3 part of the RA-MOBILITY study (NCT01061736) in adults with active, moderate-to-severe RA with inadequate responses to methotrexate (MTX). 1 Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids. This analysis focuses on the impact of sarilumab on HRQoL, fatigue, and sleep, all of which were predefined secondary endpoints at Week 24 among patients who had a patient reported outcome (PRO) measured at that time point. Overall work impairment due to RA was assessed at Week 12.

Methods: The intent-to-treat population included 1,197 patients who were randomized 1:1:1 to receive placebo + MTX, sarilumab 150 mg every two weeks (q2w) + MTX or 200 mg q2w + MTX. The Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F), Sleep-Related and Sleep-VAS, and Work Productivity and Activity Impairment (WPAI) questionnaires were assessed at baseline, Week 12 (WPAI only), and Week 24.

Results: Statistically significant improvements versus placebo + MTX in SF-36 T-Scores for Physical Component Summary (PCS) and Mental Component Summary (MCS), all 8 domains of SF-36, FACT-F and Sleep-VAS were reported by patients receiving sarilumab 150 mg + MTX and 200 mg q2w + MTX at Week 24. Sarilumab exceeded the minimum clinically important difference (MCID) in all SF-36 summary and domain scores (PCS and MCS: 2.5; 8 domains: 5.0), FACT-F (3.0) and Sleep-VAS (4.1) scores in both active treatment groups (Table 1, Bordered). Improvements evident at Week 24 were sustained through Week 52. Statistically significant improvements in WPAI % overall work impairment due to RA scores were reported for 150 mg + MTX group at Week 12.

Table 1. Adjusted mean change from baseline in WPAI scores (intention-to-treat population).

<table>
<thead>
<tr>
<th></th>
<th>Adjusted mean change from baseline (95% CI)</th>
<th>ABA + MTX (n=119)</th>
<th>ABA monotherapy (n=114)</th>
<th>MTX (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis Mth 12</td>
<td>-1.30 (-2.68, -0.02) (p=0.05)</td>
<td>-2.68 (214.98, 0.02)</td>
<td>-1.28 (213.26, 0.04)</td>
<td>-1.61</td>
</tr>
<tr>
<td>Mth 18</td>
<td>-1.37 (-2.74, -0.01) (p=0.05)</td>
<td>-2.23 (214.98, 0.14)</td>
<td>-1.46 (214.98, 0.03)</td>
<td>-2.30</td>
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</table>

*p=0.015 for treatment difference vs MTX (95% CI): p for the estimate of treatment difference did not cross 0.
Conclusion: In this Phase 3 trial, patients with active RA receiving either dose of sarilumab q2W + MTX reported clinically meaningful change from baseline in all HRQoL and fatigue scores at Week 24, which were maintained through Week 52. Statistically significant benefit was also reported in sleep and “overall work impairment due to RA” for sarilumab 150 mg q2W + MTX dose.

Table 1. HRQoL, Fatigue, WPAI-% overall work impairment due to RA, and Sleep-VAS at Baseline, Week 12 (for WPAI only), and Week 24

<table>
<thead>
<tr>
<th>PRO</th>
<th>Placebo</th>
<th>Sarilumab 150 mg + MTX</th>
<th>Sarilumab 200 mg + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS</td>
<td>Baseline mean</td>
<td>50.2</td>
<td>50.4</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>5.07</td>
<td>4.86</td>
<td>4.83</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>-2.38 (4.630, 0.901)</td>
<td>3.07 (1.978, 4.242)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>SF-36 MCS</td>
<td>Baseline mean</td>
<td>36.1</td>
<td>36.2</td>
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<tr>
<td>Mean change from baseline</td>
<td>3.94</td>
<td>3.92</td>
<td>3.79</td>
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<tr>
<td>LSM difference, 95% CI</td>
<td>0.99 (1.705, 3.696)</td>
<td>2.89 (1.628, 4.354)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SF-36 PF</td>
<td>Baseline mean</td>
<td>49.1</td>
<td>49.1</td>
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<tr>
<td>Mean change from baseline</td>
<td>6.29</td>
<td>6.30</td>
<td>6.27</td>
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<tr>
<td>LSM difference, 95% CI</td>
<td>0.0009</td>
<td>&lt;0.0001</td>
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<tr>
<td>SF-36 RP</td>
<td>Baseline mean</td>
<td>34.3</td>
<td>34.3</td>
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<tr>
<td>Mean change from baseline</td>
<td>3.69</td>
<td>3.67</td>
<td>3.67</td>
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<tr>
<td>LSM difference, 95% CI</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
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<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>SF-36 SF</td>
<td>Baseline mean</td>
<td>39.5</td>
<td>39.5</td>
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<tr>
<td>Mean change from baseline</td>
<td>3.75</td>
<td>3.74</td>
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<td>LSM difference, 95% CI</td>
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<td>&lt;0.0001</td>
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<tr>
<td>p-value</td>
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<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>SF-36 VT</td>
<td>Baseline mean</td>
<td>41.1</td>
<td>41.1</td>
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<tr>
<td>Mean change from baseline</td>
<td>4.93</td>
<td>4.93</td>
<td>4.93</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>-2.07 (5.080, 3.566)</td>
<td>-1.37 (2.647, 5.507)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&gt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SF-36 SF</td>
<td>Baseline mean</td>
<td>38.4</td>
<td>38.4</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>3.48</td>
<td>3.46</td>
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<tr>
<td>LSM difference, 95% CI</td>
<td>0.0011</td>
<td>&lt;0.0001</td>
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<tr>
<td>SF-36 RE</td>
<td>Baseline mean</td>
<td>35.6</td>
<td>35.6</td>
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<tr>
<td>Mean change from baseline</td>
<td>4.50</td>
<td>4.50</td>
<td>4.50</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>0.62 (1.236, 1.759)</td>
<td>0.70 (1.800, 2.597)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0023</td>
<td>&lt;0.0001</td>
<td></td>
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<td>SF-36 MH</td>
<td>Baseline mean</td>
<td>37.1</td>
<td>37.1</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>4.29</td>
<td>4.29</td>
<td>4.29</td>
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<tr>
<td>LSM difference, 95% CI</td>
<td>0.0018</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>Baseline mean</td>
<td>20.4</td>
<td>20.4</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>6.49</td>
<td>9.1</td>
<td>10.16</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>3.07 (1.552, 4.083)</td>
<td>3.51 (2.092, 4.611)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>WPAI- % overall work impairment due to RA</td>
<td>Baseline mean</td>
<td>51.5</td>
<td>49.2</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-9.27</td>
<td>-17.84</td>
<td>-18.00</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>-0.606 (-17.144, -2.368)</td>
<td>-7.228 (-14.854, 0.397)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0217</td>
<td>0.0631</td>
<td></td>
</tr>
<tr>
<td>Sleep VAS</td>
<td>Baseline mean</td>
<td>54.5</td>
<td>53.7</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-16.89</td>
<td>-23.17</td>
<td>-23.07</td>
</tr>
<tr>
<td>LSM difference, 95% CI</td>
<td>-6.778 (-10.734, -2.821)</td>
<td>-6.891 (-10.826, -2.955)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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Background/Purpose: In this 48-week, double-blinded, non-inferiority trial, 353 methotrexate suboptimal-responders were randomized to two treatment strategies, either the addition of sulfasalazine and hydrochloroquine (triple therapy [T]) or the addition of etanercept (E). Participants without marked improvement in DAS28 at 24 weeks switched to the alternate treatment, while maintaining the blind. This created 4 treatment subgroups: no switch (T-only, E-only), and switch (T-E, E-T). At 48 weeks, treatment blind was broken. Follow-up data on major study outcomes from the observational sub-cohort of participants who consented to long term f/u is presented.

Methods: DAS28 scores, joint assessments, laboratory values, visual analog scale (VAS), HAQ, Health Utilities Index (HUI), EQ5D, and changes in therapy (grouped as either any conventional DMARDs or to any biologic) were collected every 24 weeks up to week 120 or end of study. The last participants enrolled had minimal potential for follow-up, decreasing overall mean follow-up. We compared two follow-up groups: participants on E at 48 weeks (E-only and T-E) who then changed to a biologic compared to participants on T at 48 weeks (T-only and E-T) who then changed to a biologic. Study measure results were compared by simple ANOVA at each follow-up time across the four treatment subgroups. The stability of measures over time within each subgroup was assessed by repeated measures ANOVA.

Results: Of the 353 participants, 289 with 48 week data agreed to extend follow-up. Treatment subgroups consisted of 106 T-only, 103 E-only, 42 T-E, and 38 E-T. Data were available on 213 (74%), 168 (58%), and 162 (56%) at 72, 96, and 120 week, respectively. For week 120, data available within the subgroups ranged from 46% to 59%. With respect to DAS28, the censoring patterns appeared completely at random (at each time the null hypothesis was not rejected). Measures of joint assessment, laboratory values, VAS, HAQ, HUI, and EQ5D were stable over time within subgroups. DAS28 scores and various component scores were slightly higher over time among switchers than non-switchers, but not significant (NS). Within sub-cohort, no symptom or disability index rose significantly over time. 218 patients had follow-up data on medication use on or after 48 weeks. In this group at week 48, 90% of 101 patients who ended the study on T continued on DMARDs compared to 48% of the 117 patients who ended the study on E and continued on biologics. Of those who changed treatment at week 48, more changed from E to a DMARD than from T to a biologic (chi-square test p < 0.01). After 48 weeks medication change rates remained similar in the two groups.

Conclusion: In this observational cohort, major study outcomes including DAS28 remained stable over time. Those patients who switched therapy at week 24 of the interventional trial had slightly higher DAS28 and component scores. Censoring from the treatment subgroups was similar to the overall cohort indicating that censoring was independent of treatment assignment. Of those with post-study medication data, there was a larger change to DMARDs than to biologics immediately after ending the study. The reasons for this are being explored.

Rituximab Done! What’s Next in RA? Ulrich A. Walker1, Veronika K. Jaeger2, Katerina Chatzidionysiou3, Merete Lund Hetland4, Ellen Margrethe Tomsic5, Ronald van Vollenhoven6 and Cem Gabay7. 1Department of Rheumatology, University Hospital Basel, Basel, Switzerland, Basel, Switzerland, 2Karlova University Hospital, Stockholm, Sweden, Stockholm, Sweden, 3Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, Aarhus, Denmark, 4DANBIO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, Glostrup, Denmark, 5Charles University, Prague, Czech Republic, Prague, Czech Republic, 6ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, Helsinki, Finland, 7Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal on behalf of the Rheumatic Diseases Portugal Register, Lisbon, Portugal, 8University Medical Centre Ljubljana, Ljubljana, Slovenia, Ljubljana, Slovenia, 9University Hospitals of Geneva/SCQM Registry, Geneva, Switzerland, Geneva, Switzerland.

Background/Purpose: The optimal strategy to use biologics after rituximab (RTX) in RA is unknown. We therefore aimed to evaluate the effectiveness of different biologics after RTX treatment.

Methods: The CERRERA registry, a prospective, longitudinal, multinational database of RA patients (Pts) treated with RTX was analyzed with respect to the effectiveness of tumor necrosis factor alpha inhibitor (TNFi), abatacept (ABA) or tocilizumab (TCZ) as a new biologic after RTX. Pts were included, if they had stopped RTX no longer than 6 months prior to the new biologic, had a baseline (BL) visit within 21 days of commencement of new biologic, and at least 1 follow up visit. BL characteristics were compared across biological classes and between TCZ mono and TCZ combination therapy (methotrexate (MTX) and/or leflunomide (LEF)).

Results: The inclusion criteria were met by 265 Pts. Demographic and disease characteristics did not differ across treatment groups (Table). Pts on TCZ had a significantly greater decline of DAS28 after 6 months of treatment (Figure 1). This effect was also seen after adjusting for prednisone use and the number of previous biologics. DAS28 scores in Pts on TCZ were 1.0 (95% CI 0.2–1.7) and 1.8 (95% CI 1.1–2.6) lower than in Pts on TNFi or ABA, respectively. Similarly, the CDAI was 7.2 (95% CI 0–15) and 7.5 (95% CI 0–15) points lower in Pts on TCZ than on TNFi or ABA. Pts with TCZ more frequently had a good EULAR response than Pts with TNFi or ABA (66% vs 31% & 14%, p<0.001). Overall, Pts reported a lower HAQ after 6 months of treatment (p<0.001), though the decline did not differ between treatment groups. When comparing TCZ mono with TCZ combination therapy, DAS28 and CDAI and EULAR response did not differ. The drug retention rates did not differ between all treatments (Figure 2).

Conclusions: In this observational cohort study, TCZ provided a better control of RA activity than ABA or TNFi in Pts who discontinued RTX. There was no difference in effectiveness between TCZ given as mono therapy and TCZ given in combination with non-biologic DMARDs.

Table: Baseline characteristics by treatment groups in patients who had stopped RTX. Characteristics between TNFi, ABA and TCZ were compared by χ², Fisher’s exact, ANOVA or Kruskal Wallis tests as appropriate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TNFi</th>
<th>ABA</th>
<th>TCZ Mono</th>
<th>TCZ Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous 1</td>
<td>32.0 (17.1)</td>
<td>17.0 (12.0)</td>
<td>17.0 (12.0)</td>
<td>17.0 (12.0)</td>
</tr>
<tr>
<td>RA duration (years)</td>
<td>5.0 (3.0–7.0)</td>
<td>5.0 (3.0–7.0)</td>
<td>5.0 (3.0–7.0)</td>
<td>5.0 (3.0–7.0)</td>
</tr>
<tr>
<td>RA (CRP) (mg/L)</td>
<td>3.0 (2.0–5.0)</td>
<td>3.0 (2.0–5.0)</td>
<td>3.0 (2.0–5.0)</td>
<td>3.0 (2.0–5.0)</td>
</tr>
<tr>
<td>Anti-CCP positive (%)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
<td>70.3 (60.0–80.0)</td>
</tr>
<tr>
<td>Number of previous 2</td>
<td>12.0 (8.0–16.0)</td>
<td>12.0 (8.0–16.0)</td>
<td>12.0 (8.0–16.0)</td>
<td>12.0 (8.0–16.0)</td>
</tr>
<tr>
<td>RA (ESR) (mm/h)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>HAQ</td>
<td>4.0 (3.0–5.0)</td>
<td>4.0 (3.0–5.0)</td>
<td>4.0 (3.0–5.0)</td>
<td>4.0 (3.0–5.0)</td>
</tr>
</tbody>
</table>

Disclosure: U. A. Walker, Roche, UCB, MSD, Pfizer; V. K. Jaeger, None; K. Chatzidionysiou, None; M. L. Hetland, None; E. M. Hauge, None; K. Pavelka, MSD, AbbVie, Pfizer, UCB, Roche, Amgen, Menarini, BMS; D. C. Nordström, Roche Pharmaceuticals; H. Canhao, AbbVie, MSD, Pfizer, Roche and UCB; M. Tomsic, Roche Pharmaceuticals; R. van Vollenhoven, AbbVie, BMS, GSK, Pfizer, Roche, UCB; A. Biert, Biotest, BMS, GSK; F. Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex; C. Gabay, Roche, Merck, and AbbVie; Roche, AbbVie, Pfizer, BMS, Sanofi-Aventis, Merck, AB2 Bio, Roche, ABBVie, Pfizer, BMS, Sanofi-Aventis, Merck, AB2 Bio, S.
Rheumatic Diseases, Bucharest, Romania, 2Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania, 3Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania, 4Dr. Ion Stoia’ Clinical Center of Rheumatic Diseases, Bucharest, Romania, 5University of Medicine and Pharmacy, Cluj-Napoca, Romania, 6Clinical County Hospital, Craiova, Craiova, Romania, 7Constanta Municipal Hospital, Constanta, Romania, 8Colentina Clinical Hospital, Bucharest, Romania, 9Victor Babes’ University of Medicine and Pharmacy, Timisoara, Romania, 10T-G-Popa Center for Biomedical Research, Iasi, Romania, 11Recovering Clinical Hospital, Iasi, Romania.

**Background/Purpose:** The concept of achieving tight control of rheumatoid arthritis (RA) and treating to target has been well established. It focuses on early diagnosis, aggressive treatment and regular monitoring, thus leading to positive outcomes in a significant number of patients with RA who achieve remission. The primary aim of this study was to evaluate the sustained clinical efficacy of multiple courses of rituximab (RTX) in patients with active RA despite treatment with a TNF inhibitor in routine clinical practice in Romania.

**Methods:** In this open-label, multicenter, prospective observational study (REPEAT), patients were treated with initial (2×1000 mg IV, at 2 weeks apart) and subsequent RTX courses. Clinical assessments, including 28-joint count disease activity score (DAS 28), were performed at baseline (before RTX initiation), and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. Statistical analyses were carried out using STATA SE/11 software. Kruskal-Wallis test for disease activity stages across evaluations, Cuzick’s test for trend analysis, and cumulative clinical response compared to the previous one, were in line with the REM and LDA criteria (HDA, Ryder Disease Activity). Statistical analyses tested the effects of grouping treatments by class and broadening and narrowing inclusion criteria.

**Results:** 1087 patients with active RA and inadequate response to at least one TNF inhibitor, who received an initial RTX treatment were included. Their average age at entry was 56.2 ± 11.2 years (mean ± SD) and 86% were women. 929 patients (85.5%) had only one anti-TNF treatment, whereas 158 (14.5%) had more than one. Percentages of remission and LDA are presented below. The Kruskal-Wallis test between evaluations was used, P < 0.0001, as well as Ntrend for trend across evaluations, P < 0.0001.

**Conclusion:** The data show continuous improvement of clinical response after each retreatment course with RTX. Each RTX course led to an increased and cumulative clinical response compared to the previous one, being in line with treat to target principle and EULAR/ACR recommendations.

**Disclosure:** C. Codreanu, None; R. Ionescu, None; I. Ancuta, None; C. Mogosan, None; S. Rednic, None; P. Ciurea, None; M. Suta, None; M. Parvu, None; A. Balanescu, None; M. Bojinca, None; D. Nemes, None; C. Ancuta, None; E. Reuz, None.

**1527**

**Efficacy of Biologic Treatments in Early Active Rheumatoid Arthritis: An Indirect Comparison.** Laura Sawyer 1, Stacey Chang 1, Alex Diamantopoulos 2 and Fred Dejoungheere 1.

1Symmetron Limited, London, United Kingdom, 2Symmetron Limited, Herts, United Kingdom. 1F. Hoffmann-La Roche, Basel, Switzerland.

**Background/Purpose:** To date, no head-to-head trials have been conducted comparing the efficacy of biologic treatments for early active rheumatoid arthritis (ERA). Here, we evaluated the effectiveness of tocilizumab (TCZ) compared to infliximab (IFX) and adalimumab (AD), the latter with and without concomitant methotrexate (MTX), or bDMARDs alone, in combination, in adult patients with moderate to severe ERA who have not been treated with methotrexate (MTX) or bDMARDs.

**Methods:** A literature review was undertaken to identify randomized controlled trials (RCTs) of bDMARDs and bDMARDs in patients with ERA (duration < 3 years) that reported efficacy outcomes, including the proportion of patients achieving American College of Rheumatology (ACR) scores of 20, 50, 70, and 90 and disease activity score (DAS28)–defined remission (DA28 < 2.6). Study data were pooled using Bayesian network meta-analysis techniques. For ACR response, data were analyzed using a fixed-effects (FE) ordered probit model, which makes efficient use of ordered categorical data and guarantees coherent prediction of multinomial response probabilities. For DAS28 remission, data were analyzed with an FE binomial logit model. The analysis included only results for treatments in licensed doses. Sensitivity analyses tested the effects of grouping treatments by class and broadening and narrowing inclusion criteria.

**Results:** We included 16 RCTs of bDMARDs (MTX, sulfasalazine [SSZ], hydroxychloroquine [HCQ]), bDMARDs (abatacept [ABT], adalimumab [AD], etanercept [ETN], infliximab [IFX], golimumab [GOL], and TCZ), and TCZ (infliximab [Tofa]). Results indicate that bDMARDs + MTX, triple therapies and TCZ and Tofa in monotherapy significantly increased response across all ACR categories versus MTX. (Figure). Probabilities of ACR response to bDMARDs + MTX were broadly similar, with no significant differences between agents. Probabilities of ACR response to
bDMARDs in monotherapy were more varied, with a trend toward higher values for Tofa and TCZ than for ETN or ADA. Only a subset of studies reported DAS remission. Results show that treatment with Tofa or any bDMARD (± MTX) except ADA alone improved the likelihood of DAS remission versus MTX. TCZ (± MTX) generated the highest probability of remission among bDMARD agents and was significantly more effective than all other bDMARDs (± MTX) and Tofa. Results across both outcomes were robust to alternative grouping of interventions and to change in the inclusion criteria.

Conclusion: Based on ACR response, the expected efficacy of bDMARDs + MTX, Tofa and TCZ monotherapy, and triple bDMARD therapy appears comparable in early RA. TCZ and Tofa in monotherapy are more effective than ADA alone and are likely to be more effective than ETN alone. TCZ ± MTX is expected to have the highest probability of generating DAS.


1528 Efficacy and Safety of MK-8457, a Novel SYK Inhibitor for the Treatment of Rheumatoid Arthritis in Two Randomized, Controlled, Phase 2 Studies. Ronald van Vollenhoven1, S. B. Cohen2, Philip Meeze3, Charles G. Peterfy4, Wolfgang Spieler5, Judith Boice6, Sean Curtis7, Qing Li8, Ruji Yaoa, Richard Baumgarten9 and Holly Wenga. 1The Karolinska Institute, Stockholm, Sweden, 2Lepetopix Clinical Research Center, Dallas, TX, 3University of Washington, Seattle, WA, 4Spirae Sciences LLC, Boca Raton, FL, 5ZeO OR GmbH Zentrum für Forschung, Zebert, Germany, 6Meck Research Laboratories, Whitehouse Station, NJ, 7Meck & Co., Inc, Whitehouse Station, NJ, 8Meck & Co., Inc., Whitehouse Station, NJ.

Background/Purpose: Novel, targeted small-molecular medications are needed in the treatment of rheumatoid arthritis (RA). MK-8457 is a novel inhibitor of spleen tyrosine kinase (SYK) and zeta-chain-associated protein kinase (ZAP70) that is being investigated as an RA treatment. Methods: Two Phase 2, multicenter, double-blind, placebo-controlled trials were conducted in RA subjects (≥ 18 years old). Study 1 was an adaptive study in subjects with active RA despite treatment with methotrexate (MTX) and included M RI; Study 2 included subjects with active RA and an inadequate response or intolerance to anti-TNF-α therapy. Subjects in both studies were randomized to MK-8457 100 mg BID + MTX or placebo + MTX for 24 weeks. This dose has 99% inhibition of human CD63 biomarker. The primary endpoints were the American College of Rheumatology 20 (ACR20) response at Week 12 in Study 1 and change from baseline in the Disease Activity Score 28 (DAS28) based on C-reactive protein (CRP) at Week 12 in Study 2. ACR 50 and ACR 70 were also evaluated. Subjects were eligible to continue open-label safety extensions for up to 100 weeks upon completion of the initial 24-week treatment period. Safety was monitored by physical examination, vital signs, safety labs, and adverse event (AE) reporting.

Results: Both studies were discontinued early due to serious infections. At the time of study discontinuation, there were 82 subjects (mean age 55 years; 77% female; baseline mean DAS28 5.98) randomized to MK-8457 (n=41) and placebo (n=41) in Study 1. In Study 2, 56 subjects (mean age 59 years; 77% female; baseline mean DAS28 6.12) were randomized to MK-8457 (n=30) and placebo (n=26). Statistically significant efficacy improvement was observed with MK-8457 in Study 1 (MTX-IR), but not in Study 2 (TNF-IR) (Table). Study 1 also showed efficacy on ostelitis and synovitis on MRI. At termination, Study 2 only had 31 subjects with Week 12 data; therefore, there was little power to assess efficacy endpoints. There were 27% (MK-8457) vs 10% (placebo) with non-infection gastrointestinal (GI) AEs in Study 1, and; 27% (MK-8457) vs 4% (placebo) with GI AEs in Study 2. In Studies 1 and 2, there were 6 serious respiratory infections (5 pneumonia and 1 bronchitis) and 1 serious case of enterocolitis; 1 subject with presumed opportunistic infection died during the Study 1 extension. The combined serious infection rate per 100 patient-years was 16.3. There were no significant changes in blood pressure in the MK-8547 treated groups.

Conclusion: MK-8457 improved efficacy in subjects with an inadequate response to MTX (Study 1), but not in subjects who failed anti-TNF-α therapy (Study 2), although Study 2 was limited to a small sample size. A high rate of serious infections was observed leading to the termination of both studies suggesting a potential increased infection risk with high degree of SYK and/or ZAP70 inhibition.

Table: Efficacy Endpoints at Week 12

<table>
<thead>
<tr>
<th>Study 1 (MTX-IR)</th>
<th>Placebo</th>
<th>MK-8457</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>24.4%</td>
<td>68.3%</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>4.9%</td>
<td>36.6%</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>4.9%</td>
<td>19.5%</td>
</tr>
<tr>
<td>DAS28 CRP</td>
<td>1.23</td>
<td>0.87</td>
</tr>
<tr>
<td>Key Endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M (SD)</td>
<td>12-Week MRI Score (Change from Baseline)</td>
<td></td>
</tr>
<tr>
<td>Osteitis</td>
<td>2.12</td>
<td>1.71</td>
</tr>
<tr>
<td>Synovitis</td>
<td>3.02</td>
<td>2.34</td>
</tr>
<tr>
<td>Erosion</td>
<td>1.61</td>
<td>1.31</td>
</tr>
<tr>
<td>GOL + MTX</td>
<td>2.34</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Disclosures: R. van Vollenhoven, AbbVie, Bristol-Myers Squibb, Glaxo Smith Kline, Pfizer, Roche, and UCB; S, AbbVie, Biotech, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Lilly, Merck, Pfizer, UCB, and Vertex; S, B. Cohen, A. Mogen, Biogen-IDEC, Bristol-Myers Squibb, Centocor, Genentech, Johnson & Johnson, Pfizer, Merck, and Roche; S, P. Mease, AbbVie, A. Mogen, Biogen-IDEC, Bristol-Myers Squibb, Celgene, Covagen, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex; S, AbbVie, A. Mogen, Biogen-IDEC, Bristol-Myers Squibb, Celgene, Covagen, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex.
Evaluation of the Pharmacokinetics and Safety of the Interactions Between the Anti-Interleukin-6 Monoclonal Antibody Sirukumab and Cytchrome P450 (CYP) Enzymes. The goal of the study was to evaluate: 1) the effect of sirukumab on the pharmacokinetics of probe substrates for CYP3A4, CYP2C9, CYP2C19, and CYP1A2 in patients with active rheumatoid arthritis (RA), a disease in which IL-6 is elevated; 2) the safety of a single subcutaneous high dose of sirukumab in RA patients.

Methods: This was an open-label, Phase 1 study in men and women 18-85 years of age, diagnosed with RA and with a screening CRP >8.0 mg/L. Twelve patients, genotyped to exclude poor metabolizers of CYP2C9 and CYP2C19, were enrolled. Patients received oral “cocktail” administrations of CYP probe substrates (midazolam, warfarin, omeprazole and caffeine) at weeks -1, 1, 3, and 6 weeks relative to a single subcutaneous dose of 300 mg sirukumab. Serum sirukumab concentration and antibodies to sirukumab were measured. Safety was monitored through 7 weeks after sirukumab administration. Plasma levels of 4-hydroxycholesterol were measured.

Results: AUC_{inf} of each probe substrate before and after sirukumab treatment showed that exposure to midazolam, warfarin, omeprazole and caffeine decreased after sirukumab administration. Mean plasma levels of CYP2C19 activity in RA patients treated with sirukumab were reduced modestly (<50%) at 1, 3 and 6 weeks after sirukumab treatment, CRP decreased after sirukumab administration. Mean plasma levels of 4-hydroxycholesterol showed an increase of about 25% over time, but the ratio of 4-hydroxycholesterol to cholesterol did not change. All 12 patients reported at least one non-serious adverse event, the two most frequent ones being laboratory abnormalities and mild injection site reactions. No new safety findings were observed and no SAEs were reported.

Conclusion: Consistent with its intended suppression of IL-6 effects, treatment with sirukumab may reverse IL-6-mediated suppression of CYP enzymes in RA patients. CRP decreased after sirukumab administration. Mean plasma levels of 4-hydroxycholesterol increased by about 25% over time, but the ratio of 4-hydroxycholesterol to cholesterol did not change. All 12 patients reported at least one non-serious adverse event, the two most frequent ones being laboratory abnormalities and mild injection site reactions. No new safety findings were observed and no SAEs were reported.

Table 1: Mean (SD) values for AUC_{inf} of each probe substrate before and after sirukumab treatment

<table>
<thead>
<tr>
<th>Probe Substrate</th>
<th>Pre-sirukumab</th>
<th>1 week after sirukumab</th>
<th>3 weeks after sirukumab</th>
<th>6 weeks after sirukumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{inf} (ng*h/mL) Day 7</td>
<td>AUC_{inf} (ng*h/mL) Day 15</td>
<td>AUC_{inf} (ng*h/mL) Day 29</td>
<td>AUC_{inf} (ng*h/mL) Day 50</td>
<td></td>
</tr>
<tr>
<td>Change*</td>
<td>Change*</td>
<td>Change*</td>
<td>Change*</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>10.67 (24.29)</td>
<td>34.34 (13.89)</td>
<td>30.62 (15.76)</td>
<td>35.33 (15.33)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>3720 (3623)</td>
<td>1037 (1372)</td>
<td>45.21 (13.05)</td>
<td>41.25 (12.08)</td>
</tr>
<tr>
<td>S-warfarin</td>
<td>1256 (4930)</td>
<td>3800 (3045)</td>
<td>18.16 (14.96)</td>
<td>18.14 (14.75)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>13899 (10534)</td>
<td>15747 (10036)</td>
<td>20 15958 (15794)</td>
<td>17 14796 (13003)</td>
</tr>
</tbody>
</table>

*calculated based on geometric mean ratio

Disclosure: D. de Vries, Janssen Research and Development, LLC, 3; Y. Zhuang, Janssen Research and Development, LLC, 3; S. Marciniak, Janssen Research and Development, LLC, 3; Z. Xu, Janssen Research and Development, LLC, 3; D. Chen, Janssen Research and Development, LLC, 3; H. M. Davis, Janssen Research and Development, LLC, 3; F. Leon, Janssen Research and Development, LLC, 3.

1530

Autoimmune and Inflammatory Arthritis.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease which results from a breakdown of immune tolerance. Despite their efficacy current RA therapeutics, including biologic and non-biologic DMARDs, generally require chronic administration with the associated risk of adverse effects. The concept of therapeutic tolerance states that it should be possible to reprogram unwanted immune responses, including autoimmunity, and reset the immune system to self-tolerance. Although the concept has been achieved in animal models of autoimmunity and transplantation it has not yet been convincingly demonstrated in humans. We have developed a potentially tolerogenic therapy, autologous tolerogenic dendritic cells (tolDC), and now report the results of a phase 1 safety trial in patients with inflammatory arthritis. The secondary objectives were to assess tolerability and feasibility; exploratory objectives include preliminary evidence of potential efficacy including biomarkers.

Methods: This was an ascending dose, randomised, controlled, unblinded phase I study. Participants had a chronic inflammatory arthritis (75% RA) with an actively inflamed knee joint. Background therapy was maintained throughout the trial. There were three dosing cohorts of 1 million, 3 million and 10 million tolDC; controls received saline washout only. Following screening, participants underwent leukapheresis and leukocytes were transferred to a GMP facility. CD14+ monocytes were positively selected and tolDC differentiated according to our published methods. During differentiation tolDC were loaded with autologous synovial fluid as autologen. After 7 days tolDC were administered arthroscopically into the inflamed knee joint following saline washout. Synovial biopsies were taken arthroscopically at baseline and again 14 days later, when intra-articular glucocorticoid was administered for persistent inflammation. The primary endpoint of the study was the proportion of patients experiencing a flare of target knee joint inflammation within 5 days of tolDC administration (knee flare). Secondary endpoints were patient acceptability and the success rate of tolDC preparation.

Results: TolDC were successfully manufactured from 9 patients. The product marginally failed quality control in a tenth case. No knee flares were observed in patients or controls. In most participants there was residual inflammation at day 14 arthroscopy except for two patients in 10 million tolDC cohort. There was one SAE (flare of RA on day 70, requiring hospital admission and subsequent pneumonia) and several AEs, most of which were deemed unrelated to therapy. Patient acceptability of the intervention was high.

Conclusion: We have performed a phase 1 study of intra-articular tolDC in patients with inflammatory arthritis. The intervention appeared safe, feasible and acceptable to participants. We are currently planning tracking studies, to study the fate of administered cells, and biomarker analysis. 1. Harvey RA, Anderon AE, Isaacs JD, Hilken CM. Generation and characterisation of therapeutic tolerogenic dendritic cells for rheumatoid arthritis. Ann Rheum Dis 2010;69:2042–2050.

Disclose: G. Bell, None; A. E. Anderson, None; J. Dilibb, None; R. Harry, None; E. McColl, None; A. Dickinson, None; C. Hilken, None; J. D. Isaacs, None.
Results: We enrolled 60 patients, 56% were women, mean age 48 ± 16 years. In 50 (84%) patients with AS, 99 test (86%) for ADL level and anti-ADL-Ab in 10 patients (16%), diagnosed of PsA, 16 (14%) test was done.

For the whole patients: the average time of treatment was 9.5 ± 9.6 years and the average time on treatment with ADL 1.7 ± 1.4 years; in 38 (63%) patients, ADL was the first biological drug administered; the mean BMI was 27 and the prevalence of anti-ADL-Ab was 30% (18 patients: 14 - 28% patients with AS and 4 - 40% - patients with PsA).

In patients with anti-ADL-Ab versus patients without anti-ADL-Ab, we obtained significantly higher level of ADL (11.5 ± 5.3 vs 0.12 ± 0.2; p < 0.0001), less BASDAI response (2.7 ± 1.8 vs 5.5 ± 2.0; p < 0.0001), less ASDAS level (1.8 ± 0.6 vs 3.5 ± 2.6; p = 0.0008) and less time on treatment with ADL (2.2 ± 1.4 vs 0.8 ± 0.4; p < 0.0001). Although the 35% patients without anti-ADL-Ab was treated with DMARDs and only 10% of patients with anti-ADL-Ab, there was not statistical differences (p = 0.2). The cut-off level of ADL in patients with AS to achieve an ASDAS≤2.1 was 5.4 mg/L, with AUC of 82.9% (sensitivity: 91%; specificity: 75%).

In pts with arthritis flare, disease activity decreased again (mean DAS 28: 2.45 vs 3.85, p = 0.009) after returning to the iv administration of the drug (after a mean of 38.2 days).

One patient discontinued the sc formulation for the onset of related side-effects (headache and nausea) not reported with the iv administration.

Conclusion: although the safety profile of the sc formulation of A batacept seems to confirm the data previously obtained with the iv use of the drug, a high rate of our patients complained a reduced efficacy and needed the return to the traditional way of administration.

We failed to identify clear risk factors that may help toward the selection of pts to which propose the formulation switch. However, if an arthritic flare occurs, the return to the iv administration seems to ensure a good control of the disease again. Therefore, the efficacy of the molecule does not seem to be compromised by an eventual switch failure.

### Table 1. Characteristics in responders and non-responders patients in relation with ASDAS results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n=42)</th>
<th>Non-Responders (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASDAS ≤ 2.1</strong></td>
<td><strong>21</strong></td>
<td><strong>21</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>ADL level, mean ± SD</td>
<td>11.0 ± 4.4</td>
<td>17.4 ± 4.1</td>
<td>2.01</td>
</tr>
<tr>
<td>Anti-ADL-Ab (%)</td>
<td>20%</td>
<td>71%</td>
<td>0.006</td>
</tr>
<tr>
<td>BASDAI, mean ± SD</td>
<td>2.5 ± 1.5</td>
<td>5.7 ± 1.8</td>
<td>0.008</td>
</tr>
<tr>
<td>DMARD (%)</td>
<td>17</td>
<td>40</td>
<td>0.1</td>
</tr>
<tr>
<td>Time (years on ADL, mean ± SD)</td>
<td>1.7 ± 1.2</td>
<td>1.2 ± 1.1</td>
<td>0.09</td>
</tr>
</tbody>
</table>

(*a patient with a detectable low level of ADL and the anti-ADL-Ab was demonstrated using acid dissociation technique*).

**Conclusion.** Cut-off level of ADL in patients with AS to achieve an ASDAS≤2.1 was 5.4 mg/L. Prevalence anti-ADL-Ab in AS was 28%. Anti-ADL-Ab is correlated significantly with lower level of ADL, BASDAI and ASDA1 results and less time on treatment. 4. Patients responders have occasionally anti-ADL-Ab, and significantly higher serum concentrations of ADL than non-responders.

This study has a grant from Spanish Society for Rheumatology.

### Disclosure
J. Rosas, None; F. Linares-Tello, None; J. M. Senabre-Gallego, None; C. Santos-Ramirez, None; E. Salas-Heredia, None; X. Barber, None; G. Santos-Soler, None; J. Molina, None; M. Garcia-Carrasco, None; A. Pons, None; C. Cano, None; G. Aire-MB, None.

### 1532

**Efficacy of the Subcutaneous Formulation of Abatacept/Orencia in Rheumatoid Arthritis, a Single-Center Italian Experience.** Rossella Reggia1, Franco Franceschini2, Angela Tinca2 and Ilaria Cavazzana3.1 AO Spedali Civili, Rheumatology and Clinical Immunology Unit, Brescia, Italy; 2Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

**Background/Purpose:** Abatacept is a selective T cell costimulation modulator indicated for moderately to severely active Rheumatoid Arthritis (RA). Since August 2013 is available in Italy the new subcutaneous (sc) formulation, that consists in a fixed dose of 125 mg of the drug, administered once weekly. Four clinical trials demonstrated an efficacy and a safety profile comparable to those obtained with the intravenous (iv) administration.

Aim of our work was to analyze the clinical response of a series of patients (pts) with RA treated with monthly iv infusion and then converted to the sc formulation.

**Methods:** We included 48 pts with RA, converted to the sc formulation of Abatacept from October 2013 to April 2014. We divided them into two groups, depending on their need to return to the iv administration for the appearance of a disease flare. The main clinical and serological features of the two groups were compared using the Chi-square, T-test or the Mann-Whitney test when appropriate.

**Results:** Pts converted to the sc formulation were the 48.5% of all cases receiving Abatacept therapy in our Unit. No pts received the iv "loading dose". Eleven pts (22.9%) returned to the iv administration due to a disease flare (mean DAS 28: 2.35 vs 3.85, p=0.005), after a mean of 7.3 injections (range 4-14). The remaining 38 (77.1%) continued with the sc formulation. The compared parameters between the two groups are summarized in Table 1.

**Accepted feature**

<table>
<thead>
<tr>
<th>Analyzed feature</th>
<th>Pts who maintained the sc formulation n=38 (77.5%)</th>
<th>Pts who returned to iv formulation n=11 (22.5%)</th>
<th>p:</th>
</tr>
</thead>
<tbody>
<tr>
<td>M age (years)</td>
<td>58.8</td>
<td>55.1</td>
<td>ns</td>
</tr>
<tr>
<td>Positivity for Rheumatoid Factor (RF)</td>
<td>n=34; (92%)</td>
<td>n=10; (91%)</td>
<td>ns</td>
</tr>
<tr>
<td>Positivity for anti-citrullinated protein antibodies (ACPA)</td>
<td>n=21; (70%)</td>
<td>n=8; (60%)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean disease duration (months)</td>
<td>1.4 years</td>
<td>1.21.2 years</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous iv therapy duration (months)</td>
<td>20.8</td>
<td>17</td>
<td>ns</td>
</tr>
<tr>
<td>Body M ax Index (BMI)</td>
<td>24.2</td>
<td>26.1</td>
<td>ns</td>
</tr>
<tr>
<td>Smokers</td>
<td>n=4; (10.5%)</td>
<td>n=3; (30%)</td>
<td>ns</td>
</tr>
<tr>
<td>DMARDs in association</td>
<td>n=33; (89.5%)</td>
<td>n=10; (90%)</td>
<td>ns</td>
</tr>
<tr>
<td>Previous use of biological agents</td>
<td>n=25; (65.8%)</td>
<td>n=8; (72.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>N’ of different biological agents used in the past: mean; [SD]</td>
<td>1.7; [1.6]</td>
<td>1.7; [2.3]</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Conclusion:** Abatacept as first biological agent n=13; (34.2%) n=3; (27.3%) ns

**Remission of the disease at sc therapy start**

**N’ of different biological agents used in the past:** mean; [SD]

**Aiv: intravenous, sc: subcutaneous, DMARDs: disease-modifying antirheumatic drugs, SD: standard deviation, ns: not significant.**

**Disclosure:** R. Reggia, None; F. Franceschini, None; A. Tincan, None; I. Cavazzana, None.

### 1533

**Study of One Vial (400mg) per Body Infusion of Tocilizumab in Patients with Active Rheumatoid Arthritis.** Hiroshi Uda, Koji Shimematsu and Osamu Sariki. Higashiosaka City General Hospital, Higashiosaka, Japan.

**Background/Purpose:** The treatment of active rheumatoid arthritis (RA) patients are usually started with synthetic disease modifying antirheumatic drugs (DMARDs), but when adequate response are not achieved, biologics (TNFα blockage) are introduced. Tocilizumab (TCZ) is one of useful biologics and the infusion dose of TCZ was setted at 8mg/kg. The residues of TCZ fluid were always discarded. The procedure of sucking and discharging of TCZ is troublesome and dispose of TCZ residue is uneconomical. The fixed dose injection become majority of biologies administration, but fixed dose of biologies infusion has not been attempted to date. The present study is carried out to clarify that one vial (400mg) of TCZ infusion per body (weight >50kg) is effective in the patients with active RA.

**Methods:** The RA patients who showed inadequate response to synthetic and biologic DMARDs other than TCZ and whose body weight was between 50 to 100kg were enrolled in the present study. The patients discontinued biologies before starting TCZ, and one vial (400mg) per body infusion of tocilizumab every 4 weeks (OBOTO study) was added to synthetic DMARDS. The clinical assessments and blood tests were also carried out every 4 weeks. To the patients who did not achieve clinical remission by one vial (400mg) of TCZ, predinsolone (PSL) and/or methotrexate were added. The patients who achieved clinical remission in 12 months were estimated as responder and others were as non-responders. To the patients who achieved clinical remission, we tapered the dose of PSL and/or DMARDs. We followed up the patients at least for 5 years.

**Results:** Total of 106 patients was enrolled in the present study. Male and female were 25 and 81 respectively. Seventy-four patients achieved good response, 21 patients achieved moderate response and 11 patients were non-responders. DAS28 remission was achieved in 59 patients. The body weight of the patients enrolled was between 92 to 50 kg and the mean body weight of 71 kg.
weight of responders and non-responders did not differ significantly. A t-test the clinical remission was achieved. PSL and/or DMARDs were decreased. In five years, 12 patients were treated TCZ alone without any synthetic DMARDs or corticosteroids and kept the condition more than 4 years. The rest of responders received either or both PSL (1 to 7.5 mg/day) and MTX (2 to 8mg/week). To the patients who could not achieve clinical remission, dose escalation of TCZ was not attempted in the present study. Serious adverse events including tuberculosis or death were not found. The overall incidence of adverse events of one vial (400mg) of TCZ was less than those of 8mg/kg infusion.

Conclusion: We provide evidence that one vial (400mg) of TCZ infusion is effective in active RA patients whose body weight is over 50 kg. The finding of OBOTO study is quite useful for taking care of active RA patients both financially and technically.

Disclosure: H. Uda, None; K. Shimematu, None; O. Saiki, None.

1534 Disease Severity and Treatment of Rheumatoid Arthritis: A Comparative Study Between Sudanese and Swedish. Amir Elishaie1, Abdalla D Eikhalifa2, Thomas Welttoft3, M usa Nur4, Elnour Elagib4, Mawahib Aledrissy4, Sahwa Elbagri4 and Johan Rönnelid1,2. 1MD, PhD, Uppsala, Sweden, 2MD, PhD, Gävle, Sweden, 3MD, FRCP, Karinhult, Sweden, 4MD, D M internal Medicine, Karinhult, Sudan, 4, M, PhD student, Uppsala, Sweden, 5, Uppsala University, Uppsala, Sweden.

Background/Purpose: To perform a comparative study concerning clinical characteristics and treatment between Sudanese and Swedish RA outpatients.

Methods: A 286 Sudanese and 542 Swedish RA outpatients diagnosed according to 1987 ACR classification criteria were recruited between December 2008 and September 2010 and compared concerning clinical presentation, treatment and laboratory findings including IgM RF.

Results: Age at inclusion, disease duration and median age at disease onset were all significantly lower among the Sudanese patients (p<0.0001). When stratified concerning age of inclusion, Swedish patients between 41-50 years had however a significantly lower age of onset, with a similar trend for all age groups above 30 years. Levels of ESR and number of affected joints were significantly higher among Sudanese RA patients. The proportion of IgM RF positivity was significantly lower among Sudanese RA patients (p<0.0001). Higher proportions of Sudanese RA patients were treated with methotrexate and DMARD combinations but none of them on biologics. Sudanese patient used lower doses of methotrexate and sulfasalazine (p<0.0001) and higher doses of prednisolone (p<0.0001) than Swedish patients. The female preponderance was more striking among Sudanese RA patients. The proportion of smoking was non-existent among the Sudanese compared to 66% among the Swedish RA patients (p<0.0001).

Conclusion: Sudanese RA patients have significantly higher disease activity and are often IgM RF seronegative. Together with reports from Uganda and Cameroon our data indicate a cluster of highly active seronegative RA in central Africa.

Disclosure: A. Elishaie, None; A. D Eikhalifa, None; T. Welttoft, None; M. Nur, None; E. Elagib, None; M. Aledrissy, None; S. Elbagri, None; J. Rönnelid, None.

1535 Use of Rituximab Compared to Anti-TNF Agents As Second and Third Line Therapy in Patients with Rheumatoid Arthritis. A Report from the rhumadata® Clinical Database and registry. Denis Choquette1, Denis Choquette2, Isabelle Fortin1, Boulos Harou1, Jean-Pierre Petelletier1, Edith Villemure2, Marie-Anais Rémillard1, IsabelleFortin1, Diane Sauvageau1 and Louis Coupal1. 1Institut de rhumatologie de Montréal (IRM), Montréal, QC, 2Centre d’ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, 3Centre de rhumatologie de l’est du Québec (CREQ), Rimouski, QC.

Background/Purpose: The order of use of biologic agents is still a question for debate. Phase III trial data in MTX-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Registries offer a unique opportunity to prospectively monitor the effectiveness of these agents in a clinical setting. We aim to assess if patients with rheumatoid arthritis (RA) treated with abatacept after failure of a first line agent (MTX-IR) have a different drug survival rate than patients similarly treated with adalimumab, etanercept or infliximab.

Methods: Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as second or third biologic agents on or after January 1st 2007 was extracted and subjects taking either ADA, ETA or INF were pooled to form the anti-TNF cohort. Baseline demographics including age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, DAS 28 ESR and SDAI. Five-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM, CORQ, and CREQ.

Results: The data from 226 RA patients were extracted, 153 and 73 having respectively failed a first and a second anti-TNF agent. No clinically significant differences in baseline variables were observed between treatment groups in second and third intention. The 5 year retention rates of second line RIT and anti-TNF use were 74% and 36% respectively (Log-rank p=0.002). In patients having failed two anti-TNF, subsequent use of RIT and anti-TNF agents respectively demonstrated 5 year retention rates of 48% and 24% (Log-rank p=0.004). Although numerically superior (74% vs 48%) second line use of RIT did not reach statistical difference when compared to third line usage.

Conclusion: As a second line agent, in TNF-IR patients, RIT demonstrates a better 5 year retention rate than anti-TNF agents. As third line therapy, RIT is also statistically superior to anti-TNF agents. Although no statistically significant difference was demonstrated between second and third line RIT use, it is evident that positioning RIT as second line offers a better long term outcome.

Disclosure: D. Choquette, None; J. P. Raynauld, None; J. P. Pelletier, None; B. Harou1, None; A. D Elkhalifa, 2, Abbvie; 5, A. D. Elkhalifa, 2, Abbvie, 5, AbbVie, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Jansen Pharmaceutica Product, L. P., 5, Jansen Pharmacuetica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB, 5, L. Besette, None; E. Villemure, None; M. A. Rémillard, None; I. Fortin, None; D. Sauvageau, None; L. Coupal, None.

1536 Comparing Abatacept to Adalimumab, Etanercept and Infliximab As First Line Agents in Patients with Rheumatoid Arthritis. Experience from the Rhumadata® Clinical Database and Registry. Denis Choquette1, Louis Bessette2, Isabelle Fortin1, Boulos Harou1, Jean-Pierre Petelletier1, Jean-Pierre Raynauld2, Marie-Anais Rémillard1, Diane Sauvageau1, Edith Villemure1 and Louis Coupal1. 1Institut de rhumatologie de Montréal (IRM), Montréal, QC, 2Centre d’ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, 3Centre de rhumatologie de l’est du Québec (CREQ), Rimouski, QC.

Background/Purpose: The order of use of biologic agents is still a question for debate. Phase III trial data in MTX-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Registries offer a unique opportunity to prospectively monitor the effectiveness of these agents in a clinical setting. We aim to assess if patients with rheumatoid arthritis (RA) treated with abatacept after failure of a first line agent (MTX-IR) have a different drug survival rate than patients similarly treated with adalimumab, etanercept or infliximab.

Methods: RA patients prescribed a first biologic agent after January 1st 2007 were included in the present analysis. We extracted a cohort formed of all patients prescribed abatacept (ABA), adalimumab (ADA), etanercept (ETA) or infliximab (INF) as their first biologic agent. Baseline demographics for this cohort included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluation (VAS), TJC, SJC, DAS 28 ESR and SDAI. Person-years of treatment were also compared across biologic agents. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM, CORQ, and CREQ.

Results: A total 340 patients were included in the cohort. No clinically significant differences in baseline characteristics were noted between treatment groups. The 5 year retention rate of ADA, ABA, ETA and INF post MTX Failure were 64%, 40%, 49% and 42% without significant statistical differences (Log-rank p=0.29).

Conclusion: A batacept, adalimumab, etanercept and infliximab after MTX failure have similar 5-years retention rates.

Disclosure: D. Choquette, None; L. Besette, None; I. Fortin, None; B. Harauoi, Abbvie; 2, Abbvie; 5, A. Megen, 5, A. Megen, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Jansen Pharmaceutica Product, L. P., 5, Jansen Pharmacuetica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB, 5, L. Besette, None; E. Villemure, None; M. A. Rémillard, None; I. Fortin, None; D. Sauvageau, None; L. Coupal, None.
Clinical Characteristics of RA Patients Newly Prescribed Tofacitinib Citrate (tofacitinib) in the United States after Food and Drug Administration Approval: Results from the Corrona US Rheumatoid Arthritis Registry, Arthur Kavanaugh*, George W. Reed, Katherine C. Saunders, Andrew S. Koenig, Jamie Geier, Joel M. Kremer, Jeffrey D. Greenberg, University of California San Diego, La Jolla, CA, 2Corrona, LLC, Southborough, MA, 3Pfizer, Inc., Collegeville, PA, 4Pfizer, Inc., New York, NY, 5Albany Medical College and the Center for Rheumatology, Albany, NY, 6New York University School of Medicine, New York, NY, 7Johns Hopkins University, Baltimore, MD.

Background/Purpose: To provide initial characterization of the patients prescribed tofacitinib during the early period after United States (US) Food and Drug Administration (FDA) approval (11/6/2012).

Methods: Rheumatoid Arthritis (RA) patients in the Corrona registry initiating tofacitinib through 3/1/2014 were identified. As a comparator, RA patients with no history of tofacitinib use initiating any biologic agent between 11/6/2012-3/1/2014 were also identified. Patient characteristics at the time of initiation are summarized and compared between groups. Continuous covariates are compared using a rank-sum test; categorical covariates are compared using a chi-square test.

Results: Over the study period, there were 299 RA patients newly prescribed tofacitinib and 2418 newly prescribed biologic disease modifying antirheumatic drugs (bDMARD) in the registry. Clinical characteristics are summarized in the Table 1. Tenderness and swelling joint counts and clinical disease activity index (CDAI) scores were similar for tofacitinib and bDMARD initiators, as were the distribution of CDAI scores (i.e. high/moderate disease activity). However, tofacitinib initiators had a significantly higher health assessment questionnaire (HAQ) scores. In addition, the mean disease duration was significantly longer for initiators of tofacitinib (13.9 yrs) versus bDMARDs (9.9 yrs, p<0.001). Tofacitinib initiators also had a higher median (IQR) number of prior biologic drugs (tofacitinib 3 (2–4) versus bDMARDs 1 (0–2)); use of monotherapy and combination DMARD therapies differed among tofacitinib versus bDMARD users (p<0.001), with monotherapy more commonly used for tofacitinib (43%) versus bDMARD (27%) users.

Conclusion: A analysis of this US-based cohort reflects prescriber patient selection decisions. The RA patients with long-standing severe disease and multiple prior biologics have tended to be the patients for whom tofacitinib has been initiated to date compared with those starting a bDMARD during the same time period, although prescribing is not limited to patients with moderate/high disease activity. Monotherapy and combination treatment strategies differed among tofacitinib versus bDMARD treated patients. These factors may impact assessment of the comparative effectiveness and safety of tofacitinib versus other RA therapies during longitudinal followup.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tofacitinib</th>
<th>Biologic DMARDs</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>N = 299</td>
<td>N = 2418</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56.9 (12.17)</td>
<td>57.14 (13)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>57 (50–65)</td>
<td>58 (49–66)</td>
<td></td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>92.94%</td>
<td>89.84%</td>
<td>0.06</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>7.47 (7.47)</td>
<td>7.83 (7.48)</td>
<td>0.3</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>5.04 (5.04)</td>
<td>5.67 (5.66)</td>
<td>0.08</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.2 (0.71)</td>
<td>1.04 (0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDAI</td>
<td>20.88 (13.64)</td>
<td>21.97 (14.42)</td>
<td>0.31</td>
</tr>
<tr>
<td>Remission</td>
<td>5.67%</td>
<td>5.85%</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* p-value calculated using rank test for continuous variables and chi-square test for categorical variables. SD, standard deviation; IQR, inter quartile range; HAQ, health assessment questionnaire; CDAI, Clinical Disease Activity Index; RA, rheumatoid arthritis; DMARD, Disease modifying anti-rheumatic drug; MTX, methotrexate; bDMARD, non-biologic disease modifying anti-rheumatic drug.

Disclosure: A. Kavanaugh, Abbvie, Amgen, Jansen, L.P., UCB, 2; G. W. Reed, Corrona, LLC, 3; K. C. Saunders, Corrona, LLC, 3; A. S. Koenig, Pfizer, Inc., 1; Pfizer, Inc., 3; J. M. Kremer, Corrona, LLC, 3; Corrona, LLC, 1; A. Bvieve, Amgen, BMS, Lilly, Pfizer, UCB, Antares, Medac; research support from same companies except BMS and Medac; J. D. Greenberg, Corrona, LLC, 1; Corrona, LLC, 3; AstraZeneca, Celgene, Novartis and Pfizer; C. O. Bingham III, BMS, Jansen, Meboblad, Pfizer, UCB, 2; Abbievle, Amgen, BMS, Celgene, EMD/Serono, Genentech/Roche, Jansen, Lilly, Novartis, NovoNordisk, Pfizer, UCB, 5.

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Sustained Clinical Benefit with Multiple Courses of Rituximab in Second Line for All Rheumatoid Arthritis Patients Irrespective to the Inhibitor of Tumour Necrosis Factor Previously Used.

Ioan Ancuta*, Ruxandra Ionescu, Catalin Codreanu, Anda Balanescu, Elena Rezus, M. Maria Suta, Paulina Ciurea, Mihaela Milicescu, Dan Nemes, Corona A, 2, UCB, 5; J. P. Pelletier, None; E. Villeneuve, None; J. P. Raynauld, None; M. A. Rémiillard, None; D. Sauvageau, None; E. Villeneuve, None; L. Coupal, None.

Background/Purpose: In the last decade, biological therapy changed dramatically treatment options for rheumatoid arthritis (RA). However, a significant number of patients failed to maintain the initial response to a TNF blocker. More information is needed regarding efficacy and safety of multiple courses of biologics administered over extended periods of time. To assess the clinical benefit of subsequent courses with Rituximab (RTX) in patients with moderate to severe active RA after the failure to different TNF inhibitors used in routine clinical practice in Romania.

Methods: REPEAT is an open-label, multicenter, prospective observational study started in 2010, patients were treated with RTX at each 6 months. Clinical efficacy was assessed at baseline and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. Clinical assessments included disease activity (DAS-28), visual analogue scale (VAS) scores, Δ DAS-28 and Δ VAS. The previous anti-TNF treatments were: adalimumab (ADA), etanercept (ETA) and infliximab (INF). Statistical analyses: STATA SE 11.0 software. Comparison between all treatments and evaluations ANOVA and Nptrend for trend across evaluations.

Results: A total of 1087 adult patients with active RA and inadequate response to at least one TNF Inhibitor received initial RTX treatment. In our cohort, 929 (95.5%) patients had only one anti-TNF treatment (no switch): 210 (19.3%) patients received ADA, 318 (29.3%) received ETA and 401 (36.9%) received INF and the rest of 158 (14.5%) had more than one. As a second TNF inhibitor, 59 (5.42%) patients received ADA, 63 (5.79%) received ETA and 36 (3.31%) received INF; Median Δ DAS-28 values for all patients (1087) and each groups ADA, ETA, INF as first TNF inhibitors were: 5.76; 6.05; 5.75; 6.56 at baseline; 3.98; 4.07; 4.11; 3.84 at 6 months; 3.43; 3.43; 3.48; 3.33 at 12 months, 2.98; 3.00; 3.11; 2.89 at 18 months, 2.79; 2.72; 2.85; 2.75 at 24 months, 2.67; 2.55; 2.69 at 30 months and 2.57; 2.56; 2.41; 2.6 at 36 months. The median Δ DAS28 values for the group (158) who received a second TNF inhibitor, 5.66; 3.935; 3.56; 2.91; 2.85; 2.71 and 2.57
followed the same linear decrease across evaluations at baseline. 6:12:18: 24:30 and 36 months. ANOVA test between treatment and evaluations: P < 0.0001, between previous treatment. P = 0.0014. DAS-28 score has been improved for all groups of patients, independent from the TNF - inhibitor used as previous treatment. The VAS score was improved in the same manner, independent to previous treatment. ANOVA test between treatment and evaluations P < 0.0001, between evaluations P < 0.0001, test between previous treatment P = 0.0003.

Conclusion: In our study, Rituximab have demonstrated to be a reliable therapeutic option for all patients regardless the TNF inhibitor used in first line (adalimumab, etanercept or infliximab).

Disclosure: I. Ancuta, None; R. Ionescu, None; C. Codreanu, None; A. Balanescu, None; E. Reus, None; M. Suta, None; P. Ciurea, None; M. Milicescu, None; D. Nemes, None; C. Ancuta, None; M. Bojinca, None; M. Parvu, None; H. Popoviciu, None.

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Relation Between Number of Previous Anti TNF Agents and Clinical Response in Rheumatoid Arthritis Patients Treated with Rituximab. Daniele Opris, Diana Mazliu, Violeta Bojinca, Andreea Borangiu, Andra Balanescu, Denisa Predeteanu and Ruxandra Ionescu. Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania.

Background/Purpose: Debate is still ongoing regarding rituximab (RTX) as a first or second line biologic therapy. The objective of present study is to assess correlations between patient’s characteristics, including previous treatments with drug level, clinical response and further evolution.

Methods: A group of 62 consecutive rheumatoid arthritis (RA) patients treated with RTX according to National Guideline (2 iv infusions of 1 g separated by 2 weeks, every 6 months) were followed for 2 years. All patients were previously diagnosed according to ACR 1987 or ACR/EULAR 2010 criteria. Demographic data, clinical (number of tender and swollen joints) and laboratory (ESR, CRP, C reactive protein, RF, -hematoid factor, ACPA - anti-cyclic citrullinated peptide) variables were collected at baseline and at each reevaluation. RA activity was evaluated in all patients by using DAS28 4v, Simplified Disease Activity Index (SDAI). All clinical evaluation was performed by two independent assessors. RTX drug level and anti drug antibodies were measured just before a new infusion using Progenika kits (Promonitor®-RTX, Promonitor®-anti-RTX). Patients were excluded if between baseline and last reevaluation there had a change in their treatment regimen. The study was approved by local Ethics Committee and all patients gave written informed consent before inclusion. Statistical analysis was performed using SPSS statistical software, version 20.0.

Results: Mean rituximab treatment duration in the cohort was 41.79±27.76 months. All patients had M ethotrexate associated. No anti drug antibodies were found. During evaluation period 25 patients (40.32%) had signs of inadequate response to treatment. At baseline, 9 (36%) of these patients had undetectable drug level. At that moment there was no difference between patients with detectable and undetectable drug level regarding DAS28 (3.65±1.12 vs 3.45±1.19, P = 0.678) and SDAI (20.15±7.17 vs 21.7±9.6, P = 0.845), nor in their treatment duration (48.8±53.4 vs 27.7±13.7, P = 0.294). At follow-up, 6 months from dosing RTX, patients with detectable drug level had significantly lower DAS28 (mean DAS28 2.93±1.2 vs 2.27±1.47, P = 0.01) and SDAI (mean 12.33±14.13 vs 14.83±20.51, P = 0.033). Significantly higher number of patients with detectable rituximab level had anti citrullinated antibodies (P = 0.021) and were rheumatoid factor positive (P = 0.009). Number of previous anti TNF agents correlated to rituximab level (r = 0.514, P = 0.009). 62% of patients with detectable rituximab level were non-responders to two or more anti TNF agents. All patients with undetectable drug level had only one anti TNF agent as previous biologic treatment.

Conclusion: Significant differences were found in clinical response in patients depending on the rituximab level and number of previous anti TNF agents used. RTX detectable drug level and 2 or more anti TNFs correlated with better clinical response at follow-up. This result support the actual guidelines for RA treatment regarding rituximab as a second line biologic agent.

Disclosure: D. Opris, None; D. Mazliu, None; V. Bojinca, None; A. Borangiu, None; A. Balanescu, None; D. Predeteanu, None; R. Ionescu, None.

1540

Treatment Patterns of Biologics Used in Rheumatoid Arthritis and Ankylosing Spondylitis in the US Veterans Population. Brian Sauer1, Chia-Chen Teng2, Tao He1, Jiawen Leng2, Chao-Chin Lu3, Neel Shah4, David J. Harrison5, Derek Tang6 and Grant W. Cannon7. 1Salt Lake City VA and University of Utah, Salt Lake City, UT, 2Salt Lake City VA and University of Utah, Salt Lake City, UT, 3Agen Inc., Thousand Oaks, CA.

Background/Purpose: Biologics used for rheumatoid arthritis (RA) and ankylosing spondylitis (AS), including tumor necrosis factor blockers, are a key area of focus for Veterans Affairs (VA) Pharmacy Benefits Programs. This study describes treatment patterns with etanercept (ETN), adalimumab (ADA), and infliximab (IFX) in US veterans with RA or AS during the first year of treatment.

Methods: National VA pharmacy, administrative, and clinical databases were used for this analysis. Eligibility criteria included ≥1 claim for ETN, ADA, or IFX from Jan 1, 2008 to Dec 31, 2011 preceded by at least 180 days of enrollment in the VA. The first drug and date that met this criterion was the index drug and date. Patients had to be ≥18 years of age on their index date; have ≥360 days of enrollment following their index date; and have ≥1 claim with an ICD-9-CM diagnosis of RA or AS prior to or within 30-days after their index date. Patients with a diagnosis of psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, Crohn’s disease, ulcerative colitis, non-Hodgkin’s lymphoma, or chronic lymphocytic lymphoma, prior to or within 30-days of their index date; a claim for their index biologic prior to their index date; who used a biologic prior to its receiving approval for that condition; or who had implausible dosing (≥200% of the maximum labeled dose) were excluded.

Treatment patterns were classified based on whether or not patients were persistent on their index agent for the 360 days after their index date. Non-persistence was defined as a ≥45 day gap in days of supply on their index agent or a claim for a non-index biologic. Non-persistent patients were further categorized based on the first observed event after non-persistence: switching, a claim for a biologic other than their index biologic; restarting, another claim for their index biologic after the ≥45 day gap, or discontinued no subsequent claims for any biologic following the gap.

Results: ETN, ADA, and IFX were the index biologic for 2,109, 2,035, and 263 veterans with RA and 286, 422, and 46 veterans with AS. Approximately half of all patients with RA were persistent on therapy for the entire year; 49.3% of ETN, 51.4% of ADA, and 52.5% of IFX. Persistence in AS was lower (ETN, 42.0% and ADA, 40.0%), but higher with INF, 56.4%. In both RA and AS, switching rates were numerically higher in IFX users (RA: 18.6%; AS: 15.2%) compared with ETN (RA: 11.8%, AS: 10.1%) and ADA (RA: 10.3%; AS: 12.8%). Restarting was more common with ETN and ADA than INF in both RA and AS. Discontinuation rates were similar (11.9–14.0%) across agents in both RA and AS.

Conclusion: Overall, persistence during the first year of therapy for RA and AS was relatively low, 40.0–56.5%. Gaps in therapy occurred in 26.3–34.6% of patients taking self-injected agents, but only 15.5–16.3% of patients taking INF. More work is needed to understand the reasons for non-persistence in this population.

<table>
<thead>
<tr>
<th>Disease and Treatment Patterns</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA All</td>
<td>N = 2,109</td>
<td>N = 2,035</td>
<td>N = 263</td>
</tr>
<tr>
<td>Persistent</td>
<td>49.3%</td>
<td>51.4%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Non-Persistent</td>
<td>50.7%</td>
<td>48.6–53.8%</td>
<td>46.4–50.9%</td>
</tr>
<tr>
<td>Restart After a ≥45 day gap</td>
<td>12.0%</td>
<td>10.7–13.4%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Switch Biologic Therapy</td>
<td>11.8%</td>
<td>10.4–13.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td>AS All</td>
<td>N = 286</td>
<td>N = 422</td>
<td>N = 46</td>
</tr>
<tr>
<td>Persistent</td>
<td>42.0%</td>
<td>43.2–47.7%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Non-Persistent</td>
<td>58.0%</td>
<td>52.3–64.8%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Restart After a ≥45 day gap</td>
<td>13.3%</td>
<td>9.4–17.2%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Switch Biologic Therapy</td>
<td>10.3%</td>
<td>6.6–13.6%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

Disclosure: B. Sauer, Agen Inc, 2; C. C. Teng, Amgen Inc, 7; T. He, Agen Inc, 2; L. Leng, Agen Inc, 2; C. C. Lu, Amgen Inc, 2; N. Shah, Amgen, 3; A. I., Amgen, 1; D. J. Harrison, Amgen, 3; A. M., Amgen, 3; D. Tang, Amgen, 3; M. G. W. Cannon, Amgen Inc, 2.
**Background/Purpose:** In the pathogenesis of rheumatoid arthritis (RA), T helper cells can differentiate into functionally distinct subsets, leading to the persistent inflammation and immune abnormality associated with the interactive activation between T cells and B cells. However, little is known about pathological T cell subset targeted by biologic DMARD (bDMARD) therapy. We identified patients who had continued their initial treatment for 5 years (allowing pauses <90 days). Univariate logistic regression was used to identify factors associated with 5 years persistent treatment - covariates included age, disease duration, gender, number of previously used non-biologic DMARDs, comorbidity, TNF-type, co-medication, steroid use, disease activity score (DAS) 28, erythrocyte sedimentation rate (ESR), patient global assessment, tender and swollen joints, current smoking and Health Assessment Questionnaire (HAQ). Age, gender and variables with p-value <0.25 were included in a multivariate model and a backward section was performed to fit the final model.

**Results:** We included 666 patients starting TNFi (table). At 5 years, 312 (46.8%) patients were still on their initial treatment. Gender, disease duration, TNF-type, comorbidity, tender joints, current smoking and HAQ were relevant predictors in univariate analysis (p<0.25). Concomitant MTX was not a predictor, neither in the whole cohort or when stratified by TNFi-type, but only 14 patients received infliximab (IFX) as monotherapy. Male gender, absence of baseline comorbidity and use of ETN or adalimumab (ADA) rather than IFX were independently associated with persistent treatment at 5 years (Table). HAQ, disease duration, tender joint count or current smoking at 5 years were not significant predictors in the multivariate model.

**Conclusion:** Among this severe cohort of patients with PsA who initiated a TNFi prior to 2007, almost 50 percent were still on their initial treatment at 5 years. The only patient characteristics predicting this were gender and baseline comorbidity status which limits applicability to clinical practice. Combinant MTX was not a significant predictor of long-term treatment persistence, suggesting an absence of a beneficiary effect across all TNFi therapies, opposed to that seen in rheumatoid arthritis.

**Disclosure:** S. Nakayamada, None; S. Kubo, None; M. Yosihikawa, None; N. Iwamoto, None; Y. Yonou, None; M. Miyazaki, None; K. Saito, None; Y. Tanaka, BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbvie and Daiichi-Sankyo, 2, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei, 5, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei, 6, B.

**Table** Baseline variables and logistic regression predicting continued treatment at 5 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Univariate analysis</th>
<th>Final multivariate model</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females (n%)</td>
<td>352 (52.9)</td>
<td>0.54 (0.40-0.74)</td>
<td>0.55 (0.40-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.83 (11.00)</td>
<td>1.01 (0.99-1.02)</td>
<td>1.01 (1.00-1.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12.73 (8.75)</td>
<td>1.02 (1.00-1.04)</td>
<td>1.02 (1.00-1.04)</td>
<td></td>
</tr>
<tr>
<td>Previously used DMARDs (n/%)</td>
<td>3 (2.4)</td>
<td>0.92 (0.74-1.14)</td>
<td>0.89 (0.74-1.03)</td>
<td></td>
</tr>
<tr>
<td>TNFi (n/%) on Etanercept</td>
<td>365 (54.8)</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>296 (46.9)</td>
<td>0.52 (0.37-0.75)</td>
<td>0.55 (0.38-0.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>105 (15.8)</td>
<td>0.87 (0.53-1.34)</td>
<td>0.89 (0.57-1.39)</td>
<td>0.622</td>
</tr>
<tr>
<td>Current smoker (n%)</td>
<td>111 (21.0)</td>
<td>0.62 (0.41-0.95)</td>
<td>0.62 (0.41-0.95)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities (n/%)</td>
<td>366 (54.8)</td>
<td>0.62 (0.46-0.85)</td>
<td>0.60 (0.44-0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Co-medication (n/%)</td>
<td>190 (28.5)</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>MTX (n/%)</td>
<td>396 (58.5)</td>
<td>0.87 (0.61-1.33)</td>
<td>0.87 (0.61-1.33)</td>
<td></td>
</tr>
<tr>
<td>Other (n/%)</td>
<td>80 (12.0)</td>
<td>0.70 (0.41-1.19)</td>
<td>0.70 (0.41-1.19)</td>
<td></td>
</tr>
<tr>
<td>Baseline steroid use (n/%)</td>
<td>156 (23.4)</td>
<td>0.84 (0.59-1.21)</td>
<td>0.84 (0.59-1.21)</td>
<td></td>
</tr>
<tr>
<td>Global (0-100)</td>
<td>70.97 (20.99)</td>
<td>1.00 (0.99-1.01)</td>
<td>1.00 (0.99-1.01)</td>
<td></td>
</tr>
<tr>
<td>DAS 28</td>
<td>6.05 (1.19)</td>
<td>0.98 (0.85-1.11)</td>
<td>0.98 (0.85-1.11)</td>
<td></td>
</tr>
<tr>
<td>Tender joints (28 point-count)</td>
<td>13.17 (1.29)</td>
<td>0.98 (0.86-1.01)</td>
<td>0.98 (0.86-1.00)</td>
<td></td>
</tr>
<tr>
<td>Swollen joints (28 point-count)</td>
<td>8.4 (12.12)</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.98-1.03)</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>33 (38-57)</td>
<td>1.00 (1.00-1.01)</td>
<td>1.00 (1.00-1.01)</td>
<td></td>
</tr>
<tr>
<td>HAQ</td>
<td>1.88 (1.3.8-2.25)</td>
<td>0.72 (0.57-0.92)</td>
<td>0.72 (0.57-0.92)</td>
<td></td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td>Inefficacy (n%)</td>
<td>125 (35.3)</td>
<td>0.62 (0.41-0.95)</td>
<td></td>
</tr>
<tr>
<td>Adverse events (n%)</td>
<td>102 (28.8)</td>
<td>0.62 (0.41-0.95)</td>
<td>0.62 (0.41-0.95)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, angina, MI, stroke, epilepsy, asthma, chronic obstructive airway disease, peptic ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OR = Odds ratio**  
**Recall: University of Manchester, Manchester, United Kingdom, 6 Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, 7 British Society for Rheumatology, London, United Kingdom.**
Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Sustained Improvements in the Signs and Symptoms of PsA in DMARD-naive Patients: Results from a Phase 3, Randomized, Controlled Trial. 

Monday, November 17

### Table 1. Efficacy Outcomes at Week 52 in Patients Receiving APR From Baseline (Data as Observed)

<table>
<thead>
<tr>
<th>APR20</th>
<th>APR30</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 132</td>
<td>n = 141</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APR20</th>
<th>APR30</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20, n/</td>
<td>70/131</td>
<td>81/138</td>
</tr>
<tr>
<td>n (%)</td>
<td>53.4</td>
<td>58.7</td>
</tr>
<tr>
<td>ACR50, n/</td>
<td>35/129</td>
<td>44/138</td>
</tr>
<tr>
<td>n (%)</td>
<td>27.1</td>
<td>31.9</td>
</tr>
<tr>
<td>ACR70, n/</td>
<td>18/131</td>
<td>25/138</td>
</tr>
<tr>
<td>n (%)</td>
<td>13.7</td>
<td>18.1</td>
</tr>
<tr>
<td>SJC (0–76)</td>
<td>9.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Median % change</td>
<td>-89.4</td>
<td>-100.0</td>
</tr>
<tr>
<td>TJC (0–78)</td>
<td>Baseline, median</td>
<td>17.0</td>
</tr>
<tr>
<td>Median % change</td>
<td>-67.1</td>
<td>-66.7</td>
</tr>
</tbody>
</table>

Note: The n reflects the number of patients who completed 52 weeks; actual number of patients available for each endpoint may vary. Baseline values presented were based on the patients who had data at Week 52. n/m = number of responders/number of patients with sufficient data for evaluation.

### Conclusion

Apremilast demonstrated clinically meaningful, sustained improvements in the signs and symptoms of PsA in DMARD-naive patients. APR demonstrated an acceptable safety profile and was generally well tolerated.

### Disclosures

K. M. Fagerli, None; K. D. Watson, None; J. Packham, None; D. P. Symmons, None; K. L. Hyrich, Pfizer Inc, 9, AbbVie Immunology Pharmaceuticals, 9; On behalf of the BSRBR, Pfizer Inc, Abbvie, UCB, Merck, Roche, 2.

### Background/Purpose

Apremilast (APR), an oral phosphodiesterase 4 inhibitor, helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 4 compared the efficacy and safety of APR with placebo in patients with active PsA who were DMARD-naive.

### Methods

Patients were randomized (1:1:1) to placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30). Patients whose swollen and tender joint counts (SJC and TJC) had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial APR dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. The analysis comprises data from Weeks 0 to 52.

### Results

At baseline, median PsA duration among patients in the full analysis set, overall, was 1.1 years; median SJC was 9.0 and median TJC was 16.0. At Week 16, significantly greater proportions of patients receiving APR achieved modified ACR 20 response (primary endpoint) (placebo: 15.9%); APR20: 28.0% [P = 0.0062]; APR30: 30.7% [P = 0.0010] and modified ACR 50 response (placebo: 4.5%; APR20: 11.4% [P = 0.0173]; and APR30: 11.4% [P = 0.0181]). ACR 70 response was observed in 1.1%, 4.0%, and 4.0% of patients receiving placebo, APR20, and APR30, respectively. Median percent change in SJC at Week 16 was significantly greater with APR compared with placebo (−16.7%); APR20: 50.0% [P = 0.0001]; APR30: 42.9% [P = 0.0001]). Median percent change in TJC at Week 16 was also significantly improved with APR compared with placebo (−8.3%); APR20: −29.5% [P = 0.0007]; APR30: −33.3% [P = 0.0001]). At Week 52, modified ACR20/ACR50/ACR70 response was achieved by 53.4%/27.1%/13.7% and 58.7%/31.9%/18.1% of patients continued treated with APR20 or APR30, respectively, from baseline. Among these patients, improvements in SJC/TJC were observed over 52 weeks; at Week 52 median percent change in SJC/TJC was −89.4%/-67.1% (APR20) and −100.0%/-66.7% (APR30). Consistent results were demonstrated in patients randomized to placebo at baseline and re-randomized to APR20 or APR30 at Week 16 or 24 who completed Week 52 (Table). The most common adverse events (AEs) reported among patients receiving either APR dose during the placebo-controlled period were nausea (12.6%), diarrhea (9.4%), and headache (6.0%). The nature and severity of AEs did not change with long-term exposure through 52 weeks.

### Conclusion

Over 52 weeks, APR demonstrated clinically meaningful, sustained improvements in the signs and symptoms of PsA in DMARD-naive patients. APR demonstrated an acceptable safety profile and was generally well tolerated.

### Disclosures

A. Wells, Celgene Corporation, 2; A. O. Adeboye, None; J. A. Aelion, A. Roda, A. Stara Zeneva, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Janseen, Eli Lilly, Merck, Mesoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Biosciences, Sanofi-Aventis, Takeda, 2; Ardea, A. Stara Zeneva, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Janssen, Eli Lilly, Merck, Mesoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Biosciences, Sanofi-Aventis, Takeda, 5, AbbVie, Amgen, and UCB, 8; P. Bird, Celgene Corporation, 2; A. Kivitz, Amgen, Janssen, Eli Lilly, Novartis, Pfizer Inc, and UCB, 2; Amgen, Janssen, Eli Lilly, Novartis, Pfizer Inc, and UCB, 8; F. Liéto, Celgene Corporation, 2; Celgene Corporation, 5; P. Sarzi-Puttini, Abbvie, MSD, Roche, UCB and Alpha-Wasserstein, 2; C. Hu, Celgene Corporation, 3; Celgene Corporation, 1; R. M. Stevens, Celgene Corporation, 1; Celgene Corporation, 3; C. J. Edwards, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2; Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5; AbbVie, GlaxoSmithKline, Pfizer Inc, and Roche, 8.

### Background/Purpose

Psoriatic Arthritis (PsA) and Psoriasis (PsO) are associated with substantial economic and comorbidity burdens. However, the burden among PsO patients comorbid with PsA has not been evaluated in the biologics era. This study aimed to compare the comorbidity burden, healthcare resource utilization, and costs between moderate-to-severe PsO patients comorbid with PsA and matched controls.

### Methods

Aults (18–64 years) with ≥2 distinct PsO diagnoses (ICD-9-CM: 696.1) were identified in the OptumHealth Reporting and Insights claims database (01/2007–03/2012). Moderate-to-severe PsO patients were selected as those receiving ≥1 systemic or phototherapy during the 12-month study period following the index date (randomly selected date after the first PsO diagnosis); PsO patients comorbid with PsA (PsO+PsA cases) were further selected as those with ≥2 distinct PsO diagnoses (ICD-9-CM: 696.0) between 01/2007 and the index date or during the 12-month study period. Controls were free of PsO and PsA in the entire claims history and matched 1:1 with PsO+PsA cases on age, gender, and geographic region. All patients had at least 12 months of continuous enrollment after the index date. Multivariate regression models were performed to examine the impact of PsO+PsA on comorbidities, medication use, and healthcare utilization and costs between cases and controls, adjusting for demographics, index year, insurance type, non-PsO/PsA related comorbidities. Adjusted cost differences between cases and controls were also estimated.

### Results

A total of 1,230 matched pairs of PsO+PsA patients and controls were selected, with mean age 48.5 years and 52.1% of male. During the 12-month period, PsO+PsA patients had significantly higher disease burden in major PsO/PsA related comorbidities assessed than controls, with the top 4 most common being hypertension (35.8% vs. 23.5%), hyperlipidemia (34.6% vs. 28.5%), rheumatoid arthritis (16.6% vs. 0.7%) and diabetes (15.9% vs. 10.0%). Controlling for between-group differences, PsO+PsA patients had more number of prescription medications filled (IRR = 2.3), and were more likely to have any inpatient admission (OR = 1.6), emergency department (OR = 1.3), and outpatient visit (OR = 62.7) compared with controls (all p < 0.05). Additionally, PsO+PsA patients incurred significantly higher total hospital, and medical costs (adjusted annual costs differences: $23,160, $17,696 and $5,077 per patient, respectively, all p < 0.01) than controls.

### Conclusion

Compared with matched controls without PsO and PsA, moderate-to-severe PsO patients comorbid with PsA were more likely to have PsO/PsA-related comorbidities and incurred significantly higher healthcare utilization and costs.

### Disclosures

S. R. Feldman, Causa Technologies, Medical Quality Enhancement Corp., 1; Causa Technologies, 4, Doak, Pfizer Inc, Pharmaderm, and SkinMedica, Inc., 9;
Better Performance of the Leaps and Spardcc Enthesitis Indices Compared to the Mases in Patients with Peripheral Spondyloarthritis during Treatment with Adalimumab. Philip Mease1,2, K. L. Winthrop2, Lang Chen3, William Smith2, Benjamin Chan3, Fenglong Xie4, Allison Taylor5, Ronac Mantani6, Frank I Scott7, James D Lewis8 and Jeffrey R Curtis9.1University of Alabama at Birmingham School of Public Health, Birmingham, AL, 2Oregon Health and Science University, Portland, OR, 3AbbVie Inc., North Chicago, IL, 4University of Alabama at Birmingham, Birmingham, AL, 5University of Pennsylvania, Philadelphia, PA, 6Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Peripheral spondyloarthritis (psPA) is characterized by arthritis, enthesitis, and/or dactylitis. Enthesitis is considered a core outcome domain for SpA; however, there is no clear recommendation which of the available enthesitis tools should be used. The objective of this analysis was to evaluate the validity of different enthesitis indices in patients (pts) with non-psoriatic psPA during treatment with adalimumab (ADA).

Methods: ABILITY-2 is a multicenter phase 3 study. Eligible pts were ≥18 yrs, fulfilled a SAS pSPA criteria, and had active disease. Pts were randomized to ADA 40 mg every other week (wk) or placebo (PBO) for 12 wks followed by 144 wks of open-label ADA. 29 enthesitis sites based on Leeds (range 0–6) and SPARCC (Spondyloarthritis Research Consortium of Canada, 0–16) enthesitis indices, and the MASES (Maastricht Ankylosing Spondylitis Enthesitis Score, 0–13) were assessed during the study. Discriminatory ability and sensitivity to change of enthesitis indices at wk 12 were calculated: mean differences from BL to wk 12 in ADA vs PBO-treated pts with corresponding 95% confidence limits, standardized mean differences, and Guyatt’s effect sizes. Presence of enthesitis at each anatomical enthesitis site at BL and proportion of sites that show resolution or new onset enthesitis from BL to wk 12, ADA vs PBO, were analyzed.

Results: 165 pts (ADA 84/PBO 81) were randomized. At BL 143 (87%) had ≥1 enthesitis site. The Leeds and SPARCC enthesitis scores showed higher discriminatory ability and sensitivity to change compared to the MASES (Table). Individual enthesitis site analysis suggests that in the overall population, the proportion of change from BL to wk 12 at the following sites may have higher discriminatory ability to other more axial sites: Achilles tendon (ADA 52.8% vs PBO 13.5%), greater trochanter (42.6% vs 6.8%), lateral epicondyle humerous (63.9% vs 0%), and medial epicondyle humerus (51.2% vs 0%). Among enthesitis sites positive at BL, a greater proportion showed resolution at wk 12 among pts on ADA in the Achilles tendon (ADA 60.4% vs PBO 36.5%, P = 0.019), medial epicondyle humerus (73.2% vs 48.7%, P = 0.038), and lateral epicondyle humerus (52.8%, P = 0.023). Among sites negative at BL less new onset enthesitis was observed with ADA at the following sites: Achilles tendon (ADA 3.6% vs PBO 10.9%, P = 0.041), lateral epicondyle (4.7% vs 15.1%, P = 0.006), greater trochanter (3.4% vs 14.4%, P = 0.005), quadriceps insertion patella (1.5% vs 7.0%, P = 0.034), and medial condylo femoral (1.6% vs 9.2%, P = 0.009).

Table: Enthesitis Index Mean Change (±SD) [95% CL] from Baseline to Week 12, ADA, and Guyatt’s Effect Size

<table>
<thead>
<tr>
<th>Site</th>
<th>ADA vs PBO</th>
<th>Mean Difference (ADA–PBO)</th>
<th>SD</th>
<th>Guyatt’s Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeds</td>
<td>−2.93 (±2.25)</td>
<td>−0.45 (±1.27)</td>
<td>0.73</td>
<td>−1.07</td>
</tr>
<tr>
<td>−1.69 (±1.22)</td>
<td>−0.80 (±1.36)</td>
<td>0.42</td>
<td>−0.91</td>
<td></td>
</tr>
<tr>
<td>−1.01 (±0.51)</td>
<td>−0.18 (±0.92)</td>
<td>0.78</td>
<td>−0.99</td>
<td></td>
</tr>
<tr>
<td>SPARCC</td>
<td>−2.83 (±2.46)</td>
<td>−0.83 (±1.70)</td>
<td>1.00</td>
<td>−1.35</td>
</tr>
<tr>
<td>−2.47 (±1.95)</td>
<td>−1.23 (±2.13)</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>−2.02 (±2.47)</td>
<td>−0.93 (±2.04)</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>MASES</td>
<td>−2.63 (±2.75)</td>
<td>−0.63 (±2.45)</td>
<td>0.32</td>
<td>−0.84</td>
</tr>
<tr>
<td>−2.76 (±2.50)</td>
<td>−0.95 (±2.10)</td>
<td>0.53</td>
<td>−0.85</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<th>Site</th>
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<tr>
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<td>−0.91</td>
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</tr>
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<td>−0.18 (±0.92)</td>
<td>0.78</td>
<td>−0.99</td>
<td></td>
</tr>
<tr>
<td>SPARCC</td>
<td>−2.83 (±2.46)</td>
<td>−0.83 (±1.70)</td>
<td>1.00</td>
<td>−1.35</td>
</tr>
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<td>−2.47 (±1.95)</td>
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<td>−2.02 (±2.47)</td>
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<tr>
<td>MASES</td>
<td>−2.63 (±2.75)</td>
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<td>−0.84</td>
</tr>
<tr>
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<td>−0.95 (±2.10)</td>
<td>0.53</td>
<td>−0.85</td>
<td></td>
</tr>
</tbody>
</table>

Among patients who had score ≥1 for that index. CL, confidence limit; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SD, standard deviation; SMD, standardized mean difference; SPARCC, Spondyloarthritis Research Consortium of Canada.
Background/Purpose: To assess the treatment effect of ustekinumab on fatigue using data from PSUMIT 2.

Methods: Adult patients with active psoriatic arthritis (PsA) despite DMARD (N = 132) and/or previous treatment with biologics (N = 180) were randomized to receive ustekinumab 45mg, 90mg, or placebo (PBO) at wks 0, 4, and q12wks thereafter through week 40. PBO-treated patients crossed over to receive ustekinumab 45mg at weeks 24, 28 and q12wks through week 40. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue, 0–52) and the vitality scales of SF-36 health survey questionnaire (SF-36 VT, 0–100). High scores indicate low severity in fatigue. Clinically meaningful improvement was defined as ≥ 4 point increase in FACIT-Fatigue or ≥ 3 point increase in SF-36 VT score from baseline. Disease activity was measured by disease activity score using 28 joints (DAS28), and physical function was measured using Health Assessment Questionnaire (HAQ).

Results: At baseline, patients had a mean FACIT-Fatigue score of 25.8 and had a mean SF-36 VT score of 36.9, which was significantly below the values of the U.S. normal population (50), indicating severe fatigue. Both FACIT-Fatigue and SF-36 VT scores were significantly correlated with improvement in DAS28 (r = 0.42, 0.38, respectively) and HAQ (r = 0.62, 0.51, respectively) at week and baseline, and the improvements in FACIT-Fatigue and SF-36 VT scores were significantly correlated with improvement in DAS28 (r = 0.45, 0.43, respectively) and improvement in HAQ scores (r = 0.43, 0.41, respectively) at week 24. At week 24, patients who received ustekinumab achieved statistically significantly greater improvement in FACIT-Fatigue score (4.35 vs. 0.86, p = 0.002) and in SF-36 VT score (3.87 vs. 0.67, p = 0.004) compared with PBO. Compared to PBO, a greater proportion of ustekinumab-treated patients achieved a clinically meaningful improvement in FACIT-Fatigue (49% vs. 25.5%) or SF-36 VT (45% vs. 29.9%) (all p < 0.01). No significant differences were observed between the ustekinumab 45 and 90mg groups. The treatment effect on fatigue was consistent across biologically-experienced and DMARD-experienced patients, and maintained through week 52. Patients who were randomized to PBO and switched to active treatment at week 24 achieved comparable improvement at week 52.

Conclusion: Ustekinumab therapy significantly reduces the symptom of fatigue in patients with active PsA. Clinically meaningful improvement in fatigue was observed within 3 doses of ustekinumab therapy.


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The Swedish Early Psoriatic Arthritis (SWEPSA) Registry 5-Year Follow-Up: Slow Radiographic Progression with Highest Scores in Male Feet and In Patients with Baseline X-Ray Abnormalities. 

Elke Theander; Tomas Hugmark; Ulla Lindqvist; Per T. Larsson; Anika Telemann; Gerd-M arie Aalenius and Mats Gjejer.

Skane University Hospital Malmö, Lund University, Malmö, Sweden, 2Falu Hospital, Falun, Sweden, 3Department of Medical Sciences, Rheumatology, University Hospital, Uppsala University, Uppsala, Sweden, 4Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden, 5Svenhus Rheumatological Hospital Oskarstrom, Sweden, 6Department of Public Health and Clinical Medicine, Rheumatology, Umeå University Hospital, Umeå, Sweden, 7Skåne University Hospital, Lund, Center for Medical Imaging and Physiology, Lund, Sweden.

Background/Purpose: To describe early X-ray findings in psoriatic arthritis (PsA) patients from the SwePSA registry using the Wassenberg score, evaluate progression of structural damage, analyze correlations to clinical disease parameters and identify predictors of progressive radiographic joint disease.

Methods: Out of 197 SwePSA patients followed for 5 years, 72 (38% of the women and 35% of the men) had radiographs of hands and feet performed.
at the 5-year follow-up. According to the SwePsA protocol hand and feet radiographs should be performed in polyarticular disease or when these joints showed signs of inflammation at baseline, and repeated during follow-up. Reading (M G) in chronological order was centralized. Clinical data were collected according to the SwePsA protocol.

**Results:** Mean (SD) baseline age of the 43 women and 29 men was 48.7 (15.0) and 46.4 (14.5) years respectively. While in the total SwePsA cohort women had higher clinical disease activity (Theander et al, ARD 2014), in this sub-cohort mean baseline DAS28 (DAPSA) were similar in women and men (3.94 / 22.27 and 3.73 / 21.63, respectively, ns). However, radiographic abnormalities were more pronounced in men:

- **Baseline x-rays:** Total Wassenberg score was 0 (no abnormalities) in 55% of women and 46% of men. Scores over 10 were unusual and only found in one woman and one man. Mean (SD) total scores for women and men at baseline were 1.38 (2.44) vs 3.05 (4.04) respectively, \( p = 0.039 \).
- **5-year follow-up x-rays:** Total score was 0 in 42% of women but only in 17% of men (\( p = 0.018 \)). Scores over 10 at 5 years were found in 7.2% of women and in 17% of men. Mean (SD) total scores for women and men were 3.37 (4.85) vs 7.79 (12.46), \( p = 0.034 \), erosion scores 0.85 (1.78) vs 3.41 (8.20), \( p = 0.051 \), proliferation scores 2.55 (3.49) vs 4.62 (4.92), \( p = 0.041 \). Feets scores at 5-year follow-up were 0.84 (2.13) vs 2.35 (3.92). In women and men, \( p = 0.028 \), hand scores 2.58 (3.74) vs 5.55 (8.53), \( p = 0.047 \).

Baseline and 5-year scores were highly correlated (for total scores: Spearman rho 0.752, \( p = 0.000 \)). Baseline total score correlated with ESR (rho: 0.364, \( p = 0.004 \)) and 5-year score with swollen joint count (rho 0.310, \( p = 0.000 \)). Higher B27 positive HLA showed a trend to be associated with lower total score (rho -0.285, \( p = 0.058 \)).

Male gender and total baseline score were the only predictors of radiographic abnormalities after 5 years: OR (male/female): 4.42 (95% CI: 2.23–8.75) vs 1.52 (0.74–3.11), \( p = 0.003 \). The only baseline Wassenberg score was an independent predictor of radiographic progression. Inflammatory activity, inflammatory markers, joint counts, delay before inclusion and smoking did not predict 5-year Wassenberg score. None of the 15 patients with the highest scores/progression had received anti-TNF-blockers.

**Conclusion:** Radiographic progression in early PsA is slow in general, early prevalent in male feet and predicted by baseline radiographic findings. Thus scoring of hand and feet x-rays at baseline cannot be substituted by clinical signs, especially not in men.

**Disclosure:** E. Theander, Abbvie Sweden, 2; T. Husmark, Abbvie Sweden, 2; U. Lindqvist, Abbvie Sweden, 2; P. T. Larson, Abbvie Sweden, 2; A. Telemann, Abbvie Sweden, 2; G. M. Alenius, Abbvie Sweden, 2; M. Geijer, Abbvie Sweden, 2.
tion 5A ("Wash & dry your entire body") showed the highest correlation, specifically with pain.

The majority of HAQ questions were significantly associated with the need for help within their corresponding ability category, with the exception of questions Q3B, Q3C, Q4B, Q5C and Q8B.

The results of factor analysis showed that 2 (Q1A and Q3B) out of the 20 HAQ questions accounted for 61.5% of its matrix variance, suggesting that the question on the ability to "dress, tie shoe laces and do buttons", as well as the question on the ability to "lift a full cup or glass" may be the main drivers of HAQ variability.

Conclusion: Variability exists in the correlation of individual HAQ questions with patient and physician reported Psa measures. Pain and PIGA are significantly associated with the various domains of HAQ, while clinical outcomes (SJ, C28 and TJC28) and MDGA are less important. Among Psa patients, the HAQ is driven by components related to dressing and grooming and to eating abilities, suggesting that Psa patients may be facing different challenges than RA patients. This may have implications from an occupational health perspective and in the design of a shorter self-report instrument more suitable for Psa patients.

Table 1. Correlation* between Individual HAQ Questions and Psa Outcome Measures

<table>
<thead>
<tr>
<th>HAQ Questions</th>
<th>Pain</th>
<th>PIGA</th>
<th>SJ C28</th>
<th>TJC28</th>
<th>MDGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing and Grooming (Q1 A/B)</td>
<td>0.57/0.42</td>
<td>0.53/0.37</td>
<td>0.35/0.28</td>
<td>0.39/0.35</td>
<td>0.46/0.33</td>
</tr>
<tr>
<td>Activities (Q2 A/B)</td>
<td>0.51/0.56</td>
<td>0.56/0.56</td>
<td>0.29/0.27</td>
<td>0.37/0.37</td>
<td>0.42/0.40</td>
</tr>
<tr>
<td>Eating (Q3 A/B/C)</td>
<td>0.41/0.68/0.41</td>
<td>0.30/0.30/0.42</td>
<td>0.20/0.26/0.31</td>
<td>0.30/0.28/0.37</td>
<td>0.30/0.26/0.37</td>
</tr>
<tr>
<td>Walking (Q4 A/B)</td>
<td>0.51/0.57</td>
<td>0.46/0.50</td>
<td>0.29/0.32</td>
<td>0.33/0.38</td>
<td>0.43/0.43</td>
</tr>
<tr>
<td>Hygiene (Q5 A/B/C)</td>
<td>0.67/0.40/0.53</td>
<td>0.40/0.40/0.44</td>
<td>0.28/0.20/0.25</td>
<td>0.34/0.36/0.32</td>
<td>0.30/0.30/0.31</td>
</tr>
<tr>
<td>Reach (Q6 A/B)</td>
<td>0.38/0.37</td>
<td>0.40/0.53</td>
<td>0.20/0.29</td>
<td>0.20/0.35</td>
<td>0.36/0.40</td>
</tr>
<tr>
<td>Grip (Q7 A/B/C)</td>
<td>0.34/0.43/0.34</td>
<td>0.30/0.30/0.30</td>
<td>0.28/0.28/0.27</td>
<td>0.37/0.35/0.39</td>
<td>0.29/0.35/0.27</td>
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<tr>
<td>Activities (Q8 A/B/C)</td>
<td>0.56/0.57/0.55</td>
<td>0.53/0.50/0.53</td>
<td>0.27/0.27</td>
<td>0.37/0.38/0.40</td>
<td>0.40/0.40/0.42</td>
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<tr>
<td>HAQ-DI score</td>
<td>0.67</td>
<td>0.63</td>
<td>0.38</td>
<td>0.38</td>
<td>0.51</td>
</tr>
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</table>

* Levels of correlation are Weak: r 0.40 - 0.69; Moderate: r 0.40 - 0.69; Strong: r 0.40 - 0.69; Very Strong: r 0.70 - 0.90.

References

Table 1. Workplace and household productivity over 96 wks in the RAPID-Psa trial (RS population; LOCF)

<table>
<thead>
<tr>
<th>WPS responses</th>
<th>C2P 200mg Q2W</th>
<th>C2P 400mg Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>M mean</td>
<td>Median</td>
<td>M mean</td>
</tr>
<tr>
<td>Productivity at workplace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work days missed due to arthritis per month [a]</td>
<td>BL</td>
<td>2.0</td>
</tr>
<tr>
<td>Days with work productivity reduced by ≥50% due to arthritis per month [a, b]</td>
<td>BL</td>
<td>5.2</td>
</tr>
<tr>
<td>Level of arthritis interference with work productivity (0–10 scale) [a, c]</td>
<td>BL</td>
<td>4.4</td>
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<tr>
<td>Household productivity and social participation (all patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household work days missed due to arthritis per month</td>
<td>BL</td>
<td>5.9</td>
</tr>
<tr>
<td>Household workdays with productivity reduced by ≥50% due to arthritis per month [b]</td>
<td>BL</td>
<td>7.1</td>
</tr>
<tr>
<td>Days missed family/social/leisure activities due to arthritis per month</td>
<td>BL</td>
<td>5.6</td>
</tr>
</tbody>
</table>

[a] Based only on employed patients at the specific visit; pts employed at BL (CZP 200mg Q2W/CZP 400mg Q4W). [b] Does not include work days missed counted in the previous question; [c] 0–10 scale, 0 = no interference and 10 = complete interference.

Disclosure A. Kavanaugh, Abbott, Amgen, BMS, Pfizer, Roche, Janssen, UCB Pharma, 2; D. D. Glidman, Abbott, Bristol Myles Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, and UCB Pharma, 2, Abbott, Bristol Myles Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, and UCB Pharma, 5; D. van der Heijde, Abbott, Amgen, AstraZeneca, Aegerion, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, 5, Imaging Rheumatology bv, 9; O. Pucurar, UCB Pharma, 3; P. Mease (Abbott) A044W, Amgen, Biogenicdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB Pharma, Vertex, 2; (Abbott) A044W, Amgen, Biogenicdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB Pharma, 8.
Background/Purpose: Early non-response to biologic therapy has been shown to be associated with a low probability of long-term response in rheumatoid arthritis and psoriasis. However, to date there is a shortage of data regarding early identification of non-responders in psoriatic arthritis (PsA). Such analyses may help avoid unnecessary exposure, increase cost-effectiveness and improve the chance of achieving long-term treatment goals. Here we aim to assess the association between disease activity (DA) and clinical response (CR) during the first 12 weeks (wks) of treatment, and attainment/lack of attainment of treatment targets at Wk48 in PsA patients (pts) receiving certolizumab pegol (CZP).

Methods: The relationship between DA state during the first 12 wks of treatment, and M inal Disease Activity (minDA) or DA at Wk48 (CRP <2.6 at Wk48) was assessed post hoc using data from the RAPID-Psa study (NCT01087788). DA state was defined using either DAS28(CRP) values: <2.6, 2.6–3.2, 3.2–5.1, >5.1; or PsARC response/non-response. Descriptive analyses are based on all pts randomized to CZP from Wk0. Pts that discontinued treatment during the first 12 wks were excluded from the analysis. For remaining pts, missing data were imputed using LOCF for DA at Wk48 and PsARC, and NRI for minDA.

Results: A relationship between Wk2 DA state and Wk48 minDA was observed, with 68% (17/25) of pts with DAS28(CRP) <2.6 at Wk2 achieving Wk48 minDA, compared with 10% (5/52) of pts with Wk2 DAS28(CRP) >5.1. This trend was maintained at Wk12, by which point more pts had lower DA. 73% (57/78) of pts with Wk12 DAS28(CRP) <2.6 achieved Wk48 minDA, compared to 0% (0/26) of pts with Wk12 DAS28(CRP) >5.1 (Table A). When Wk48 DAS28(CRP) <2.6–a less stringent target that excludes enthesis and skin manifestations - was used, a similar trend was observed, but more pts in each category achieved the target; however, still only 4% (1/26) of pts with Wk12 DAS28(CRP) >5.1 attained Wk48 DAS28(CRP) <2.6 (Table B). CR at Wk12 was also associated with likelihood of attaining minDA at Wk48: Of 153/256 (60%) CZP pts that achieved Wk12 DAS28(CRP) 0.6–1.2, 50% (76/153) achieved Wk48 minDA, compared to 32% (17/53) of pts with Wk12 DAS28(CRP) CR 0.6–1.2 and 12% (6/50) of Wk12 non-responders (DAS28(CRP) CR >0.6). PsARC response at Wk2 was also associated with Wk48 outcomes: 10.7% (6/56) of Wk12 PsARC non-responders achieved Wk48 minDA, compared to 47.7% (95/199) of Wk12 PsARC responders.

Conclusion: Using DA state and CR level at an early stage of CZP treatment, it was possible to identify PsA pts unlikely to achieve long-term treatment goals. This early identification may enable physicians adopting a treat-to-target strategy to determine early on when to change therapy in pts not responding to CZP.

References:
1. van der Heijde D, J Rheum 2012;39(7):1326–1333
5. Disclosure: P. Mease, AbbVie, Amgen, Biogen-Dicke, BMS, Celgene, Cresco, Genentech, Janssen, Lilly, Meck, Novartis, Pfizer, UCB Pharma, Verto; 2. R. Fleischmann, Genentech Inc, Roche, AbbVie, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, MSD, Novartis, Biogen-Dicke, AStellas, AstraZeneca, Janssen, 20; Roche, AbbVie, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, Novartis, AStellas, AstraZeneca, Janssen; 3. O. Davies, UCB Pharma; 4. D. van der Heijde, AbbVie, Amgen, AStrella, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Osuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Verto, 5. Imaging Rheumatology bv, S.

Early and Sustained Modified PsARC Response in Psoriatic Arthritis Patients Treated with Ustekinumab: Results from 2 Phase 3 Studies. 1

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Tuesday, November 18

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**Background/Purpose:** To report the safety of ustekinumab (UST) from the psoriatic arthritis (PsA) development program.

**Methods:** Safety data through up to 2yr of follow-up were pooled from Ph3 for the analysis of overall safety endpoints. Data were pooled from Ph2(n=146) and Ph3 for AEs of interest. In Ph3, adult PsA pts (PSUMMIT I (n=615), PSUMMIT II (n=312)) with active disease (≥5 SJC and ≥10 TJC; CRP≥0.3 mg/dL [ULN 1.0 mg/dL]) despite DMARD and/or NSAID or previously treated with DMARD and/or NSAID, and prior anti-TNF therapy (PSUMMIT II only) were randomized to UST 45mg, 90mg, or PBO at wks 0, 4, and q12wks; at wk16, pts with ≤50% improvement in SJC and TJC entered blinded EE (PBO→UST 45mg; UST45mg→90mg; 90mg→90mg). PBO pts crossed over to UST45mg at wks24 and 28 and q12wk dosing. No crossover from DMARDs to UST was allowed. 620 pts were entered blinded EE (PBO→UST 45mg; UST45mg→90mg; 90mg→90mg). PBO pts crossed over to UST45mg at wks24 and 28 and q12wk dosing. No crossover from DMARDs to UST was allowed. 620 pts were entered blinded EE (PBO→UST 45mg; UST45mg→90mg; 90mg→90mg). PBO pts crossed over to UST45mg at wks24 and 28 and q12wk dosing. No crossover from DMARDs to UST was allowed.

**Results:** In Table 1, Event rates of overall AEs, infections, and SAEs, were comparable among PBO and UST during the PhB-PBO-controlled period; rates remained comparable through 2yrs of follow-up. Rates of AEs leading to d/c were higher in PBO. Overall AE rates were not impacted by baseline MTX or prior anti-TNF usage. 1 squamous cell carcinoma (90mg), 1 serious infection leading to death/PCI/IMT was reported during PBO-controlled period. With up to 2yrs of follow-up, rate of infections was similar in 90mg vs 45mg grps; 0.57/100PY in 90mg vs 0.61/100PY in 45mg grps. All other AEs were not impacted by baseline MTX or prior anti-TNF usage. 1 squamous cell carcinoma (90mg), 1 serious infection leading to death/PCI/IMT was reported during PBO-controlled period. With up to 2yrs of follow-up, rate of infections was similar in 90mg vs 45mg grps; 0.57/100PY in 90mg vs 0.61/100PY in 45mg grps. All other AEs were not impacted by baseline MTX or prior anti-TNF usage.

no dose effects were observed (1.15 vs 0.24 for 45mg and 90mg, resp). No cases of active TB or serious opportunistic infections, RPLS, demyelination, anaphylaxis or serum sickness-like reactions were reported.

**Conclusion:** Pooled safety data showed that UST was well tolerated at both doses with up to 2yrs of follow-up without new safety signals. The safety profile of UST in the PsA clinical development program was generally comparable to that observed in the psoriatic population.

### Table 1: A disease Adverse Rates per 100 PY of Follow-up (95% CI)

<table>
<thead>
<tr>
<th>AE</th>
<th>PBO 45mg</th>
<th>UST 45mg</th>
<th>PBO 90mg</th>
<th>UST 90mg</th>
<th>PBO 45mg</th>
<th>UST 90mg</th>
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<tr>
<td>Overall AEs</td>
<td>109/100</td>
<td>113/100</td>
<td>114/100</td>
<td>113/100</td>
<td>144/100</td>
<td>144/100</td>
</tr>
<tr>
<td>Serious AE</td>
<td>11/100</td>
<td>9/100</td>
<td>9/100</td>
<td>10/100</td>
<td>11/100</td>
<td>11/100</td>
</tr>
<tr>
<td>Pts treated (n)</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
</tr>
<tr>
<td>Pts randomized (n)</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
<td>379</td>
</tr>
<tr>
<td>Serious infects</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 1.5)</td>
<td>(0.0, 1.5)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
</tr>
<tr>
<td>Serious malignancies</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
</tr>
<tr>
<td>Serious other</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
</tr>
<tr>
<td>Death</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
<td>(0.0, 2.1)</td>
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</tbody>
</table>

**Disclosure:** M. C. Genovese, Amgen Inc., 2, Amgen Inc., 5; P. Mease, Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 2, AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 5, AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, and UCB, 8; M. W. Greenwald, Amgen Inc., 2, C. T. Ritchlin, Amgen, Janssen, Novartis, Pfizer, UCB, 2, AbbVie, Amgen, Cipher, Crescendo, Janssen, Lilly, Novartis, Pfizer, and UCB, 5, AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, and UCB, 8; A. A. Beaulieu, Amgen Inc., 2, A. A. Deodhar, AbbVie, Amgen, Biogen Idec, Janssen, Novartis, Pfizer, and UCB, 2, AbbVie, Amgen, Cipher, Crescendo, Janssen, Lilly, Novartis, and Pfizer, 5, R. Neumann, Amgen Inc., 1, Amgen Inc., 3; J. Feng, Amgen Inc., 1, Amgen Inc., 3; N. Erondu, Amgen Inc., 1, Amgen Inc., 3; A. Nirula, Amgen Inc., 1, Amgen Inc., 3.

**Outcomes based on available data up to week 52 from the ongoing study included American College of Rheumatology 20% response (ACR20), ACR50, changes in DAS 28, CDAI, and ACR response components. Safety was assessed by monitoring adverse events (AEs).**

**Results:** The majority of enrolled subjects (113 brodalumab and 55 placebo) were female (64%), white (94%), and rheumatoid factor negative (92%). Mean age, weight, and duration of PsA at baseline were 52 years, 91 kg, and 9 years, respectively. 156 subjects entered the OLE (52 prior placebo, 53 prior 140 mg, 51 prior 280 mg). ACR20 and ACR50 response rates (observed), which were higher in brodalumab arms than in placebo at week 12, continued to improve and were sustained through week 52 across all groups (Figure 1). Improvements in DAS 28, CDAI, and several ACR components, observed from baseline to week 12, continued through week 52.

During the OLE (through week 52), 142 subjects reported AEs; most frequently reported (≥5% of subjects in any treatment group) were nasopharyngitis, arthralgia, psoriatic arthropathy, upper respiratory tract infection, bronchitis, nausea, sinusitis, and oropharyngeal pain. Ten subjects reported serious adverse events during the OLE through week 52: including 1 case each of acute myocardial infarction, invasive ductal breast carcinoma, metastatic lung cancer, melanoma, pyelonephritis, and streptococcal septic arthritis. Exposure adjusted AE rates (per 100 subject years) were 706 (all brodalumab) and 757 (placebo). Exposure adjusted SAE rates were 11 (brodalumab) and 8 (placebo). No deaths, clinically significant neutropenia (≥ Grade 2), or mycobacterial/fungal/opportunistic infections were reported.

**Conclusion:** Brodalumab treatment was associated with significant clinical response with continued improvement from weeks 12 to 52.
of baseline "extreme" scores on treatment outcome for etanercept and placebo.

**Methods:** Patients with non-radiographic axial spondyloarthritis participated in a randomized clinical trial and received double-blind etanercept 50 mg or placebo weekly. For this analysis, patients were divided into those who did vs. those who did not have extreme scores at baseline. Extreme baseline scores were defined as the highest quintile for enthesis score (>6), and/or scores >0 on 3 of 5 BASDAI items (morning stiffness duration was excluded). Depression was evaluated using the Hospital Anxiety and Depression Scale, depression subscale (HADS-D). Treatment outcome was the Assessment of SpondyloArthritis in Children (ASAS) 40 response rate at week 12.

**Results:** Of the 213 patients at baseline, 35 (16%) met only enthesis criteria, 31 (15%) met only BASDAI criteria, and 12 (6%) met both criteria, and 135 (63%) met neither criteria. Patients with extreme enthesis and/or BASDAI scores vs. those without were more likely to have moderate to severe depression at baseline (20/68 (29%) vs. 10/118 (9%) of patients had HADS-D score ≥11 (P<0.001). For patients with vs. without extreme scores, no significant difference existed in week 12 ASAS 40: etanercept 13/41 (32%) vs. 21/60 (35%); placebo 5/36 (14%) vs. 12/68 (18%).

**Conclusion:** Extreme enthesis and/or BASDAI scores correlated with depression at baseline, but did not have an effect on week 12 ASAS 40 in either the etanercept or placebo treatment group.

**Disclosure:** M. Dougados, Pfizer Inc, 2; Pfizer Inc, 5; H. J. Jones, Pfizer Inc, 1; Pfizer Inc, 3; A. Szumski, Pfizer Inc, 5; L. I. Logeart, Pfizer Inc, 1; F. C. Coudreau, Pfizer Inc, 1; M. Dougados, Pfizer Inc, 3.

### 1559

**Long Term Improvements in Physical Function are Associated with Improvements in Dactylitis, Enthesitis, Tender and Swollen Joint Counts, and Psoriasis Skin Involvement:** Results from a Phase 3 Study of Ustekinumab in Psoriatic Arthritis Patients. Arthur Kavaslaroglu, Lluís Puig Sanz, Alice B. Gottlieb, Christopher T. Ritchlin, Shu Li, Yin You, Ali M, Mandelsohn, Michael Song, Proton Rahman, and Iain B. McNees.

**University of California San Diego, La Jolla, CA, 1; Universitat Autònoma de Barcelona, Barcelona, Spain, 2; Tufts Medical Center, Boston, MA, 3; University of Rochester Medical Center, Rochester, NY, 4; Janssen Research & Development, LLC, Spring House, PA, 5; Imperial University of New Zealand, St. John's, NF, 6; University of Glasgow, Glasgow, United Kingdom.

**Background/Purpose:** To evaluate the association of improvements in tender and swollen joint counts (TJ, SJ) and psoriasis skin involvement, and dactylitis/enthesitis (in patients affected at baseline) with improvement in physical function using data from the ustekinumab (UST) PSUMMIT 1 trial in psoriatic arthritis (PsA) pts.

**Methods:** Adult PsA pts (n=615) with active disease (>5 SJ and/or >5 TJ) of peripheral origin were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks. Pts with prior anti-TNF agents were excluded. Stable concomitant MTX was permitted but not mandated. At wk16, pts with <5% improvement in TJC and SJ entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). PBO-treated patients subsequently crossed over to UST45mg at wk24. Pts received q12wks dosing to wk88, with final efficacy evaluation at wk100 and safety assessment at wk108. The percent change from baseline in enthesis score, dactylitis score, TJ and SJ by HAQ responder status (response defined as achieving ≥0.3 point improvement from baseline) was assessed at wks 52 and 100. The correlation between change from baseline in HAQ and percent change from baseline in TJC, SJ, enthesis, and dactylitis were also determined at wks 52 and 100.

**Results:** At baseline; mean (median) TJ and SJ values were 23.5 (20.0) and 12.3 (10.0), respectively. 441 (71.7%) and 296 (48.1%) patients had enthesis or dactylitis at baseline, respectively; 440 (71.7%) patients had >3 SLS psoriasis skin involvement. Improvements in TJ, SJ, enthesis, and PASI scores were generally greater in HAQ responders compared with non-responders at both wks 52 and 100 (Table). Significant correlations were demonstrated between the HAQ change from baseline with percent change in outcomes for all parameters for all outcomes (Table) at wk52 and wk100. In addition, associations were observed at earlier time points, including at wk28. Depression was evaluated using the Hospital Anxiety and Depression Scale, depression subscale (HADS-D). Treatment outcome was the Assessment of SpondyloArthritis in Children (ASAS) 40 response rate at week 12.

**Conclusion:** Based on this post-hoc analysis of the PSUMMIT 1 population, improvements in physical function as measured by HAQ were associated with improvements in TJ, SJ, dactylitis and enthesis, and these correlations were observed as early as week 24 and continued through week 100. Improvement in skin disease was also associated with improvements in HAQ.

#### Table: Summary of percent change from baseline at wk52 and wk100 in HAQ responders; randomized patients at baseline (mean[median])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wk52 Responders</th>
<th>Wk100 Responders</th>
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<tbody>
<tr>
<td>HAQ</td>
<td>Responders</td>
<td>Responders</td>
</tr>
<tr>
<td>TJ</td>
<td>N=90</td>
<td>N=90</td>
</tr>
<tr>
<td>SJ</td>
<td>N=90</td>
<td>N=90</td>
</tr>
<tr>
<td>enthesis</td>
<td>N=90</td>
<td>N=90</td>
</tr>
<tr>
<td>dactylitis</td>
<td>N=90</td>
<td>N=90</td>
</tr>
<tr>
<td>-0.19 (0.19)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

**Disclosure A. Kavanaugh, AbbVie, 2; Amgen, 2; Roche Pharmaceuticals, 2; Pfizer Inc, 2; Janssen Pharmaceuticals Product, L.P., 2; UCB, 2; BMS, 2; Astellas, 2; L. Puig Sanz, AbbVie, 2; Amgen, 2; Celgene, 2; Janssen Research & Development, LLC, 2; Merck & Co., 2; A. B. Gottlieb, AbbVie, 2; Amgen, 2; Astellas, 2; K. A. Flughoff, and Pfizer, 2; A. T. Ritchlin, AbbVie, 2; Amgen, 2; Astellas, 2; K. A. Flughoff, and Pfizer, 2; C. T. Ritchlin, Amgen, 2; Janssen, 2; C. T. Ritchlin, Amgen, 2; Janssen, 2; N. Sehl, 2; T. R. Rennemark, 2; H. Jones, 2; W. B. Kassim, 2; I. B. McInnes, 2; E. M. Kuper, 2; M. Schmalzing, 2; H. Gnann, 5; D. Diamant, 5; S. Hervás, 6; and C. T. Ritchlin, 5.


**Goethe-University Frankfurt, Frankfurt, Germany, 1; Fraunhofer Institute for Molecular Biology and Applied Ecology, 1; University of Medicine and Pharmacology, 1; University of Frankfurt/Main, 1; University of Würzburg, Würzburg, Germany, 2; Abbvie Deutschland GmbH & Co. K.G., Wiesbaden, Germany, 3; Abteilung Biostatistik, GKM Gesellschaft für Therapieforschung mbH, München, Germany, 4; University Hospital Heidelberg, Heidelberg, Germany, 5; University Hospital Schleswig Holstein Campus Lübeck, Lübeck, Germany.

**Background/Purpose:** Osteoporosis is an important comorbidity in patients with rheumatic diseases, but risk factors for osteoporosis in Psoriatic Arthritis (PsA) patients have not been explored.

**Methods:** We evaluated baseline characteristics of active PsA patients enrolled in a German observational multicenter study with aadalimumab (ADA). Multiple logistic regression analyses were utilized to identify risk factors for osteoporosis. Risk factors were confirmed in a validation cohort.

**Results:** At baseline, 60% of patients in the initial PsA cohort (N=1467) had osteoporosis as indicated by medical history. Logistic regression analysis (1194 patients with adequate data for modeling) found that age, systemic glucocorticoid use and rheumatoid factor (RF) seropositivity were significantly associated with osteoporosis. As the association between RF status and osteoporosis has been previously described in PsA, we evaluated a second cohort of PsA patients (N=1762) to determine whether this association could be verified. As in the initial cohort, positive RF status was associated with a >2-fold increase in the risk of osteoporosis in patients with PsA in the same range as use of glucocorticoids. The rate of osteoporosis was 5.4% (168/3102) in the total cohort and 12.1%
(35/290) in RF-positive patients. Analysis of typical PsA-features like confirmed nail involvement, enthesis and dactylitis and active psoriasis suggests that it is unlikely that the RF-positive PsA patients were misdiagnosed RA-cases. The full set of predictors of osteoporosis of the full cohort (2956 patients with adequate data) is shown in Table 1. Negative predictors were male gender and higher functional (FFbH) scores.

**Conclusion:** RF seropositivity is an independent risk factor for osteoporosis in active PsA patients. Other variables that increase the risk of osteoporosis are steroid use, older age, longer disease duration, recent hospitalization, female gender, and worse functional status.

### Baseline Weight and BMI on ACR20 and HAQ-DI Response: Pooled Apremilast, an Oral Phosphodiesterase 4 Inhibitor, and the Impact of

Baseline weight and body mass index (BMI) on clinical response to APR over 24 weeks for patients with active PsA and physical function were observed across a broad range of baseline weight and BMI values. Results suggest that no dose adjustment is required to account for baseline body weight or BMI.

### Results from 3 Phase 3, Randomized, Controlled Trials.

**Baseline weight (kg)**

<table>
<thead>
<tr>
<th>APR</th>
<th>Placebo n = 496*</th>
<th>APR n = 500*</th>
<th>APR n = 497*</th>
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<tbody>
<tr>
<td>&lt;70</td>
<td>34/108 (31.5)</td>
<td>34/108 (31.5)</td>
<td>44/121 (36.4)</td>
</tr>
<tr>
<td>70–85</td>
<td>311 (23.9)</td>
<td>17/109 (15.6)</td>
<td>41/116 (35.3)</td>
</tr>
<tr>
<td>85–100</td>
<td>39/113 (29.3)</td>
<td>44/174 (27.6)</td>
<td>66/170 (38.8)</td>
</tr>
<tr>
<td>≥100</td>
<td>311 (23.9)</td>
<td>7/40 (17.5)</td>
<td>15/39 (35.9)</td>
</tr>
</tbody>
</table>

**Baseline BMI (Kg/m²)**

<table>
<thead>
<tr>
<th>APR</th>
<th>Placebo n = 496*</th>
<th>APR n = 500*</th>
<th>APR n = 497*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>34/108 (31.5)</td>
<td>34/108 (31.5)</td>
<td>44/121 (36.4)</td>
</tr>
<tr>
<td>25–30</td>
<td>383 (28.8)</td>
<td>28/125 (22.4)</td>
<td>48/174 (27.6)</td>
</tr>
<tr>
<td>30–35</td>
<td>496 (27.6)</td>
<td>24/152 (15.8)</td>
<td>66/170 (38.8)</td>
</tr>
<tr>
<td>35–40</td>
<td>189 (34.5)</td>
<td>17/109 (15.6)</td>
<td>39/113 (34.5)</td>
</tr>
<tr>
<td>≥40</td>
<td>311 (23.9)</td>
<td>7/40 (17.5)</td>
<td>15/39 (35.9)</td>
</tr>
</tbody>
</table>

**Mean Change in HAQ-DI at Week 16 (LOCF)**

<table>
<thead>
<tr>
<th>APR</th>
<th>Placebo n = 496*</th>
<th>APR n = 500*</th>
<th>APR n = 497*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100</td>
<td>0.09 (0.22)</td>
<td>0.16 (0.22)</td>
<td>0.20 (0.22)</td>
</tr>
<tr>
<td>≥85</td>
<td>0.16 (0.23)</td>
<td>0.12 (0.22)</td>
<td>0.16 (0.22)</td>
</tr>
<tr>
<td>≥70</td>
<td>0.13 (0.23)</td>
<td>0.12 (0.22)</td>
<td>0.15 (0.23)</td>
</tr>
<tr>
<td>≥60</td>
<td>0.12 (0.23)</td>
<td>0.11 (0.22)</td>
<td>0.15 (0.23)</td>
</tr>
<tr>
<td>≥50</td>
<td>0.10 (0.23)</td>
<td>0.10 (0.22)</td>
<td>0.15 (0.23)</td>
</tr>
</tbody>
</table>

**The n reflects the number of randomized patients.**

**Discussion:** Apremilast, an Oral Phosphodiesterase 4 Inhibitor, and the Impact of Baseline Weight and BMI on ACR20 and HAQ-DI Response: Pooled Results from 3 Phase 3, Randomized, Controlled Trials.

**Apremilast, an Oral Phosphodiesterase 4 Inhibitor, and the Impact of Baseline Weight and BMI on ACR20 and HAQ-DI Response:**

### ACR20 Response at Week 16 (NRI)¶, m/n% (¶LOCF)

<table>
<thead>
<tr>
<th>APR</th>
<th>Placebo n = 496*</th>
<th>APR n = 500*</th>
<th>APR n = 497*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>22/107 (20.6)</td>
<td>34/108 (31.5)</td>
<td>44/121 (36.4)</td>
</tr>
<tr>
<td>70–85</td>
<td>311 (23.9)</td>
<td>17/109 (15.6)</td>
<td>41/116 (35.3)</td>
</tr>
<tr>
<td>85–100</td>
<td>39/113 (29.3)</td>
<td>44/174 (27.6)</td>
<td>66/170 (38.8)</td>
</tr>
<tr>
<td>≥100</td>
<td>311 (23.9)</td>
<td>7/40 (17.5)</td>
<td>15/39 (35.9)</td>
</tr>
</tbody>
</table>

**Conclusion:** APR demonstrated a favorable treatment effect in patients with active PsA. Comparable improvements in the signs and symptoms of PsA and physical function were observed across all weight and BMI ranges (Table). These treatment effects were generally maintained at Week 24.

### Clinical Response to APR: Comparison with Placebo

Apremilast is a phosphodiesterase 4 inhibitor that helps to regulate the immune response that causes inflammation and pain in patients with PsA. Despite prior dose-modifying antirheumatic drugs (DMARDs) and/or biologics, including biologic failures. We assessed the impact of baseline weight and BMI on clinical response to APR over 24 weeks in a pooled analysis.

### Methods

Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline BMI, gender, and disease duration. Patients who were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial APR dose at Week 24. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30.

### Results

1,493 patients were randomized, received ≥1 dose of study medication (placebo: n = 496; APR20: n = 500; APR30: n = 497), and were comparable across treatment groups for demographics, disease characteristics, and prior/concurrent therapy. At a baseline, mean (SD) weight was 85.7 (20.6) kg and mean (SD) BMI was 29.9 (6.5) kg/m². At Week 16, a significantly greater proportion of patients receiving APR20 or APR30 achieved a modified ACR20 response vs placebo (primary endpoint) in all 3 PALACE trials. APR30 was associated with significant improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI) score vs placebo at Week 16 (key secondary endpoint) across all 3 trials. At Week 16, similar ACR20 response rates and improvements in HAQ-DI scores were observed across all weight and BMI ranges (Table). A favorable treatment effect for both APR treatment groups vs placebo was observed, irrespective of baseline body weight or BMI. Overall, the treatment effect was dose-dependent, with greater effects generally observed in APR30 patients over APR20 patients. These treatment effects were generally maintained at Week 24.

### Conclusion

The results from these trials suggest that APR could be an effective and well-tolerated treatment option for patients with active PsA.

**Disclosure:** G. A. Schett, Abbott, Celgene Corporation, Roche, and UCB, 2; Abbott, Celgene Corporation, Roche, and UCB, 5; P. M. Mease, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, UCB, Celgene Corporation, Novartis, and Roche, 2; Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, Pfizer Inc, and UCB, 8; D. D. Gladman, Abbvie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 2; Abbvie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 5; A. Kavamura, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene Corporation, Controz-Janssen, Pfizer Inc, Roche, and UCB, 2; A. O. Adebaio, None, J. J. Gomez-Reino, Bristol-Myers Squibb, Pfizer Inc, Roche, Schering-Plough, and UCB SA, 9; Bristol-Myers Squibb, Roche, Schering-Plough, and Wyeth, 3; Roche and Schering-Plough, 3; J. Wollenhaupt, Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 2; Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, Roche, and UCB, 5; M. Cutolo, Actelion, Bristol-Myers Squibb, and Sanofi-Aventis, 2; Atezolizumab, Bristol-Myers Squibb, and Sanofi-Aventis, 5; L. E. Lespessailles, Amgen, Eli Lilly, Novartis, and Servier, 2; Amgen, Eli Lilly, Novartis, and Servier, 2; C. H. Hu, Celgene Corporation, 3; Celgene Corporation, 1; R. M. Stevens, Celgene Corporation, 1; Celgene Corporation, 3; C. J. Edwards, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2; Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5; Abbott, GlaxoSmithKline, Pfizer Inc, and Roche, 8; C. A. Birbara, Amgen, Bristol-Myers Squibb, Incyte, Eli Lilly, Merck, and Pfizer Inc, 2.
Psoriasis Longitudinal Assessment and Registry: Global Update upon Full Enrollment. Bruce Strober¹, Alan Menter², Craig Leonard³, Lyn Guenther⁴, Kavitha Goyal⁵, Wayne Langhoff⁶, Steve Calabro⁷, and Steve Fakharzadeh⁸. ¹University of Connecticut Health Center, Farmington, CT, ²Baylor Research Institute, Dallas, TX, ³Central Dermatology, St. Louis, MO, ⁴The Guenther Dermatology Research Centre, London, ON, ⁵Janssen Services, LLC, Horsham, PA, ⁶Janssen Research and Development, LLC, Spring House, PA, ⁷Janssen Services, LLC, Spring House, PA.

Background/Purpose: To report the baseline demographics and clinical characteristics of participants enrolled in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study.

Methods: PSOLAR is a multicenter, prospective, longitudinal, observational study initiated by the FDA designed to follow psoriasis patients for 8 years in academic and community settings. Eligible patients are ages 18+ years, have a diagnosis of psoriasis and are currently receiving or are candidates to receive systemic therapies for psoriasis. Demographics and medical/family history are collected at enrollment, including self-reported diagnosis of psoriatic arthritis. Evaluations at 6 month intervals include adverse events, disease activity, quality of life, economic status, healthcare utilization and interval therapies.

Results: PSOLAR is fully enrolled, with sites in North America, Latin America, and Europe having recruited 12 095 patients as of 23 August 2013. Baseline characteristics at enrollment were as follows: mean age 48.6 years, median age 49.0 years; 13% were ≤55 years of age; 54.9% male; 82.9% white; mean body mass index (BMI) 30.9 (SD 7.2); and mean psoriasis duration 17.5 years (SD 13.5 years). Psoriatic arthritis was self-reported in 35.7% of patients and 96.9% of patients had plaque-type psoriasis. Mean and median historical peak psoriasis activity as measured by PGA were 3.1 and 3.0 respectively, and mean physicians’ global assessment (PGA) score 2 (SD 1.2). Psoriasis medications (current and historical) included topical agents [22]. Limitations: Rates have not been adjusted for demographic and clinical differences among treatment groups and are subject to attribution rules.

Conclusion: In the current evaluation, reflecting a median duration of 2.5 years of follow-up, cumulative unadjusted rates of malignancies in PSOLAR are comparable across treatment groups. The most frequently reported malignancies in the registry are similar to those in the general population. Evaluation of malignancies with accruing longitudinal exposure will be informative.

Disclosure: D. Fiorinotto, Janssen Scientific Affairs, LLC, 2; M. Lebwohl, Janssen Scientific Affairs, LLC, 2; V. Ho, Janssen Scientific Affairs, LLC, 2; R. Langley, Janssen Scientific Affairs, LLC, 2, K. Goyal, Janssen Scientific Affairs, LLC, 3; S. Fakharzadeh, Janssen Scientific Affairs, LLC, 3; S. Calabro, Janssen Scientific Affairs, LLC, 3; W. Langhoff, Janssen Scientific Affairs, LLC, 3.

Long-Term (104-Week) Safety Profile of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial and Open-Label Extension. Philip Mease¹, A dewale O. Adeboja², Dafna D. Gladman³, Juan J. Gómez-Reino⁴, Stephan Hall⁵, Arthur Kavanaugh⁶, Eric Lespes-sailles⁷, Georg A. Schett⁸, Kamal Shah⁹, Randall M. Stevens¹⁰, Lichen Teng¹¹ and Jürgen Wollenhaupt¹². ¹Swedish Medical Center and University of Washington, Seattle, WA, ²University of Sheffield, Sheffield, United Kingdom, ³University of Toronto, Toronto Western Hospital, Toronto, ON, ⁴Hospital Clinico Universitario, Santiago, Spain, ⁵Monash University, Melbourne, Australia, ⁶University of California San Diego, La Jolla, CA, ⁷University of Orléans, Orléans, France, ⁸University of Erlangen-Nuremberg, Erlangen, Germany, ⁹Celgene Corporation, Warren, NJ, ¹⁰Schön Klinik Hamburg Elbek, Hamburg, Germany.

Background/Purpose: Apremilast (APR), a phosphodiesterase 4 inhibitor, helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 1, a phase 3 randomized trial with an open-label extension, compared the efficacy/safety of APR with placebo (PBO) in pts with active PsA despite prior conventional DMARDs and/or biologics.

Methods: Pts were randomized (1:1:1) to receive PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Pts whose swollen/tender joint counts had not improved ≥20% at Wk 16 were considered non-responders and were re-randomized (1:1) to APR20 or APR30 (PBO pts) or continued on their initial dose (APR pts). At Wk 24, all remaining PBO pts were randomized to APR20 or APR30. Double-blind APR treatment continued to Wk 52; pts could continue to receive APR during an open-label, long-term treatment phase. The analysis reports safety findings from the APR-exposure period (Wks 0 to 104).

Results: Pts were randomized and received ≥1 dose of study medication (PBO: n = 168; APR20: n = 168; APR30: n = 168). A total of 4900
Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA).

**Results:** In the pooled PALACE 1-3 population, a significantly greater proportion of patients receiving APR 20 and APR 30 achieved a modified ACR20 response vs placebo at Week 16 (placebo: 18.8%; APR 20: 32.0% [P < 0.0001]; APR 30: 37.0% [P < 0.0001]) (primary endpoint). At Week 16, significant improvements were observed with APR 20 and APR 30 (PALACE 1-3, pooled) for multiple patient-reported outcomes compared with placebo (APR 20: and APR 30, respectively): least-squares (LS) mean changes in Health Assessment Questionnaire-Disability Index (HAQ-DI) (−0.07; −0.16 [P = 0.0009]; and −0.21 [P < 0.0001], visual analog scale (VAS) (−5.8; −10.7 [P = 0.0009]; and −12.7 [P < 0.0001]), 36-Item Short-Form Health Survey version 2 (SF-36v2) physical component summary (PCS) (1.9; 3.3 [P < 0.0001]; and 3.9 [P < 0.0001]), and SF-36v2 Physical Functioning (PF) domain (1.3; 2.7 [P = 0.0057]; and 3.6 [P < 0.0001] scores). APR 30 also significantly improved the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at Week 16 (1.1; 1.5 [P = N.S.]; and 3.5 [P < 0.0001]). In patients initially randomized to APR who completed Week 52, improvements were sustained at Week 52 across the individual studies (Table). The most common adverse events reported for up to 24 weeks of APR treatment were diarrhea (12.2%), nausea (10.1%), and headache (8.0%) (PALLAS 1-3; pooled). The safety profile of APR through 52 weeks was similar to that observed with APR for up to 24 weeks of treatment.

**Conclusion:** Among patients continuously treated with APR, sustained clinically meaningful improvements in patient-reported outcome measures of pain, physical function, and fatigue were observed through Week 52. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 104 wks, with no new safety concerns identified with long-term exposure. These data continue to support that specific laboratory monitoring is not needed with APR.

**Background/Purpose:** Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics, including biologic failures.

**Methods:** Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR 20 or APR 30 if they were initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining placebo patients were re-randomized to APR 20 or APR 30. This analysis reports data up to 52 weeks.

**Results:** In the pooled PALLAS 1-3 population, a significantly greater proportion of patients receiving APR 20 and APR 30 achieved a modified ACR20 response vs placebo at Week 16 (placebo: 18.8%; APR 20: 32.0% [P < 0.0001]; APR 30: 37.0% [P < 0.0001]) (primary endpoint). At Week 16, significant improvements were observed with APR 20 and APR 30 (PALLAS 1-3, pooled) for multiple patient-reported outcomes compared with placebo (APR 20: and APR 30, respectively): least-squares (LS) mean changes in Health Assessment Questionnaire-Disability Index (HAQ-DI) (−0.07; −0.16 [P = 0.0009]; and −0.21 [P < 0.0001], visual analog scale (VAS) (−5.8; −10.7 [P = 0.0009]; and −12.7 [P < 0.0001]), 36-Item Short-Form Health Survey version 2 (SF-36v2) physical component summary (PCS) (1.9; 3.3 [P < 0.0001]; and 3.9 [P < 0.0001]), and SF-36v2 Physical Functioning (PF) domain (1.3; 2.7 [P = 0.0057]; and 3.6 [P < 0.0001] scores). APR 30 also significantly improved the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at Week 16 (1.1; 1.5 [P = N.S.]; and 3.5 [P < 0.0001]). In patients initially randomized to APR who completed Week 52, improvements were sustained at Week 52 across the individual studies (Table). The most common adverse events reported for up to 24 weeks of APR treatment were diarrhea (12.2%), nausea (10.1%), and headache (8.0%) (PALLAS 1-3; pooled). The safety profile of APR through 52 weeks was similar to that observed with APR for up to 24 weeks of treatment.

**Conclusion:** Among patients continuously treated with APR, sustained clinically meaningful improvements in patient reported-outcome measures of pain, physical function, and fatigue were observed through Week 52. APR demonstrated an acceptable safety profile and was generally well tolerated through 52 weeks.

**Impact of APR on Parameters of Pain, Disability, and Fatigue at Week 52 (Data as Observed)**

<table>
<thead>
<tr>
<th>Metric</th>
<th>PALACE 1</th>
<th>PALACE 2</th>
<th>PALACE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APR 20</strong></td>
<td>APR 30</td>
<td>APR 30</td>
<td>APR 30</td>
</tr>
<tr>
<td><strong>Week 52</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAQ-DI (0-3)</strong></td>
<td>−0.33</td>
<td>−0.22</td>
<td>−0.09</td>
</tr>
<tr>
<td><strong>Pain VAS (0-100 mm)</strong></td>
<td>−17.8</td>
<td>−20.3</td>
<td>−13.5</td>
</tr>
<tr>
<td><strong>SF-36v2 PCS (0-100)</strong></td>
<td>7.8</td>
<td>13.0</td>
<td>10.5</td>
</tr>
<tr>
<td><strong>SF-36v2 PF (0-100)</strong></td>
<td>7.0</td>
<td>7.8</td>
<td>6.2</td>
</tr>
<tr>
<td><strong>FACIT-fatigue (−52)</strong></td>
<td>4.8</td>
<td>4.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Note: The n reflects the number of patients who completed 52 weeks; actual number of patients available for each endpoint may vary. *Increase indicates improvement; †Decrease indicates improvement.

**Disclosure:** D. D. Gladman, Abbott, Amgen, Celgene, Janssen, Pfizer, UCB, 2; Abbvie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 5; V. Strand, Affirme Pharmaceuticals, Inc., 5; A. Kavaanah, Abbott, Amgen, Bristol-Myers Squibb, Celgene Corporation, Centocor-Janssen, Pfizer Inc, Roche, and UCB, 2; P. Mease, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, and UCB, 2, A. O. Adebajo, None; D. D. Gladman, Abbvie, Amgen, Celgene, Janssen, Pfizer, UCB, 2; Abbvie, Amgen, BMS, Celgene, Eli Llyly, Janssen, Novartis, Pfizer, UCB, 5; J. J. Gomez-Reino, Bristol-Myers Squibb, Pfizer Inc, Roche, Schering-Plough, and UCB SA, 9; Bristol-Myers Squibb, Roche, Schering-Plough, and Wyeth, 9; Roche and Schering-Plough, 2; S. Hall, Celgene Corporation, Pfizer, UCB, Bristol-Myers Squibb, GlaxoSmithKline, Roche, Jansen, Novartis, Merck, 2; Cellgene Corporation, Pfizer, UCB, Bristol-Myers Squibb, GlaxoSmithKline, Roche, Jansen, Novartis, Merck, 5; A. Kavanaugh, Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor-Janssen, Pfizer Inc, Roche, and UCB, 2; E. Lespesailles, Amgen, Eli Lilly, Novartis, and Servier, 2; A. M. Cutolo, Janssen, Novartis, and Servier, 8; G. A. Schett, Abbott, Celgene Corporation, Roche, and UCB, 2; A. Abbott, Celgene Corporation, Roche, and UCB, 2; S. K. Shah, Celgene Corporation, 1; Celgene Corporation, 3; R. M. Stevens, Celgene Corporation, 1; Celgene Corporation, 3; J. J. Wollenhaupt, Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 2; Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 5.

**1565**

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Improvement of Pain, Fatigue, and Disability in Patients with Psoriatic Arthritis: Results from 3 Phase 3, Randomized, Controlled Trials. Dafna D. Gladman1, Vibeke Strand2, Arthur Kavaanah1, Philip M. Casey3, Christopher J. Edwards1, Maurizio Cutolo4, Frederic Liote5, Paul Bird6, Randall M. Stevens1, Lichen Tang1, Maria Hochfeld7, and Georg A. Schett8.

1University of Toronto, Toronto Western Hospital, Toronto, ON, 2Stanford University, Portola Valley, CA, 3University of California San Diego, La Jolla, CA, 4Swedish Medical Center and University of Washington, Seattle, WA, 5University Hospital Southampton, Southampton, United Kingdom, 6Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, 7University Paris Diderot, Paris, France, 8Combined Rheumatology Practice, Kogarah, Australia, 9Celgene Corporation, Warren, NJ; 10University of Erlangen-Nuremberg, Erlangen, Germany.
The Efficacy and Safety of Biological Disease Modifying Anti-Rheumatic Drugs and Apremilast in the Treatment of Psoriatic Arthritis: A Systematic Review and Meta-Analysis. Arthur N. Lau, Michael Zoratti, Alfred Cividino, William Bensen, Jonathan D. Adachi, and Christopher Edwards. McMaster University, Hamilton, ON, 2Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, 3NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

**Background/Purpose:** Currently, there are a number of effective therapies for psoriatic arthritis (PsA). The objective of this systematic review was to assess the efficacy (PSARC, ACR 20/50/70 and PASI 75 response) and adverse event profile (AEs) (any AEs, serious AEs, and infection rate) of using TNF inhibitors or new therapies including Ustekinumab and Apremilast to treat active PsA.

**Methods:** This review included all published/unpublished RCTs comparing biologics or Apremilast to placebo in PsA patients. Multiple mechanisms of action (MOA) were included: TNF inhibitor (Adalimumab, Certolizumab, Etanercept, Infliximab and Golimumab), IL12/23 inhibitor (Ustekinumab) and PDE4 inhibitor (Apremilast). The databases MEDLINE (n=245), EMBASE (n=1551) and CENTRAL (n=223) were searched. Conference abstracts from the ACR and American Academy of Dermatology (2009–13) were hand searched. Two reviewers independently screened titles/abstracts/full text for eligibility. Data extraction and risk of bias assessment were performed in duplicate using Cochrane’s Risk of Bias assessment tool.

**Results:** 18 RCTs (543 participants) met our criteria. Ustekinumab and Apremilast were pooled, the risk ratio (RR) for achieving PSARC, ACR20, 50, 70, and PASI 75 respectively for the TNF, PDE4 and IL12/23 inhibitors. RR of achieving ACR20 response (24wk) by MOA is shown in figure 1. Low heterogeneity (I^2=65%) was explained by a priori subgroup analysis (by MOA). When comparing TNF ACR20 (12-16wk) response by MOA, the RR was 2.99 (95% CI: 2.91-5.46), 2.03 (95% CI: 1.70-2.42) and 2.08 (95% CI: 1.66-2.59) respectively for the TNF, PDE4 and IL12/23 inhibitors. RR of achieving ACR 20 response (24wk) by MOA is shown in figure 1. Low heterogeneity (I^2 < 40%) was seen for the outcomes ACR50, 70 at 12–16/24 wk respectively, suggesting there may be comparable efficacy of each MOA class for these outcomes. There was no significant increase in risk for any AEs or severe AEs, except a mild increase in risk of infections at 24 wk (RR = 3.14, 95% CI: 1.10-9.32).

**Conclusion:** TNF inhibitors, Ustekinumab & Apremilast all appear to produce significant benefits on joint and skin disease for individuals with PsA. The safety profile, aside from a slight increased risk of infections, appears acceptable. When comparing the three MOAs, the TNF inhibitors appeared most effective in achieving an ACR20 response at 12-16wk. However, by 24wk there was no significant difference between TNF inhibition and Apremilast. A significant difference remained between TNF inhibition and Apremilast. Ustekinumab and Apremilast whilst head to head trials are needed to definitively draw such conclusions, incorporating additional RCTs in future analyses will provide greater power to characterize this relationship.

**Disclosure:** A. N. Lau, Amgen, Roche, 2, Amgen, Roche, 8, Amgen, Roche, 2, M. Zoratti, None; A. Cividino, Celgene, Abbvie, 5; W. Bensen; Janssen Inc.; S. D. Adachi, None; C. Edwards, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5, A. Blatto, Glaxo-SmithKline, Pfizer Inc, and Roche, 8.

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The Spectrum of Autoimmune Ophthalmic Manifestations in Psoriatic Disease. Sergio Schwartzman, A. Kolomoyer, and David Chu. Hospital for Special Surgery, New York, NY, University of Pittsburgh, Pittsburgh, PA, Rutgers, Newark, NJ.

**Background/Purpose:** Psoriatic arthritis is characterized by the presence of psoriasis with or without an association of extra-dermal manifestations. Inflammatory forms of arthritis are the most common comitant findings in this continuum but not infrequently other organ systems manifest involvement. There is a dearth of primary literature on autoimmune ocular manifestations in patients with Psoriasis (Ps) and Psoriatic arthritis (PsA) although the prevalence of uveitis in PsA has been documented to be as high as 25%. The purpose of this study is to describe the pattern of ocular inflammation in patients with psoriatic disease.

**Methods:** Retrospective chart review of ocular manifestations in patients with Ps and PsA from two tertiary care centers in the United States specializing in autoimmune ophthalmic disease. Data was collected on age, gender, ethnicity, associated autoimmune disease, ocular manifestations, HLA Typing, systemic immunomodulating agents and ocul therapy.

**Results:** 20 patients were identified with the following characteristics:

<table>
<thead>
<tr>
<th>Age in years at Diagnosis of Ophthalmic Disease mean +/- SD</th>
<th>Male/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.9 SD +/- 14.4</td>
<td>5/15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hispanic</td>
</tr>
<tr>
<td>2. African Americans</td>
</tr>
<tr>
<td>3. Caucasians</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psoriatic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Ps</td>
</tr>
<tr>
<td>14. PsA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Systemic Illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Sarcoid</td>
</tr>
<tr>
<td>2. RA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pattern of PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Oligoarticular</td>
</tr>
<tr>
<td>2. Axial</td>
</tr>
<tr>
<td>1. Polysarticular</td>
</tr>
<tr>
<td>(not available in 3 pts)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ophthalmic Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Anterior Uveitis</td>
</tr>
<tr>
<td>3. Panuveitis</td>
</tr>
<tr>
<td>2. Scleritis</td>
</tr>
<tr>
<td>1. Ectopisits</td>
</tr>
<tr>
<td>3. Sclerouveitis</td>
</tr>
<tr>
<td>2. PUK</td>
</tr>
<tr>
<td>1. Vasculitis</td>
</tr>
<tr>
<td>1. Multifocal Choroiditis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Systemic and Local Steroids</td>
</tr>
<tr>
<td>2. Sulfasalazine</td>
</tr>
<tr>
<td>3. Methotrexate</td>
</tr>
<tr>
<td>4. Cyclosporin</td>
</tr>
<tr>
<td>5. Amlimumab</td>
</tr>
<tr>
<td>6. Infliximab</td>
</tr>
<tr>
<td>7. Certolizumab</td>
</tr>
<tr>
<td>8. Etanercept</td>
</tr>
<tr>
<td>9. Cytoxan</td>
</tr>
<tr>
<td>10. Rituximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Patients Requiring More than One Immunomodulatory Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

**Conclusion:** The breadth and severity of ocular manifestations in patients with Ps and PsA is diverse. This is the largest cohort of patients with autoimmune ophthalmic manifestations and psoriatic disease described to date. There are several unique features of this cohort:

1. 30% of patients had only skin disease.

2. Although it appears that anterior uveitis is the most common autoimmune ocular manifestation of this group of diseases in this cohort of patients it tends to be chronic, differentiating this ocular manifestation from the pattern in Ankylosing Spondylitis.

3. 33% of patients had an overlap of two underlying systemic autoimmune diseases.

4. When ocular manifestations do occur in patients with psoriatic disease, they tend to be more severe and require more than one immunomodulatory therapy.

5. The most common pattern of PsA in patients with autoimmune ophthalmic disease is the olioarticular form.


**Disclosure:** S. Schwartzman, A. Kolomoyer, and D. Chu. Aobbt Immunology Pharmaceuticals, 5, Aobbt Immunology Pharmaceuticals, 8, Janssen Pharmaceuticals, L.P., 5, Janssen Pharmaceuticals, L.P., 8, Genentech and Biogen IDEC Inc., 5, Genentech and Biogen IDEC Inc., 8, ucmb, 5, ucmb, 8, Amgen, 8, antares, 8, Pfizer Inc, 5, Paizer, 8, A. Kolomoyer, None; D. Chu, Xoma Corporation, 5, Sanofi-Aventis Pharmaceutical, 2, Biogen IDEC, 5, Bausch & Lomb, 5, alcon, 8, Allergan, 2.
Joint Damage Is Not Associated with Smoking Status in Patients with Psoriatic Arthritis. Hernán Maldonado-Ficco, A-rane Thavaneswaran, Vinoth Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The association between smoking and radiographic progression has been established in axial spondyloarthritis and rheumatoid arthritis (RA) but this association has not been established in psoriatic arthritis (PsA). The aim of this study was to determine the effects of cigarette smoking on clinical joint damage in patients with psoriatic arthritis.

Methods: From 1306 PsA patients followed prospectively between 1978 and 2014 as part of an observational cohort, a total of 1107 that started treatment after the first visit was included in the current study. We defined clinical damage as limitation of movement of more than 20% of the range that is not related to a joint effusion, the presence of flexion contractures, fused or flail joints, or evidence of surgery in a particular joint. We used clinical damage as it is assessed at each protocol visit and we have previously demonstrated that clinical joint damage in linked to radiological joint damage. We evaluated the smoking status at the baseline visit up until the first development of clinical joint damage. Smoking status was defined as “non-smoker”, “past smoker” and “current smoker”. Time to development of joint damage was assessed using a Cox Regression Analysis to determine the factors predictive of clinical damage, including age, sex, dactylitis and smoking status, joint counts, treatment and HLA B*27 status.

Results: A mong the 1107 patients, 55.6% were males, with a mean age of 46 years, duration of psoriasis 17.4 years and the duration of PsA 8.4 years at baseline. 55.6% of the patients were non-smokers, 24.4% were past smokers and 12.4% were current smokers. 7.9% of the patient had clinical joint damage and 26% had dactylitis at baseline. Males, HLA B*27 positivity, higher age at diagnosis of PsA, clinical damage at baseline, dactylitis and swollen joints were associated with a higher probability of developing clinically damaged joints whereas current and past smokers at baseline were associated with a lower probability of developing clinically damaged joints compared to non-smokers.

Conclusion: Unlike what occurs in RA and ankylosing spondylitis, the clinical damage in PsA was not associated with smoking status but was associated with disease-specific features.

Disclosure: H. Maldonado-Ficco, None; A. Thavaneswaran, None; V. Chandran, None; D. D. Gladman, None.

1569 Persistence of Biological Therapy in Psoriatic Disease: Results from the Psoriasis Longitudinal Assessment and Registry. Alan Menter, Kim Papp, Gerald G. Krueger, Mathias Augustin, Francisco Kerdel, Elinda Gooderham, Steve Fakharzadeh, Wayne Langhoff, Jan Sermon1, Steve Calabro2 and David Pariser3. 1Baylor Research Institute, Dallas, TX; 2Probioty Medical Research, Waterloo, ON; 3University of Utah, Salt Lake City, UT; 4Janssen Scientific Affairs, LLC, 2; 5Janssen Services, LLC, 3; 6Janssen Scientific Affairs, LLC, 2; 7Amgen, 8Janssen Scientific Affairs, LLC, 2; 9AbbVie, Allergan, Celgene, Eli Lilly, Galderma, Kythera, Leo Pharma, Merck, Novartis, and Pfizer, 9AbbVie, Amgen, Astellas, Galderma, Janssen, Leo Pharma, Novartis, and Pfizer, 9& K. Goyal, Janssen Scientific Affairs, LLC, 3; 10S. Fakharzadeh, Janssen Scientific Affairs, LLC, 3; 11W. Langhoff, Janssen Scientific Affairs, LLC, 3; 12J. Sermon, Janssen Cilag, 3; 13S. Calabro, Janssen Scientific Affairs, LLC, 3; 14D. Pariser, Janssen Scientific Affairs, LLC, 2.

Background/Purpose: People with psoriatic arthritis (PsA) have an increased risk for several comorbidities that negatively impact quality of life and survival. Defining the relationships between comorbidities and PsA characteristics may help identify subsets of PsA patients at high risk for comorbidities. The objective of this study was to determine if PsA severity or duration associated with the number of comorbidities.

Methods: This was a cross-sectional study of PsA participants in the Utah Psoriasis Initiative Registry. Data were collected with questionnaires, interviews, and examinations between 1/22/2010 and 4/21/2014. Disease severity measures included a functional assessment (BASFI), a quality of life instrument (Psoriasis Quality of Life (PsAQOL)), and disease activity measures, (68 tender joint count (TJC), 66 swollen joint count (SJC)), BASDAI, Physical Global, Patient Global, and a cutaneous physician global assessment multiplied by the body surface area (PGAxBSA). To analyze PsA duration, a proportional odds logistic regression model was used to test for an association between PsA duration and number of comorbidities (0, 1–2, or ≥3 comorbidities), after adjustment for age, gender, race, body mass index (BMI), TJC, and SJC. For severity assessments, a general linear model was used to test for differences in the mean score for each instrument after adjusting for age, gender, race, BMI, and PsA duration.

Results: PsA was diagnosed and phenotyped by a rheumatologist in 190 participants (Table 1). Compared to participants with PsA duration 15 years had higher mean numbers of comorbidities, but the difference was statistically significant only in the group with duration of 5–15 years (Table 2). The number of comorbidities was associated with BASFI (Table 3), but not with measures of quality of life or disease activity (data not shown).

Conclusion: Higher numbers of comorbidities may be associated with longer PsA duration and functional limitations as measured by BASFI. Anticipated analysis of a larger number of participants in a multi-center comorbidity project will provide a better understanding of the relationships between comorbidities, PsA duration, and PsA severity.
Table 1. Demographics, disease characteristics, and comorbidities (n=170-190)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>&lt;5 years</th>
<th>5-15 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>46.0 (12.3)</td>
<td>49.0 (14.0)</td>
<td>54.7 (12.8)</td>
</tr>
<tr>
<td>Female</td>
<td>43 (56.6)</td>
<td>27 (46.1)</td>
<td>30 (51.7)</td>
</tr>
<tr>
<td>Caucasian Race</td>
<td>73 (93.2)</td>
<td>54 (98.2)</td>
<td>55 (98.4)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>30.3 (8.7)</td>
<td>30.5 (8.8)</td>
<td>30.4 (8.9)</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0</td>
<td>0</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>1 (1.3)</td>
<td>1 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic heartburn/reflux</td>
<td>13 (17.1)</td>
<td>14 (25.5)</td>
<td>15 (25.9)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>12 (15.8)</td>
<td>11 (20.0)</td>
<td>14 (24.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (7.9)</td>
<td>10 (18.2)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Osteoporosis/osteopenia</td>
<td>5 (6.6)</td>
<td>8 (14.5)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>COPD/emphysema</td>
<td>1 (1.3)</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td>3 (3.9)</td>
<td>2 (3.6)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (2.6)</td>
<td>4 (7.3)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>COPD (lymphoma)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>5 (6.6)</td>
<td>1 (1.8)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (6.6)</td>
<td>7 (12.7)</td>
<td>11 (19.0)</td>
</tr>
<tr>
<td>Osteoarthritis/osteoarthritis</td>
<td>5 (6.6)</td>
<td>8 (14.5)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>1 (1.3)</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0</td>
<td>0</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Restless leg syndrome</td>
<td>5 (6.6)</td>
<td>2 (3.6)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (7.9)</td>
<td>10 (18.2)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>12 (15.8)</td>
<td>11 (20.0)</td>
<td>14 (24.1)</td>
</tr>
<tr>
<td>Chronic heartburn/reflux</td>
<td>13 (17.1)</td>
<td>14 (25.5)</td>
<td>15 (25.9)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>8 (10.5)</td>
<td>7 (12.7)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (1.3)</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 (1.3)</td>
<td>3 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (22.4)</td>
<td>18 (32.7)</td>
<td>12 (20.7)</td>
</tr>
</tbody>
</table>

Table 2. Number of comorbidities and PsA duration (n=190)

<table>
<thead>
<tr>
<th>PsA duration</th>
<th>4.0</th>
<th>4.5</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of comorbidities</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No MSC (n)</td>
<td>724</td>
<td>527</td>
<td>527</td>
</tr>
<tr>
<td>MSC - self reported (n)</td>
<td>840</td>
<td>672</td>
<td>514</td>
</tr>
<tr>
<td>MSC Known (n)</td>
<td>158</td>
<td>108</td>
<td>87</td>
</tr>
<tr>
<td>MSC - other reported (n)</td>
<td>724</td>
<td>527</td>
<td>527</td>
</tr>
<tr>
<td>Overall (n)</td>
<td>624</td>
<td>534</td>
<td>527</td>
</tr>
</tbody>
</table>

Table 3. Number of comorbidities and BASFI (n=170)

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>0.000</th>
<th>1.73 (0.86-3.48)</th>
<th>0.128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of comorbidities</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0-15</td>
<td>100</td>
<td>99.8</td>
<td>99.7</td>
</tr>
<tr>
<td>16-20</td>
<td>100</td>
<td>99.8</td>
<td>99.7</td>
</tr>
</tbody>
</table>

Table 1. Musculoskeletal complaints (MSC) in the study population

Table 2. Prevalence of PsA

<table>
<thead>
<tr>
<th>All Patients</th>
<th>All Responders</th>
<th>Eligible Participants</th>
<th>Evaluated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2649</td>
<td>n = 1722</td>
<td>n = 890</td>
<td>n = 527</td>
</tr>
<tr>
<td>Prevalence (n = 116)</td>
<td>Prevalence new cases (n = 54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (%)</td>
<td>4.4 (3.7-5.2)</td>
<td>2.0 (1.6-2.7)</td>
<td></td>
</tr>
<tr>
<td>Responders (%)</td>
<td>6.7 (5.6-8.0)</td>
<td>3.1 (2.4-4.1)</td>
<td></td>
</tr>
<tr>
<td>Psoriasis patients with MSC (n = 836)</td>
<td>13.8 (11.6-14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5 (5.0-8.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: 649 psoriasis (PsO) patients from 97 GPs were invited (Table 1). Of the 1722 responders (65.0%), 890 (51.7%) were willing to participate of which 672 (75.5%) reported MSC at the telephone interview (TI) and 527 were clinically evaluated. 145 out of the 672 patients dropped out between TI and the visit, mostly without giving any reason. The 832 patients that did not want to participate reported MSC in 19.7% (n = 164) on the reply slip. Among the 527 patients we found 54 new cases of PsA (10.2%): inflammatory arthritis (n = 11), axial disease (n = 37), confirmed by US and a combination of symptoms (n = 3). Another 62 existing PsA patients were identified. This led to a prevalence of 6.7% among PsO patients that responded (n = 1722) and 4.4% among all invited PsO patients (n = 2649) assuming no additional cases in the non-responders (Table 2).

Conclusion: Among psoriasis patients with musculoskeletal complaints in primary care (n = 836) the prevalence of PsA is estimated to be 13.8% (95% CI 11.6%-16.2%), which would decrease to 4.4% (95% CI 3.7%-5.2%) among all PsO patients if no additional cases would be observed in the non-responders. Besides 54 of the 116 cases (46.6%) hadn’t been diagnosed before our study, this indicates underdiagnosis of PsA in primary care.

Table 2. Number of comorbidities and PsA duration (n=190)

<table>
<thead>
<tr>
<th>PsA duration</th>
<th>Adjusted OR (95% CI)</th>
<th>p value before adjustment</th>
<th>Adjusted OR (95% CI)</th>
<th>p value after adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5-15 years</td>
<td>1.29 (0.94-1.77)</td>
<td>0.12</td>
<td>1.29 (0.94-1.77)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>1.69 (1.25-2.27)</td>
<td>0.00**</td>
<td>1.69 (1.25-2.27)</td>
<td>0.00**</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, race, body mass index, tender joint count, & swollen joint count.
the efficacy and safety of APR with placebo (PBO) in patients with active PsA who were DMARD-naive. We evaluated the impact of APR treatment over 52 weeks on enthesitis and dactylitis among PALACE 4 patients.

**Methods:** Patients were randomized (1:1:1) to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining PBO patients were re-randomized to APR20 or APR30. The analysis comprises data from Weeks 0 to 52. Enthesitis was evaluated based on MASES (range 0–13), which indicates the number of painful entheses out of 13 entheses sites. The dactylitis count (range 0–20) is the number of digits (hands and feet) with dactylitis present; each dactylitis was scored as 0 (dactylitis absent) or 1 (dactylitis present).

**Results:** At Week 16, a significantly greater proportion of patients receiving APR20 or APR30 achieved the modified ACR20 response vs PBO (primary endpoint). In patients initially randomized to APR and with enthesitis (n=228) or dactylitis (n=173) at baseline, APR was associated with improvements in enthesitis and dactylitis over 52 weeks, as evidenced by reductions in MASES and dactylitis count. At Week 16, median percent changes in MASES were 0% (PBO), −20.0% (APR20; P=0.2948), and −50.0% (APR30; P=0.0008). In patients initially randomized to APR and completing 52 weeks, median percent changes in MASES were −66.7% (APR20) and −75% (APR30) (Table); 39.6% (APR20) and 45.9% (APR30) of patients achieved a score of 0, indicating no pain at any of the entheses assessed. Median percent changes in dactylitis count at Week 16 were −50.0% (APR20; P=0.0043), and −69.2% (APR30; P=0.0149). In patients initially randomized to APR and completing 52 weeks, both doses resulted in a median 100% decrease in the dactylitis count; a dactylitis count of 0 was achieved in 68.6% (APR20) and 68.8% (APR30) at Week 52. *MASES ranges from 0 to 13, with 0 indicating no pain at any assessed entheses.*

**Conclusion:** Among patients continuously treated with APR through 52 weeks, sustained improvements in both enthesitis and dactylitis were observed in patients with active PsA, who had enthesitis or dactylitis at baseline. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 weeks.

Enthesitis and Dactylitis at Week 52 in Patients Receiving APR. From Baseline

<table>
<thead>
<tr>
<th>MASES</th>
<th>APR 20 n=91</th>
<th>APR 30 n=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, median</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Median % change from baseline</td>
<td>−66.7</td>
<td>−75.0</td>
</tr>
<tr>
<td>Patients achieving score of 0, %</td>
<td>39.6</td>
<td>45.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dactylitis count</th>
<th>n=70</th>
<th>n=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, median</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Median % change from baseline</td>
<td>−100</td>
<td>−100</td>
</tr>
<tr>
<td>Patients achieving score of 0, %</td>
<td>68.6</td>
<td>68.8</td>
</tr>
</tbody>
</table>

The n represents the number of patients with a baseline >0 and a value at Week 52. MASES ranges from 0 to 13, with 0 indicating no pain at any assessed entheses and 13 indicating pain at all assessed entheses. Dactylitis count is the sum of all scores for each of the 20 digits, with each digit scored as 0 (absence) or 1 (presence) of dactylitis.

**Disclosure:** C. J. Edwards, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 3, Abbott, GlaxoSmithKline, Pfizer Inc, and Roche; B. J. A. Aelion, Astra, Astrazeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Jansen, Eli Lilly, Merck, Medoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Bionceiences, Sanofi-Aventis, Takeda, 2, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Jansen, Eli Lilly, Merck, Medoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Bionceiences, Sanofi-Aventis, Takeda, 3, AbbVie, Amgen, and UCB; B. A. O. Abidin, None; A. K. Iwitz, A. M. Johnson, Jansen, Eli Lilly, Novartis, Pfizer Inc, and UCB; 2, A. M. Johnson, Eli Lilly, Novartis, Pfizer Inc, and UCB; 5, Pfizer Inc, 8, B. P. Bird, Celgene Corporation, 2; C. Hu, Celgene Corporation, 3; C. E. Stevens, Celgene Corporation, 1; R. M. Stevens, Celgene Corporation, 1; Z. Wells, Celgene Corporation, 2.

**Background/Purpose:** Higher rates of obesity in psoriatic arthritis (PsA) compared to rheumatoid arthritis (RA) have been described. Obesity, C-reactive protein (CRP) and inflammatory arthritides itself are known risk factors for cardiovascular disease. Obesity is also shown to affect response to therapy in patients with inflammatory arthritis. This study aimed to compare BMI in RA, PsA, and axSpA and additionally to examine for possible correlation between BMI and CRP in these diseases.

**Methods:** All the RA, PsA and axSpA patients that visited the outpatient clinic during the year 2013 were included. The RA patients had a diagnosis verified by the treating rheumatologist, the PsA patients all fulfilled the Classification for Psoriatic Arthritis (CASPAR) criteria and the axSpA patients all fulfilled the ASAS classification criteria for axSpA. BMI was calculated as the patient’s weight in kilograms divided by height in meters, squared. CRP was assessed by turbidimetry (mg/L). The unadjusted analyses of BMI and CRP were performed using analyses of variance (ANOVA) with post-hoc tests (Tukey HSD) for homogeneity of variance. The analyses were performed by use of a General Linear Model with adjustments for age, sex, smoking, years of education, disease duration and multiple comparisons (Bonferroni). Correlation analysis of BMI and CRP was performed by use of Spearman’s rho.

**Results:** A total of 1045 RA, 351 PsA and 314 axSpA patients were included. Respectively, mean (SD) age was 62.9 (13.9), 55.2 (12.3), 48.2 (12.8) years, mean disease duration 12.5 (10.6), 9.9 (8.0), 13.2 (11.7) years, mean years of education 11.5 (3.6), 12.4 (3.6), 12.9 (3.5) years, percentages currently smoking 20.7, 18.6, 23.6 % and percentage females 68.0, 49.0 and 34.1%. In both unadjusted and adjusted analyses the PsA patients had significantly higher mean BMI compared to the RA and axSpA patients. The male PsA patients had significantly higher BMI than the RA and the axSpA patients in the unadjusted analyses, but this difference was only significant for the PsA patients compared to the RA patients in the adjusted analyses. For females the PsA patients had significantly higher BMI than the RA and the axSpA patients both in the unadjusted and in the adjusted analyses, there was only a significant correlation between BMI and CRP for females (rho=0.18, p<0.001).

**Conclusion:** In our population of patients with inflammatory arthritides, PsA patients were significantly more obese than RA and axSpA patients. These differences were more pronounced for female patients. A weak correlation between CRP and BMI was found, but only for females. Both CRP and obesity are independent cardiovascular risk factors. Given the increased risk of cardiovascular events in inflammatory arthritis, obesity represents a potentially important modifiable risk factor.

**Disclosure:** B. Michelsen, None; A. P. Diamantopoulos, None; A. Kavanaugh, None; G. Haugenbeek, None.

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**Background/Purpose:** We believe that the prevalence of spondyloarthritides, especially psoriatic arthritis is higher than published in literature. Most of those patients are undiagnosed or diagnosed with different diseases. Enthesitis is the primary pathology of spondyloarthritides particularly psoriatic arthritis. It was suggested that enthesitis was an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. Additionally, subclinical enthesisology was detected more frequently

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in patients with psoriatic arthritis than those with psoriasis. We hypothesized that individuals with psoriatic nail changes would have a larger magnitude of enthesitis than those with normal nails. To support this hypothesis, we aimed to determine the association between psoriatic nail changes and enthesitis as well as the frequencies of both.

Methods: We examined the hand nails of university students for psoriatic nail changes, including pitting, leukonychia, longitudinal and horizontal ridging, pitting, subungual hyperkeratosis, onycholysis, splinter hemorrhages, red spot and oil drop. All students underwent manual palpation of 14 enthesial sites (quadriceps to patella, patella to tibia, Achilles, plantar fascia, medial epicondyly, lateral epicondyly, supraspinatus) that were described in the Spondylarthritides Research Consortium of Canada (SPARCC) Enthesitis Index. A additionally, tendons of spinous processes of thoracic vertebræ and sacroiliac joints were recorded.

Results: Three hundred seventy-seven university students (240 female, 137 male) who are attending to the faculties of medicine (229 students) and of dentistry (148 students) were included in this study. Two hundred thirty-two (61.6%) of 377 students had at least one psoriatic nail change. Less specific nail changes for psoriasis such as leukonychia, horizontal and longitudinal ridging were very common among the university students (Table 1). Pitting was observed in 52 (13.8%) students. Eighty-eight (23.3%) of 377 participants had at least one tender enthesial point. The most frequently affected enthesial site was supraspinatus insertion (Table 2). Students with pitting or any other psoriatic nail changes had a greater number of tender enthesial points than those with normal nails (p = 0.002 and p = 0.006, respectively).

Conclusion: Pitting was detected more frequently than published in the literature among university students and pitting or any other psoriatic nail changes correlated with tender enthesial points.

Table 1. Psoriatic nail changes in university students

<table>
<thead>
<tr>
<th>Nail change</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukonychia</td>
<td>136 (36.1)</td>
</tr>
<tr>
<td>Horizontal ridging</td>
<td>62 (16.4)</td>
</tr>
<tr>
<td>Longitudinal ridging</td>
<td>58 (15.4)</td>
</tr>
<tr>
<td>Pitting</td>
<td>52 (13.8)</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>19 (5.0)</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>18 (4.8)</td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Red spot</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Oil drop</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 2. Frequency of affected enthesial points in university students

<table>
<thead>
<tr>
<th>Enthesial points</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraspinatus</td>
<td>55 (14.6)</td>
</tr>
<tr>
<td>Thoracic vertebrae</td>
<td>27 (7.2)</td>
</tr>
<tr>
<td>Sacralis</td>
<td>20 (5.3)</td>
</tr>
<tr>
<td>Lateral epicondyly</td>
<td>20 (5.3)</td>
</tr>
<tr>
<td>Medial epicondyly</td>
<td>18 (4.8)</td>
</tr>
<tr>
<td>Achiilles</td>
<td>12 (3.2)</td>
</tr>
<tr>
<td>Quadriceps to patella</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Patella to tibia</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Plantar fascia</td>
<td>8 (2.1)</td>
</tr>
</tbody>
</table>

Discussion: A. E. Yuwel, None; M. Pamukcu, None; E. Durukan, None; B. Tsou, None; B. Batman, None; O. Ozkan, None; A. Kocak, None.

1575

The Association Between Obesity and Disease Phenotype in Psoriatic Arthritis. Lhi Eder, Cheryl Rosen, Vinod Chandran* and Dafna D. Gladman*.

Background/Purpose: Obesity is associated with an increased risk of developing psoriatic arthritis (PsA) in patients with psoriasis. This study aimed to assess whether obesity is associated with a distinct phenotype of PsA.

Methods: A cross-sectional analysis was performed among patients with early PsA (<2 years from the diagnosis) from a large PsA clinic and compared them to patients with psoriasis alone (PsC). Patients with PsA met the CASPAR criteria. Patients with PsC were examined by a rheumatologist to exclude the presence of arthritis. The participants were assessed according to a standardized protocol. Demographic, clinical and radiographic information was retrieved from the clinic database. The primary predictor was Body Mass Index (BMI) at the first visit to the clinic that was classified to normal (BMI<25), overweight (BMI 25-30), or obese (BMI>30). The association between BMI and clinical and radiographic outcomes was assessed using Cochran-Armitage and linear trend tests.

Results: A total of 305 early PsA and 498 PsC patients were analyzed. Higher BMI was associated with older age (years) at onset of PsA (Normal: 38±14, Overweight: 44±14, Obese: 47±11, p=0.003) and psoriasis (Normal: 27±17, years, Overweight: 29±15, Obese: 32±15, p=0.009). A similar trend was observed in patients with psoriasis alone, higher BMI was associated with older age (years) at onset of psoriasis (Normal: 28±16, Overweight: 39±16, Obese: 32±16, p=0.01). In addition, a longer delay (years) from the onset of symptoms to the time of the diagnosis was found in overweight and obese patients (Normal: 2.8±5.8, Overweight: 3.9±10, Obese: 6.9±4, p=0.02). No difference was observed in the pattern and severity of the skin, nail or joint manifestations across the three BMI groups. Patients with higher BMI were more likely to have new bone formation at the pelvic and heel entheses (each <0.001) however no difference was observed in the extent of radiographic erosive damage. The frequency of overweight and obesity was higher in PsA compared to psoriasis alone only among participants who were older than 40 years of age (Table 1) while no difference in BMI was observed among younger individuals.

Conclusion: Obesity may mark a distinct phenotype of PsA. Higher BMI is associated with older onset of PsA and psoriasis. This finding may suggest that obesity predisposes to late-onset psoriatic disease but has little role in the development of early onset disease.

The association between BMI and PsA vs. Psoriasis by age group

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age ≤40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA (N=120)</td>
<td>45 (37.5%)</td>
<td>47 (39.2%)</td>
<td>28 (23.3%)</td>
<td>0.21</td>
</tr>
<tr>
<td>PsC (N=184)</td>
<td>84 (45.7%)</td>
<td>63 (34.2%)</td>
<td>37 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA (N=183)</td>
<td>35 (18.9%)</td>
<td>64 (34.6%)</td>
<td>86 (46.5%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>PsC (N=314)</td>
<td>91 (29%)</td>
<td>129 (41.3%)</td>
<td>94 (29.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: L. Eder, None; C. Rosen, None; V. Chandran, None; D. D. Gladman, None.

1576

Reversal of Damage in Psoriatic Arthritis. Amir Haddad, Ker-Ai Lee, Arane Thavaneswaran, Vinod Chandran, Richard J. Cook and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON, University of Waterloo, Waterloo, ON.

Background/Purpose: Psoriatic arthritis could lead to severe damage and disability. However, cases of improvement in joint damage over time have been reported in the literature. We aimed to determine the prevalence of damage reversal in a large cohort of patients with psoriatic arthritis and to identify predictors of this unique feature.

Methods: In a cohort of PsA patients established in 1978, radiographic assessments are made every two years with readings by at least 2 investigators. A consensus rating according the modified Steinbrocker scoring (mSSS) method classifies each of 42 hand and foot joints on a 0–4 scale where grade 0 = normal, 1 = juxtaarticular osteopenia or soft tissue swelling, 2 = erosion, 3 = erosion and joint space narrowing and 4 = total destruction. Reversal of damage was defined as a decrease in the total mSSS confirmed on second and third readings. Disease characteristics of the study population were presented using descriptive statistics. A transitional multistate model was applied to investigate ratios of transition intensities in the Steinbrocker staging of each joint, with a working independence assumption used for joints within the same patient. A reversible Markov model was applied to investigate predictors for damage reversal and progression including age, sex, disease duration, the number of actively inflamed joints at baseline and treatment with MTX and biologics in the course of follow up.

Results: Of 537 PsA patients with baseline and at least 1 follow-up radiographs with all available data 56.2% were males, had a mean (SD) age of 43.7 (12.7) and disease duration of 7.0 (8.3) years. 32.4% and 66.9% were treated with DMARDs and biologics, respectively. 373 patients developed at least 1 damaged joint: 117/537 patients (21.8%) had evidence of reversal in damage in at least one joint. Of the 20,307 assessed joints in 537 patients, 339 joints had improvement in damage, of whom the majority 213 out of 348 transitions were from mSSS 2 to 1 and had an intensity score of 0.025 (0.022, 0.029) as opposed to the highest estimated progression rate of 0.061 (0.055, 0.067). 164 joint improvement occurred before treatment with biologicals in 63
patients, of whom the majority 104/166 transitions were also from mSS 2 to 1. When analyzing the data on the 89.965 patient-joint assessments, treatment with biologics was a predictor for transition to a state of joint improvement (RR = 2.25 (1.79-2.83) P = 0.0001) and less for joint progression (RR = 0.67 (0.61,0.74) P = 0.0001).

Conclusion: A number of patients have reversal in damage (21.8%), which occurred in 1.7% of the assessed joints. Treatment with biologics is a predictor for joint improvement and less progression of damage. Transitions of joint improvement were observed also in patients not treated with biologics.

Disclosure: A. Haddad, None; K. A. Lee, None; A. Thavaneswaran, None; V. Chandran, None; R. J. Cook, None; D. D. Gladman, None.

1577

Value and Prediction of Minimal Disease Activity in Patients with Psoriatic Arthritis. Arthur Kavanagh1, Philip Meeze2, Laura C. Coates3 and Dafna D. Gladman1. 1University of California San Diego, La Jolla, CA, 2Swedish Medical Center and University of Washington, Seattle, WA, 3NIHR Leeds Musculoskeletal Biomedical Research Unite, Leeds, United Kingdom.

Background/Purpose: The prediction of treatment outcomes based on early response could be useful in guiding clinicians to adjust therapy. The objective was to determine whether week 12 SJC and TJC, DAS28, CDAI and RAPID3 scores are predictive of achievement of a minimal disease activity (MDA) target at wk 24 in patients (pts) with Psoriatic Arthritis (PsA) and to evaluate patient-reported outcomes (PROs) associated with achieving MDA.

Methods: This post hoc analysis used pt data from ADEPT, a double blind randomized trial of adalimumab (ADA) versus placebo (PBO) in pts with moderate to severely active PsA and an inadequate response to NSAIDs. Pts who achieved MDA at wk 24 were termed "achievers", while those who did not were termed "non-achievers" (NAs). PROs studied in association with MDA were: quality of life by DLQI and SF-36 scores (total, with moderate to severely active PsA and an inadequate response to NSAIDs. Evaluation of PROs was performed at baseline and wk 12, and mean synovitis scores at wk 24 were determined by ROC analysis, negative and positive predictive values (NPV/PPV).

Results: At wk 24, 24/62 pts (38.7%) on ADA treatment, and 4/60 pts (6.7%) on PBO treatment achieved MDA. While radiographic progression was low, overall, in the ADEPT trial, achievees had no progression compared to mild progression in NA, although this difference was not statistically significant (p = 0.201). Achievers also had higher total SF-36 scores (81.6 ± 10.7 vs. 75.8 ± 10.3, p < 0.001), SF-36 PCS (51.0 ± 7.2 vs. 35.0 ± 10.8, p < 0.001) and FACIT scores (43.5 ± 8.2 vs. 33.8 ± 9.8, p < 0.001), SF-36 MCS (50.6 ± 10.6 vs. 35.0 ± 12.2, p < 0.05). There was no difference in the SF-36 MCS and DLQI scores of achievees compared to that of NA. MDA achievees had lower mean SJC at wk 24 (28.1 ± 21.2, p = 0.001) and SJC at wk 24 than NAs, and greater improvement from BL to wk 12 in mean SJC 76 ± 10.7 and TJC 78 ± 29.3 scores. Wk 12 DAS28, CDAI and RAPID3 all predicted wk 24 MDA with an AUC of 0.85 and ROC area under the curve of 0.94 (table). Wk 12 TJC was a slightly better predictor than wk 12 SJC, with 28 joint-counts having similar accuracy to 78 joint-counts. All of the criteria cut points, as determined by ROC analysis, had high NPV for wk 24 MDA (table).

Wk 12 criterion Area under the ROC curve (CL) PPV NPV

TJC28 0.98 (0.93, 0.99) 0.60 0.90
TJC78 0.90 (0.86, 0.97) 0.61 0.99
SJC28 0.89 (0.82, 0.89) 0.61 0.96
SJC76 0.84 (0.76, 0.91) 0.46 0.96
DAS28 0.96 (0.92, 0.99) 2.84 0.75 0.97
CDAI 0.97 (0.94, 1.00) 10.00 0.80 0.97
RAPID3 0.95 (0.90, 1.00) 1.30 0.75 0.97

Conclusion: In pts with PsA, the achievement of MDA was associated with improvements in HRQoL, physical function and fatigue. Wk 12 composite scores such as CDAI or RAPID3 remission and DAS28(CRP) LDA, as well as SJC and TJC had good ability to predict the likelihood of achieving MDA at wk 24, with 28 joint-counts being as informative as 78 joint counts in this analysis. These quick and convenient tools can be used to guide treatment decisions at an early timepoint.


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Abatacept Improves Synovitis As Assessed By Magnetic Resonance Imaging (MRI) in Psoriatic Arthritis - Preliminary Analysis from a Single Centre, Placebo-Controlled, Crossover Study. A. Kavanaugh1, E. J. Heffernan2, M. Haroon3, P. Gallagher4, A. Baker5, M. Cooney5, and O. Fitzgerald6. 1St. Vincent’s University Hospital, Dublin, Ireland, 2Cork University Hospital, Cork, Ireland.

Background/Purpose: The abatacept is a soluble, fully human fusion protein which selectively inhibits T-cell activation via the CD80/CD86:CD28 co-stimulation pathway and decreases serum levels of inflammatory cytokines and proteins implicated in the pathogenesis of psoriatic arthritis (PsA). Improvement in skin psoriasis has been shown with abatacept treatment previously with greatest reduction in PASI using 3 mg/kg dose. It has been proposed that 10 mg/kg of abatacept, the approved dose for rheumatoid arthritis may be an effective treatment choice for PsA.

The objectives of the study were (1) to study both skin and joint-related clinical outcomes prior to and 6 months after introducing abatacept treatment in PsA; (2) to investigate MRI changes of an inflamed knee joint over time in PsA patients on abatacept.

Methods: Biologics treatment-naive PsA patients fulfilling the CASPAR criteria with active disease for >3 months (>3 swollen and >3 tender joints) with clinical synovitis of a knee and the presence of a psoriatic skin lesion were enrolled to the study. Patients were randomised to receive abatacept 3mg/kg or placebo infusion on day 1, 15 and 29; thereafter abatacept 10mg/kg was administered every 28 days for 5 months. A stable dose of methotrexate (7.5–25 mg/week) for >3 months prior to randomization was the only concomitant DMDA permitted in the study. Ga-enhanced MRI of the same inflamed knee was performed at baseline, and 6 months and scored using the PsA MRI RIS method by one consultant radiologist. For the semi-quantitative method each knee was divided into 4 anatomical regions; medial (MED) and lateral (LAT) parapatellar recesses, intercondylar notch (ICN) and suprapatellar pouch (SPP). A synovitis score ranging from 0 to 3 was assigned to each region and then added for a total synovitis score (MRS) ranging from 0 to 12 per knee.

Results: 15 patients (8 female) 7 male) with mean age of 44.6 ± 14.6 years were randomized by June 2014. Four (27%) patients were on methotrexate, the remainder did not receive any DMARDs during the study. At baseline, mean DAS28-ESR was 4.9 ± 3.0 and DAS28-CRP was 4.7 ± 0.9. Median PASI, HAQ, PsAQoL and DLQI were 3.6 (0–16.2), 1.0 (0–2.125), 10 (1–17) and 3 (0–27) respectively. Mean synovitis scores at MED, LAT, ICN and SPP regions were 2.07 (±0.9), 2.21 (±0.9), 1.4 (±0.8) and 1.85 (±1.0) respectively at baseline, mean MRS was 7.6 (±3.4).

As per EULAR criteria 87.5% of patients responded to the treatment at 6 months and 75% were good responders. Patients’ TJC68, SJC68, duration of morning stiffness, global health score, DAS28-ESR, DAS28-CRP, HAQ and PsAQoL reduced significantly at 6 months compared to baseline. Median MRS decreased over the study period and was significantly lower at 6 months compared to baseline (p = 0.016).

Conclusion: Six months of abatacept treatment reduced synovitis scores as assessed by MRI. The results of our study suggest that 10 mg/kg of abatacept is a potent treatment option in PsA.

Disclosure: A. Kavanaugh, None; E. J. Heffernan, None; M. Haroon, None; P. Gallagher, None; A. M. Baker, None; M. Cooney, None; O. Fitzgerald, Pfizer, Abbott, BMS, MSD, Roche, UCBB, 2. Pfizer, Abbott, BMS, MSD, Janssen, Roche, 5.

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Background/Purpose: A premarket (APR) is a PDE4 inhibitor that helps regulate the immune response. PALACE 1, 2, and 3 assessed the efficacy and safety of APR in pts with active psoriatic arthritis (PsA) despite prior DMARDs and/or biologics. We evaluated weight change from BL in PALACE 2, and 3.

Methods: Pts were randomized (1:1:1) to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Wk 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if initially randomized to placebo, or continued on their initial apremilast dose. At Wk 24, all remaining PBO patient, patients randomized to APR20 or APR30 were considered non-responders and were required to be re-randomized (1:1) to PBO or the same APR exposure. This analysis comprises data for the PBO-controlled period (Wks 0 to 24) and the APR-exposure period (Wks 0 to ≥52) up to cutoff date, 3/1/2013.

Results: During the PBO-controlled period, 495 pts received PBO, 501 received APR20, and 497 received APR30. At cutoff, 720 pts had received APR20 and 721 had received APR30. At BL, mean/median weight was 86.4/84.0 (PBO), 86.4/84.0 (APR20), and 84.5/83.0 (APR30) kg. Weight decrease was observed to a greater extent as an AE in a small proportion of pts during both the PBO-controlled (PBO: 0.4%; APR20: 1.0%; APR30: 1.4%) and APR exposure (APR20: 1.4%; APR30: 1.8%) periods. No pts in the PBO-controlled and 2/1,441 pts (APR20: 1; APR30: 1) in the APR-exposure period discontinued due to weight decrease. An additional analysis using observed weight measurements collected at selected visits assessed changes from BL weight. In the PBO-controlled period, most pts remained within 5% of their BL weight (PBO: 92.1%; APR20: 83.5%; APR30: 86.4%). A larger proportion of APR-treated pts experienced any weight loss (APR20: 57.9%; APR30: 56.8%) vs PBO (40.1%). Weight loss >5% was experienced by 3.9% (PBO), 12.7% (APR20), and 11.0% (APR30) (Table). At the end of the PBO-controlled period, mean/median weight change from BL was 0.09/0.0 (PBO), -1.16/-0.60 (APR20), and -0.96/0.60 (APR30) kg. In the APR-exposure period (Wks 0 to ≥52), most pts remained within 5% of their BL weight (APR20: 77.6%; APR30: 75.8% (APR20) and 71.1% (APR30)) experienced weight loss. Weight loss did not lead to any overt medical sequelae or manifestations through the APR-exposure period. In an analysis to determine the relationship between weight loss and GI AEs, weight loss was not associated with diarrhea or nausea/vomiting.

Conclusion: APR was associated with a small rate of weight decrease reported as an AE. The incidence of observed weight loss was higher with APR vs PBO, although most pts remained within 5% of their BL weight. APR exposure period did not appear to be dose-dependent and did not lead to overt clinical sequelae. No association between weight loss and incidence of other AEs, including GI AEs, was apparent.

Disclosures: P. Mease: Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 2; Consulting fees from: AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 5; Speakers bureau for: AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, and UCB, 5; D. D. Gladman: AbbVie, A. AbbVie, A. Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 2; AbbVie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 5; A. Kavanagh: Abbott, Amgen, Astra-Zeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor, Janssen, Pfizer Inc, Roche, and UCB, 2; A. O. Adeabao, J. Gomez-Reino, 2; Belimumab, 2; Biogen, 2; Bristol-Myers Squibb, Pfizer Inc, Roche, Schering-Plough, and UCB SA, 9; Bristol-Myers Squibb, Roche, Schering-Plough, and Wyeth, 9; Roche and Schering-Plough, 2; J. Wollenhaupt: Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 2; Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 5; G. A. Schett: Abbott, Celgene Corporation, Roche, and UCB, 5; K. Shah, Celgene Corporation, 1; Celgene Corporation, 3; C. Hu, Celgene Corporation, 3; Celgene Corporation, 1; R. M. Stevens, Celgene Corporation, 1; Celgene Corporation, 3; C. Edwards, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2; Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5; Abbott, Glaxo-SmithKline, Pfizer Inc, and Roche, 8; C. A. Birbara, Amgen, Bristol-Myers Squibb, Incyte, Eli Lilly, Merck, and Pfizer Inc, 2.

S968
**Inflammatory Back Pain in Psoriasis and Psoriatic Arthritis Is Suggestive of Undiagnosed Spondyloarthropathies.** Majeed Khraiishi, Heather Jones and Arentte Szumski.

**Background/Purpose:** Patients with psoriasis (Ps) and/or psoriatic arthritis (PsA) may have clinical features suggestive of axial skeletal abnormalities and should be assessed for the presence of spondyloarthropathies (SpA). The purpose of this post-hoc analysis from 2 clinical trials is to assess the prevalence, demographic and disease characteristics of Ps patients with and without MRI evidence of sacroiliac (SI) abnormalities or axial involvement. We also investigated how common screening questionnaires perform in detecting inflammatory back pain (IBP) that may be suggestive of SpA.

**Methods:** From the PRESTA trial, the medical history of patients with Ps and PsA were analyzed for axial involvement. From the PREPARE trial, patients with Ps who had baseline MRI were analyzed and characteristics assessed between those with and without MRI evidence of SI abnormalities (SI+/−). Results of the PASQi and TOPAS questionnaires in the PREPARE trial were assessed for patient-reported IBP and compared with their respective patients’ SI findings to determine possible trends in each IBP+/− and SI+/− group.

**Results:** In the PRESTA trial, 747 patients with Ps/PsA were evaluated and 41% (304/747) had axial involvement. Those with axial involvement had a longer duration of PsA, greater Ps-affected BSA, and higher PASI, DAS28, TJC, SJC, HAQ, EQ-5D scores than those without (Table 1). A total of 168 Ps patients with MRI were analyzed in the PREPARE trial; 47% were SI+ who tended to be older with a lower Ps-affected BSA than those who were SI− (Table 1). Only 43% (38/88) of Ps patients who were SI+ were also diagnosed with PsA. IBP was evaluated in 128 patients from the PREPARE trial with the PASQi and ToPAS questionnaires of which 45% (57/128) were IBP+ and 33% (19/57) of those were SI+.

**Conclusion:** Patients with spinal involvement tended to be older with longer disease duration. Patients with Ps, with or without a PsA diagnosis, may exhibit clinical features of SpAs. These findings suggest that patients should be evaluated carefully for the presence of entities such as non-radiographic axial SpA and radiologic evidence of SI regardless of PsA diagnosis or reported IBP. The PASQi and ToPAS questionnaires detected 1/3 of Ps/PsA patients who reported IBP were SI+ which may be useful in detecting the possibility of SpAs.

**Table 1:** Baseline characteristics for patients with and without SI and axial involvement in the PRESTA and PREPARE clinical trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PRESTA*</th>
<th>PREPAREb</th>
<th>P-valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.4 (10.4)</td>
<td>51.2 (12.9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>8 (42.1)</td>
<td>31 (75.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>0.369</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (94.7)</td>
<td>39 (95.1)</td>
<td>0.824</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.3)</td>
<td>2 (4.9)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Otherd</td>
<td>1 (5.3)</td>
<td>2 (4.9)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (4.9)</td>
<td>29.2 (5.1)</td>
<td>0.012</td>
</tr>
<tr>
<td>PSQI diagnosis, n (%)</td>
<td>10 (52.6)</td>
<td>16 (42.1)</td>
<td>0.330</td>
</tr>
<tr>
<td>Duration of PsA, years</td>
<td>7.1 (5.9)</td>
<td>11.6 (6.8)</td>
<td>0.723</td>
</tr>
</tbody>
</table>

**Table 2:** Baseline characteristics for the presence/absence of IBP and/or SI abnormalities in the PREPARE study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IBP+/SI+(n=19)</th>
<th>IBP−/SI+(n=43)</th>
<th>IBP+/SI−(n=38)</th>
<th>IBP−/SI−(n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.4 (10.4)</td>
<td>51.2 (12.9)</td>
<td>45.2 (11.9)</td>
<td>44.9 (12.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>8 (42.1)</td>
<td>31 (75.6)</td>
<td>17 (44.7)</td>
<td>17 (56.7)</td>
<td>0.018</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>0.369</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (94.7)</td>
<td>39 (95.1)</td>
<td>32 (84.2)</td>
<td>25 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.3)</td>
<td>2 (4.9)</td>
<td>5 (12.2)</td>
<td>5 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Otherd</td>
<td>1 (5.3)</td>
<td>2 (4.9)</td>
<td>5 (12.2)</td>
<td>5 (16.7)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (4.9)</td>
<td>29.2 (5.1)</td>
<td>30.4 (6.4)</td>
<td>27.2 (5.2)</td>
<td>0.120</td>
</tr>
<tr>
<td>PSQI diagnosis, n (%)</td>
<td>10 (52.6)</td>
<td>16 (42.1)</td>
<td>10 (33.3)</td>
<td>15 (50.0)</td>
<td></td>
</tr>
</tbody>
</table>

All values mean (standard deviation) unless otherwise specified. *P-values for continuous values are calculated using ANOVA comparing means between groups; P-values for categorical values use the chi-square test. **Includes those with missing values. Based on physical exam, medical history, and laboratory findings. Based on medical history. **BMI=body mass index; PASI=psoriasis area severity index; PS=psoriatic arthritis; SI=sacroiliac.

**Disclosure:** M. Khraiishi, None; H. Jones, Pfizer Inc.; A. Szumski, Pfizer Inc. 3.
Table 1. Clinical features at baseline and last follow up in patients with high and low PWV group

<table>
<thead>
<tr>
<th>Low PWV</th>
<th>Baseline</th>
<th>High PWV</th>
<th>p value</th>
<th>Low PWV</th>
<th>High PWV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>18 (50.0%)</td>
<td>18 (50.0%)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.6 ±10.0</td>
<td>55.6 ±10.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA duration (years)</td>
<td>7.5 ±6.8</td>
<td>11.0 ±7.5</td>
<td>0.041</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 ±4.0</td>
<td>24.6 ±3.3</td>
<td>0.184</td>
<td>25.7 ±3.6</td>
<td>22.9 ±3.1</td>
<td>0.028</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>133 ±23</td>
<td>139 ±21</td>
<td>0.226</td>
<td>122 ±13</td>
<td>133 ±16</td>
<td>0.003</td>
</tr>
<tr>
<td>Framingham 10-year risk</td>
<td>13 ±39.4</td>
<td>23 ±67.6</td>
<td>0.020</td>
<td>2 ±15.6</td>
<td>8 ±22.2</td>
<td>0.085</td>
</tr>
<tr>
<td>CVD risk &gt;10%</td>
<td>2 (6-0)</td>
<td>1 (6-0)</td>
<td>0.112</td>
<td>1 (6-0)</td>
<td>1 (6-0)</td>
<td>0.011</td>
</tr>
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</table>

Disclosure: J. Shen, None; Q. Shang, None; Y. Y. Laung, None; E. Li, None; T. Y. Zhu, None; L. S. Tam, None.

1583

Screening for PsA in Primary Care: Psoriasis Patients with Musculoskeletal Complaints with PEST, PASE & EAR.

M. C. Karreman1, A.E.A.M. Weel1, M. van der Ven1, M. Vis1, I. Tchetverikov2, M. Wakkee3, T.E.C. Nijsten1, J.M.W. Hazes3 and J.J. Luime1, 1Erasmus University Medical Center, Rotterdam, Netherlands, 2Albert Schweitzer Hospital, Dordrecht, Netherlands.

Background/Purpose: Psoriatic Arthritis (PsA) is a progressive inflammatory joint disease that can lead to severe joint damage. New treatment strategies can be very effective in early stages of the disease. This requires early recognition of the symptoms to be PsA. Several screening tools have been developed to enhance early recognition. However, most were developed in secondary care, while early recognition should ideally take place in primary care.

Our objective was to evaluate the screening performance of the PEST, PASE and EAR tool to identify psoriatic arthritis among primary care psoriasis patients with recurrent spells of musculoskeletal complaints (MSC).

Methods: We conducted a cross-sectional study in adult primary care patients with psoriasis who reported recurrent spells of MSC. Patients were selected by IPCG code S91 for psoriasis and the presence of recurrent spells of MSC (joints, enthesis or low back pain) was determined by telephone interview. Patients completed the PEST, PASE & EAR questionnaires before clinical evaluation by a trained research nurse. A assessments included PASI, LEI/MASES, 66/68-joint count and the presence of nail-pсорiasis. If clinical evaluation suggested the presence of arthritis or axial disease, or ultrasound (US) evaluation showed Power Doppler signal in an enthesis, patients were referred to the rheumatologist.

A PsA case was defined by fulfilling the CASPAR criteria. Sensitivity and specificity were determined for the PEST and EAR cut off as 2.5 and PASE cut off as 44 as well as ≥47.

Results: 480 psoriasis patients participated with a mean ±SD age of 55.9 ±13.9 years and 50.8% being male (Table 1). We found 54 new cases of PsA (10.2%). A mong the cases the skin was slightly more affected and more tender joints were reported, while nails were affected evenly compared to the non-cases. The PEST had a true positive rate of 63.9%, and a false positive rate of 30.0%, for the EAR this was 87.0% and 67.1%. The PASE had a true specificity were determined for the PEST and EAR cut off 2.5 and EAR cut off ≥44 were significantly lower mean CPDAI, BASDAI, DAS28, CDAI, SDAI and DAS28-CRP.

Conclusion: Sensitivity and specificity were determined for the PEST and EAR tool to identify psoriatic arthritis among primary care psoriasis patients with recurrent spells of musculoskeletal complaints (MSC).

Table 1 Characteristics of the study population (n=480)

<table>
<thead>
<tr>
<th>Non-Cases (n=426)</th>
<th>Cases (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>56.0 ±14.0</td>
</tr>
<tr>
<td>% M en</td>
<td>50.5</td>
</tr>
<tr>
<td>TJ C median (IQR)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>SJ C median (IQR)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>PASI median (IQR)</td>
<td>2.2 (0-9-4)</td>
</tr>
<tr>
<td>Nail abnormalities (%)</td>
<td>64 (15.2)</td>
</tr>
<tr>
<td>EARP median (IQR)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>PEST median (IQR)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>PASE median (IQR)</td>
<td>41 (33-49)</td>
</tr>
</tbody>
</table>

Table 2 Sensitivity & Specificity of Screening Tools for PsA among primary care psoriasis patients

<table>
<thead>
<tr>
<th>Cut off</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEST</td>
<td>≥3</td>
<td>63.0 (48.7-75.7)</td>
</tr>
<tr>
<td>EARP</td>
<td>≥3</td>
<td>87.0 (75.1-94.6)</td>
</tr>
<tr>
<td>PASE</td>
<td>≥44</td>
<td>63.0 (48.7-75.7)</td>
</tr>
<tr>
<td></td>
<td>≥47</td>
<td>55.6 (41.4-69.1)</td>
</tr>
</tbody>
</table>

Disclosure: M. C. Karreman, None; A. E. A. M. Weel, None; M. van der Ven, None; M. Vis, None; I. Tchetverikov, None; M. Wakkee, None; T. E. C. Nijsten, None; J. M. W. Hazes; None; J. J. Luime, Pfizer bv, 2.

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Evaluation of the Patient Acceptable Symptom State in Patients with Psoriatic Arthritis.

Pinar Celini1, Dilek Solmaz2, Murat Keser3, Ismail Sarı3, Nurullah Akkoc1, Fatos Onen1, Dokuz Eylul University School of Medicine, Izmir, Turkey, Namik Kemal University School of Medicine, Tekirdag, Turkey.

Background/Purpose: The Patient Acceptable Symptom State (PASS), a single-question outcome, has been defined as an absolute level of patient well-being, which was used in the evaluation of treatment efficacy in several rheumatologic diseases. We aimed to evaluate the acceptability, reliability and discriminant capacity of the PASS in patients with psoriatic arthritis (PsA).

Methods: This study included PsA patients who fulfilled the CASPAR criteria. Disease activity was assessed in the patients by using “Composite Psoriatic Disease Activity Index (CPDAI)”, “Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)”, “Patient Global” and “Disease Activity Score (DAS)”. “Psoriasis Area Severity Index (PASI)” was used for the measurement of severity of psoriasis and high-sensitive C-reactive protein (hs-CRP) level was measured as laboratory parameter of disease activity. Other follow-up parameters such as “Bath Ankylosing Spondylitis Functional Index (BASFI)”, “Health Assessment Questionnaire (HAQ)”, “Psoriasis Area Quality of Life (AQoL)” were also included in the study.

PASS (+) and PASS (-) groups were compared for demographic features and disease severity parameters using Mann-Whitney U test. Stepwise logistic regression was used to assess the contributors to PASS. DAS28 thresholds were estimated with receiver operating characteristic (ROC) curve analysis. Cut off levels targeting the 75th percentile of the cumulative distribution were also determined.

Results: There were 101 PsA patients (34 male, 67 female; mean age: 46.8 ±11.5). Eighteen (17.8%) patients had predominantly axial disease, 52 (51.5%) had predominantly peripheral disease and 31 (30.7%) had mixed symptoms. Thirty-four (33.6%) of 101 patients were in PASS. The patients with an acceptable status had significantly lower mean CPDAI, BASDAI, DAS28-CRP, PASI and disease scores than the others (Table 1). The significant contributor to PASS was BASDAI (r=-0.343 Exp(8): 0.71; p<0.001). PASS (+) 75th percentile thresholds were 4.3 for BASDAI (sensitivity:70.6%, specificity: 64%) and 4.0 for CPDAI (sensitivity:76.5%, specificity: 54%).

Conclusion: PASS can be considered as a method in determination of PsA disease activity in the future.

Table 1. Clinical and demographic features of the PASS (+) and PASS (-) PsA patients

<table>
<thead>
<tr>
<th>PASS (+) (n=34)</th>
<th>PASS (-) (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>47.9 ± 12.3</td>
</tr>
<tr>
<td>Male, n; %</td>
<td>13.38 ± 21.3</td>
</tr>
<tr>
<td>Education (years), mean ± SD</td>
<td>9.1 ± 4.1</td>
</tr>
<tr>
<td>CPDAI, mean ± SD</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>BASDAI, mean ± SD</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>EASE2CRP, mean ± SD</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>PASI, mean ± SD</td>
<td>5.8 ± 7.4</td>
</tr>
<tr>
<td>C-reactive protein, mean ± SD</td>
<td>104 ± 13.1</td>
</tr>
<tr>
<td>hs-CRP, mean ± SD</td>
<td>2.2 ± 1.1</td>
</tr>
<tr>
<td>HAQ, mean ± SD</td>
<td>0.4 ± 0.5</td>
</tr>
<tr>
<td>ASQoL, mean ± SD</td>
<td>5.7 ± 5.8</td>
</tr>
<tr>
<td>Patient global, mean ± SD</td>
<td>2.85 ± 2.8</td>
</tr>
</tbody>
</table>

TJC=Tender Joint Count, SJC=Swollen Joint Count, PASI=Psoriasis Area Severity Index, P=0.05
Presence of Swollen and Tender Joints in Patients Fulfilling Minimal Disease Activity Criteria. Joséfa Marín1, María L. Acosta Felgueroso2, Leandra Ferrerya-Garrot3, Santiago Ruta1, and Enrique R. Soriano3. 1Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 2Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 3Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 4Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires. Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Minimal disease activity (MDA) is a composite measure created for patients with psoriatic arthritis (PsA) that encompasses many clinically important aspects of PsA: arthritis, psoriasis, enthesis, pain, patient-assessed global disease activity, and physical function. A patient is considered to be in MDA if fulfills 5/7 criteria. In theory, a patient could be in MDA, but still have several tender and/or swollen joints. Objectives: 1) To evaluate the number of patients fulfilling MDA criteria that still have several tender/swollen joints, and 2) To analyze the components of MDA that contribute most to prevent patients achieving MDA.

Methods: Consecutive patients with PsA (CASPAR criteria) were included, and all components of MDA score were assessed by a single experienced Rheumatologist. Patients were classified as in MDA if they fulfilled 5/7 criteria (tender joint count (TJC); 0–68 ≤ 1; swollen joint count (SJC); 0–66 ≤ 1; PASI ≤ 1 or BSA ≤ 3%; pain patient visual analog scale (VAS); 0–100 ≤ 15; patient global assessment of disease activity (PsGA); VAS; 0–100 ≤ 20 mm; Health Assessment Questionnaire (HAQ); 0–3 ≤ 0.5; and tender entheseal points (0–13) ≤ 1). Percentage of patients with ≥ 2 tender and/or swollen joints within patients in MDA was calculated. We also calculated the percentage of patients not fulfilling each one of the criteria for those patients with 4 out of 7 MDA criteria.

Results: 83 patients were included. Patient’s characteristics according to MDA status are shown in the Table. Among the 41 patients fulfilling MDA criteria, only one patient (2.4%) showed more than 2 tender joints (3 tender joints), and two other patients showed ≥ 2 swollen joints (one patient two and one patient three swollen joints). Altogether 7.4% of patients, fulfilling MDA criteria presented a clinically significant number of tender/swollen joints. Among patients fulfilling MDA criteria, only 24% fulfilled all 7 criteria, and 32% and 43% fulfilled 6 and 5 criteria respectively. Of those patients not in MDA status, 17 (40.5%) fulfilled 4/7 criteria. Among those patients, the criteria most often not fulfilled were: patient pain visual score VAS ≤ 15 = 100%; PaG A VAS ≤ 20 mm = 76.5%; and PASI ≤ 1 = 65%. Only 29%, 18%, 6% and 6% did not fulfilled tender joint count, HAQ, swollen joint count and entheseal tenderness criteria, respectively.

Conclusion: Although possible in theory, only a minority of patients fulfilling MDA criteria present a clinically significant number of tender and/or swollen joints. In patients that were close to fulfill MDA criteria patient’s VAS scores (pain and disease activity) and PASI were the most frequent reasons to fail short to MDA status.

Disclosure: J. Marín, None; M. L. Acosta Felgueroso, None; L. Ferrerya-Garrot, None; S. Ruta, None; J. Rosa, None; E. R. Soriano, None.

Quantitative Proteomic Analysis of Synovial Fluid and Skin Identifies Putative Psoriatic Arthritis Biomarkers. Daniela Crețu1, Kun Liang4, Dafna D. Gladman2, Eleftherios Diamandis4 and Vinod Chandran3. 1University of Toronto, Mount Sinai Hospital, Toronto, Canada, Toronto, ON, 2University of Waterloo, Waterloo, ON, 3University of Toronto, Western Hospital, Toronto, ON, 4University of Toronto, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is a unique form of arthritis occurring in 30% of psoriasis patients. There is a high prevalence of undiagnosed PsA in psoriasis patients; therefore identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate referral to a rheumatologist. Potential PsA biomarkers likely originate in sites of inflammation, such as inflamed joints and skin, and subsequently enter systemic circulation. We hypothesize that quantitative proteomic analysis of synovial fluid (SF) and skin obtained from PsA patients, will generate a comprehensive list of proteins specific to PsA, facilitating the identification of potential PsA screening biomarkers.

Methods: SF was obtained from swollen knee joints of 10 PsA patients, and age/sex matched early osteoarthritis (OA) controls. Likewise, skin biopsies were obtained from involved and uninvolved skin of 10 PsA, and 10 age/sex matched psoriasis patients. Using strong cation exchange chromatography, followed by tandem mass spectrometry, we characterized the proteomes of pooled SF and pooled skin samples. Extracted ion current (XIC) intensities were used to calculate protein abundance ratios, and utilized to classify upregulated proteins. Selected reaction monitoring (SRM) assays were developed to quantify these potential PsA markers in individual patient samples. Identified markers were quantitatively measured in serum samples from 33 PsA and 15 PsC patients, using commercially available or in-house developed enzyme-linked immunosorbent assays (ELISA).

Results: We quantified a total of 443 and 1922 proteins in SF and skin extracts, respectively, but only 17 proteins represented upregulated proteins in PsA SF, while 47 proteins were specifically elevated in PsA-derived skin. SRM validation confirmed that 12 and 8 proteins were indeed elevated in an independent set of PsA SF and involved PsA skin, respectively. Based on the fold change between PsA and controls, the associated P-values, and the cellular localization, we ranked the proteins, and selected the following putative markers for validation in the serum - S100A9, M2BP, CDSL, MMP3, CRP, EPO, POSTN, and ITGB5. Only ITGB5 (1.2±0.5 compared to 0.8±0.6; P=0.007), M2BP (553±150.9 compared to 453.0±115.0; P=0.027), EPO (19.6±12.3 compared to 13.7±12.2; P=0.035), and MMP3 (3.4±3.4 compared to 1.8±1.1; P=0.046) were significantly elevated in PsA serum compared to PsC.

Conclusion: Proteomic analysis of PsA SF and skin has identified 20 candidate biomarkers, and 4 of these have been confirmed in serum following a small-scale validation. In the future, these markers must be validated in a larger and independent sample cohort, in order to identify their clinical utility in PsA patients. Additionally, these proteins may also uncover aspects of PsA pathobiology that are currently unknown.

Disclosure: D. Crețu, None; K. Liang, None; D. D. Gladman, AbbVie Canada, 5; E. Diamandis, None; V. Chandran, AbbVie, 5.

The Economic Impact of Psoriatic Arthritis in Toronto, Ontario. Dafna D. Gladman, Melissa Yu, Michal Bohnadnowicz, Arane Thavaneswaran and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: This study aimed to quantify the direct and indirect costs of psoriatic arthritis (PsA) at a single center in Toronto, Ontario and to assess whether these costs varied with respect to socioeconomic status. Methods: Participants were identified from the Psoriatic Arthritis Clinic at Toronto Western Hospital in Toronto, Ontario. To be included in the study, patients fulfilled the Classification criteria for Psoriatic Arthritis (CASPAR) and attended the clinic for ≥ 1 year. Participants were excluded if they were <18 years old or if they were non-English speakers.

Consented participants completed a questionnaire that included healthcare utilization, out-of-pocket expenses, and productivity losses in the preceding 12 months. Results from this survey were supplemented with a chart review of participants’ prescription costs, and a survey of the past year, demographic information, socioeconomic characteristics, and disease severity measures. Direct costs were estimated according to the Ontario Drug Benefit Formulary, Ontario Health Insurance Plan, or industry averages. Indirect costs were estimated from productivity losses due to sick days or early
retirement. Age, sex, education, marital status, employment status and household income were used as indicators of socioeconomic status. The relationship between cost of PsA and socioeconomic status was assessed using the Kruskal-Wallis test, with significance of p < 0.05.

Results: Of the 188 patients included in the study, the mean annual direct cost of PsA was $15,802 per patient, of which $5,499 and $10,219 accounted for non-pharmacologic and pharmacologic costs, respectively. Women, un-employed, and lower income patients had significantly higher pharmacologic costs, whereas patients under the age of 65 had significantly higher pharmacologic costs compared to their counterparts. Thirteen % of patients were unemployed due to psoriatic arthritis, with an average 3.3 years of lost employment.

Conclusion: This study showed that PsA generates a substantial economic burden for patients in Toronto, Ontario. This burden is composed of healthcare resource consumption as well as productivity loss due to early retirement. Furthermore, age, sex, employment status, and income are all significantly associated with the direct cost of PsA. Information from this study will help to estimate the cost-effectiveness of new PsA medications and to allocate healthcare resources more effectively to certain socioeconomic groups in need.

Disclosure: D. D. Gladman, None; M. Yu, None; M. Bohdanowicz, None; A. Thavaneswaran, None; V. Chandran, None.

1588
Resistance Training in Patients with Psoriatic Arthritis Improves Functional, Disease Activity and Quality of Life. Diego Roger Silva1, Fabio Jennings2, Emilia Moreira3 and Jamil Natour4. 1Universidade Federal de Sao Paulo, Sao Paulo, Brazil, 2Escola Paulista de Medicina/Universidade Federal de Sao Paulo, Sao Paulo, Brazil.

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, defined as the association of inflammatory arthropathy and skin psoriasis. The literature is still very scarce with regard to non-pharmacological treatments for patients with PsA, specially physical exercise.

Objective: The aim of this study was to assess the effectiveness of resistance training in improving functional capacity, muscle strength, quality of life and disease activity in patients with PsA.

Methods: Forty-one patients aged between 18 and 65 years with diagnosis of psoriatic arthritis were selected to this study. The patients were randomized into two groups: intervention group and control group. The intervention group (IG) underwent resistance exercise twice a week, for twelve weeks. The control group remained on the waiting list with the conventional drug therapy. The outcome measurements were: BASFI and HAQ-S for functional capacity, one maximum-repetition test (1RM) for strength (1RM), SF-36 questionnaire for general quality of life; and BASDAI and DAS-28 for disease activity. The evaluations were done by a blinded evaluator at baseline (T0), 6 weeks (T6) and 12 weeks (T12) after the beginning of the study.

Results: At baseline the groups were homogeneous regarding clinical and demographic characteristics. The IG significantly improved functional capacity measured by HAQ-S and disease activity measured by BASDAI, compared to CG, at week 12. Regarding quality of life, the IG improved the domains “pain” and “general health status” compared to CG (p < 0.05). There was improvement in muscular strength in almost all exercises in IG, except in the exercise for biceps. In the CG, the improvement in strength was observed only on “crucifix” (bilateral) and “leg extension” (bilateral) exercises. However, there was statistical differences between groups only on exercise “leg extension” (right side) in favor of IG.

Conclusion: Resistance training is effective in improving physical capacity, disease activity and quality of life of patients with psoriatic arthritis. The clinical improvements were not coupled to significant changes in muscular strength.

Disclosure: D. R. Silva, None; F. Jennings, None; E. Moreira, None; J. Natour, None.

1589
Risk of Opportunistic Infection and Herpes Zoster Infection in a Psoriasis/Psoriatic Arthritis Cohort. Kevin L. Winthrop1, Lang Chen2, John Basham3, Benjamin Chan1, Huifeng Yun1, Sarah Siegel1, and Jeffrey R. Curtis3. 1Oregon Health & Science University, Portland, OR, 2University of Alabama at Birmingham, Birmingham, AL, 3Oregon Health and Science University, Portland, OR, 4University of Alabama at Birmingham School of Public Health, Birmingham, AL, 5The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Psoriasis/Psoriatic arthritis (PsO/PsA) often requires treatment with systemic agents. Some of these agents are associated with infectious adverse events. Few studies have described the background incidence of opportunistic infections (OIs) or Herpes zoster (HZ) infections, in a cohort of PsO/PsA patients.

Methods: We used the US Medicare dataset from 2006-2011 to identify a large cohort of PsA and PsO patients. We defined PsA and PsO as those with ≥1 rheumatologist-diagnosis code for psoriatic arthritis (ICD 9 78.969) or ≥1 dermatologist-diagnosis code for psoriasis (ICD 9 696.1) respectively, collectively, by a prescription for etanercept (ETA), cyclosporine (CIC), ustekinumab (UST), adalimumab (ADA), methotrexate (MTX) or ultraviolet light (UV) therapy. Patients had at least 6 months of continuous Medicare enrollment prior to the first date of exposure to these therapies. We excluded patients with organ transplantation, human immunodeficiency virus infection, advanced kidney and liver disease, or cancer with a 183-day period prior to cohort inception. Pairwise propensity scores (PS) were calculated and used to control for potential differences between comparator treatments. We used validated-claims based algorithms to identify OIs and HZ events among exposure groups. Patient exposures were censored at time of serious infection, death, end of study, loss of coverage, or 90 days following end of treatment exposure whichever came first. For OIs and for HZ, we calculated crude incidence rates in all exposure groups, and used Cox-proportional hazard regression models to calculate hazard ratios for these outcomes between exposure groups while adjusting for PS quintile.

Results: We identified 10,261 PsA individuals and 31,052 PsO individuals. Of the PsA cohort, there were fewer than 11 OI infections yielding an overall incidence rate of 1.5 (95% CI: 0.7–3.0) per 1,000 py, while the PsO cohort also had fewer than 11 OI infections with an overall incidence rate of 1.5 (95% CI: 0.6–3.0) per 1,000 py. For HZ, there were 82 HZ infections in the PsA cohort yielding an overall incidence rate of 16.1 (95% CI: 12.8–20.0) per 1,000 py. In the PsO cohort, the incidence rate was 1.5 (95% CI: 13.3–30.2) per 1,000 py for the UV therapy group. For the ETA group of the PsO cohort, there were fewer than 391 HZ infections with an overall incidence rate of 13.0 (95% CI: 11.8, 14.4) per 1,000 py. The incidence rate ranged from 11.1 (95% CI: 7.4–16.7) per 1,000 py for the CIC group to 14.3 (95% CI: 2.2–16.7) per 1,000 py for the MTX group. Rates of HZ infection were similar by exposure groups, but were higher than rates found in rheumatoid arthritis patients of the same age. For both the PsA and PsO cohorts, there were no significant associations by treatment type for either OI or the HZ infection, even when compared to the UV therapy group.

Conclusion: Among Medicare enrollees with PsO or PsA, biologic treatments were not associated with an increased risk of either OIs or HZ compared to non-biologic treatment (e.g. UV light).

Disclosure: K. L. Winthrop, Pfizer Inc, 5, Pfizer Inc, 2, Insmed, 2, Insmed, 5, UCBI, 5, Roche Pharmaceuticals, 5, Abbvie, 5, LS Chen, None; J. Baddley, BMS, 2, Merck, 5, Abbvie, 5, Ch. Cheon, None; H. Yun, Amgen; 2, S. Siegel, None; J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONE, Amgen, Pfizer, BMS, Crescendo, ABBVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONE, Amgen, Pfizer, BMS, Crescendo, ABBVie, 5.

1590
Apremilast, an Oral Phosphodiesterase 4 Inhibitor, is Associated with Long-Term (104-Week) Improvements in Patients with Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial. Arthur Kavanaugh1, A. deawale O. Abedarab2, Dunia D. Gladman1, Juan J. Gomez-Reino3, Stephon Hall4, Eric Lepescheski5, Philip Maze6, Georg A. Scheif6, ChiaChii Hu6, Randall M. Stevens7 and Jürgen Wellenhaus6. 1University of California San Diego, La Jolla, CA, 2University of Sheffield, Sheffield, United Kingdom, 3University of Toronto, Toronto Western Hospital, Toronto, ON, 4Hospital Clinico Universitario, Santiago, Spain, 5Cabinri Health and Monash University, Melbourne, Australia, 6University of Orleans, Orleans, France, 7Swedish Medical Center and University of Washington, Seattle, WA, 8University of Erlangen-Nuremberg, Erlangen, Germany, 9Cell-gene Corporation, Warren, NJ, 10Schön Klinik Hamburg Eilbek, Hamburg, Germany.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor that may modify the immune response, has been shown effective in psoriatic arthritis (PsA). PALACE 1 compared the efficacy and safety of APR with placebo in patients with active PsA despite prior conventional DMARDs and/or biologics, including biologic failures.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline
DMARD use (yes/no). Patients whose swollen and tender joint counts (SJC and TJC) had not improved by \(\geq 20\%\) at Week 16 were considered non-responders and were required to be re-randomized (1:1 to APRA or APRA30 if they were initially randomized to placebo, or continued on their initial DMARD dose). At Week 24, all remaining placebo patients were re-randomized to APRA20 or APRA30. Double-blind APRA treatment continued to Week 52; patients could continue to receive apremilast during an active treatment, long-term phase of up to 4 years, for a total follow-up of up to 5 years. Efficacy in patients randomized to apremilast at baseline and with evaluable data at Week 52 and Week 104 is described herein (analysis: as observed).

**Results:** 504 patients were randomized and received \(\geq 1\) dose of study medication (placebo: \(n = 168\); APRA20: \(n = 168\); APRA30: \(n = 168\)). At Week 52, modified ACR20 response was achieved by 63.0% and 54.6% of patients who were initially randomized to APRA20 or APRA30 from baseline, respectively. Among patients who were randomized to APRA at baseline, improvements were sustained over the next 104 weeks for multiple endpoints (Table), including (1) modified ACR20/A CR50/ARCR70 of 61.3%/29.8%/16.0% (APRA20) and 66.3%/35.6%/19.8%, respectively (APRA30); (2) median percent change in SJC/TJC of \(-88.9\%/-80.5\%\) (APRA20) and \(-87.5\%/-76.7\%\) (APRA30); (3) mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) of \(-0.33\) (APRA20) and \(-0.43\) (APRA30), and greater than 50% achieving minimal important differences \(\geq 0.30\); (4) mean change in 28-joint Disease Activity Score (DAS-28) of \(-1.61\) (APRA20) and \(-1.89\) (APRA30); and (5) achievement of DAS <2.6 in 35.1% (APRA20) and 38.5% (APRA30) of patients. Consistent results were demonstrated in patients randomized to placebo at baseline and re-randomized to APRA20 or APRA30 at Week 16 or 24 who completed Week 104. No new safety signals were observed with treatment through 104 weeks.

**Conclusion:** Over 104 weeks, APRA demonstrated sustained clinically meaningful improvements in the signs and symptoms of PsA, physical function, and associated skin symptoms. ACR 20 response at Week 104 was 66% for APRA30. APRA continued to demonstrate an acceptable safety profile and was generally well tolerated.

**Outcomes at Week 52 and Week 104 (Data as Observed)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Week 52</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APRA20</strong></td>
<td>0.120</td>
<td>0.125</td>
</tr>
<tr>
<td>ACR20, n (%)</td>
<td>75/119  (63.0)</td>
<td>57/93 (61.3)</td>
</tr>
<tr>
<td>ACR50, n (%)</td>
<td>29/127 (23.1)</td>
<td>30/120 (25.0)</td>
</tr>
<tr>
<td>ACR70, n (%)</td>
<td>18/117 (15.4)</td>
<td>19/116 (16.6)</td>
</tr>
<tr>
<td>SJC median % change</td>
<td>78.3</td>
<td>77.8</td>
</tr>
<tr>
<td>TJC median % change</td>
<td>69.2</td>
<td>62.5</td>
</tr>
<tr>
<td>HAQ-DI (0–3), mean change</td>
<td>-0.32</td>
<td>-0.32</td>
</tr>
<tr>
<td>DAS-28 (CRP), mean change</td>
<td>-1.40</td>
<td>-1.31</td>
</tr>
<tr>
<td>PAS-75 (0–100), n (%)</td>
<td>15.0 (23.1)</td>
<td>13.0 (21.3)</td>
</tr>
</tbody>
</table>

**Results:**

- **Baseline**: 504 patients were randomized and received \(\geq 1\) dose of study medication (placebo: \(n = 168\); APRA20: \(n = 168\); APRA30: \(n = 168\)). At Week 52, modified ACR20 response was achieved by 63.0% and 54.6% of patients who were initially randomized to APRA20 or APRA30 from baseline, respectively. Among patients who were randomized to APRA at baseline, improvements were sustained over 104 weeks for multiple endpoints (Table), including (1) modified ACR20/A CR50/ARCR70 of 61.3%/29.8%/16.0% (APRA20) and 66.3%/35.6%/19.8%, respectively (APRA30); (2) median percent change in SJC/TJC of \(-88.9\%/-80.5\%\) (APRA20) and \(-87.5\%/-76.7\%\) (APRA30); (3) mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) of \(-0.33\) (APRA20) and \(-0.43\) (APRA30), and greater than 50% achieving minimal important differences \(\geq 0.30\); (4) mean change in 28-joint Disease Activity Score (DAS-28) of \(-1.61\) (APRA20) and \(-1.89\) (APRA30); and (5) achievement of DAS <2.6 in 35.1% (APRA20) and 38.5% (APRA30) of patients. Consistent results were demonstrated in patients randomized to placebo at baseline and re-randomized to APRA20 or APRA30 at Week 16 or 24 who completed Week 104. No new safety signals were observed with treatment through 104 weeks.

- **Conclusion:** Over 104 weeks, APRA demonstrated sustained clinically meaningful improvements in the signs and symptoms of PsA, physical function, and associated skin symptoms. ACR 20 response at Week 104 was 66% for APRA30. APRA continued to demonstrate an acceptable safety profile and was generally well tolerated.
purpose was to determine the predictive value of clinical features to predict joint damage in PsA.

**Methods:** The study was conducted in a large prospective cohort of patients with PsA who are assessed according to a standard protocol that includes detailed clinical evaluation every 6 months and radiographic evaluation every 2 years. Patients who had at least 2 radiographs were included in this study. Radiographic joint damage progression was defined as increase in the count of radiographically damaged joints between 1st and 2nd radiographs or any of the following: MCP, PIP, DIP, MTPs and 1st IP of toes (total 42 joints). The following clinical variables at the time of first radiographic assessment were evaluated as predictors: age, sex, age at diagnosis of psoriasis and PsA, duration of psoriasis and PsA, PASI, active, swollen, clinically damaged and radiographically damaged joint count, dactylitis, presence of axial disease, ESR, SF-36, HAQ, NSAID, DMARD and biologic use at baseline, HLA-B*27 and HLA-C*06. Univariate PASI, active, swollen, clinically damaged and radiographically damaged joint count, dactylitis, presence of axial disease, ESR, SF-36, HAQ, NSAID, DMARD and biologic use at baseline, HLA-B*27 and HLA-C*06 positive. Their SF-36 PCS was 36.5 and HAQ 0.8. In univariable analyses older age, age at diagnosis of psoriasis, duration of psoriasis and PsA, active, swollen, clinically damaged and radiographically damaged joint counts, dactylitis, axial arthritis, ESR, HAQ, and treatment with DMARDS were associated with radiographic progression ($p < 0.05$). The predictors independently associated with radiographic progression in a multivariate reduced model are shown in Table 1. The area under the curve of the ROC curves was 0.71.

**Results:** 656 (380 males) with a mean age of 43 years, age at onset of psoriasis 28 years and of PsA 37 years were included. At the time of the first radiograph these patients had 11 active, 5 swollen, 9 clinically damaged and radiographically damaged joints and the PASI score was 5.3. The mean ESR was 23 mm/hr, Hb 139 g/dl, platelet count 268,000/microL and CRP 3.2. The NLR significantly correlated with SJC ($r = 0.12$, $p < 0.0001$), PASI ($r = 0.15$, $p < 0.0001$), ESR ($r = 0.24$, $p < 0.0001$), HB ($r = -0.18$, $p < 0.0001$) and platelet count ($r = 0.15$, $p < 0.0001$). Multivariate linear regression analysis showed that NLR ($β = 0.16$, $p = 0.01$), PASI ($β = 0.11$, $p = 0.003$) were independently associated with SJC. Similarly, multivariate linear regression analysis showed that NLR ($β = 0.41$, $p < 0.0001$) and ESR ($β = 0.11$, $p = 0.007$) were independently associated with PASI score.

**Conclusion:** NLR has a potential as a marker of disease activity in PsA independent of traditional acute phase reactants. Further evaluation to determine threshold of abnormal values in the context of psoriatic disease, as well as prognostic value in predicting joint damage and cardiovascular disease is required.

**Disclosure:** V. Chandran, None; A. Thavaneswaran, None; D. D. Gladman, None.

**1594**

**Persistence of Low Disease Activity after Tumor Necrosis Factor Inhibitor Withdrawal in Patients with Psoriatic Arthritis.**

**Doquyen H. Huynh,**1 Carol J. Etzel,2 Vanessa Cox,2 Philip Meece2 and Arthur Kavanaugh3.

1UC San Diego School of Medicine, San Diego, CA, 2Corrona, LLC., Southborough, MA, 3CORRONA, Inc, Southborough, MA, 4CORRONA, Seattle, WA, 5UCSD School of Medicine, La Jolla, CA.

**Background/Purpose:** The increased use of tumor necrosis factor inhibitors (TNFi) has improved clinical outcomes for psoriatic arthritis (PsA) patients and made low disease activity (LDA) and remission viable treatment goals. Due to factors such as pharmacoeconomic considerations, concern for long term side effects, and patient preferences, there has been increasing interest in the possibility that TNFi may be discontinued by patients achieving remission or LDA, with maintenance of clinical benefit. The purpose of this study is to determine the duration of clinical benefit among PsA patients discontinuing TNFi while in LDA, and to identify patient characteristics and disease related factors that may be associated with prolonged clinical benefit.

**Methods:** An observational cohort study of PsA patients in the CORRONA registry who discontinued TNFi use after achieving LDA. LDA was defined as CDAI $\leq 10$ and skin psoriasis physician global assessment $\leq 20/100$. Patients were considered to have lost clinical benefit if: 1) increase in CDAI to $> 10$; 2) increase in skin assessment to $> 20$; or 3) increase in concomitant DMARD or prednisone doses or start of DMARD, prednisone, or biologic agents. Clinical data were collected at baseline (the time of TNFi discontinuation) and at loss of clinical benefit or the last clinic visit. Kaplan Meier analyses were used to estimate duration of clinical benefit. Both unvariable and multivariable Cox proportional hazard analyses were used to evaluate characteristics associated with duration of benefit.

**Results:** Of 5945 PsA patients in CORRONA, 325 discontinued TNFi while in LDA and had follow up data available. Mean age was 52.6 years, mean BMI 30.1, mean duration of PsA 9.8 years, and 51.9% were female. 52.6% of patients discontinued their 1st TNFi, and 31.1% discontinued their 2nd TNFi. Mean duration of TNFi use was 1.5 years. 53.5% used TNFi as monotherapy, 42.2% used concomitant MTX; 29% took low dose prednisone. 146 patients lost clinical benefit, due to: increased CDAI (31.5%), initiation of or increase in DMARD (32.2%), TNFi restart (6.8%), initiation or increase in prednisone (9.6%) or worsening skin disease (15.8%). The median time to loss of benefit was 29.2 months. 179 patients still had persistent benefit at their last clinic visit. Patients with higher disease activity at TNFi discontinuation had increased risk of losing clinical benefit (hazard ratios [HR] for: CDAI $> 3.2$ vs $\leq 3.2$ - HR 1.43 ($p = 0.032$), patient global assessment $> 5$ vs $\leq 5$ - HR 1.7 ($p = 0.007$), moderate vs low DAS - HR 1.65 ($p = 0.017$). Interestingly smokers had significantly higher risk for loss of benefit (HR vs non-smokers 1.76; $p = 0.027$) in both unvariable and multivariable analysis. Number of TNFi used and overweight or obese status did not significantly affect loss of benefit.

**Conclusion:** PsA patients who achieve LDA on treatment may maintain clinical benefit after discontinuation of TNFi. Patients with higher disease activity at the time of discontinuation and smokers may have less success at stopping therapy.

**Disclosure:** D. H. Huynh, None; C. J. Etzel, Corrona, 3; V. Cox, Corrona, 3; P. Meece, Corrona, 9; A. Kavanaugh, None.
Economic Evaluation of Sequencing Strategies in the Treatment of Psoriatic Arthritis in the United States. Thomas Tencer1, Zoe Clancy1, Helene Cawston2, Sandrine Cure3 and Frank Zhang4; 1Celgene Corporation, Warren, NJ; 2OptumInsight, Nanterre, France; 3OptumInsight, Uxbridge, United Kingdom.

Background/Purpose: In the treatment of psoriatic arthritis (PsA), switching between alternative biologic treatments is common. A cost-effectiveness model was developed to assess the impact of placing apremilast, a new oral treatment, before biologics in PsA patients who had failed conventional disease-modifying antirheumatic drug therapy, from a U.S. payer perspective.

Methods: A lifetime Markov state transition cohort model was developed to compare 2 treatment sequences in the base-case: apremilast followed by adalimumab followed by etanercept versus adalimumab followed by etanercept. Patients who failed etanercept were assumed to receive best supportive care (BSC) as the last line of treatment. Response to therapy was assessed using the Psoriatic Arthritis Response Criteria (PsA-ARC) at the end of the clinical trial periods, ranging from 12 to 16 weeks depending on drug. Non-responders moved to the next line of therapy. A 16.5% annual dropout rate was assumed for each drug. Therapy efficacy inputs were obtained from a meta-analysis and trial results. Drug costs were sourced from 2013 Wholesale Acquisition Costs prices, and a 3% annual discount rate was applied to costs and quality-adjusted life-years (QALYs). A premilast was assumed to be priced at a discount to biologics. Utilities were estimated from the Health Assessment Questionnaire and Psoriasis Area and Severity Index response using a previously published regression equation.

Results: The apremilast arm provided an additional 2.53 years with a PsA-RC response and an additional 0.78 QALYs. Total time spent on the biologics was reduced by 0.34 years and time spent in BSC was reduced by 2.85 years. Under base-case assumptions, placing apremilast before biologics was found to be the dominant strategy (costs reduced by $28,794). Sensitivity analyses indicated that several parameters (e.g., cost of BSC and baseline utility) influence the incremental cost-effectiveness ratio. Similar results were obtained with different biologic drugs in the sequence.

Conclusion: Placing apremilast before biologics is a cost-saving strategy in the treatment of PsA.

Disclosure: T. Tencer, Celgene Corporation, 3; Z. Clancy, Celgene Corporation, 2; H. Cawston, Celgene Corporation, 2, OptumInsight, 3; S. Cure, Celgene Corporation, 2, OptumInsight, 3; F. Zhang, Celgene Corporation, 3.

Clinical Characteristics and Outcome of Golimumab Treatment Differ Between Bio-naïve and Patients Previously Exposed to Biologicals. Nationwide Results on Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and Other Spondylarthritides (SpA).

Saeed Saevadsdottir1, Michèle Santacaterina, Carl Turesson2, Helena Forsblad3, Lennart Jacobsson4 and Staffan Lindblad5; 1Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; 2Karolinska Hospital, Stockholm, Sweden; 3Karolinska Institutet, Stockholm, Sweden; 4Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden; 5The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: Golimumab is a TNF inhibiting biological drug that was approved in Sweden in 2010 for the treatment of RA, PsA and AS. Our previous analyses have demonstrated similar drug adherence as for other TNF-inhibitors and better adherence in bio-naïve patients (Saevadsdottir S et al, ACR 2013). Given that, the aim of the current study in an updated dataset with longer follow-up time, was to investigate the differences in clinical characteristics and drug survival probability between golimumab treated patients that were bio-naïve compared to those previously exposed to biologicals, separately for patients with RA, PsA, AS as well as other SpA.

Methods: Data were retrieved for all patients initiating golimumab treatment in 2010–2013 from the nationwide SRQ register. A survival analysis (Kaplan Meier) was performed over 24 months with right censoring and log-rank test of equality across strata.

Results: Of 2106 patients initiating golimumab treatment during the study period, 849 (40%) had RA, 454 (22%) PsA, 303 (14%) AS, 242 (12%) SpA and 258 (12%) had other diagnoses. The proportions of women in RA/PsA/AS/SpA patient groups were 78%/50%/29%/55%, respectively; and their median age at baseline was 54/48/42/40 years. In patients with RA/PsA/AS/SpA, the proportions receiving golimumab as the first biological treatment were 48%/46%/42%/40%; and the proportions receiving concurrent disease-modifying anti-rheumatic drugs (DMARDs) were 76%/64%/32%/47%.

Several baseline characteristics differed between bio-naïve patients (0) and those previously exposed to biological treatment (1-2 or 3+ biologic drugs, see Table 1, parameters showing significant difference in each disease are mentioned below). Bio-naïve patients were less likely to have concurrent treatment with DMARDs (PsA, AS), prednisolone and NSAID (all); and they reported fewer HAQ, RA, PsA, SpA, DAS28 (RA, PsA), inflammatory markers (CRP/ESR: RA, SpA), VAS-global health (RA, PsA, SpA) and VAS-pain (RA) at baseline. Furthermore, bio-naïve were more likely to be male (RA, PsA), older (RA, PsA, AS) and with short disease duration (RA, AS, SpA).

The drug survival probability over 24 months was also higher in bio-naïve patients (RA, AS, trend for PsA) but less so for SpA.

Conclusion: In this real-life nationwide cohort, patients starting golimumab as their first biologic were treated with co-medication to a lesser extent, but had more favorable prognostic factors, and better drug survival over two years compared to those previously treated with other biologics. Patterns were similar for the various rheumatologic diseases treated with golimumab. It is of major importance to take previous biologic exposure into account when evaluating new biologic treatments in patients with PsA.

Table 1. Clinical characteristics of patients receiving golimumab treatment 2010–2013 in Sweden.

<table>
<thead>
<tr>
<th>Number of previous biologics</th>
<th>RA</th>
<th>PsA</th>
<th>AS</th>
<th>Other SpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disclosure: S. Saevadsdottir, None; M. Santacaterina, None; C. Turesson, Unrestricted research grants from Abbvie, Pfizer and Roche; 2, Advisory Boards: Bristol-Myers Squibb, MSD, Pfizer, Roche; S. Forsblad, None; L. Jacobsson, None; S. Lindblad, None.

Work Productivity Improvement Associated with Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results of a Phase 3, Randomized, Controlled Trial.

Thomas Tencer1, Stan Li1 and Vibeke Strand2; 1Celgene Corporation, Warren, NJ; 2Biopharmaceutical Consultant, Portola Valley, CA.

Background/Purpose: Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the aberrant immune response that causes the joint symptoms, systemic inflammation, and skin disease associated with psoriatic arthritis (PsA). The Work Limitations Questionnaire (WLQ) measures the degree to which employed individuals are experiencing limitations on the job due to their health problems, as well as health-related productivity loss. The PALACE 1
study compared the efficacy and safety of APR with placebo in patients with active PsA despite prior or concurrent conventional disease-modifying antirheumatic drugs (DMARDs) and/or prior biologics. The objective of the current analysis was to assess the effect of APR on work productivity and work limitations of employed patients in the PALACE 1 study.

**Methods:** Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Treatment efficacy was assessed at Week 16 based on the intent-to-treat population. Employed patients completed the WQ, a 25-item questionnaire that assesses the impact of chronic health conditions on work performance and productivity, at baseline and Week 16. Work limitations were categorized into 4 domains, which were then used to calculate the WQ index: physical demands (PDS), mental demands (MDS), time management demands (TMS), and output demands (ODS). Improvement in the WQ index, and its 4 domains, is represented by a negative change from baseline. Improvement in work productivity is represented by a positive improvement in percentage of productivity loss.

**Results:** 504 patients were randomized (mean age: 50.4 years; 49.4% male). Of these 261 who were both employed and completed at least 1 component of the WQ were analyzed. At Week 16, APR20 and APR30, vs. placebo, were associated with a greater mean change from baseline in PDS (−1.58 vs. −1.24, p=0.01), MDS (−2.22 and −5.18 vs. 1.15, p=0.01), TMS (−0.53 vs. −1.76 and 4.25, p=0.01), and ODS (−3.45 and −1.67 vs. −1.34, p=0.02), resulting in a greater mean improvement in the WQ index (−0.01 vs. −0.03 vs. 0.00), which corresponds to a higher median percent improvement in productivity loss (18.9% vs. 3.72%). Higher productivity improvements were also observed among APR20 and APR30 and responders at Week 16—PDS (−2.36 and −2.67 vs. −1.26, p=0.01), MDS (−1.78 vs. −1.63 and −1.11, p=0.04), TMS (−1.43 vs. −1.83, p=0.02), and ODS (−1.56 vs. −1.67, p=0.04), respectively—resulting in a higher mean improvement in the WQ index (−0.03 vs. −0.03 vs. 0.00), which corresponds to a higher median percent improvement in work productivity (57.9% and 46.8%), respectively.

**Conclusion:** APR20 and APR30 increased work productivity and improved work limitations among patients active PsA who were not adequately controlled with prior or concurrent conventional DMARDs and/or prior biologics.

**Disclosure:** F. Zhang, Biogen Idec, 5; H. Przepiera-Bedzak, None; K. Fischer, None. M. Brzozoski, None.

**1599**

**Serum Fetuin-A, Intercellular Adhesion Molecule-1 and Interleukin-18 Levels in Ankylosing Spondylitis and Psoriatic Arthritis.** Hanna Przepiera-Bedzak1, Kataryzna Fischer2 and Marek Brzozoski.1 1Department of Rheumatology and Internal Diseases Pomeranian Medical University in Szczecin, Szczecin, Poland, 2Independent Laboratory of Rheumatological Diagnostics, Pomeranian Medical University in Szczecin, Szczecin, Poland.

**Background/Purpose:** In recent years, increased incidences of metabolic disorders have been observed in patients with systemic inflammatory rheumatic diseases. Fetuin-A, Intercellular Adhesion Molecule-1 (ICAM-1) and interleukin-18 (IL-18) have been implicated in the endophthalic function and atherosclerosis. The aim of the study was to investigate serum levels of fetuin-A, ICAM-1 and IL-18 in ankylosing spondylitis (AS) and psoriatic arthritides (PsA).

**Methods:** We studied 123 patients and 20 controls. We recorded: age, sex, disease duration, treatment type, history of metabolic disorders, VAS, BASTDAI, PASI, BMI, waist-hip ratio. Blood was collected for analysis of fetuin-A, ICAM-1, IL-18, IL-6, IL-23, VEGF and EGF by ELISA method. We assessed lipid profile, CRP and ESR. This work was supported by a grant from the National Science Centre in Poland (UMO-2011/03/B/NZ5/0192).

**Results:** A total of 59 AS (43.5±12.9 years; 36 F/23 M) patients were studied. Serum fetuin-A, ICAM-1 and IL-18 levels were significantly higher in patients compared to controls (p<0.005).

No differences were found in serum fetuin-A, ICAM-1 and IL-18 levels in AS and PsA patients.

Serum fetuin-A positively correlated with triglycerides (r=0.3; p=0.02) and VEGF (r=0.3; p=0.02) in AS and with IL-23 (r=0.2; p=0.05) and VEGF (r=0.3; p=0.04) in PsA patients.

Serum ICAM-1 positively correlated with IL-6 (r=0.3; p=0.007) and ESR (r=0.3; p=0.007) in AS and with IL-6 (r=0.2; p=0.05) in PsA patients.

Serum IL-18 positively correlated with CRP (r=0.25; p=0.05), cholesterol (r=0.4; p=0.01), triglycerides (r=0.4; p=0.04) and BSAFI (r=0.3; p=0.02) in AS and with IL-6 (r=0.3; p=0.03) and VEGF (r=0.3; p=0.04) in PsA patients.

No differences were found in comparison of subjects to treatment type regarding to serum fetuin-A, ICAM-1 and IL-18 levels in AS and PsA patients.

**Conclusion:** Serum fetuin-A, ICAM-1, IL-18, levels were increased and correlated with disease activity in AS and PsA patients. Serum fetuin-A and IL-18 correlated with triglycerides in AS patients.

**Disclosure:** H. Przepiera-Bedzak, None; K. Fischer, None; M. Brzozoski, None.
Is There a Role for Inflammasome Activation in PsA Pathogenesis and Its Comorbidities?

Rodolfo Perez Alamino1, Raquel Cuchacovich2, A. Zea3 and Luis R. Espinoza4. 1LSUHSC, New Orleans, LA, 2LSU Medical Center, New Orleans, LA, 3Stanley Cancer Center, New Orleans, LA.

Background/Purpose: New data has emerged about the role of the inflammasome in psoriasis and psoriatic arthritis (PsA). The assembly of the inflammasome components in innate immune cells (monocytes) results in the rapid activation of Caspase-1, which cleaves pro-IL-1. Inflammasome activation in monocytes results in the cleavage of pro-IL-1β and IL-18, which are key effectors on the initiation and amplification of the innate immune response in PsA pathogenesis. Therefore, it was decided: 1) To determine whether inflammasome activation occurs in monocytes of PsA patients and; 2) To determine the relationship between inflammasome activation with disease activity and metabolic syndrome in these patients.

Methods: After informed consent, 13 PsA patients (CASPAR criteria) and 16 age-matched healthy individuals attending to the outpatient Rheumatology clinic were enrolled. Demographic, laboratory and clinical data was recorded. Disease activity was determined by DAS-28 score. Blood pressure, diabetes history, lipid profile and waist circumference data were included. Metabolic syndrome (MS) was defined following the International Diabetes Federation (IDF) criteria. Purified monocytes were plated and stimulated for 18 h with LPS (100ng/ml) in presence or absence of Caspase-1 inhibitor. CD14 and Caspase-1 expression was analyzed by flow cytometry. Cell lysates and supernatants were collected for determination of Caspase-1 and NLRP3 protein by Western blot and cytokine levels by ELISA, respectively. Student’s test and Mann-Whitney tests were used for statistical analysis.

Results: Sixty two percent (62%) of patients were females, mostly (77%) Caucasians. The mean age was 45.15 (SD 9.7) years and mean disease duration was 6.7 (SD 5.5) years. Ten patients presented with active disease, mean DAS28 3.25 (SD 1.2). Metabolic syndrome was present in 77% of patients.

The percentage of CD14+/Caspase-1 was numerically higher in PBMC, monocytes from PsA patients compared to normal controls (33.5 ± 13 vs. 22.5 ± 11.3, respectively), although difference did not reach statistical significance (p<0.1). Caspase-1 expression was confirmed by Western blot. No differences were found regarding cytokine levels. Purified monocytes from PsA patients displayed a robust inflammatory response after LPS stimulation where Caspase-1, NLRP3, IL-1β and IL-18 were highly expressed. Neither Caspase-1 nor cytokine expression were associated with disease activity. In a subset of PsA patients with MS, there was a trend to higher IL-1β levels (19.4 ± 24.8 vs. 4.1 ± 6.6) (p=0.08).

Conclusion: In this pilot study, PsA patients showed an enhanced expression of inflammasome activation, although difference did not reach statistical significance. Further studies including a larger number of patients are needed to truly establish a role of inflammasome activation in PsA pathogenesis and associated comorbidities.

Disclosure: R. Perez Alamino, Genentech and Biogen IDEC Inc.; 2, Pfizer; 2, Bristol-Myers Squibb; 2, R. Cuchacovich, None; A. Zea, None; L. R. Espinoza, None.

Are There Gender Specific Differences in Patient Characteristics at Baseline by Gender

Table 1: Patient Characteristics at Baseline by Gender

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)/%</th>
<th>Male</th>
<th>Female</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: years</td>
<td>48.6 (10.8)</td>
<td>48.9 (8.9)</td>
<td>0.862</td>
<td></td>
</tr>
<tr>
<td>Disease duration: years</td>
<td>6.9 (7.4)</td>
<td>6.8 (10.8)</td>
<td>0.980</td>
<td></td>
</tr>
<tr>
<td>C-Reactive Protein (CRP): mg/L</td>
<td>11.1 (14.4)</td>
<td>15.7 (23.8)</td>
<td>0.342</td>
<td></td>
</tr>
<tr>
<td>Patient Global (PtGA): VAS mm</td>
<td>58.6 (27.0)</td>
<td>55.0 (28.9)</td>
<td>0.168</td>
<td></td>
</tr>
<tr>
<td>Physician Global (MGDA): NRS 0–10</td>
<td>5.6 (2.0)</td>
<td>6.0 (2.3)</td>
<td>0.369</td>
<td></td>
</tr>
<tr>
<td>Pain: VAS mm</td>
<td>43.9 (25.6)</td>
<td>49.1 (26.1)</td>
<td>0.355</td>
<td></td>
</tr>
<tr>
<td>Morning stiffness: min</td>
<td>61.4 (48.1)</td>
<td>55.2 (42.2)</td>
<td>0.527</td>
<td></td>
</tr>
<tr>
<td>HAO-DI</td>
<td>0.92 (0.58)</td>
<td>1.43 (0.66)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>TJC28</td>
<td>5.0 (5.0)</td>
<td>6.8 (5.4)</td>
<td>0.105</td>
<td></td>
</tr>
<tr>
<td>SJC28</td>
<td>3.4 (4.0)</td>
<td>4.0 (3.16)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>PASI</td>
<td>4.2 (1.6)</td>
<td>2.4 (1.7)</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>DAS28</td>
<td>3.8 (1.6)</td>
<td>4.6 (1.5)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Prior biologic (&lt;6 months)</td>
<td>23.8%</td>
<td>14.3%</td>
<td>0.245</td>
<td></td>
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<tr>
<td>Concomitant DMARD</td>
<td>71.4%</td>
<td>78.6%</td>
<td>0.434</td>
<td></td>
</tr>
<tr>
<td>Concomitant corticosteroid</td>
<td>11.9%</td>
<td>4.1%</td>
<td>0.163</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Overall, some significant differences in disease parameters were observed between genders in AS and PsA at anti-TNFF initiation. Female AS patients experience greater functional impairment compared to men. Female PsA patients, in addition to higher HAQ, also show greater disease activity as measured by DAS28. These results suggest that female patients appear to receive their first biologics at a higher level of disease activity. Whether this represents a gender bias in prescribing, or a gender based difference in the acceptance of biologic treatment, requires additional research.

References

**1602**

**Th9 Cells in Inflammatory Cascades of Autoimmune Arthritis.** Siba Raychaudhuri, Anupam Mitra, A nanya Datta Mitra, Christine Abria and Smriti K. Raychaudhuri. 1Univ California Davis/VA Sac, Davis, CA, 2VA Sacramento Medical Center, Mather, CA.

**Background/Purpose:** Interleukin (IL)-9, a member of IL-2 cytokine family was recently attributed to a novel CD4 T cell subset termed Th9 cells in the murine system. It is secreted by naive CD4+ T cells in response to TGF-β and IL-4. IL-9 can also be secreted by Th17 cells and itself induces Th17 cells to differentiate and regulate autoimmune and inflammatory diseases by enhancing their secretion of IL-17. These observations provoked us to elucidate their pathogenic role of IL-9 in autoimmune arthritis.

**Methods:** From peripheral blood and synovial fluid (SF) of psoriatic arthritis (PsA) (n = 8), rheumatoid arthritis (RA) (n = 10), and osteoarthritis (OA, n = 10) patients, mononuclear cells were obtained and magnetically sorted for CD3+ T cells. IL-9 levels in SF and serum were measured by enzyme linked immunosorbent assay (ELISA). Proliferative effect of human recombinant IL-9 (rIL-9) on CD3+ T cells of peripheral blood and SF was assessed by MTT (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide, a yellow tetrazol) and CFSE dilution (Carboxyfluorescein succinimidyl ester) assays. The CD3+ cells from peripheral blood were activated with anti-CD3/CD28 cocktail.

**Results:** IL-9 levels were significantly elevated in SF and serum of PsA patient and RA patients as compared to SF and serum of OA patients (Figure 1). Further we demonstrated that activated synovial T cells of PsA and RA patients produced significantly more IL-9 than those of OA patients. In MTT and CFSE dilution assays, rIL-9 (MTT, OD: 0.642 ± 0.02) induced significant proliferation of CD3 + T cells of peripheral blood (Figure 2) and SF (Figure 3) derived from RA and PsA patients compared to media. Further, initial observations suggest that IL-9 receptor ab inhibits IL-9 induced proliferation of the activated SF derived T cells in inflammatory arthritis.

**Conclusion:** Our data showed that serum and SF of PsA and RA patients have higher concentration of IL-9 than matched OA controls. Moreover, rIL-9 induced marked proliferation of RA and PsA derived activated CD3+ T cells of SF from RA and PsA patients. Thus, IL-9 is likely to play a critical role in the inflammatory cascades of autoimmune arthritis. More importantly IL-9 provides a unique target to develop therapy for PsA patients where we do not have many options like in RA.

**Disclosure:** S. Raychaudhuri, None; A. Mitra, None; A. Datta Mitra, None; C. Abria, None; S. K. Raychaudhuri, None.

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**1603**

**Effect of Methotrexate on the Immunogenicity of TNF Inhibitors in Spondyloarthritis Patients.** Alejandro Villalba, Chaimada Plasencia-Rodriguez, Diana Peiteado, Laura Nuño, Gema Bonilla, Alejandro Balsa, Emilio Martin-Mola and Dora Pascual-Salcedo. 1Hospital La Paz - IdiPaz, Madrid, Spain, 2Hospital La Paz - IdiPaz, Madrid, Spain, 3Hospital La Paz, Madrid, Spain, 4Hospital Universitario La Paz, Madrid, Spain, 5La Paz University Hospital, Madrid, Spain.

**Background/Purpose:** The spondyloarthritides (SpA) patients treated under TNF inhibitors (TNFi) with detectable antidrug antibodies (ADA) often develop loss of efficacy. Concomitant therapy with methotrexate (MTX) appears to reduce the the immunogenicity of biological drugs. Our aim was to analyze if the use of combined therapy with MTX and TNFi can reduce the incidence of ADA and whether its effect is MTX dose dependent in SpA patients.

**Methods:** In this retrospective observational study, 162 SpA patients (including ankylosing spondylitis, Psoriatic Arthritis, SpA associated with inflammatory bowel disease and undifferentiated SpA) were included. The patients are treated with infliximab (Ifx) or adalimumab (Ada). The presence of ADA was measured at baseline and before each administration by ELISA to complete a follow up of 3 years. The patients were divided into two groups [MTX-15 (dose < = 15 mg/week) and MTX + 15 (> = 15 mg/week)] to study the influence of baseline MTX dose on immunogenicity. The statistical analysis was performed using SPSS 11.

**Results:** Of the eighty nine out of 162 (54.9%) patients were male. Eighty five out of 162 (52.5%) patients received Ifx and 77 out of 162 (47.5%) Ada. The mean duration of treatment was 13.38 ± 9.19 years to Ifx and 12.71 ± 10.46 years for Ada. Forty five patients received MTX weekly at baseline [25/85 (29.4%) in Ifx and 20/77 (26%) in Ada]. The mean dose of MTX was 15.9 ± 4.76 mg/week. Twenty nine out of 162 (17.9%) patients developed ADA, and ADA presence was significantly higher in SpA patients on Ifx therapy [21/85(24.7%) in Ifx vs 8/77 (10.4%) in Ada, p = 0.018]. The presence of ADA was less frequent in SpA patients taking MTX [3/45 (6.7%) with MTX vs 26/117 (22.2%) without MTX, p=0.022]. No statistically significant differences were observed in the influence of baseline MTX dose on the ADA appearance in Ifx: 2/18 (11.1%) in MTX-15 vs 1/9 (11.1%) in MTX-15, P=1.00; in Ada: 1/24 (4.1%) in MTX-15 vs 0/0 (0%) in MTX-15, P=1.00.

**Conclusion:** In this cohort of SpA patients treated with Ifx and Ada, the use of MTX has a preventive effect on the ADA development. However, the baseline MTX dose is not a determinant factor to get this effect. Further prospective studies are needed to confirm these data.

**Disclosure:** A. Villalba, None; C. Plasencia-Rodriguez, Pfizer Inc, 2; D. Peiteado, None; L. Nuño, None; G. Bonilla, None; A. Balsa, Pfizer Inc, 8; E. Martin-Mola, Pfizer Inc, 8; Abbie, 8; U.C.B., 8; Roche Pharmaceuticals, 8; D. Pascual-Salcedo, Pfizer Inc, 2.

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**1604**

**IFN-γ (Th1), IL-4 (Th2), and IL-15 (Th15) Are Elevated in Pre-Clinical SLE and Predict Transition to Classified Disease Prior to Appearance of Autoantibodies or Clinical Criteria.** Rufei Lu, Melissa E. Munroe, Joel M. Guthridge, Krista M. Bean, Dustin Fifer, John B. Harley, Judith A. James and Michael P. Keitt. University of Oklahoma Heart Health Center, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK, 3Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, 4Walter Reed National Military Medical Center, Bethesda, MD.

**Background/Purpose:** Systemic Lupus Erythematosus (SLE) is a clinically diverse autoimmune disease that often begins with a pre-disease period of autoantibody production and symptom accrual. Identifying reliable and biologically relevant predictors for future SLE onset could contribute to understanding disease pathogenesis, discovering disease-specific targetable pathways and facilitating prevention of this debilitating disorder.

**Methods:** To assess potential mechanistic pathways dysregulated early in lupus autoimmunity and to identify serum biomarkers that can accurately
forecast SLE development, we measured 13 autoantibodies and 34 circulating soluble mediators including cytokines, chemokines, and soluble receptors in serially collected serum samples from time points before and after meeting ACR classification in 55 individuals who subsequently developed SLE and 60 matched healthy controls.

Results: Elevated IL-4 (median, 13.9 vs 2.67 pg/mL), IL-5 (median, 51.14 vs 11.18 pg/mL), and IFN-γ levels (median, 9.12 vs 0.81 pg/mL) are present in subsequent SLE patient sera long before the disease classification (≥3.4 years) (compared to the healthy controls, p = 0.03). Path analysis shows that the elevation of IL-4 and IL-5 likely precede development of the majority of lupus specific autoantibodies. Random forest modeling during the preclinical period identified IFN-γ (Th1), IL-4 (Th2), and IL-5 (Th1) as reliable predictors of future SLE onset of SLE with only a 3.27% out of bag (OOB) prediction error. The best set of predictive biomarkers after disease classification includes IFN-γ, IL-4, IL-5 MCP-3, and TGF-β (0.78% OOB classification error).

Conclusion: These results suggest that dysfunctional Th1 related pathways likely potentiate autoantibody production during the pre-clinical period and abnormal elevations in Th2 cytokine levels exacerbate immune dysregulation. This longitudinal case-control retrospective study has not only provided a panel of SLE predictors to help develop prevention strategies, but strengthened the hypothesis that dysregulated Th1 and Th2 pathways are involved in early SLE pathogenesis.

Disclosure: R. Lu, None; M. E. Munroe, None; J. M. Guthridge, None; K. M. Bean, None; D. Fihs, None; J. B. Harley, None; J. A. James, None; M. P. Keith, None.

1605
Elevated Regulatory Mediators and Interferon Gamma Associated Responses, but Not Interferon Alpha, BLyS or IP-10, Accompany High-Titer Anti-Ro Autoantibodies in Asymptomatic Mothers of Children with Neonatal Lupus. Peter M. Izmirly1, Robert M. Clancy2, Melissa Munroe3, Sara Rasmussen3, Amit Saxena4, Jose U. Scher5, Alkaterini Thanou6, Stan Kamp7, Joan T. Merrill8, Jill P. Buyon9, and Judith James10. 1New York University School of Medicine, New York, NY. 2Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Mothers of children with neonatal lupus offer a unique opportunity to study the drivers and consequences of autoantibody production in the absence of ongoing maternal inflammation/damage or concurrent immunotherapeutics since many of these women are clinically asymptomatic with high titer anti-Ro antibodies identified solely by disease in the child. This study was initiated to assess the contribution of soluble mediators in the innate, adaptive and effector arms of the immune system to the production of anti-Ro responses independent of other autoantibodies or established systemic lupus erythematosus (SLE), Sjogren’s syndrome (SS) or rheumatoid arthritis (RA).

Methods: Soluble mediators (N = 32) were examined including cytokines, chemokines, and soluble receptors using validated multiplex bead-based (xMAP) or enzyme-linked immunosorbent assays in serum from 44 anti-Ro positive women within 5 years of a pregnancy complicated by either heart block (N = 36) or skin rash (N = 8). Autoantibodies were measured by Bio-Rad Bioplex A N A 2 2 0 0 and recombinant and native Ro/50/52 proteins by ELISA. Antibodies to dsDNA, Sm, and RNP were all negative. Based on questionnaire, phone interview, and review of medical records, 18 mothers were completely asymptomatic, 8 had either photosensitivity or Raynauds, and 18 had a combination of mild complaints, including arthralgias and cutaneous symptoms and did not fulfill SLE (ACR or SLICC) SS or RA criteria. Comparisons were made with sera obtained from 156 healthy controls and 94 SLE patients (30 = anti-Ro positive).

Results: Compared to healthy controls, asymptomatic/undifferentiated anti-Ro positive mothers had significant (p < 0.001) alterations in 21 of 32 tested mediators. These mothers had higher levels of IFN γ and associated molecules (MIG, MIP-1α) (p < 0.001) than ANA negative healthy controls at levels that were comparable with SLE patients. However, levels of IFNα and associated molecules important in SLE (BLyS, IP-10) were much lower in anti-Ro positive mothers than SLE patients, and similar to healthy controls (p < 0.001). These anti-Ro positive mothers also had higher levels of Th17 (IL-17A, IL-21, IL-6), Th1 (IL-2, TNFa), Th2 (IL-4, IL-6), shed TNF receptors (TNFR1, TNFR2, SCID40L) and regulatory responses (IL-1RA) compared to healthy controls (p < 0.001). In addition, these anti-Ro positive mothers had dramatically higher levels of IL-1RA, and TGFβ compared to SLE patients including those with anti-Ro (p < 0.0001). No significant differences in soluble mediator levels were noted between anti-Ro positive mothers who were completely asymptomatic and those with mild rheumatic symptoms.

Conclusion: High titer anti-Ro positive asymptomatic neonatal lupus mothers have dysregulated levels of soluble mediators across several inflammatory and immune pathways; however, BLyS and IP10, which appear temporally important in transition to clinical SLE, are not elevated. This cohort provides a unique opportunity to dissect critical pathways resulting in autoimmunity absent overt disease, thus guiding the development of targeted therapeutics for decreasing anti-Ro antibodies and risk of neonatal lupus, as well as providing insights into lupus pathogenesis.

Disclosure: P. M. Izmirly, None; R. M. Clancy, None; M. Munroe, None; S. Rasmussen, None; A. Saxena, None; J. U. Scher, None; A. Thanou, None; S. Kamp, None; J. T. Merrill, None; J. P. Buyon, None; J. A. James, None.

1606
Profiling a Broad Range of Autoantibodies in Healthy and Systemic Lupus Erythematosus Revealed Autoantibody Patterns Associated with Autoantibody Transition and Disease Activity. Quan-Zhen Li1, Lili2, Edward Wakeland3, Prithvi Raj4, Honglin Zhu5, Xiaoxia Su6, Mei-Yi An4 and Indu Raman1. 1University of Texas Southwestern Medical Center, Dallas, TX. 2University of Texas Southwestern Medical Center, Dallas, TX. 3Yiang Hospital of Hunan Medical Univ, Changsha, China.

Background/Purpose: Autoantibodies targeting to nuclear antigens are serological hallmarks of SLE, however, the processing of autoantibody production during the transition from normal to autoimmunity and the pathogenicity of the autoantibodies related with the disease activities are still unclear.

Methods: In this study, we first measured the serum anti-nuclear antibody (ANA) in 2,353 healthy controls (HC) and 500 SLE patients by ELISA. We then screened the levels of IgG and IgM autoantibodies (autoAbs) targeting a broad range of nuclear and non-nuclear antigens using proteomic microarrays bearing 95 autoantigens, in a cohort of 121 well defined SLE patients and the same number of matched HCs. For a subset of samples, we also measured the IgG subtype of A U A B using autoantigen arrays.

Results: An ANA testing showed a positivity of 92.5% in SLE, in which 78% with高水平 ANA titers (≥ 1:160) and 14.5% with low ANA titer to ANA (20-40 AU). A subset of HCs also exhibited positive ANA among which 9% with high titer (≥ 40 AU). Autoantibody array analysis revealed high prevalence of IgG autoAbs in SLE patients, the average number of positive IgG autoAbs in SLE were 28.5 and over 95% of SLE harbor more than 5 autoAbs, comparing with average of 3 IgG autoAbs with only 25% have more than 5 autoAbs in HCs (p < 0.05). A group of 19 IgG autoAbs targeting to various nuclear antigens (dsDNA, chromatin, nucleosome, histone, Sm, RNP, PCNA, CENP-B, etc.) were identified to be significantly enriched in SLE patients by clustering analysis. The prevalence of IgG autoantibodies against DNA antigens (dsDNA, ssDNA, chromatin, nucleosome, histone) were most significantly associated with disease activity (SLEDAI) and lupus nephritis (r = 0.56, p < 0.001) in SLE. Among the normal populations, the young females (age 20-45) with high ANA (> 20) tend to carry more IgG autoAbs than other groups, however, majority of the IgG autoAbs identified in HCs were those targeting to non-nuclear antigens, such as cell matrix (collagens, alpha-actinin, heparin sulfate, etc.) and phospholipid proteins (cardiolipin). The ANA negative NCs showed low positivity for both IgG and IgM autoAbs, however, the ANA positive NC exhibited higher IgM specificities targeting to 33 non-nuclear and nuclear antigens whereas in SLE the IgM autoAbs reaction were relatively lower. Interestingly we noticed a subgroup of SLE patients who have active disease (SLEDAI > 10) with lupus nephritis exhibited strong positivity for both IgG and IgM autoantibodies against DNA-associated antigens (dsDNA, ssDNA, chromatin, nucleosome, histone). IgA autoAbs were detected in 17 (out of 30) SLEs, preferably targeting to RNA-associated antigens (Ro, La, Sm/RNP and Ribo phosphoproteins).
Interestingly, 3 of the ANA - SLE who have no IgG autoAbs showed positive IgA autoantibodies.

Conclusion: Breach in immune tolerance in normal population was usually accompanied by production of autoantibodies against non-nuclear antigens and the transition from IgM to IgG autoAbs was an indication of increased pathogenicity of the autoantibodies. IgG autoantibodies against nuclear antigens especially DNA associated antigens were closely related with the disease activity and renal damage in SLE.

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1607

B Cell and Neutrophil-Related Transcripts Predict and Characterize a Lupus Flare. Mikhail Olferiev1, Kyriakos A. Kirou2 and Mary K. Crow2. 1HSS, New York, NY, 2Hospital for Special Surgery, New York, NY.

Background/Purpose: Lupus flare reflects an increase of disease activity that is associated with significant morbidity and accumulation of tissue damage. Prediction and prevention of lupus flare is an important goal of lupus research and, ultimately, clinical management. Our aim was to identify perturbations in molecular and cellular mechanisms that precede and coincide with lupus flare.

Methods: PBMC samples, clinical and laboratory data were collected longitudinally from 19 patients meeting ACR criteria for SLE. From 2 to 8 visits/patient (total 90 data points) were analyzed. All patients experienced at least one SLEDAI flare. Patients did not receive biologic agents during flare visits, but therapy was otherwise uncontrolled. Transcriptional profiles were obtained for each visit using Affymetrix HG U133Plus 2.0 GeneChips (by Novo Nordisk). SLENA-SLEDAI, BILAG and physician global assessments were compared to identify a point of maximum disease activity (flare). The flare point was set as day 0 for each patient over a 2 year interval. The remaining visits were arranged by time before or after flare. An mRNA profile for each transcript was established using the smoothing-spines mixed effect model (BerK M., 2012). All fitted models were classified by hierarchical clustering, and obtained clusters were studied using the gene-enrichment profiler database (Xavier lab; Benita Y. et al., 2010) and the DAVID v6.7 database to link functionally-related transcripts. The selected cell-specific or function-related genes were refitted and dynamic changes over one year intervals preceding and following flare were characterized.

Results: From 22190 transcripts, the models were successfully fit for 3189 transcripts. Clustering identified 9 major patterns over the observed time course. Most striking was the rise of 8 cell-related transcripts, including IRF4, SPIB, CD19, CD22, and CD79b, as early as 180 days before lupus flare. Subsequently, transcripts expressed in the myeloid lineage [mannose receptor (MRCl/CD206), CLEC10A/CD301, GPR137B] and those linked to lymphosomal function [N-acetylglactosaminidase (NAGA), acid phosphatase 2 (ACP2), scavenger receptor class B (SCARB2), and endolyn (CD164)] were decreased. B cell-related transcripts rapidly declined immediately prior to flare, while a distinct transcript cluster, including SIGLEC5/CD170, FPR1, ILIR2, SLC11A1, CR1, C1R, emerged and coincided with flare. B cell enrichment profiles identified those transcripts as highly expressed in blood neutrophils. The mean level of neutrophil-related transcripts correlated with SLEDAI and BILAG scores at time of flare (R = 0.49 and R = 0.44, respectively; p < 0.001 for both).

Conclusion: Despite the clinical heterogeneity that characterizes flare in individual patients, a common sequence of molecular events was observed preceding and during lupus flares. Strikingly, changes in the B cell population were observed as early as 6 months before flare. Similarly, perturbations in myeloid lineage transcripts occurred prior to flare. An increase in neutrophil-related transcripts is an indicator of lupus flare and correlates with disease activity at time of flare.

Disclosure: M. Olferiev, None; K. A. Kirou, None; M. K. Crow, None.

1608

Erythrocyte C4d and Antibodies to Anti-C1q Are Associated with Proteinuria in Lupus Nephritis. Jill P. Buyon1, 2, R. Ramsey-Goldman2, Richard Furie2, 3, Chaim Putterman4, Kenneth Kalunian5, John Conklin6, Tyler Dervieux6. 1New York University School of Medicine, New York, NY, 2Northwestern University Feinberg School of Medicine, Chicago, IL, 3North Shore-LIJ Health System, Great Neck, NY, 4Albert Einstein College of Medicine, Bronx, NY, 5UCSD School of Medicine, La Jolla, CA, 6Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: Biomarkers of renal response in patients with systemic lupus erythematosus (SLE) may provide clues to pathogenesis and drive translation to treatment. This study was initiated to evaluate the association between renal activity and the changes in erythrocyte bound complement C4d product (EC4d), anti-C1q, anti-dsDNA antibodies and low complement.

Methods: The study enrolled 289 SLE patients (mean age 40 years, 92% females) meeting the 1982 ACR classification criteria. All patients were evaluated at one time point as part of a cross-sectional study and a subset of 34 patients (mean age 34 years, 94% female) were followed monthly for an average of 9 months. Among patients enrolled in this study, the presence of proteinuria was defined by the renal domain on the SLENA-SLEDAI (increase > 0.5 g thus implies active and not chronic proteinuria). For the longitudinal study, proteinuria was defined using the random protein to creatinine ratio (expressed as g/g). Complement protein levels (C3 and C4) were determined using immunoturbidimetry, antibodies to anti-C1q and anti-dsDNA were determined by ELISA and EC4d was determined using flow cytometry (expressed as mean fluorescence intensity [MFI]). Statistical analyses consisted of non-parametric tests, and Chi-square tests. Longitudinal changes in urine protein as a function of the change in the biomarkers were evaluated using generalized linear mixed models effects using random intercept and fixed slopes.

Results: Among 289 SLE, 12% presented with proteinuria at the time of the clinical assessment. Higher EC4d levels were observed in the 34 SLE patients who presented with proteinuria compared to those who did not (median 21 MFI [interquartile range, IQR: 15–29] vs 12 MFI [IQR: 7–22], p = 0.01). A normal EC4d levels (> 20 MFI) were found in 62% of patients with proteinuria compared to 27% of patients without (p = 0.001). In contrast, the presence of the low complement component of the SLENA-SLEDAI domain was not significantly different between the groups (53% versus 36% p = 0.08). Neither Anti-C1q nor anti-dsDNA antibodies differentiated between the two groups at baseline. Among the 34 SLE patients followed monthly, a decrease in EC4d levels to lower than 20 MFI was associated with a concomitant decrease of 0.7 g/g urine protein to creatinine ratio (p = 0.0018) (Table). Similarly, the decrease in anti-C1q levels to lower than 80 units was accompanied by decreased proteinuria (p = 0.0015). Normalization of low complement or loss of anti-dsDNA was non-significantly associated with proteinuria (p > 0.19). In multi-variate analysis both EC4d and anti-C1q were independently associated with proteinuria (p < 0.01).

Conclusion: These data suggest that longitudinal changes in EC4d and anti-C1q levels track with changes in proteinuria. EC4d correlates more strongly with proteinuria than traditional measures of complement.

Table: Mixed model effect estimates

<table>
<thead>
<tr>
<th>Estimate (SEM)</th>
<th>g/g</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC4d≤20 MFI</td>
<td>-0.70 ± 0.22</td>
<td>0.0018</td>
</tr>
<tr>
<td>Anti-C1q≤80 units</td>
<td>-1.12 ± 0.35</td>
<td>0.0015</td>
</tr>
<tr>
<td>Normal Complement (C3/C4)</td>
<td>-0.33 ± 0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Loss of anti-dsDNA</td>
<td>+0.07 ± 0.29</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Disclosure: J. P. Buyon, Exagen, 2; R. Ramsey-Goldman, Exagen, 2; R. Furie, Exagen, 2; C. Putterman, Exagen, 2; Exagen, 5; K. Kalunian, Exagen, 2; Exagen, 5; J. Conklin, Exagen, 3; T. O'Malley, Exagen, 3; D. Barken, Exagen, 3; T. Dervieux, None.

1609

Dissection of the Type I Interferon Response in Systemic Lupus Erythematosus: Serum IFNα is Elevated in Lupus Nephritis and Correlates with IFN Score; IFNβ is Elevated in Mucocutaneous Disease. Julie Ducoux1, Fabien Colao4, Séverine Nieuwland1, Patrick Blanco4, Thierry Defrance3, Pierre Vandepapelere7, Géraldine Groud-Vogel2, Frédéric A. Houssiau1 and Bernard R. Lauwerys1. 1Université catholique de Louvain, Brussels, Belgium, 2NEOVACS SA, Paris, France, 3CHU Bordeaux, Bordeaux, France, 4INSERM, Lyon, France.

Background/Purpose: Type I interferons play a role in the pathogenesis of systemic lupus erythematosus (SLE), but their mechanisms of action are still not fully understood. In this study, we measured serum concentrations of IFNα, IFNβ and IFNω in a cross-sectional cohort of SLE patients followed at a single center, and investigated whether they correlate with clinical or biological indices of disease activity. The link between serum IFNα and IFNω...
signature in SLE whole blood cells was further evaluated in a prospective set of samples from patients included in the IFN-α kinoid study.

Methods: Sera from 178 patients with SLE were harvested during a visit at the Lupus Clinic, and stored at −80°C. Serum IFN-α, IFN-β and IFN-ω was measured by ELISA. BILAG scores, serum C3 and double-stranded DNA antibody titers were retrieved from the medical records. A clive mucocutaneous disease was defined based on the presence of a mucocutaneous BILAG A, B or C. Because persistent hematuria results in a renal BILAG B score, only renal BILAG A was considered for the definition of active renal disease.

Whole blood transcriptome (GeneChip HGU133Plus 2.0 chips) and serum IFN-α concentrations were determined at day 0, 112 and 168 in an additional cohort of 28 patients (SLEDAI between 4 and 10) included in the IFN-α kinoid trial. Statistical analyses (Mann-Whitney tests and Spearman correlations) were performed using Prism 5.0 software.

Results: 14 out of 178 patients had active renal disease, and 33 had active mucocutaneous disease. Out of them, 7 displayed both renal and mucocutaneous disease activity.

Serum IFN-α and IFN-β, but not IFN-ω, were significantly higher in the presence of a renal BILAG A. However, when patients with simultaneous renal and mucocutaneous involvement were discarded, only serum IFN-α remained significantly higher in the presence of active renal disease (median concentration 4.53 versus 0 pg/ml, p < 0.0001).

Similarly, serum IFN-β and IFN-ω, but not IFN-α, were significantly higher in the presence of a mucocutaneous BILAG A, B and C. However, when patients with simultaneous mucocutaneous and renal involvement were discarded, only serum IFN-β remained significantly higher in the presence of active mucocutaneous disease.

There was a low, albeit significant correlation between serum IFN-α and serum dsDNA titers or C3 concentrations. In the set of patients included in the IFN-α kinoid trial, the IFN signature score displayed a strong and significant correlation with serum IFN-α concentrations (Spearman r = 0.54, p < 0.0001).

Conclusion: Our data indicate for the first time that the type I interferon response in SLE is different according to the affected system. The IFN signature score observed in SLE whole blood cells is driven by IFN-α. Increased IFN-α in systemic and renal disease and IFN-β in mucocutaneous disease indicate that distinct pathogenic mechanisms are involved in these different manifestations of the disease.

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1610 New Autoantigens Associated with Lupus Nephritis. Sachiko Onishi1, Yuki Tanaka2, Tatsuhiko Miyazaki3, Jun Ishizaki2, Takuya Matsumoto1, Endy Adhan1, Hitoshi Yamash1, Koichi Suemori1, Katsufumi Okura1, Masaki Yasukawa1 and Hitoshi Hasegawa2. 1Ehime University Graduate School of Medicine, Toon, Japan, 2Ehime University, Toon, Japan, 3Gifu University Hospital, Gifu, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the production of a variety of autoantibodies and is considered a prototype immune complex disease. Anti-dsDNA antibodies contribute to the pathogenesis of lupus nephritis (LN). However, since anti-dsDNA antibodies are not sufficient for the diagnosis, prognosis or evaluation of disease activity, other autoantibodies associated with LN need to be identified. Using an N-terminal biotinylated protein library (BPL) we screened for autoantigens reacting with LN patient sera and then further characterize these autoantigens.

Methods: We screened for autoantigens using the AlphaScreen method with the sera from 3 SLE patients with different disease complications; thrombocytopenia, nephritis or serositis. A nitgens used for screening were created using the 2286 cDNA library from a wheat cell-free protein production system in the Ehime University Cell-Free Sciences and Technology Research Center. The proteins characteristic of nephritis were selected, and immunoprecipitation was performed using serum from patients with LN. Immunohistochemical staining of renal tissues was carried out with antibodies against proteins positive in the immunoprecipitation. The specificity of the identified autoantigens was analyzed by an enzyme-linked immunosorbent assay (ELISA) with serum from approximately 250 patients with various autoimmune diseases such as polymyositis/dermatomyositis, systemic sclerosis, and rheumatoid arthritis.

Results: We screened 66 proteins which reacted with LN patient sera at a high level. Of these, ten proteins showed strong reaction specifically to SLE sera with immunoprecipitation. Immune complex deposition of these ten proteins was confirmed by immunohistochemical staining of renal biopsy tissue and autopsy renal tissue of LN. Clear deposition of 2 proteins, ribosomal RNA processing 8 (RPRP8) and transition protein 1 (TPN1), was seen in some renal tissues. ELISA analysis showed that RPRP8 and TPN1 reacted to the sera from some SLE patients but have little or no reaction with those from other autoimmune diseases. In addition, anti-RPRP8 and anti-TNP1 antibodies were detected in 5 and 7 out of 11 LN patients, respectively.

Conclusion: The AlphaScreen method using BPL created by wheat cell-free protein synthesis was useful for activity screening. We have identified RPRP8 and TNP1 as new LN autoantigens. RPRP8 and TNP1 may play an important role in the pathogenesis of LN.

Disclosure: S. Onishi, None; Y. Tanaka, None; T. Miyazaki, None; J. Ishizaki, None; T. Matsumoto, None; E. Adnan, None; H. Yamash1, None; K. Suemori, None; T. Okura, None; M. Yasukawa, None; H. Hasegawa, None.

1611 Modular Transcriptional Neutrophil Signature As Predictors of Nephritis and of Its Severity in SLE Patients. Noemie Jourde-Chiche Sr.1, Stephanie Burutey1, Nathalie Bardin1, Elizabeth Wilhel1, Bertrand Gondouin1, Scott Prenelli2, Bertrand Dussol2, Gilles Kapanaki3, Jean-Robert Harlei4, Y von Berland1, Vignette Pascala5, Damien Chassubela6 and Laurent Chiche1.

1Aix-Marseille Université - APHM, Marseille, France, 2APHM, Marseille, France, 3Hopital de la Conception, Marseille, France, 4BRI, Seattle, WA, 5bri, seattle, WA, 6A.P. Maltese, Marseille, France.

Background/Purpose: Lupus nephritis (LN) is a serious complication of SLE. Reliable biomarkers to assess and/or predict renal involvement in SLE patients are needed. The aim of this study was to better assess the link between blood transcriptional signatures and LN.

Methods: Consecutive SLE patients (ACR criteria) were followed-up prospectively. Blood samples were split in: group 1, samples collected at the time of a biopsy-proven LN with active lesions, either proliferative (class III or IV) or not (class II or V); group 2, patients sampled at the time of an extra-renal flare; group 3, patients sampled at their first clinically quiescent visit (no flare or treatment modification in the past 60 days and SLEDAI ≤4).

Results: In addition to the IFN-related modules (M1.2, M3.4 and M5.12), modular repertoire analysis in SLE patients revealed a strong upregulation of M5.15, a module of 24 transcripts annotated “neutrophil”. There was no significant correlation between IFN modules and M5.15 activity. At the individual level, spearman correlations between modules and SLEDAI were significant for M5.12 (r = 0.25, p = 0.03), but not for M5.15 (r = 0.21, p = 0.09). M5.15, however, was the only module strongly associated with LN (Wilcoxon test p = 0.009), although there was a trend for M5.12 (p = 0.099). M5.15 was not associated with cutaneous, articular or hematological flares.

Results: In addition to the IFN-related modules (M1.2, M3.4 and M5.12), modular repertoire analysis in SLE patients revealed a strong upregulation of M5.15, a module of 24 transcripts annotated “neutrophil”. There was no significant correlation between IFN modules and M5.15 activity. At the individual level, spearman correlations between modules and SLEDAI were significant for M5.12 (r = 0.25, p = 0.03), but not for M5.15 (r = 0.21, p = 0.09). M5.15, however, was the only module strongly associated with LN (Wilcoxon test p = 0.009), although there was a trend for M5.12 (p = 0.099). M5.15 was not associated with cutaneous, articular or hematological flares.

Conclusion: Modular repertoire analysis demonstrates that neutrophil signature in SLE patients is correlated with the occurrence and severity of lupus nephritis and may help in the design of disease prognostic and/or activity biomarkers.

Disclosure: N. Jourde-Chiche Sr., None; S. Burutey, None; N. Bardin, None; E. Whalen, None; B. Gondouin, None; S. Prenelli, None; B. Dussol, None; G. Whalen, None; B. Gondouin, None; S. Prenelli, None; B. Dussol, None; G.
1612

Deficient Repair of DNA Double-Strand Breaks and Increased Apoptosis in Patients with Lupus Nephritis. Vassilis Soulouios1 and Petros P. Sifakis1. 1Institute of Biology, Medical Chemistry and Biotechnology, National Hellenic Research Foundation, Athens, Greece, Athens, Greece, 2First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece.

Background/Purpose: Accumulation of apoptotic cells leads to excessive autoantigen presentation and autoantibody formation in autoimmunity, whereas efficient repair of DNA double-strand breaks (DSBs) is essential to avoid apoptosis. Efficient repair of DNA double-strand breaks (DSBs) is essential to avoid apoptosis in peripheral blood mononuclear cells.

Methods: We found that the intrinsic DNA damage and the DNA repair capacity using γH2AX foci measurement by confocal microscopy and comet assay, as well as the induction of apoptosis following ex vivo treatment with genotoxic drugs (cispłat, melphalan) were evaluated in peripheral blood mononuclear cells from lupus nephritis patients (n = 6). Healthy individuals (n = 10), age- and gender-matched to patients were served as controls.

Results: We found that the intrinsic DNA damage was significantly higher in lupus patients than in healthy volunteers (p < 0.01). Particularly using γH2AX foci assay, patients showed γH2AX foci values of 15.8 ± 2.3 arbitrary units, while healthy controls only 3.0 ± 1.4 units. Also, using comet assay, the percentage of the γH2AX positive cells was 13.6 ± 1.8 in lupus patients and 4.6 ± 0.9 in healthy controls. Moreover, the genotoxic agent-induced apoptosis rates were significantly higher in lupus than in control cells (p < 0.01). That is, melphalan dose as low as 9.9 ± 4.9 μg/ml was sufficient to induce detectable levels of apoptosis in lupus patients, while healthy controls required doses of 32.3 ± 7.7 μg/ml. The corresponding values for cispłat treatment were 29.8 ± 8.3 μg/ml and 67.7 ± 5.5 μg/ml, respectively. Finally, following ex vivo treatment of mononuclear cells with a genotoxic agent, DSBs repair efficiency was inversely correlated with the apoptosis rates of these cells, being significantly lower in lupus than in control patients (p < 0.01). That is, melphalan-induced DNA damage was removed with τ1/2 = 9.1 ± 2.4 h in healthy controls and 53.3 ± 7.6 h in lupus patients, with the corresponding values for cispłat-induced damage being 4.2 ± 1.5 h and 25.4 ± 5.9 h, respectively. Results in lupus cells were not associated with individual disease activity level or treatment modalities at the time of study.

Conclusion: We demonstrated that circulating mononuclear cells from lupus nephritis patients are characterized by higher intrinsic DNA damage and profoundly reduced DSBs repair capacity. Since failure to repair DNA lesions such as DSBs leads to mutations, genomic instability and induction of apoptosis, these results suggest a novel mechanism by which deficient repair of DSBs may contribute to the induction of systemic autoimmunity.

Disclosure: V. Soulouios, None; P. P. Sifakis, None.

1613

Circulating microRNAs As Candidate Biomarkers of Diagnosis in Systemic Lupus Erythematosus. Ju Hyung Jung1, Jai Young Jeon2, Bong-Sik Kim1, Young-Chan Choe1,2. 1Ajou University School of Medicine, Suwon, South Korea, 2Ajou University School of Medical Science, Suwon, South Korea.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by polyclonal B-cell activation and elevated production of pathogenic autoantibodies. MicroRNAs (miRNAs) are short, noncoding RNAs that regulate gene expression on the posttranslational level, which can be measured in the circulation, and are emerging as novel biomarkers in various diseases. However, a systematic analysis of circulating miRNAs in SLE patients has been rarely addressed. We attempted to identify circulating miRNAs associated with the susceptibility to SLE in Korean populations, and to elucidate their significance in clinical phenotypes of SLE.

Methods: Blood samples were collected from Korean SLE patients (n = 40) at the rheumatology clinic, Ajou University Hospital. The microRNA PCR arrays identified miRNAs differentially expressed in SLE patients and NC. For the microRNA PCR arrays, we isolated total RNA from plasma samples of 10 SLE patients and 10 NC.

The RNAs were pooled in each sample group (n = 10) with an equal amount of RNAs. A miRNA expression profiling analysis was performed and compared between SLE patients and NC. To verify the microRNA PCR arrays results, we performed the quantitative real-time PCR in samples from SLE patients (n = 70) and NC (n = 40).

Results: Nine miRNAs were differentially expressed in plasma between SLE patients and NC by miRNA PCR array. The plasma expression level of hsa-miR-17-5p, hsa-miR-13a-3p, hsa-miR-21-5p, hsa-miR-29a-3p, hsa-miR-92a-3p, hsa-miR-223-5p, and hsa-miR-30e-5p were up-regulated in the SLE patients compared to the NC. The plasma expression level of hsa-miR-26b-5p and hsa-miR-150-5p were down-regulated in the NC patients compared to the SLE. hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p were significantly up-regulated in plasma from patients with SLE by quantitative real-time PCR. Especially, the hsa-miR-223-3p was significantly associated with oral ulcer (p < 0.001) and lupus anticoagulant (p = 0.031).

Conclusion: Our data suggest that plasma hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p may be novel important promising biomarkers in the diagnosis of SLE. These novel and promising markers warrant validation in larger prospective studies.

Disclosure: J. Jung, None; J. J. Jeon, None; B. S. Kim, None; H. A. Kim, None; C. H. Suh, None.

1614


Background/Purpose: Interferon (IFN) responsiveness is central to SLE pathogenesis and increased expression of IFN regulated genes (the ‘IFN signature’) is associated with active disease. Clinical utility of the IFN signature is unclear, and refinement to define further patient subgroups may improve disease management. Toll-like receptor (TLR) activation leads to IFN induction. To increase understanding of the role of IFNs in SLE pathobiology, and connectivity between IFN and TLR signaling, functional profiling of immune signaling downstream of IFNα, IFNγ and TLR modulators in peripheral blood mononuclear cells (PBMC) of SLE donors was performed and compared with signaling in healthy donors (HD).

Methods: Single Cell Network Profiling (SCNP) is a multiparametric flow cytometry based technology that enables simultaneous analysis of signaling networks in multiple immune cell subsets. PBMC from 60 SLE patients (meeting ACR criteria (2007), SELENA SLEDAI ≥6) and 59 HD were profiled by SCNP, interrogating IFN modulated JAK-STAT signaling and TLR modulated signaling relevant to SLE. CD4+/−/CD45RA+/−IFNα, IFNγ and TLR modulators in peripheral blood mononuclear cells (PBMC) of SLE donors was performed and compared with signaling in healthy donors (HD).

Results: IFNα and IFNγ modulated p-STAT1, -3 and -5 signaling was more heterogeneous in SLE vs HD. An SLE subgroup demonstrated low IFNα signaling, and high IFNγ signaling in lymphocytes and monocytes. Based on low IFNα and high IFNγ, we performed p-STAT1, -3 and -5 signaling. The SLE-IFN subgroup was defined as outside the 95 percentile (z-score >−1.96) of HD, comprising 20 of 60 SLE samples.

The SLE-IFN subgroup was 9.4-fold more likely to be positive for anti-dsDNA antibodies (Fisher’s exact test p-val<0.001), consistent with published data on the IFN signature and its link to disease activity, and
supporting the clinical relevance of this observation. Significant associations with ANA Ab positivity (p = 0.04), report of a new rash (p = 0.03) and age (p = 0.04) were also identified. No significant associations with other clinical or demographic parameters were identified.

Strikingly, the members of the SLE–IFN subgroup displayed higher TLR7/8 modulated signaling in B cells (Wilcoxon test p = 0.003–0.03, depending on the intracellular readout), and dendritic cells (p = 0.03), but not in monocytes. Moreover, TLR9 signaling was lower in B cells (p = 0.02), and TLR12 and TLR4 modulated signaling was lower in monocytes (p = 0.003–0.01).

Conclusion: These data identify potential connectivity in immune signaling across cell subsets and signaling pathways that underlie disease pathobiology and further define SLE donor subgroups. Refinement of the IFN signature in SLE through SCNP may facilitate the clinical applicability of the signature to better inform patient stratification for treatment options.


1615
MIR-127-3p As a Novel Regulator of Type I Interferon Signaling Pathway in SLE. Bo Qu, Xiao Han and Nan Shen. Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) & Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China, Shanghai, China.

Background/Purpose: Type I interferon (IFN) is a critical pathogenic factor in Systemic Lupus Erythematosus (SLE) and its associated nephritis, as elevated IFN inducible genes have been found in the kidney tissues and deficiency of IFN receptor protects lupus mouse model from developing nephritis. Reduced miR-146a is in part the reason for uncontrolled IFN response in peripheral blood cells of SLE. However, we are not clear if there are abnormally expressed kidney miRNAs that are responsible for the overactivated IFN response in the renal tissue of SLE. Our previous miRNA profiling data showed that miR-127-3p was one of the most reduced miRNAs in renal biopsies of lupus nephritis patients, raising the question whether miR-127-3p plays a role in IFN signaling. In this study, we explored the regulatory function of miR-127-3p in IFN signaling and its therapeutic effects on SLE.

Methods: miR-127-3p was quantified by RT-qPCR. Interferon-stimulated response element (ISRE)-luciferase reporter assay and western blotting were used to investigate the function of miR-127-3p. Genes affected by miR-127-3p were identified by microarray (chemical modified miRNA inhibitors) and were used to inhibit the function of miR-127-3p to validate its function. We administrated agomir (chemical modified miRNA mimic) into pristane induced lupus mouse model to investigate the in vivo function of miR-127-3p.

Results: To test its function in IFN signaling, we transfected miR-127-3p together with ISRE-luciferase reporter plasmids into HeLa cells and then stimulated the cells with IFN. We found that miR-127-3p inhibited IFN induced phosphorylation of STAT1 and STAT2, which are two major upstream molecules that activate ISRE mediated gene expression. We further revealed that most of the IFN inducible genes were inhibited by miR-127-3p in HeLa cells. In addition, in human primary renal mesangial cells, loss of function of miR-127-3p augmented IFN signaling including enhanced ISRE mediated reporter gene expression, stronger phosphorylation of STAT2 and elevated expression of IFN inducible genes. By ribonucleaseprotein Immuno-Precipitation assay, we identified JAK1, the upstream tyrosine kinase of STAT1 and STAT2, as the target of miR-127-3p. To elucidate the mechanism of reduced miR-127-3p, we screened several inflammatory factors and found that IFN inhibited miR-127-3p in renal cells. What’s more, we injected IFN into the mice and found that IFN inhibited the expression of miR-127-3p in their kidneys. To test its therapeutic effects, we examined a short-term phenomenon, pulmonary hemorrhage (PH), in pristane induced lupus mouse model and found that administrating miR-127-3p alleviated PH and inhibited IFN inducible gene Mx1 in peripheral blood cells.

Conclusion: Our study shows renal miR-127-3p can inhibit IFN signaling, indicating a new mechanism of overactivated IFN response in the kidney of SLE. Preliminary in vivo data suggest miR-127-3p has therapeutic potential in SLE. Ongoing mouse model studies about the effects of miR-127-3p on lupus nephritis will give us more insights into its therapeutic potential.

Disclosure: B. Qu, None; X. Han, None; N. Shen, None.

1616
Functional Profiling of PBMC from SLE Patients Versus Healthy Subjects Identifies Subgroups with Disease-Associated Dysfunctional Signaling. Rachel Hawtin1, Wouter Korver2, Erik Evesen3, Diane Longo4, Drew Hotson5, Nikil Wale5, Andy Conroy5, Alessandra Cesano6, Barbara Mittleman7, Shirley Tu8, Matt Westfall9, Tsung Lin10, Vik Rao11, Elena Peeva12, Stephen Benoit13, Martin Hodge14, James D. Clark15, Jean-Baptiste Telliez5 and Aaron R. Winkler12, 1Noddality Inc., South San Francisco, CA, 2Noddality Inc., South San Francisco, CA, 3Pfizer Biotherapeutics Research and Development, Cambridge, MA.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multi-system rheumatic disease with widely differing clinical manifestations and outcomes. Treatment is generally immunosuppressive, with no available biomarkers to inform therapeutic selection for a given patient or disease manifestation. Profiling the immune signaling pathways in PBMCs from patients with active SLE and healthy donors (HD) enables improved understanding of pathobiology and provides a basis for rational treatment decisions.

Methods: Single Cell Pathway Analysis (SCPA) is a multiparametric flow cytometry based technology that enables simultaneous quantitative analysis of signaling networks in multiple immune cell subsets. PBMC from 60 SLE patients meeting ACR (2007) criteria with SELENA-SLEDAI scores >6 were profiled by SCPN and compared to PBMC from 59 age, gender and race matched HD in the presence and absence of modulators of immune function (10 cytokines: 5 toll-like receptor (TLR) modulators and IL-1β), B cell-specific modulators CD40L and Anti-IgD, and PMA), across B, T (CD4, CD8) and dendritic (HLA-DR, CD11b, CD123) cells, and evaluated through induced p-STAT1, p-STAT6, p-STAT5, p-STAT3 in T cell subsets, IL-2 p-STAT1, -3, -5 in B cells, monocytes, IL-4 p-STAT5 in B cell subsets, IL-10 p-STAT1 in T cell subsets, and IL-6 p-STAT3 in T cell subsets. p-STAT1 by IFNγ, IL-10 and IL-27, and IL-6 p-STAT3 was increased in SLE monocytes. TLR- p-ERK, but not NFκB signaling was increased in monocytes. SLE mDCs showed elevated TLR7/8 induced IκB degradation. Unmodulated levels of intracellular readouts and PMA-induced signaling were similar between SLE and HD, suggesting that 1. Signaling differences are not the result of elevated unmodulated levels of signaling and 2. Overall signaling capacity is not compromised in SLE.

SLE donor subgroups: Distinct signaling profiles were identified based upon multivariate analysis of signaling within the SLE population. Not only was signaling quantitatively more broadly distributed in SLE vs HD, distinct subgroups were also observed (Table 1). Associations of dysfunctional signaling with donor demographics, including belimumab treatment will be presented.

Table 1. Subgroups of SLE patients based on modulated signaling outside the range for HD.

<table>
<thead>
<tr>
<th>Modulator</th>
<th>Intracellular Readout</th>
<th>Subgroup identified with higher/lower signaling compared to HD</th>
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<tbody>
<tr>
<td>IFNα</td>
<td>p-STAT1, -3, -5</td>
<td>B cells, monocytes, T cell subsets</td>
</tr>
<tr>
<td>IFNγ</td>
<td>p-STAT1, -3, -5</td>
<td>B cells, monocytes, T cell subsets</td>
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<tr>
<td>IL-4</td>
<td>p-STAT5</td>
<td>B cell subsets</td>
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<tr>
<td>IL-6</td>
<td>p-STAT5</td>
<td>T cell subsets</td>
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<tr>
<td>IL-10</td>
<td>p-STAT1</td>
<td>M monocytes</td>
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<td>IL-10</td>
<td>p-STAT5</td>
<td>M monocytes</td>
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<tr>
<td>CD20L</td>
<td>p-STAT3, p-ATK, p-ERK</td>
<td>B cells, monocytes, T cell subsets</td>
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<td>IL-10</td>
<td>p-STAT5</td>
<td>M monocytes</td>
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<tr>
<td>IL-4</td>
<td>p-STAT5</td>
<td>B cell subsets</td>
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<td>CD20L</td>
<td>p-STAT3, p-ATK, p-ERK</td>
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</table>
Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with the development of auto-antibodies particularly against nuclear antigens. Previous studies have revealed the possible role of type I interferon, IFN-α, in disease pathogenesis. Notably the formation of immune complexes (auto-antibodies with auto-antigens) can influence the production of IFN-α via Fc receptor signaling. Hereditary homozygous deficiency in the complement protein, C1q, has shown a high penetrance of 88-93% in afflicted individuals resulting in disease development. Remarkably it was shown in recent years that C1q has the capacity to suppress immune complex mediated IFN-α production. Considering that in vivo C1q functions as the sensory adaptor in the C1 complex, we compared C1 with C1q in modulating immune complex mediated IFN-α production from peripheral blood mononuclear cells (PBMCs).

Methods: Serum samples were obtained from 15 SLE patients and assayed for the presence of auto-antibodies (anti-nucleosome) via ELISA. The monocyctic U937 cell line was UV-irradiated and the apoptotic supernatant was harvested after 24 hours. The apoptotic supernatant was incubated with SLE sera to form immune complexes. The immune complexes were pre-treated with C1 complex or, as controls, C1q or PBS. Human PBMCs, isolated from healthy donors by Ficol-hyphae density centrifugation were treated with the immune complexes for 24 hours and IFN-α production was measured by ELISA.

Results: After screening 15 SLE patients for anti-nucleosome autoantibodies, 4 patients with disease activity (SLEDAI-2K ≥ 4) and high titer of anti-nucleosome (≥60 R units/ml, where clinical cutoff ≥20 R units/ml) were selected. SLE sera were incubated with UV-irradiated U937 apoptotic supernatant to form SLE immune complexes. Human PBMCs were stimulated with SLE immune complexes and assayed for IFN-α production. Healthy control serum elicited 86.7 ± 8.0 R units/ml IFN-α (media control was 85.7 ± 3.5 R units/ml), whereas SLE patient A elicited 674.7 ± 244.3 R units/ml IFN-α, SLE patient B elicited 243.8 ± 37.0 R units/ml IFN-α (p < 0.05), SLE patient C elicited 1115.8 ± 166.5 R units/ml IFN-α (p < 0.05), and SLE patient D elicited 142.6 ± 7.4 R units/ml IFN-α (p < 0.05). SLE patient C immune complexes were treated with C1, C1q or PBS and C1 and C1q showed a dose-dependent inhibition in IFN-α induction (853.2 ± 16.3, 701.1 ± 10.0, 508.4 ± 18.6 and 192.1 ± 16.4 R units/ml respectively) as compared to PBS-treated SLE immune complex (1362.3 ± 80.5 R units/ml). Furthermore, it was noted that, at equal molar concentration of C1 and C1q, C1-treated SLE immune complex suppressed immune complex-induced IFN-α production more effectively than C1q-treated immune complex.

Conclusion: C1 is the natural complex encompassing C1q and C1-treated SLE immune complexes exhibit suppressed IFN-α induction from human PBMCs. C1 appeared to be more potent than C1q in inhibiting immune complex-induced IFN-α production showing correlation among the complement classical pathway in providing enhanced protection against SLE pathogenesis as compared with C1q alone.

Disclosure: J. Y. Leong; None. J. G. Ye; None. T. Arkachaisri; None. J. L. U; None.

1619

Interferon Dysregulation in an Academic SLE Cohort Is Associated with Distinct Signaling Differences in Blood Neutrophils Versus PBMCs.

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Background/Purpose: Interferons (IFNs) have long been implicated in the pathogenesis of systemic lupus erythematosus (SLE). However, the specific consequences of the IFN activity have not been well characterized. In this study, the biology associated with an IFN activity signature was assessed in SLE blood neutrophil and PBMC fractions.

Methods: RNA was collected from isolated blood PBMC and neutrophil fractions from a cohort of 46 SLE patients and 23 healthy
donors. The patients fulfilled both ACR and SLICC criteria for SLE and represented a clinical population with a SLEDAI range of 0-12 (median 2), with 63% treated with prednisone, a cytotoxic immunosuppressant, or both. Patients were grouped by positive or negative IFN activity by assessing 21 IFN-inducible genes in whole blood, and gene expression changes were determined by RNA sequencing. Gene expression differences were analyzed further to determine the most likely upstream mechanistic explanations for the data in each comparison. The significance of these mechanisms is based on the evaluation of two metrics: supporting gene change enrichment using a hypergeometric distribution, and directional consistency as assessed by a binomial distribution. Differential mechanisms between positive and negative IFN groups were examined in the context of those with inferred activity significantly different in SLE compared to healthy donors.

**Results:** This analysis identified mechanisms inferred to be distinctively active in positive vs. negative IFN neutrophils. Table 1 indicates the gene expression support for representative mechanisms where enrichment and directional consistency are both significant (p<0.05 vs healthy). Additionally, IFN neutrophils exhibited distinctly active biology, including IFNG, mTOR and CCL5 consistent signaling. Additionally, mechanisms preferentially associated with IFN positive neutrophils including TLR signaling and IFNA, as well as many mechanisms in common and at similar levels with IFN negative neutrophils, were also active. TGFβ1 and MAPK1 activation were distinct in negative IFN neutrophils. Mechanisms activated in PBMCs were very similar between the IFN groups, with most activated to similar extents.

**Conclusion:** Our analysis supports that in a patient population with low SLEDAI scores, the IFN activity signature in blood correlates with biological differences that predominate in neutrophils. The work permits better understanding of the impact of IFN signaling in SLE, by demonstrating different effects in neutrophil vs PBMC fractions in an academic cohort.

<table>
<thead>
<tr>
<th>Table 1. Representative mechanism association with IFN activity in neutrophil and PBMC fractions</th>
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<tr>
<td><strong>Mechanism Direction and Gene-Expression Change</strong></td>
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<tr>
<td><strong>Evidence</strong></td>
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<td><strong>Mechanism</strong></td>
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<td><strong>in Neutrophils</strong></td>
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<td>IFNA Family</td>
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<td>mTOR</td>
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<td>SPl1 (Pu.1)</td>
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<td><strong>Mechanism</strong></td>
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<td>TGFβ3</td>
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<td>IFNA Family</td>
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</table>

**Gene expression changes are defined by a least a 1.5-fold change with an FDR p-value of < 0.05 (N= Neutrophils, Pos= PBMCs, Pos+positive, Neg=negative). Arrows indicate downstream gene expression support for mechanism increase (↑), decrease (↓), or no significant change (⇔) based on the statistics in methods, followed by number of supporting gene expression changes.
A Shift Towards Trans-Signalling Explanes Relatively Low CRP Despite an Active Interleukin-6 (IL-6)/IL-6-Receptor (IL-6R) System in SLE.

Background/Purpose: IL-6 has been found increased in SLE, while CRP, which is directly stimulated by IL-6, usually remains low. We therefore analyzed the IL-6/IL-6R system in SLE.

Methods: Peripheral blood mononuclear cells (PBMC) of 41 SLE patients and 71 healthy individuals (HC) were prepared. CRP and disease activity were measured by ELISA. For determining the percentages of CD126 and CD130 positive cells, PBMC were directly stained with PE-labelled or control antibodies. For in vitro experiments on the influence on receptor expression, healthy PBMC were incubated for 24 hours with or without the addition of IL-6, IL-10, tumor necrosis factor (TNF), interferon-α (IFNα), or combinations of these cytokines. Stained cells were immediately analyzed on a Becton Dickinson FACSCalibur fluorometer, gating for lymphocytes. As a semiquantitative measure of pStat3 contents mean fluorescence intensity (mFI) was used.

Results: SLE serum IL-6 levels (median [range]) (3.6 [0.69–69.3] pg/ml) were significantly (p<0.0001) higher than those of HC (0.3 [0.12–10.5] pg/ml) and correlated with disease activity (Spearman r=0.41, p=0.01). CRP was slightly increased in SLE (1.8 [1.0–40.8] pg/ml vs 0.8 [0.3–4.8] pg/ml for HC, p<0.0001). The percentage of CD126+ lymphocytes (mean±SD) was decreased in SLE (48±16 % vs. 61±11% for HC; p<0.0001). In line with reduced receptor expression, the IL-6-induced increase in pSTAT3 was significantly reduced in SLE (Amph 40–219, 19–37, 15%, p<0.001). In a mirror image to the membrane receptor, soluble IL-6 receptor (sIL-6R) serum levels were increased in SLE (421 (241–109.6) ng/ml compared to 38.6 (16.4–80.5) ng/ml in HC, p<0.05). Moreover, sIL-6R was negatively correlated with the percentage of CD126+ lymphocytes (Spearman r=−0.35, p=0.03). In vitro stimulation assays showed that the reduction in CD126+ cells could be mimicked by combinations of IL-6 with either IFNα (−39±13 %) or TNF (−16±6 %).

Conclusion: In SLE, combinations of IFNα or TNF with IL-6, all of which are increased in response to immune complexes, apparently lead to shedding of the cellular IL-6-receptor CD126 and thus increased sIL-6R. This shifts the IL-6 systems towards trans-signalling, directing the effects of the increased IL-6 away from conventional signalling, as responsible for increased CRP, and towards effects on cells carrying gp130 only.

Disclosures: M. Skwarek, None; B. Heschel, None; J. Fantana, None; M. Aringer, Roche Pharmaceuticals, S.

1622

Th1 and Th2 Cytokines Are Associated with Cerebral Atrophy in Systemic Lupus Erythematosus.

Background/Purpose: Cerebral atrophy has been described to occur in systemic lupus erythematosus (SLE) with variable frequency. The pathophysiology of cerebral atrophy in SLE remains unclear. The proposed mechanisms that are likely due to the assault of several autoimmune system changes include circulating immune complexes, corticosteroid use, autoantibodies, and cytokine release. The aim of this study was to determine the prevalence of cerebral atrophy and to elucidate the possible role of sera Th1 (IL-12, IFN-γ, TNF-α) and Th2 (IL-4, 5, 6 and 10) cytokines levels in SLE.

Methods: Consecutive SLE patients followed at the rheumatology unit of the State University of Campinas were enrolled in this study. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Beck Depression and Beck Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Magnetic resonance imaging (MRI) scans were performed in a 3T Phillips scanner using a standard T1 protocol. Sagittal T1 weighted images were used for semiautomated volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Sera samples were obtained from all participants in the absence of infections. Th1 (IL-12, IFN-γ, TNF-α) and Th2 (IL-4, 5, 6 and 10) cytokines sera levels were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: We included 146 SLE patients (138 women; mean age of 26.60±13.42 years; range 9–67) and 91 (86women; mean age of 27.82±15.23 years; range 5–80) age and sex matched healthy controls. The median and range of cerebral volume in SLE patients was 1064.16cm³ (range 831.1–1449.24) cm³, compared to healthy volunteers 1134.46 cm³ (range 880.01–1417.59) cm³ (p<0.001). Cerebral atrophy was identified in 20 (13.69%) SLE patients and in none of controls (p<0.001). Significantly increased Th1 (IL-12 (p<0.001), IFN-γ (p<0.001), TNF-α (p<0.001)) and Th2 (IL-4 (p=0.002), IL-5 (p<0.001), IL-6 (p<0.001) and IL-10 (p<0.001)) levels were observed in SLE patients compared to controls. We observed an association between cerebral atrophy and IL-12 (p=0.044), IFN-γ (p=0.037) and IL-10 (p=0.003). We did not observe association between cerebral volume and corticosteroid or any other clinical or laboratory manifestations.

Conclusion: IL-12, IFN-γ and IL-10 were associated with cerebral atrophy in SLE, suggesting immunological basis for global atrophy in SLE. Cytokines have been highlighted as potential contributory factors to cerebral atrophy in SLE.

Disclosure: M. Postal, None; A. T. Lapa, None; K. D. O. Pelicari, None; N. A. Sinicato, None; F. A. Peres, None; W. G. Ferreira, None; R. Marin, None; L. Costallat, None; F. Cendes, None; S. Appenzeller, None.

1623

Increased CD95 (Fas) Expression on Naïve B Cells is Associated with a Switch to Double Negative and Plasma Cells in the Peripheral Blood, and Correlates with Disease Activity in Systemic Lupus Erythematosus.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by a break of tolerance to autoantigens, and polyclonal activation of B cells. We performed multicolor flow cytometry analyses of B cell subsets in SLE patients and controls, in order to increase our understanding of the B cell activation steps characteristic of the disease.

Methods: PBMC from 16 SLE patients and 5 controls were analyzed using the following flow cytometry markers: CD5, IgD, CD27, CD20, CD19, CD38, CD95 and intracellular survivin, and their control isotypes. The data were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Magnetic resonance imaging (MRI) scans were performed in a 3T Phillips scanner using a standard T1 protocol. Sagittal T1 weighted images were used for semiautomated volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Sera samples were obtained from all participants in the absence of infections. Th1 (IL-12, IFN-γ, TNF-α) and Th2 (IL-4, 5, 6 and 10) cytokines sera levels were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: We included 146 SLE patients (138 women; mean age of 26.60±13.42 years; range 9–67) and 91 (86women; mean age of 27.82±15.23 years; range 5–80) age and sex matched healthy controls. The median and range of cerebral volume in SLE patients was 1064.16cm³ (range 831.1–1449.24) cm³, compared to healthy volunteers 1134.46 cm³ (range 880.01–1417.59) cm³ (p<0.001). Cerebral atrophy was identified in 20 (13.69%) SLE patients and in none of controls (p<0.001). Significantly increased Th1 (IL-12 (p<0.001), IFN-γ (p<0.001), TNF-α (p<0.001)) and Th2 (IL-4 (p=0.002), IL-5 (p<0.001), IL-6 (p<0.001) and IL-10 (p<0.001)) levels were observed in SLE patients compared to controls. We observed an association between cerebral atrophy and IL-12 (p=0.044), IFN-γ (p=0.037) and IL-10 (p=0.003). We did not observe association between cerebral volume and corticosteroid or any other clinical or laboratory manifestations.

Conclusion: IL-12, IFN-γ and IL-10 were associated with cerebral atrophy in SLE, suggesting immunological basis for global atrophy in SLE. Cytokines have been highlighted as potential contributory factors to cerebral atrophy in SLE.
cell proliferation and anti-apoptotic marker. Finally, we observed a significant negative correlation between both CD95 (r = -0.53, p = 0.036) or survivin (r = -0.50, p = 0.048) expression in naive B cells and serum C3.

**Conclusion:** CD95 expression on naive B cells is associated with a switch to double negative and plasma cells in the peripheral blood of SLE patients. The positive correlation between CD95 and survivin expression in SLE B cell subsets confirms that CD95 is a marker of B cell activation in SLE. A titration (CD95 and survivin expression) of naive B cells correlates with disease activity. Further studies on additional cross-sectional and longitudinal samples are ongoing.

**Disclosure:** J. Ducrøe, None; S. Nieuwland, None; F. A. Houssiau, None; B. R. Lauwerys, None.

## 1624

The Role of B Lymphocyte Stimulator in Monocyte Subpopulation Differentiation in SLE

Eoghan M. M. McCarthy¹, JoAnn N. Gabbanne², Siobhán Smith³, Michele Doran³, Gaye Cunnane³, S. Donnelly³, Donough Howard³, Paul G. O’Connel³, Caroline J. effeiries² and Gráinne M. Kearn³.

¹Beaumont Hospital, Dublin, Ireland, ²Royal College of Surgeons in Ireland, Dublin, Ireland, ³St. James’s Hospital and Trinity College Dublin, Dublin, Ireland, ⁴Mater Misericordiae University Hospital, Dublin 7, Ireland.

**Background/Purpose:** Monocytes are increasingly recognised to play a key role in the pathogenesis of SLE. Different subpopulations of monocytes contribute to the disease through dysregulated pro and anti-inflammatory responses. B Lymphocyte Stimulator (BLyS) has been shown to promote disease activity in SLE however its effect on monocyte subpopulation differentiation has not previously been reported. This study sought to investigate the effect of BLyS on monocyte subpopulations in healthy controls and SLE patients.

**Methods:** 25 Patients with matched controls were recruited. CD14+ monocyte subpopulations were analysed by Flow Cytometry using the following markers: M1 CD86+ HLA-DR+; M2a CD163+ CD206+; M2b CD86+ HLA-DR+ CD163+. qPCR was utilised to investigate gene expression for the subsets markers as follows: M1 CXCL10; M2a CCL17; M2b CCL1. Serum levels of cytokines were measured by ELISA. Differences between groups were examined using the Mann Whitney.

**Results:** Following stimulation with BLyS a significant increase in the pro-inflammatory M1 and anti-inflammatory M2a monocyte subpopulations was observed in healthy controls and SLE patients with a corresponding decrease in M2b levels. Interestingly SLE patients demonstrated a trend toward increased M1 levels in both the resting state and following BLyS stimulation in comparison to control patients. With this, both SLE patients and M1 monocytes exhibited significantly enhanced HLA-DR MFI expression in the resting state and following stimulation compared to controls. Furthermore a significant increase in CD86 MFI was observed following BLyS stimulation in patients, a result not replicated in controls. No differences were observed between patients and controls with regard to the M2b subpopulation.

In keeping with the literature SLE patients exhibited significantly reduced M2a levels. Surprisingly however, following BLyS stimulation an increased percentage of M2a monocytes was observed in patients compared to healthy controls (12.7% vs 8.3%) such that the fold change from baseline in M2a monocytes between patients and controls following BLyS stimulation was significantly different (3.6 vs 1.4, p = 0.0096).

In support of this qPCR confirmed a significant increase in the M2a-associated gene CCL1 in SLE patients following stimulation, a result not replicated in controls. No absolute differences were observed in expression for the M1-associated gene CXCL10 and M2b-associated gene(CCL1).

Strikingly BLyS stimulation significantly increased the M1 subpopulation in SLE patients with evidence of immunological activity(dsDNA +ve), an observation not replicated in dsDNA -ve patients.

Finally determination of M1 and M2 subset associated cytokines by ELISA confirmed significantly enhanced levels of both CXCL10(M1) and CCL17(M2) in the serum of SLE patients with a strong correlation seen between CXCL10 and both dsDNA levels and disease activity. CCL17 demonstrated modest correlation with disease activity.

**Conclusion:** Our study highlights a heterogenous response to BLyS stimulation in both healthy control and SLE patient monocytes. SLE patient monocytes appear to have enhanced pro and anti-inflammatory responses to BLyS a finding which warrants further investigation.

**Disclosure:** E. M. McCarthy, None; J. Ní Gabhann, None; S. Smith, None; M. Doran, None; G. Cunnane, None; S. Donnelly, None; D. Howard, None; P. G. O’Connell, None; C. J. effeiries, None; G. M. Kearn, None.

## 1625

Interferon Stimulates Transglutaminase Activity on Human Monocytes and Their Microparticles

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¹Medical College of Wisconsin, Milwaukee, WI, ²Medical College of Wisconsin, Wauwatosa, WI.

**Background/Purpose:** Microparticles (MPs) are circulating membrane-bound vesicles derived from blood and endothelial cells via a highly regulated process. They are immunomodulatory and have been implicated in autoimmune and Systemic Lupus Erythematosus (SLE). We recently showed that MPs derived from SLE patients contain higher protein and activity levels of type II transglutaminase (Tgase), Tgases are protein crosslinking enzymes whose activity increases antigenicity of certain proteins. This enzyme family has been implicated in SLE pathogenesis, perhaps by stimulating autoantibody formation against such proteins as C3, which are major Tgase substrates. The cell source of MPs responsible for increased Tgase activity on SLE MPs is unknown. We explored the hypothesis that interferon, a key cytokine in SLE, could promote Tgase activity on human monocytes and their MPs.

**Methods:** MPs were isolated from non-adherent human monocyte THP-1 cells by differential centrifugation of conditioned media in cultures treated with or without 1000 U/ml interferon gamma or 10-1000 U/ml interferon alpha for 24- 72 hours. Tgase activity was measured on the MP sample and THP-1 cell layer using a standard radiometric assay. Tgase protein levels for type II Tgase and factor XIIIa were measured in cells and on MPs with Western blotting. Similar experiments were carried out with human umbilical vein endothelial cells (HUVECs) and Jurkat cells (human T lymphocytes).

**Results:** An increase in type II Tgase protein as evidenced by Western blotting was noted on the cell layer of interferon gamma treated THP-1 cells. This corresponded to a slight, 1.56 fold increase in Tgase specific activity after interferon gamma exposure at 72 hours (p=0.18). Interestingly, a dramatic increase in Tgase activity was observed on MPs from interferon gamma treated cells with specific activity increasing 5.61 fold (p=0.02) over control MPs (figure 1). There were no differences in protein levels of factor XIIIa nor were there increases in Tgase activity with thrombin treatment, which activates latent Factor XIIIa. HUVECs and Jurkat cells did not respond similarly. Interferon alpha did not increase Tgase activity on any of the cell types tested.

**Conclusion:** Interferon gamma specifically increases Tgase activity and type II Tgase protein levels on human monocytes and has marked stimulatory effects on Tgase activity on monocyte-derived MPs. Increased Tgase activity may contribute to autoantibody formation through post-translational modification of proteins, such as C3, and their location on MPs may be important. Tgase inhibitors ameliorate SLE in animal models. Our data lend additional support for Tgase inhibitors as potential therapies for SLE.

**Disclosure:** K. Carroll, None; E. Milton-Fitzgerald, None; B. Bettendorf, None; C. Gohr, None; M. E. Cronin, None; A. K. Rosenthal, None.
Autoantibodies Against High Mobility Group Box 1 (HMGB1) in Patients with SLE. Fleur Schaper, Gerda Horst, Daan van Beijeren Bergen en Henegouwen, Johan Bijzet, Karina de Leeuw, Aija Steł, Pieter C Limburg, Peter Heeringa and Johanna Westra. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: High mobility group box 1 (HMGB1) is a damage-associated molecular pattern and can be divided in three separate domains: the A Box, B Box and the acidic tail. Box A by itself serves as a competitive antagonist for HMGB1 and inhibits HMGB1 activity. In an earlier study we showed that anti-HMGB1 antibodies are present in Systemic Lupus Erythematosus (SLE) patients and may play a role in the pathogenesis of the disease, but are not present in patients with systemic vasculitis. In this study we investigate the relation between anti-HMGB1 antibodies and disease activity, renal involvement, anti-dsDNA antibodies and medication use. We performed cross-sectional and longitudinal analyses.

Methods: Seventy-one SLE patients, 25 age and sex matched healthy controls (HC), and 15 disease control patients with incomplete lupus (fulfilled less than 4 of the ACR criteria), were included in this study. All 71 SLE patients were measured during quiescent or mild (SLEDAI ≤4) disease, and 28 were also measured during an exacerbation (SLEDAI ≥5). Furthermore, in a subgroup of patients (n=11) longitudinal levels of HMGB1 were determined over a period of three years. Serum levels of anti-HMGB1 IgG and IgM were measured using an in house ELISA. Epitope recognition was measured by ELISA against Box A and B IgG. Data are presented as arbitrary units (AU).

Results: Quiescent as well as active SLE patients showed a significant increase in anti-HMGB1 IgG compared to HC (median 236 vs 339 vs 46 AU respectively). Incomplete lupus patients also had an increased anti-HMGB1 level compared to HC (p=0.03), but lower compared to SLE patients (ns). Patients recognized both Box A and Box B epitopes of the molecule. Anti-HMGB1 IgM levels were not different in patients versus controls. We did find an association with disease activity, as there was a significant decrease in Box A recognition after exacerbation (p=0.028). No differences were found comparing active patients with renal involvement to patients without for anti-HMGB1 IgG, IgM, Box A and Box B. There was also no effect of immunosuppressive medication, including hydroxychloroquine, on anti-HMGB1 levels. Finally, longitudinal values of anti-HMGB1 IgG showed similar patterns compared to anti-dsDNA and might even increase shortly before an increase in anti-dsDNA levels are seen.

Conclusion: Anti-HMGB1 antibodies seem specific for SLE, as they were significantly increased compared to HC. Interestingly, also incomplete lupus patients showed already a minor increase of anti-HMGB1 antibodies. Antibodies directed to Box A decreased after an exacerbation, indicating a correlation with disease activity. Furthermore, longitudinally levels of anti-HMGB1 seemed to increase before an increase in anti-dsDNA levels occurred, which might indicate an interesting new biomarker in the follow-up of SLE patients.

Disclosure: F. Schaper, None; G. Horst, None; D. van Beijeren Bergen en Henegouwen, None; J. Bijzet, None; K. de Leeuw, None; A. Steł, None; P. C. Limburg, None; P. Heeringa, None; J. Westra, None.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Biomarker, Translational and Nephritis Studies
Monday, November 17, 2014, 8:30 AM - 4:00 PM

1626

1626

The Global Antiphospholipid Syndrome Score (GAPSS) Differentiates Between Transient Ischemic Attack and Stroke in Patients with Antiphospholipid Antibodies. Savino Sciaccia1, Giovanni Sanna2, Veronica Murr3, Dario Roccatellet, M unther A. Khamashtaa and Maria Laura Bertolaccini1. 1Rayne Institute, St. Thomas Hospital, London, United Kingdom, 2St. Thomas’ Hospital, London, United Kingdom, 3Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, 4University of Turin (ITALY), TURIN, Italy, 5Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom.

Background/Purpose: A rtial event are frequent in the antiphospholipid syndrome (APS) and stroke is a major clinical manifestation of syndrome. Recently, we conducted a study in a large cohort of Systemic Lupus Erythematosus (SLE) patients applying a risk score for APS clinical manifestations (Global APS Score or GAPSS), demonstrating that risk profile for APS can be successfully assessed. In this study, we aimed to evaluate the clinical usefulness of the GAPSS in differentiating between transient ischemic attack (TIA) and stroke in a cohort of patients tested positive for aPL who suffered cerebrovascular events.

Methods: We included 40 consecutive SLE patients attending the Louise Coote Lupus Unit at St Thomas Hospital, London, all with a history of cerebrovascular events. Demographic, clinical and laboratory characteristics were collected. aPL profile included anticardiolipin antibodies (aCL), lupus anticoagulant (LA), anti β2 glycoprotein I antibody (anti-β2GPI), and antibodies to phosphatidylserine-prothrombin complex (aPS/PT). Cardiovascular risk factors were assessed following NICE guidelines (1). The GAPPS system was calculated for each patient (2,3).

Results: Nineteen patients (47.5%) had stroke, 16 (40%) a transient ischemic attack (TIA), defined as neurologic symptoms or signs lasting less than 24 hours by a neurologist. Five patients (12.5%) experienced both. Thirty patients (75%) fulfilled the current APS classification criteria. Higher values of GAPPS were seen in patients who experienced stroke (alone or in association with TIA) when compared to those with TIA alone (10.13±3.3 [range 5–16] vs. 6.3±4.6 [range 3–13], p=0.003). This observation was confirmed when compared patients who had a history of stroke alone with patients with TIA alone (9.95±3.29 [range 5–16] vs. 6.3±4.6 [range 3–13], p=0.029). Patients who experienced both stroke and TIA showed the highest GAPSS but the difference was only statistically significant when compared to those with TIA alone (10.8±3.63 [range 7–16] vs. 6.3±4.6 [range 3–13], p=0.03).

Conclusion: The GAPSS is a valid tool for risk stratification for ischemic manifestation in the setting of cerebrovascular events. This tool may help identifying a more “at risk” population in whom a tailored prophylaxis therapy might be beneficial.


Disclosure: S. Sciaccia, None; G. Sanna, None; V. Murr, None; D. Roccatellet, None; M. A. Khamashta, None; M. L. Bertolaccini, None.

1628

Upregulation of Myxovirus Resistance Protein 1 in Patients with Neuropsychiatric Systemic Lupus Erythematosus. Yuka Shimizu, Shinsuke Yamamoto, Koji Asai, Takashi Kurita, Sanae Shimamura, Ikuma Nakagawa, Atsushi Noguchi, Haruki Shida, Toshiyuki Watanabe, Michihito Kono, Kenji Oku, Toshiyuki Bohgaki, Olga Amengual, Tetsuya Horita and Tatsuya A. Tsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Nervous system disease is one of the most common manifestations in patients with systemic lupus erythematosus (SLE) that significantly affects morbidity and mortality. Due to the complexity of clinical presentation of neuropsychiatric lupus (NPSLE), there are no specific markers for the diagnosis or for the evaluation of disease activity. A link between type I interferon (IFN) and SLE has been established by a series of studies. Recent studies have shown up-regulated IFN-inducible genes in the peripheral blood of lupus patients, which is correlated with disease activity2,3. We previously reported that gene expression levels of Mx1 (myxovirus resistance protein 1), one of the IFN-inducible genes, was increased in lupus peripheral T cells compared with healthy controls2. But it has not been revealed how the overexpression of Mx1 affects specific organs in lupus patients. Based on the report detecting Mx protein in areas of active scars in brain tissues from patients with multiple sclerosis (MS)2, we hypothesized that Mx1 is one of the factors related to the pathogenesis or the biomarker of NPSLE.

Methods: This study comprised 20 patients with NPSLE, 9 patients with SLE who were not considered NPSLE (non-NPSLE), and 20 patients with other non-inflammatory neuropsychiatric diseases as a disease control group. We evaluated the level of Mx1 in serum and cerebrospinal fluid (CSF) by enzyme-linked immuno-sorbent assay (ELISA). There was no significant
difference in disease activity (SLEDAI) between those with NPSLE or without.

**Results:** The levels of MX1 in serum and CSF were correlated in patients with SLE (R = 0.36). The levels of MX1 in CSF were higher than that of serum in both patients with NPSLE (p = 0.05) and non-NPSLE (p = 0.05). The levels of serum MX1 were significantly higher in patients with NPSLE than in those with non-NPSLE and other non-inflammatory neuropathic diseases (p < 0.01, p < 0.001, respectively). Figure. The levels of MX1 in CSF were significantly higher in patients with NPSLE than in those with other non-inflammatory neuropathic diseases (p < 0.001).

**Conclusion:** The upregulation of MX1 was significantly correlated with NPSLE, suggesting that serum MX1 is one of the candidates of biomarker for NPSLE.

**Reference:**
1. Feng X et al.: Arthritis Rheum. 2006; 54(9), 2
2. S. Yasuda et al.: EULAR, 2009, [THU0124], 3

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**Disclosure:** Y. Shimizu, None; S. Yasuda, None; T. Kurita, None; S. Shimamura, None; I. Nakagawa, None; A. Noguchi, None; H. Shida, None; T. Watanabe, None; M. Kono, None; K. Oku, None; T. Bohgaki, None; O. Amengual, None; T. Horita, None; T. Atsumi, None.

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**1629**

**Added Value of the Determination of Anti-Ribosomal and Anti-Ku Antibodies for Diagnosis of Systemic Lupus Erythematosus.** Johannes Schulte-Pelkum1, Diana Carmona-Fernandes2, Maria Jose Santos2, Roger Albesa1 and Michael Mahler1. 1INOVA Diagnostics, Inc., 3.

**Background/Purpose:** Anti-dsDNA antibodies (aAb) are known as important serological marker to aid in the diagnosis of systemic lupus erythematosus (SLE) and are part of the ACR classification criteria. In addition, anti-ribosomal P (Rib-P) AAb are a specific diagnostic marker for SLE. Lastly, anti-Ku AAb were also described to be present with a high prevalence in SLE patients. Here we describe the evaluation of new chemiluminescent immunoassays (CIA, QUANTA Flash®) for the detection of anti-Rib-P and anti-Ku AAB, and show that testing for these AAB might add value to the diagnosis of SLE.

**Methods:** Sera (125) from patients suffering from SLE and 280 control sera including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) ankylosing spondylitis (AS) and healthy controls (HC) were tested using QUANTA Flash Ribosomal P, QUANTA Flash dsDNA, and QUANTA Flash Ku (prototype).

**Results:** 58/125 of the SLE Patients and 13/280 controls tested positive for antibodies against dsDNA corresponding to a sensitivity of 46.6% (95% CI of 37.4–55.5%) and a specificity of 95.4% (95% CI of 92.2–97.5%). 37/125 of the SLE patients and 14/280 controls tested positive for anti-Rib-P AAB corresponding to a sensitivity of 29.6% (95% CI: 21.8–38.4%) and a specificity of 95.0% (95% CI: 91.8–97.2%). In addition, 20/125 of the SLE patients and 5/280 controls sera tested positive for anti-Ku AAB corresponding to a sensitivity of 16.0% (95% CI: 10.1–23.6%) and a specificity of 98.2% (95% CI: 95.9–99.4 %). The reactivities against Rib-P and Ku show minimal overlap. Therefore, when combining the two markers, the sensitivity and specificity for SLE were 41.6% (95% CI: 32.9–50.8%) and 93.2% (95% CI: 89.6–95.9%), respectively. Table 1 part A shows a summary.

In the group of dsDNA negative samples anti-Ku (OR = 8.1) and anti-Rib-P (OR = 2.3) results could be used to discriminate SLE patients from controls. 16/67 sera from SLE patients and 18/267 control sera had a positive test result for either anti-Rib-P or anti-Ku, thus discriminating SLE from controls with a specificity of 93.3% (95% CI 89.6–96.0%). Table 1 part B shows the individual and combined sensitivities, specificities and Odd ratios.

**Table 1** Sensitivities, specificities and Odd ratios summarized (Part A: complete cohort, Part B: dsDNA negative sub cohort).

<table>
<thead>
<tr>
<th>QUANTA Flash®</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>OR</th>
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<tbody>
<tr>
<td>dsDNA</td>
<td>46.6%</td>
<td>95.4%</td>
<td>92.2–97.5%</td>
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<tr>
<td>Rib-P</td>
<td>29.6%</td>
<td>95.0%</td>
<td>91.8–97.2%</td>
</tr>
<tr>
<td>Ku</td>
<td>16.0%</td>
<td>98.2%</td>
<td>95.9–99.4%</td>
</tr>
<tr>
<td>either Rib-P or Ku</td>
<td>41.6%</td>
<td>93.2%</td>
<td>89.6–95.9%</td>
</tr>
</tbody>
</table>

**Conclusion:** Our data confirm that anti-Rib-P and anti-Ku AAB represent potentially useful biomarkers to aid in the diagnosis of SLE. Interestingly, the reactivity against these two antigens shows only minimal overlap and thus, the combination of both markers showed high sensitivity and specificity for SLE. In addition, a significant portion of anti-dsDNA negative SLE patients were positive for anti-Rib-P or anti-Ku AAB. More studies will be needed to confirm this observation.

**Disclosure:** J. Schulte-Pelkum, Inova Diagnostics, Inc., 3; D. Carmona-Fernandes, None; M. J. Santos, None; R. Albesa, Inova Diagnostics, Inc., 3; M. Mahler, Inova Diagnostics, Inc., 3.

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**1630**


**Background/Purpose:** Nuclear magnetic resonance (NMR) spectra from samples analyzed for lipoproteins also contain a peak (termed GlycA) resulting from glycosylated proteins. GlycA is not only a novel marker of inflammation but was also associated with coronary heart disease in the MESA study. Little is known about GlycA in patients with systemic lupus erythematosus (SLE).

**Methods:** We compared concentrations of GlycA in 116 patients with SLE and 83 control subjects, frequency-matched for age, sex, and race. GlycA was detected by NMR, as a signal from methyl group protons on the carbohydrate portions of glycosylated proteins. SLE disease activity index (SLEDAI) and the SLE Collaborating Clinics damage index (SLICC) were calculated. A cute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were measured using standard methods by the hospital clinical laboratory and interleukin-6 (IL-6) using a Lincoplex ELISA assays.

**Results:** Patients with SLE had higher concentrations of GlycA [398 (350–445) μmol/L] than control subjects [338 (298–393) μmol/L, p < 0.001]. In patients with SLE, concentrations of GlycA were significantly associated with ESR, CRP, IL-6, systolic and diastolic blood pressure. (Table)

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**Table 1** Sensitivities, specificities and Odd ratios summarized (Part A: complete cohort, Part B: dsDNA negative sub cohort).

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**Disclosure:** J. Schulte-Pelkum, Inova Diagnostics, Inc., 3; D. Carmona-Fernandes, None; M. J. Santos, None; R. Albesa, Inova Diagnostics, Inc., 3; M. Mahler, Inova Diagnostics, Inc., 3.
Cell Bound Complement Activation Products and Their Relationship to Disease Activity and Quality of Life Measures in Systemic Lupus Erythematosus. Richard Furie 2, Jill Piel 2, R. Ramsey-Goldman 2, Chain Putterman 3, Kenneth Kalunian 4, Tyler O’Malley 5, John Conklin 5, Lysa Abitbol 5, Kenneth Kalunian 5, Tyler O’Malley 6, John Conklin 6, C. M. Stein 2, NIH 2, Great Neck, NY, New York University School of Medicine, New York, NY, Northwestern University Feinberg School of Medicine, Chicago, IL, Albert Einstein College of Medicine, Bronx, NY, UCSF School of Medicine, La Jolla, CA, Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: To assess the association between cell bound complement activation products (CBCaPS) and measures of disease activity and quality of life in systemic lupus erythematosus (SLE).

Methods: SLE patients (1997 ACR classification criteria) with active disease as defined by an SLE disease activity 2000 index (SLEDAI 2K) ≥6 points or the presence of a 2004 British Isles Lupus Assessment Group (BILAG) index A or B score were eligible for enrollment. However, only those screened patients with elevated CBCaPS (e.g. erythrocyte C4d levels [EC4d] above 15 units) were permitted entry into the study. Clinical activity measures, consisting of a modified SLEDAI 2K (mSLEDAI 2K excludes complement and anti-dsDNA components) and a BILAG index score, and quality of life assessments (short-form 36 [SF-36]) were performed monthly for one year. Patients were also evaluated monthly for EC4d and erythrocyte C3d (EC3d), serum complement (C3/C4), and anti-dsDNA antibody concentrations at each visit. EC4d and EC3d levels were determined by flow cytometry, and the mean net fluorescence intensity (MFI) was log transformed for the analysis. Statistical analysis consisted of generalized linear mixed models with random intercept and fixed slopes.

Results: 33 patients (mean age 35 years; 94% female) were evaluated monthly for a total of 303 study visits (median 10 visits per patient, range 3-13). Anti-dsDNA positivity was observed in 61% and low complement levels in 70% of the cohort. The average (SEM) baseline EC4d and EC3d levels were 54.0±21.6 and 15.6±10.0 Net MFI, respectively, and decreased to 28.8±4.4 and 4.2±0.8 net MFI at the last visit. Similarly, the average mSLEDAI 2K and composite BILAG score (A = 0, B = 0, C = 1 point) were 6.8±0.8 and 15.7±1.6 points at baseline, respectively, and decreased to 2.8±0.8 and 8.5±1.3 points at the last visit. Mean SF-36 scores ranged from 42 (general health) to 68 (role emotional) at baseline. Generalized linear mixed models showed that the number of monthly follow up visits was significantly associated with clinical improvement (decreased mSLEDAI 2K and BILAG scores; increased SF36 scores). As presented in the Table, decreases in EC3d levels and increases in C4 levels were associated with reductions in mSLEDAI 2K and BILAG index scores, whereas increases in C3 levels were associated with reductions in mSLEDAI 2K only. The analysis also revealed that decreasing EC4d and EC3d levels were associated with improving quality of life (p<0.05) in 6/8 domains of the SF-36. Changes in C4 were not significantly associated with changes in quality of life measures. Increased C3 was associated with lower quality of life in 2/8 domains of the SF-36 (physical function and role physical).

Conclusion: Our data reveal that EC4d and EC3d levels are associated with changes in disease activity and quality of life measures in SLE.

Table Mixed model estimates

<table>
<thead>
<tr>
<th>Ec4d Log Net MFI</th>
<th>Ec3d Log Net MFI</th>
<th>C3 mg/dl</th>
<th>C4 mg/dl</th>
<th>Anti-dsDNA U/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified SLEDAI 2K</td>
<td>0.7±0.5</td>
<td>1.0±0.4</td>
<td>-0.03±0.01</td>
<td>-0.16±0.05</td>
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<tr>
<td>BILAG Index Score</td>
<td>0.0±0.8</td>
<td>0.22±0.7</td>
<td>-0.01±0.01</td>
<td>0.31±0.01</td>
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<tr>
<td>SF3d Physical Function</td>
<td>-0.7±2.3</td>
<td>-1.7±2.1</td>
<td>-0.22±0.07</td>
<td>0.08±0.21</td>
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<tr>
<td>SF3d Role Physical</td>
<td>-0.5±2.2</td>
<td>-2.2±1.7</td>
<td>-0.15±0.07</td>
<td>-0.06±0.21</td>
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<tr>
<td>SF3d Bodily pain</td>
<td>-6.6±2.8</td>
<td>-6.6±2.1</td>
<td>-0.16±0.08</td>
<td>0.18±0.27</td>
</tr>
<tr>
<td>SF3d General Health</td>
<td>0.5±1.4</td>
<td>1.2±1.1</td>
<td>-0.01±0.04</td>
<td>0.24±0.14</td>
</tr>
<tr>
<td>SF3d Vitality</td>
<td>0.4±1.8</td>
<td>5.0±1.4</td>
<td>-0.03±0.06</td>
<td>0.22±0.17</td>
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<tr>
<td>SF3d Social Functioning</td>
<td>-0.6±2.4</td>
<td>-5.6±1.8</td>
<td>-0.06±0.07</td>
<td>0.22±0.23</td>
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<tr>
<td>SF3d Role emotional</td>
<td>2.7±2.4</td>
<td>0.7±1.9</td>
<td>-0.12±0.07</td>
<td>0.33±0.23</td>
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<tr>
<td>SF3d Mental health</td>
<td>24.1±1.7</td>
<td>3.1±1.3</td>
<td>0.01±0.05</td>
<td>0.31±0.16</td>
</tr>
</tbody>
</table>

Conclusion: The association between cell bound complement activation products and disease activity and quality of life measures in SLE is significant.
vascular and those with neuropsychiatric manifestations, however, it was non-significantly lower in patients with nephritis. This may suggest that insufficiency of LX4A may be responsible for some of the systemic manifestations of SLE, making the disease progressive and more serious. Accordingly, LX4A could be an inflammatory biomarker for systemic manifestations in SLE patients.

Disclosures: M. Sedky Abdou; None, D. Effat; None, L. Mansour; None, M. mohsen Abdul Salam; None, N. abd El Baky; None.

1633 Galectin-3-Binding Protein Is Associated with Disease Activity, but Not with Atherosclerosis in SLE Patients, S. Kay1, N. Heegaard2, Anna Voss3. 1Rheumatology, Odense, Denmark, 2Clinical Biochemistry and Pharmacology, Odense, Denmark, 3Reumatology, Odense, Denmark.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD), which may be due to an increased prevalence of atherosclerosis. Atherosclerosis is recognized as being associated with chronic inflammation. SLE is characterized by activation of the innate immune system and an increased expression of type I interferon (IFN) leading to chronic inflammation. Galectin-3 binding protein (G3BP) is a putative marker of IFN activation and has recently been shown to be increased in plasma of SLE patients. The objective of this study was to quantify plasma G3BP and determine the association of G3BP and atherosclerosis in SLE.

Methods: In a population-based predominantly Caucasian cohort we recruited 80 SLE patients. Atherosclerotic burden was assessed by cardiac CT scan for coronary calcium score (CAC) and carotid duplex for carotid intima-media thickness (IMT) and plaque using the ARIC study plaque definition. The presence of atherosclerosis was defined by a CAC > 0 and/or carotid plaque. A total of 38 patients were found to be negative for atherosclerosis and 42 patients were found to be positive. The concentration of galectin-3 binding protein (G3BP, 90k/Mac-2 BP) was determined in plasma samples by a commercially available sandwich-type enzyme-linked immunosorbent assay (ELISA). Samples were diluted 1:100 and concentrations were determined by extrapolation to standard curves obtained with known concentrations of G3BP.

Results: Mean plasma galectin-3-binding protein in the entire study population was 59.94 ng/ml. Plasma galectin-3-binding protein did not significantly differ between SLE patients with atherosclerosis and without atherosclerosis. G3BP levels were significantly correlated with disease activity as expressed by SLEDAI (P = 0.02).

Conclusion: The inflammatory marker galectin-3-binding protein is not significantly associated with atherosclerosis, but we confirm its association with disease activity in SLE patients.

Disclosures: S. Kay; None, N. Heegaard; None, A. Voss; None.

1634 Thrombophilia Associated with DFS70 Antibodies, Julien Marlet1, Jean-Luc Charuel1, Isabelle Martin-Toutain1, Pascale Gilliani-Dalbin2, Zahir Amoura3, Annick Ankr2, and Makoto Miyara3. 1Pitié Salpêtrière Hospital (AP-HP), Paris, France, 2Groupe Hospitalier Pitié Salpêtrière, service d’hématologie biologique, Paris, France.

Background/Purpose: The search for antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on Hep-2 cells is routinely performed as the first step for the biological diagnosis of systemic autoimmune diseases. Anti-DFS70 antibodies are a type of ANA defined by a nuclear dense fine speckled (DFS) IIF pattern, first described in 1994. It has also been reported that anti-DFS70 antibodies were the most frequent type of ANA found in healthy individuals. We therefore conducted a retrospective study on a large number of patients tested positive for anti-DFS70 antibodies.

Methods/Patients: The first group of patients, the anti-DFS70 group, included patients selected among those undergoing routine antinuclear antibodies testing (ANA) as at the Pitie-Salpetriere hospital (Paris, France). Patient inclusion started on the 1st of July 2011 and ended on the 31st of July 2013. The criterion of inclusion was an ANA testing positive with a DFS pattern at titer higher or equal to 1:80. Anti-DFS70 antibodies were confirmed with QUANTA Flash DFS70 immunoassay (Inova diagnostics). 441 patients were included.

The second group of patients, the thrombosis group, included patients consulting in hematology at the Pitié-Salpetrière hospital (Paris, France) who were screened for the first time for a factor V Leiden mutation, a test performed only in patients with a history of thrombosis. Patient inclusion started on the 1st of January 2013 and ended on the 31st of December 2013.

Clinical history of all patients was retrospectively analyzed by clinical chart review of medical records.

Results: The anti-DFS+ group included 441 patients. The prevalence of SARD among anti-DFS+ patients was low (18%, n=81) consistent with previous reports and the majority of them were followed up in internal medicine departments (82%). Among them, 51 patients had SLE (11.6%), 9 RA (2%), 15 primary Sjögren syndrome (3.4%) 3 inflammatory myositis (0.7%) and 2 with mixed connective tissue diseases. Among the other 17 patients, 17 had multiple sclerosis (3.9%) and 16 thyroiditis (3.6%). Moreover, we observed an unexpectedly high prevalence of thrombotic events in the anti-DFS+ group (12%, 54 patients).

We thus constituted a control thrombosis group with patients followed in a single tertiary center for thrombosis. All patients referred (n=67) for the first time to the center for thrombotic events were included. Interestingly, 10.4% of patients in the thrombosis group were positive for anti-DFS antibodies.

Prevalence of arterial thrombosis and venous thrombosis in the whole DFS+ population were respectively of 2.9%, 6.1% and prevalence of obstetric syndrome (fetal loss, HELLP or pre-eclampsia) in anti-DFS+ populations was 3.3%. One patient had both arterial and venous thrombosis, another had both arterial thrombosis and obstetric syndrome and four patients had both venous thrombosis and obstetric syndrome.

Conclusion: Presence of DFS70 antibodies on ANA testing may be associated with thrombophilia.

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1635 Association Between Carrying at Least One Apolipoprotein1 Variant Allele and Hypertension in Lupus Patients with Normal Renal Function. Ashira Blazer1, H. Michael Belmonte1, Robert Clancy2, Peter M. Izmirly3 and Jill P. Buyon4. 1NYU School of Medicine, New York, NY, 2NYU Medical Center, New York, NY, 3New York University School of Medicine, New York, NY.

Background/Purpose: The apolipoprotein1 (APOL1) gene encodes a 3 domain protein found both in serum and intracellularly in endothelial cells among other cell types. Variant APOL1 has undergone positive selection as the serum protein offers advantageous traits promoting lysis of Trypanosoma Brucei conferring resistance to African Trypanosomiasis. Populations with 30% of African Americans (AA) heterozygous for the gene and 12% homozygous. The intracellular form of APOL1 is a cytokine mediated apoptosis factor. Recently homozygous status for APOL1 risk allele (RA) has been associated with non-diabetic end stage renal disease by multiple causes including Lupus Nephritis (LN). While the mechanism of disease progression has not yet been described, we hypothesize that renal vascular vasculature may lead to arterial dysfunction and renal injury. This study was undertaken to establish a relationship between carrying at least one APOL1 RA and known clinical indicators of renal vascular dysfunction in a sample of 34 AA lupus patients with average eGFR above 60 (calculated by the CKD Epi formula).

Methods: APOL1 G1 and G2 risk alleles were genotyped by PCR/DNA sequencing. All patients satisfied ACR criteria for SLE. The patients were distributed into 2 groups: those carrying 2 wild type (WT) alleles (WT/WT) and those with at least 1 RA (G1/WT, G2/WT, G1/G1, G2/G2, G1/G2). Charts were reviewed to assess clinical parameters including demographics, medical comorbidities, medications, vital signs, and laboratory values.

Results: There were 18 patients in the WT group and 16 in the risk variant (RV) group. G1 (10pt; G2/WT = 10pt; G2/G2 = 3pt; G2/G1 = 2pt; G1/G2 = 2pt; G1/G1 = 2pt). Subjects were AA (100%) and predominantly female (WT: 100%; RA: 81%). Hypertension was defined as diagnosis of HTN on chart review, taking at least 1 antihypertensive drug, or having BP over 140 systolic and/or 90 diastolic at least at 2 clinic visits. The APOL1 RA group was strongly associated with HTN with 69% of the RV group meeting criteria for HTN compared to 22% of the WT group (odds ratio: 7.7; p-value: 0.009). Subgroup analysis of 14 patients with biopsy proven LN showed a higher effect size (odds ratio: 16; p-value: 0.04). There was no significant difference in age, disease duration, disease activity, eGFR, proteinuria, or history of LN between the groups. Next the relationship between inflammation and APOL1 regulation was assessed. As a surrogate of mononuclear cells residing at
Background/Purpose: Childhood-onset Systemic lupus erythematosus (cSLE) is an autoimmune disease characterized by periods of activity and remission. There is a wide spectrum of manifestations, such as hematologic and immunologic, which are commonly found. The cytokine profile assists in the diagnosis, determination of disease activity and may predict future damage caused by the disease. To determine the serum levels of TNF-α (IL-12 and TNF-α), Th1 (IL-6 and IL-10) and Th17 (IL-17) cytokines in cSLE and to evaluate their role in different disease phenotypes.

Methods: We included 53 consecutive cSLE patients [median age 21 years (range 13–28)] and 51 age and sex-matched healthy controls [median age 20 years (6–35)]. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory in all subjects. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI)] and current drug exposures. Th1 (IL-12 and TNF-α), Th2 (IL-6 and IL-10) and Th17 (IL-17) cytokines were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: Serum IL-6 (p = 0.002), IL-10 (p = 0.028), IL-17 (p = 0.009) and TNF-α (p = 0.04) levels were increased in cSLE patients when compared to healthy controls. TNF-α levels were significantly increased in patients with active disease (SLEDAI>5) (p = 0.004), IL-6 (p = 0.006) and TNF-α (p = 0.024) levels were significantly increased in patients with nephritis and IL-10 levels were increased in patients with elevated ESR (p = 0.013). We observed that IL-17 was associated with migraine (p = 0.040) and IL-6 with thrombocytopenia (p = 0.022) and low complement (p = 0.014). IL-12 (p = 0.008) and IL-17 (p = 0.005) were associated with anxiety. No association between cytokine levels and SDI scores or medication was observed.

Conclusion: Cytokines play a central role in cSLE and may be responsible for different disease phenotype. TNF-α is associated with SLEDAI and may be a biomarker of disease activity. Th1 and Th2 responses may play a role in lupus nephritis and Th1 and Th17 may play a role in neuropsychiatric symptoms in cSLE. Longitudinal studies are needed to determine if these cytokines may be used as biomarkers in cSLE.

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1639

Serum Anti-Müllerian Hormone Levels in SLE Patients, the Disease Severity and Cyclophosphamide Reduce the Ovarian Reserve. Gerardo Marino1, Laura Messuti2, Maria Rita Gigante3, Angela Barini4, Silvia Canestri3, Antonella Barini5, Barbara Tolusso6, Elisa Gremese1 and Gian-franco Feraccioli1. 1Division of Rheumatology, Institute of Rheumatology, Institute of Biochemistry, Catholic University of the Sacred Heart, Rome, Italy. 2Department of Laboratory Medicine, Institute of Biochemistry and Clinical Biochemistry, Catholic University of The Sacred Heart, Rome, Italy.

Background/Purpose: Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age, can lead to severe organ involvement and may require prolonged immunosuppressive therapy. Anti-Müllerian Hormone is produced by the granulosa ovary cells and serum levels of Anti-Müllerian Hormone are used as a measure of ovarian reserve, reflecting the number of primary follicles. The aim of the study was to compare serum levels of AMH in a cohort of patients with SLE and healthy controls to assess whether the presence of the disease, the treatments used and/or other clinical parameters may affect the ovarian reserve.

Methods: 75 women with SLE of childbearing age, aged between 18 and 42 years and with regular menses, and 30 healthy controls age-matched (p = 0.3) were evaluated. Anti-Müllerian Hormone levels were measured in peripheral blood samples (kit AMH Gen II ELISA, Beckman Coulter). Clinical and demographic characteristics, disease duration, pattern of organ involvement and previous and current therapies were collected at the time of sampling. 14 patients (18.7%) had been treated with cyclophosphamide (cumulative dose 8.3 ± 5.4 g), and of the remaining, 36 (46.0%) with other DMARDs (mainly methotrexate, mycophenolate mofetil, cyclosporine), and 25 (33.3%) with anti-malarials only.

Results: Patients with SLE had a mean age of 30.2 ± 6.3 years, a disease duration of 8.4 ± 5.1 and 25 patients (33.3%) had a severe organ involvement (mainly renal and neurological), 14 were treated with cyclophosphamide, 11 with other DMARDs. Serum levels of AMH were comparable between patients and controls (4.3 ± 3.5 vs 5.2 ± 3.2 ng/ml, respectively, p = 0.15). Considering patients on the basis of organ involvement, patients with major organ involvement had AMH levels (3.4 ± 2.7 ng/ml) significantly lower than control subjects (p = 0.04); no difference was found between patients with minor organ involvement (AMH 4.7 ± 3.4 ng/ml) and control subjects (p = 0.45). Considering the treatments used, patients with major organ involvement treated with cyclophosphamide showed serum AMH levels lower than controls (3.3 ± 4.0 ng/ml, p = 0.04) and tendentially lower than patients not treated with cyclophosphamide (3.3 ± 4.0 vs 4.5 ± 3.0, p = 0.09). There were no associations between the use of other DMARDs than cyclophosphamide and lower AMH levels in SLE patients compared to controls.

Conclusion: In the whole cohort of SLE patients, the ovarian reserve was overall comparable to that of healthy controls, whereas a reduction of the ovarian reserve was associated with the use of cyclophosphamide and the severity of the disease.

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Conclusion: Positive anti-Smith, low C3, positive anti-dsDNA, immunosuppressant usage, proteinuria, and elevated C-reactive protein were predictors of high BLyS and may be useful clinical parameters in identifying SLE patients with high disease activity at risk of flare.

Disclosure: D. Roth, GlaxoSmithKline, 3, GlaxoSmithKline, 1; A. Thompson, GlaxoSmithKline, 3, GlaxoSmithKline, 1; T. Tang, GlaxoSmithKline, 3, GlaxoSmithKline, 1; A. Hammer, GlaxoSmithKline, 3, GlaxoSmithKline, 1; C. T. Molin, GlaxoSmithKline, 3, GlaxoSmithKline, 1.

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A Prospective Study of Vitamin D Effects on T Cells Phenotype in Patients with Systemic Lupus Erythematosus Treated with Different Regimens of Supplementation for Two Years. Silvia Piantoni, Laura Andreoli, Alessandra Zanola, Francesca Dall’Ara, Mirko Scarsi and Angela Tincani. Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Background/Purpose: Vitamin D (VD) receptor is constitutively expressed on the membrane of multiple cells, including lymphocytes. Recent studies highlight that VD may have an action on T cells, inhibiting Th1 and Th17 response and enhancing Th2 and T regulatory (Treg) function. After repeated antigenic presentation, T cells undergo different functional and phenotypical modifications, leading to the differentiation into highly experienced memory T cells (CD45RA-CCR7-) and in the total amount of CD4/H11001 significant reduction of the CD8

mononuclear cells (PBMC) was evaluated by flow-cytometry.

As the best of our knowledge, little is known about the effect of VD on CD8 T cell population and in the differentiation of memory T cells.

The aim of this study is to verify the effect of VD on the circulating levels of T cells in a cohort of SLE patients (pts).

Methods: 34 SLE pts were followed-up for 24 months. In the first year, 16 pts (group 1) were supplemented with an intensive regimen of colecalciferol (300.000UI for the first month and 50.000UI/monthly as maintenance), whereas 18 (group 2) were supplemented with a standard regimen (25.000UI monthly).

During the second year, patients switched to the other regimen.

Phenotypic analysis of peripheral T lymphocyte and the quantification of the intracytoplasmatic production of IL-4 and IFN from peripheral blood mononuclear cells (PBMC) was evaluated by flow-cytometry. Wilcoxon-signed rank test and Mann-Whitney test were used for the comparisons.

Results: At baseline, no significant difference emerged in VD levels and among main T cell subtypes in SLE pts, with the exception of CD8+CD28- T cells which were expanded in group 1 (group 1 vs. 2, 74.5 vs. 26.6 % of CD4+ T cells; p<0.01). These pts had a greater serological disease activity (group 1 vs. 2, antdsDNA = 16.6 vs. 4.1 U/ml; p=0.02).

After 24 months, an increase of the absolute number of Treg cells (CD4+CD25highCD127low) was observed, independently from the regimen of supplementation. Over two years of treatment, a progressive increase in peripheral induced (CD45RA-CCR7-) T cells and in the total amount of CD4+CD45RA+CCR7- T cells was seen in both groups, whereas a gradual significant reduction of the CD8+CD28- T cells was observed only in group 2 (Table 1-2).

In the group 1, PBMCs of 8 pts were evaluated for cytokines production at baseline and after 12 months of treatment: a reduction of γ-IFN/IL-4 (from 12.1 to 3.2; p<0.02) and IL-18 (725.2 ± 215.4 vs 479.2 ± 125.2 pg/ml, 0.01). Caspase-1 expression was confirmed by Western blot. Purified monocytes from SLE patients displayed a robust inflammatory response after LPS stimulation where Caspase-1, NLRP3, IL-1β and IL-18 were highly expressed. The production of IL-18 was reduced by 3 fold when Caspase-1 inhibitor was added to the cultures. Plasma levels of IL-18 were significantly higher in SLE clinical patients with active disease (p<0.05). Neither Caspase1- or IL-1β expression was associated with SLE clinical features and disease activity.

Conclusion: Innate immune cells in SLE patients exhibited enhanced inflammasome activation, characterized by high expression of Caspase-1, NLRP3, IL-1β and IL-18, and in-vitro suppression of IL-18 production by Caspase-1 inhibitor. These findings provide novel insights into the pathogenesis of SLE and potential new avenues to explore the development of newer therapeutic strategies in the management of the disease.

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Background/Purpose: Systemic lupus erythematosus (SLE) presents with a wide-spectrum of clinical and immunologic abnormalities. On the other hand, exciting data is emerging about the role of the inflammasome in autoimmune disorders. The non-assembled components of the inflammasome in innate immune cells (monocytes) results in the rapid activation of Caspase-1, which cleaves pro-IL-1β and pro-IL-18 to generate active forms of these cytokines. Because the precise etiology and the aberrant immune dysfunction in SLE are not completely understood, we hypothesized that: "inflammasome activation occurs in monocytes as a key element on the initiation and amplification of the innate immune response in SLE pathogenesis". Therefore, the aims of the present study were 1) To determine whether inflammasome activation occurs in monocytes of SLE patients, and 2) To determine the relationship between inflammasome-related cytokines and disease activity in these patients.

Methods: After informed consent, 13 SLE patients and 13 age-matched healthy individuals attending the outpatient arthritis clinic were enrolled. Demographic, laboratory and clinical data were recorded. A score = 6 (SLEDAI) was defined as active disease. Purified monocytes were isolated and stimulated for 18 h with LPS (100ng/ml) in the presence or absence of Caspase-1 inhibitor. CD14 and Caspase-1 expression was analyzed by flow cytometry. Cell lysates and supernatants were collected for determination of Caspase-1 and NLRP3 protein by Western blot and cytokine levels by ELISA, respectively. Student’s t test and Mann-Whitney tests were used for statistical analysis. The study was approved by the LSU IRB committee.

Results: Ninety two percent (92%) of patients were females and 67% African-Americans. Mean age was 33.2 years and mean disease duration was 10 years. Six patients presented with active disease. Lupus nephritis was diagnosed in 3 patients. The percentage of CD14+/Caspase-1 was significantly higher (p<0.02) in SLE patients compared to normal controls (70.7 ± 11.1 vs 33.5 ± 13.0, respectively). These findings were directly correlated with higher plasma levels of IL-1β (0.4 ± 0.28 vs 0.15 ± 0.24 pg/ml, p<0.05) and IL-18 (725.2 ± 215.4 vs 479.2 ± 125.2 pg/ml, 0.01). Caspase-1 expression was confirmed by Western blot. Purified monocytes from SLE patients displayed a robust inflammatory response after LPS stimulation where Caspase-1, NLRP3, IL-1β and IL-18 were highly expressed. The production of IL-18 was reduced by 3 fold when Caspase-1 inhibitor was added to the cultures. Plasma levels of IL-18 were significantly higher in SLE clinical patients with active disease (p<0.05). Neither Caspase-1 or IL-1β expression was associated with SLE clinical features and disease activity.

Conclusion: Innate immune cells in SLE patients exhibited enhanced inflammasome activation, characterized by high expression of Caspase-1, NLRP3, IL-1β and IL-18, and in-vitro suppression of IL-18 production by Caspase-1 inhibitor. These findings provide novel insights into the pathogenesis of SLE and potential new avenues to explore the development of newer therapeutic strategies in the management of the disease.

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Mycohenolic Acid and Ribavirin Induces Cytoplasmic Autoimmunogenic Rods and Rings Structures in Vivo. Gerson D Keppeke Sr., 1, Eunice Nunes2, 2, Maria Lucia Ferraz3, 3, Sandro F. Perazzoli4, 4, Mônica Prado4, 4, Edward K. L. Chan2, 5, and Luis Eduardo C. Andrade4. 1Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil, 2Univesidade Federal de São Paulo, Sao Paulo, Brazil, 3Universidade Federal de São Paulo, Sao Paulo, Brazil, 4University of Florida, Gainesville, FL.

Background/Purpose: Autoantibodies to IMD PH2 occur in Hepatitis C patients receiving ribavirin (RBV) & interferon-α (IFN-α). Anti-IMD PH2 antibodies recognize "rods and rings" (RR) cytoplasmic structures in indirect immunofluorescence on HEP-2 cells (IF-HEP-2). In vitro inhibition of
IMPDH2 by RBV or mycophenolic acid (MPA) induces RR formation. We investigate the in vivo formation of RR structures in patients and mice treated with RBV or MPA.

Methods: Sequentially retrieved RBV/IFN-α-treated HCV (n = 108) and MPA-treated Systemic Lupus Erythematosus (SLE) patients (n = 78) were tested for anti-RR autoantibodies. Peripheral blood mononuclear cells (PBMC) from 18 MPA-treated SLE and 17 RBV/IFN-α-treated HCV patients were analyzed for RR+ PBMC by double-labelling IIF with human anti-RR serum and rabbit anti-IMPDH2 IgG. Crosssections from 3 untreated and 3 RBV-treated (0.4 mg/day; 3 months) BALB/c mice were screened for RR.

Results: Forty-one (38%) HCV and none of the SLE patients presented anti-RR autoantibody (p < 0.0001). In vivo RR formation in PBMC occurred in all RBV/IFN-α-treated HCV (28.2 ± 15.2% RR+ cells) and MPA-treated SLE (23.3 ± 15.1% RR+ cells) patients (p < 0.03). The frequency of RR+ PBMC was positively correlated with the duration of treatment (r = 0.53; p < 0.01). In SLE there was no correlation with duration of treatment (r = 0.01; p = 0.95), time interval from last dose ingested prior to sample collection (r = 0.04; p = 0.86) and daily dose (r = 0.30; p = 0.21). RBV-treated mice showed widespread RR structures, with variable proportion of RR+ cells in the several tissues: spleen (21.5%), stomach (57.8%), liver (70.7%), kidney (38.8%), heart (13.3%), brain (56.2%), muscle (23.7%), skin (37.1%). Untreated mice showed RR only in spleen (16.3%) and pancreas (14.9%).

Conclusion: Ribavirin and MPA generate in vivo formation of IMPDH2-rich RR structures in PBMC from HCV and SLE patients, respectively. In addition, RBV-treated mice showed widespread formation of RR with variable proportion of RR-positive cell across all the several tissues. These findings support further studies for the investigation of the consequences of widespread RR formation in patients receiving chronic treatment with RBV or MPA, as well as the understanding of the role of in vivo RR structures on the generation of anti-IMPDH2 autoantibodies.

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Tokyo Medical and Dental University (TMU), Tokyo, Japan; 2Chiugai Pharmaceutical co., ltd, Tokyo, Japan; 3Tohoku University, Sendai, Japan; 4Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization K yushu Medical Center, Fukuoka, Japan; 5St. Luke’s International Hospital, Tokyo, Japan; 6Genentech, Inc, South San Francisco, CA.

Background/Purpose: Elevated expression of interferon(IFN)-regulated genes in peripheral blood cells has been reported in systemic lupus erythematosus (SLE) patients and is known as the IFN signature. The IFN signature in SLE patients has been correlated with disease activity. The primary objective of the present study was to determine whether the IFN signature in SLE and DLE patients has differences in expression of the IFN-regulated genes such as anti-dsDNA and anti-RNP and with disease activity. The expression of the IFN signature among SLE patients has been reported and may indicate that the patient subgroups categorized with IFN signature expression levels have distinct biological differences.

Methods: Peripheral blood samples from healthy volunteers (HV)s and SLE patients were analyzed in Japanese and American/European populations. SLE patients with SELENA-SLEDAI (SS) score >6 and without active renal nephritis, CNS or hematological disease were chosen to represent the overall IFN signature of IFN-regulated genes, and the serological biomarkers described below in Japanese SLE patients. In SLE patients with DLE the PD score, a macroarray signature described previously, was significantly higher

Disclosure: H. Kohsaka, Chugai Pharmaceutical Co., Ltd, Teijin Pharma Limited, 5; Chugai Pharmaceutical, Bristol-Myers Squibb, UCB, Astellas, Nippon-Shinyaku, Aste- lium, Abbott, abbVie, Pfizer, Kowa pharmaceutical, Ono pharmaceutical, AShahi-Kasei, Japan Blood Products Organization, Mitsubishi Tanabe Pharma, Santen Pharmaceuticals, 9; Chugai Pharmaceutical, Ono pharmaceutical, abbVie, Mitsubishi Tanabe Pharma, Eisai, Takeda Pharma Limited, Astellas, Takeda Pharmaceutical, Pfizer, Daichi Sankyo, Santen Pharmaceuticals, Actelion, Nippon Kayaku, 2; K. Kotani, Chugai pharmaceutical, 3; T. Ishii, Chugai Pharmaceuticals, abbVie, Ono pharmaceutical, Mitsubishi Tanabe Pharma, Bristol-Myers Squibb, Eisai, UCB, Janssen Pharmaceutical, Astellas, Pfizer, 8; T. Miyamura, None; M. Okada, Chugai pharmaceutical, 8; T. Aranishi, Chugai pharmaceutical, 3; R. Maciaca, Genentech inc., 3; W. P. Kennedy, Genentech inc., 3; J. Ohata, Chugai pharmaceutical, 3.

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Molecular, Cellular and Histopathologic Assessment of Baseline Characteristics of Sixteen Subjects with Discoid Lupus Erythematosus Prior to Treatment with AMG 811 (anti-IFN-γ). Barbara Sullivan1, Robert Guzman2, Christopher B. Russell1, Greg Arnold2, Michael Boedigheimer3, Connie Ma4, James Chung5, Victoria P. Worth4 and David A. Martin4,

1Amgen, Thousand Oaks, CA, 2Amgen, Seattle, WA, 3Veteran Affairs Medical Center, Philadelphia, PA.

Background/Purpose: Discoid Lupus Erythematosus (DLE), the most common chronic cutaneous form seen in LE, includes inflammation leading to scaling, telangiectasias, atrophy, and/or dyspigmentation. Elevated levels of IFN-γ mRNA have been described in DLE skin biopsy specimens, and patients with DLE have an IFN transcriptional signature in both blood and skin. AMG 811 is a human monomolacular antibody that selectively targets and neutralizes human IFN-γ, and results from a randomized, placebo-controlled, crossover study in DLE subjects have been previously reported. The current analysis is a post-hoc analysis of the safety and PK profiles with available clinical benefit. Evidence of a pharmacodynamic effect in the blood (e.g. inhibition of IFN-γ) was apparent; however, heterogeneity in skin samples prevented definitive conclusions about the effects of AMG 811 in diseased skin.

Methods: This multi-center clinical study included 16 subjects with DLE enrolled in a randomized, single-dose crossover study. DLE subjects required a history of skin biopsy consistent with the diagnosis of DLE (Gilliam and Sontheimer classification); a diagnosis of SLE (ACR criteria) was not required, however 14 of 16 subjects had both DLE and SLE. Microscopic histopathology was performed on punch biopsies obtained from discoid lesional and non-lesional areas, and the abundance of CD3+ , CD4+, CD8+, CD68 + and K167 + cells were quantitated by laser scanning cytometry. Whole blood and skin RNA and serum proteins were analyzed by microarray and ELISA, respectively.

Results: The baseline CLASI activity and damage scores ranged from 10 to 34 and 6 to 35, respectively (maximum 70), reflecting heterogeneity in the anatomic location and severity of the DLE skin involvement in this cohort. A range of microscopic pathfindings were observed including acanthosis, keratinocyte apoptosis, inflamma- tory cell infiltrates and dermal mucinosis. As with psoriasis, there was a wide range of elevated numbers of CD3+, CD4+, CD8+ T cells, CD68 + macrophages and as well as K167 + proliferating cells in the lesional skin compared to non-lesional skin. The AMG 811 PD score, a macroarray signature described previously, was significantly higher.

Disclosure: H. Kohsaka, Chugai Pharmaceutical Co., Ltd, Teijin Pharma Limited, 5; Chugai Pharmaceutical, Bristol-Myers Squibb, UCB, Astellas, Nippon-Shinyaku, Aste- lium, Abbott, abbVie, Pfizer, Kowa pharmaceutical, Ono pharmaceutical, AShahi-Kasei, Japan Blood Products Organization, Mitsubishi Tanabe Pharma, Santen Pharmaceuticals, 9; Chugai Pharmaceutical, Ono pharmaceutical, abbVie, Mitsubishi Tanabe Pharma, Eisai, Takeda Pharma Limited, Astellas, Takeda Pharmaceutical, Pfizer, Daichi Sankyo, Santen Pharmaceuticals, Actelion, Nippon Kayaku, 2; K. Kotani, Chugai pharmaceutical, 3; T. Ishii, Chugai Pharmaceuticals, abbVie, Ono pharmaceutical, Mitsubishi Tanabe Pharma, Bristol-Myers Squibb, Eisai, UCB, Janssen Pharmaceutical, Astellas, Pfizer, 8; T. Miyamura, None; M. Okada, Chugai pharmaceutical, 8; T. Aranishi, Chugai pharmaceutical, 3; R. Maciaca, Genentech inc., 3; W. P. Kennedy, Genentech inc., 3; J. Ohata, Chugai pharmaceutical, 3.
in DLE lesional skin compared with non-lesional skin. Histopathology and RNA transcript analysis revealed substantial intra- and intersubject heterogeneity between skin biopsies from DLE subjects as compared to published results from subjects with psoriasis. Pathway analysis of the transcriptome suggested differential activation of both the interferon and IL-17 pathways.

**Conclusion:** Discord subjects in this small clinical study demonstrated a high level of clinical, histologic and molecular heterogeneity at baseline, creating challenges in the interpretation of response to treatment. Analysis of clinical and/or skin biomarkers may improve understanding of the heterogeneity within DLE, and may better enable subgroup selection for assessment of response to therapeutic treatments.

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**Relationship Between ApoM/S1P Levels and Atherosclerosis in Women with Systemic Lupus Erythematosus.** Sonali Narain1, Sylvain Galvan2, Christina Christoffersen, Peiyi Yang, M. aureen A. Mcmahon, Timothy Hla3 and Jane E. Salmon1. 

1Hospital for Special Surgery, New York, NY, 2Weill Cornell College of Medicine, New York, NY, 3University of Copenhagen, Copenhagen, Denmark.

**Purpose:** SLE patients are at risk for atherosclerotic cardiovascular disease (ASCVD). In some SLE patients, high density lipoprotein (HDL) has impaired vasoprotective effects, and this “proatherogenic” HDL (piHDL) is more prevalent in those with ASCVD. The protective effect of HDL in atherosclerosis is attributable, in part, to its ability to deliver to S1P receptors on endothelial cells. Apolipoprotein M (ApoM) is a component of some HDLs and serves as a chaperone of sphingosine 1-phosphate (S1P), a critical mediator of vascular homeostasis. S1P interacts with its receptors on endothelial cells to prevent vascular injury and inflammation. We hypothesized that the ApoM/S1P axis is deregulated in SLE.

**Methods:** We performed a cross-sectional study to measure ApoM and S1P levels in SLE patients. Plasma samples were obtained from 52 SLE patients who were part of a University of California Los Angeles cohort followed for ASCVD and met at least four of eleven 1982 ACR SLE Classification Criteria (Table 1). Patients on statins or with renal failure (Cr > 2.0) were excluded. Plasma lipid levels were measured using standard methods. Measurement of pro-inflammatory HDL was performed using a cell free LDL oxidation assay. ApoM was measured using a solid phase immunoassay by mass spectrometry. Statistics were performed using GraphPad Prism 6.0 and SPSS using appropriate non-parametric tests.

**Results:** Total plasma ApoM and S1P levels were significantly lower in the SLE cohort as compared to previously published levels in healthy controls (HC). Mean ApoM level was 0.75 ± 0.28 mmol/L in lupus patients versus 0.92 ± 0.32 mmol/L in HC (p = 0.001); and mean S1P level was 47.08 ± 17.08 ng/ml in lupus patients versus 221.7 ± 84.25 ng/ml in HC (p = 0.004). There was a positive correlation between levels of ApoM and S1P (r = 0.34, p = 0.013). ApoM levels negatively correlated with body mass index (BMI) (r = −0.54, p<0.0001) and SLE disease duration (r = −0.33, p<0.017). Level of S1P was negatively correlated with BMI (r = −0.45, p<0.0002) and hs-CRP (r = −0.46, p<0.008). There was no statistically significant association of ApoM or S1P levels with piHDL status, plaque status, intimal medial thickness (IMT), smoking, age, hypertension, lipid levels, ethnicity or lifetime prednisone use. In a multivariate regression combining these variables, only BMI and disease duration was significantly associated with ApoM levels.

**Conclusion:** Although total plasma levels of ApoM and S1P in circulation appeared to be significantly lower in SLE patients, they were neither associated with cardiovascular risk factors nor established plaque or piHDL. Studies comparing ApoM/S1P levels in SLE patients with age and sex matched healthy controls and ApoM/S1P levels in lipid sub-fractions of SLE patients are ongoing. We postulate that levels of ApoM and S1P may be influenced by inflammation status of SLE patients as this has been previously reported in patients with sepsis.

**Patient Demographics**

<table>
<thead>
<tr>
<th>Gender (F:M)</th>
<th>52:0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs ± SD)</td>
<td>44.98 ± 13.2</td>
</tr>
<tr>
<td>Carotid Plaque (%, n=15)</td>
<td>92 (28.9)</td>
</tr>
<tr>
<td>SLE Disease duration (yrs ± SD)</td>
<td>12.92 ± 9.1</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>186.2 ± 37.1</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>60.23 ± 19</td>
</tr>
<tr>
<td>BMI (baseline) kg/m² ± SD</td>
<td>26.98 ± 5.8</td>
</tr>
<tr>
<td>Smoking (%, n=12)</td>
<td>45 (24.5)</td>
</tr>
<tr>
<td>Diabetes mellitus (%, n=0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension (%, n=15)</td>
<td>22 (29.9)</td>
</tr>
</tbody>
</table>

**Disclosure:** S. Narain, None; S. Galvani, None; C. Christoffersen, None; P. Yang, None; M. A. McMahon, None; T. Hla, None; J. E. Salmon, None.

### 1648

**Urinary T Cells and Macrophages Strongly Reflect the Disease Activity, Kidney Function, and the Histopathologic Classification in Patients with Lupus Nephritis.** Yoko Wada1, M. moru Sakatsume2, M. asakai Nakano3 and Ichii Narita4. 1Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, 2Department of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan.

**Background/Purpose:** Lupus nephritis (LN) is one of the common manifestations of systemic lupus erythematosus (SLE), and the occurrence of LN is considered to be a very important factor influencing the course of the disease. Although kidney biopsy is the gold standard for defining the histopathologic class of LN, it is invasive and sometimes associated with a risk of bleeding; furthermore, repeated biopsies are not always applicable in clinical practice. For this reason, some form of novel non-invasive examination would be useful for detecting renal flare-up in LN patients. We have already reported that, in patients with glucocorticosteroids, T cells and macrophages appear in the urine when there are accompanying signs of active cellular infiltration such as cellular crescent formation and diffuse interstitial cellular infiltration, but not when active inflammatory lesions are absent. In the present study, we assessed the utility of urinary immune cell analysis in patients with SLE by examining the correlation between the numbers of urinary inflammatory cells and disease activity, kidney function, and histopathologic classification of lupus nephritis.

**Methods:** Sixty-four samples from 56 patients with SLE, who had been referred to Niigata University Hospital between 2004 and 2013, were included in this study. Flow-cytometric analysis of urinary inflammatory cells was performed. Urine samples from patients undergoing biopsy were also collected when patients were under treatment. Numbers of urinary T cells or macrophages were determined by multiplying the number of viable cells in the gated mononuclear cell region in each sample by the percentage of urinary T cells or macrophages. The relationship between urinary inflammatory cells and disease activity, kidney function, and histopathologic classification was assessed.

**Results:** The number of urinary CD3-positive cells was significantly elevated in patients with both proteinuria and abnormal urinary sedimentation, related to patients with proteinuria alone or normal urinary analysis. The number of CD3-positive cells was positively correlated with serum Cr, abnormal urinary sedimentation, and SLEDAI, and negatively correlated with serum CH50, while the number of urinary CD14-positive cells was positively correlated with serum Cr. Abnormal urinary sedimentation, 24-hour urinary protein excretion, and SLEDAI. Among the 15 patients who underwent kidney biopsy, 8 showing a significant increase in the total number of CD3-positive cells and CD14-positive cells (>120 ml urine) were diagnosed as ISN/RPS class III or IV, while the remaining 7 were diagnosed as ISN/RPS class V.

**Conclusion:** These results indicate the usefulness of urinary immune cell analysis for assessment of patients with SLE.

**Disclosure:** Y. Wada, None; M. Sakatsume, None; M. Nakano, None; I. Narita, None.
Background/Purpose: Deposit of different classes of immunoglobulins is the main feature of lupus nephritis; because of its high specificity, a patient with SLE is the main feature of lupus nephritis; because of its high specificity, a patient with SLE was graded from 0 to 4. Histological features were classified according to the 2004 ISN/RPS LN criteria. Immunohistochemical analyses using anti-human CD68, CD163 or CD204 antibodies were performed for identification of activated macrophages for tissue injury, recent studies have shown that alternatively activated (M2) macrophages are involved in resolution of inflammation in animal models of kidney disease. The current study aimed to evaluate renal accumulation of macrophage phenotypes and urine soluble markers and relate them to disease activity in human lupus nephritis. Naotake Tsuboi, Nobuhide Endo, Seichi Matsuo and Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Disclosures: N. Endo, None; S. Matsuo, None; S. Maruyama, None.

Association of Glomerular Macrophage Phenotypes and Urine Soluble CD163 with Disease Activity in Human Lupus Nephritis.

Background/Purpose: In addition to the effector roles of classically activated macrophages for tissue injury, recent studies have shown that alternatively activated (M2) macrophages are involved in resolution of inflammation in animal models of kidney disease. M2 macrophages are characterized by the production of anti-inflammatory cytokines such as interleukin-10 and transforming growth factor-beta, and they are involved in tissue repair and remodeling.

Methods: Plasma, urine and kidney biopsy samples were obtained from 74 patients with LN. Histological features were classified according to the ISN/RPS LN criteria. Immunohistochemical analyses using anti-human CD68, CD163 or CD204 antibodies were performed for identification of macrophage phenotypes. Concentrations of soluble CD163 (sCD163) and MCP-1 in plasma and urine were measured by ELISA.

Results: Immunohistological analysis in LN glomeruli revealed more than 70% of CD68+ macrophages were merged with CD163+ cells and more than 90% of CD163+ cells was merged with CD68+ cells. However, CD163+ cells appeared to be more than CD68+ cells in interstitium, indicating the different origin of glomerular and interstitial CD163+ macrophages. The cell counts of CD163+ and CD204+ cells were increased in association with severity of biopsy active index (BAI) score in LN. Intersitial CD68+, CD163+ or CD204+ macrophage infiltration correlated with eGFR. Urine sCD163 level showed stronger correlation with the number of glomerular CD163 positive cell counts (r = 0.501) and BAI score (r = 0.644) than plasma sCD163 levels with both of the above (r = 0.289 and r = 0.295, respectively). Correlation of urine sCD163 with BAI was comparable to that of urine MCP-1 levels (r = 0.592) and was much better than NGAL (r = 0.174) in LN.

Conclusion: These results suggest that CD163+ or CD204+ macrophage is the dominant phenotype in kidneys of LN patients, and urine sCD163 level has a potential significance for estimation of disease activity in human LN.

Disclosures: N. Tsuboi, None; N. Endo, None; S. Matsuo, None; S. Maruyama, None.
Biomarkers of Lupus Nephritis and Ethnic Disparities in Systemic Lupus Erythematosus. Adrian Kiani1, Laurence S, Magder2 and Michelle Petri3. 1Johns Hopkins University, Baltimore, MD, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Lupus nephritis eventually occurs in 50% of Caucasian SLE patients and 75% of African-Americans. African Americans have a more severe presentation of SLE and more often progress to end stage renal disease (ESRD). We have found a number of serum and urine biomarkers that have been associated with lupus nephritis. Therefore, we compared Caucasians and African-Americans with respect to levels of these biomarkers.

Methods: Urinary tumor necrosis factor-like weak inducer of apoptosis (TWEAK), vascular cell adhesion molecule 1 (VCAM-1), monocyte chemotactant protein 1 (MCP-1) and osteoprotegerin (OPG) were measured in a longitudinal cohort of SLE patients by ELISA (R&D). We analyzed the relationship between these potential urine biomarkers and Caucasian or African-American ethnicity.

Results: Urinary TWEAK levels were higher among Caucasians than African-Americans (p<0.03). Urinary VCAM-1, MCP-1 and OPG levels were higher among African-Americans than Caucasians, but the results were not statistically significant (Table 1).

Conclusion: Systemic lupus erythematosus and lupus nephritis disproportionately affect racial/ethnic minorities. Renal outcome has not improved in African-Americans or in the South in United States. Our results show that not all urine biomarkers are worse in African-Americans. Surprisingly, urinary TWEAK was higher in Caucasians. The others, however, were higher in African-Americans. The identification of ethnicity-specific biomarkers of renal activity would allow ethnicity-specific regimens. Further larger studies are needed to corroborate our findings.

Disclosure: A. Kiani, None; L. S. Magder, None; M. Petri, None.

Serum Cystatin C As a Biomarker for Clinical Practice in Patients with Lupus Nephritis. Hua Zhou, Di Lu, Haoring Tang and Lining Wang. The First Hospital of China Medical University, Shenyang, China.

Background/Purpose: Cystatin C has been developed as a novel biomarker of renal function in last decade and thought as more sensitive than serum creatinine (sCr). However, the clinical significance of serum cystatin C (sCysC) in lupus nephritis (LN) has been rarely reported. We aim to compare serum CysC with traditional indices of renal function and SLEDAI in LN patients.

Methods: 75 patients with renal biopsy approved LN based on the ISN/RAC 2003 classification criteria were from The First Hospital of China Medical University since 2009 to 2014. sCysC (mg/L), sCr (umol/L), blood urea nitrogen (BUN, mmol/L), glomerular filtration rate (GFR, ml/min) measured by MDRD and EPI equation, serum albumin (sAlb, mg/L) and urinalysis including 24hr total protein (uTP, g/day), albumin (uAlb, g/L), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were measured before and 6 months after glucosteroid and cyclophosphamide (CTX) treatment. The correlation between sCysC and each traditional indicator were analyzed by Person and the difference of these indices before and after-treatment was analyzed by student t-test.

Results: sCysC showed closer correlation with traditional indices of renal impairment and SLE activity (Table 1). sCysC also displayed a better statistical p value in the response to the treatment of glucosteroid and CTX than sCr and BUN (Table 2).

Conclusion: The significance of sCysC should be more emphasized in clinical practice in LN patients. Prospective study needs to be contacted on the effect of early treatment giving based on the increase of sCysC but before sCr rise in large cohort of patients with lupus nephritis.
Background/Purpose: To analyze the correlation between clinical and laboratory data and type of histological injury in a cohort of patients with lupus nephritis (LN).

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Patients diagnosed with LN classes 2–5 according to the WHO classification or the ISN/RPS classification (in use since 2004) were selected for analysis. In each case, the presence of arterial hypertension, renal insufficiency (RI), nephrotic syndrome (NS), hematuria, and cylindruria was assessed at the time of the biopsy; 24-h urine protein value was also recorded.

The specificity, sensitivity, PPV, NPV, LR +, LR −, and accuracy for each of the clinical and laboratory data in order to diagnose the different histological types of LN.

Results: The diagnoses were: a) Class II M easangial proliferative lupus nephritis, 45 cases (35%); b) Class III F ocal lupus nephritis, 16 (13%); c) Class IV D iffuse lupus nephritis 49 (39%); and d) Class V M embranous lupus nephritis, 16 (13%).

The mean levels of proteinuria were: a) class II: 1.62 g/24 h; b) class III: 1.53 g/24 h; c) class IV: 2.12 g/24 d) class V: 5.15 g/24 h. The only significant differences observed were between LN class V and the other histological types of LN. Five patients had proteinuria below 0.5 g/24 h in 3 (class II and 2 class IV) and 12 had proteinuria 0.5–1 g/24 h (3 class II, 3 III, 4 IV and 2 class V).

The discriminative values of other clinical and laboratory data for the diagnosis of the different types of LN are shown in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR +</th>
<th>LR −</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>4%</td>
<td>83%</td>
<td>13%</td>
<td>61%</td>
<td>0.26</td>
<td>1.16</td>
<td>0.547</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>4%</td>
<td>78%</td>
<td>10%</td>
<td>59%</td>
<td>0.20</td>
<td>1.23</td>
<td>0.515</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>38%</td>
<td>54%</td>
<td>18%</td>
<td>54%</td>
<td>0.39</td>
<td>1.51</td>
<td>0.412</td>
</tr>
<tr>
<td>Hematuria</td>
<td>69%</td>
<td>40%</td>
<td>39%</td>
<td>70%</td>
<td>1.14</td>
<td>0.79</td>
<td>0.396</td>
</tr>
<tr>
<td>Cylindruria</td>
<td>4%</td>
<td>81%</td>
<td>12%</td>
<td>61%</td>
<td>0.24</td>
<td>1.17</td>
<td>0.359</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6%</td>
<td>86%</td>
<td>6%</td>
<td>86%</td>
<td>0.46</td>
<td>1.09</td>
<td>0.761</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>6%</td>
<td>83%</td>
<td>5%</td>
<td>86%</td>
<td>0.36</td>
<td>1.13</td>
<td>0.730</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>6%</td>
<td>60%</td>
<td>2%</td>
<td>81%</td>
<td>0.16</td>
<td>1.56</td>
<td>0.531</td>
</tr>
<tr>
<td>Hematuria</td>
<td>56%</td>
<td>35%</td>
<td>11%</td>
<td>85%</td>
<td>0.87</td>
<td>1.23</td>
<td>0.380</td>
</tr>
<tr>
<td>Cylindruria</td>
<td>13%</td>
<td>87%</td>
<td>13%</td>
<td>87%</td>
<td>0.98</td>
<td>1.00</td>
<td>0.777</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>20%</td>
<td>94%</td>
<td>67%</td>
<td>65%</td>
<td>3.14</td>
<td>0.85</td>
<td>0.500</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>35%</td>
<td>96%</td>
<td>85%</td>
<td>70%</td>
<td>8.90</td>
<td>0.68</td>
<td>0.722</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>53%</td>
<td>75%</td>
<td>58%</td>
<td>72%</td>
<td>2.15</td>
<td>0.62</td>
<td>0.666</td>
</tr>
<tr>
<td>Hematuria</td>
<td>61%</td>
<td>35%</td>
<td>38%</td>
<td>59%</td>
<td>0.94</td>
<td>1.11</td>
<td>0.452</td>
</tr>
<tr>
<td>Cylindruria</td>
<td>22%</td>
<td>94%</td>
<td>69%</td>
<td>65%</td>
<td>3.46</td>
<td>0.83</td>
<td>0.658</td>
</tr>
</tbody>
</table>

Conclusion: In our cohort of patients with MPLN, the rate of non-responders at one year following treatment reached 17%, and was associated with a high rate of transformation to higher grade nephritides. Our data highlight that renal biopsy should be repeated early in patients who fail to respond to glucocorticoid treatment in order to identify those who may require intense immunosuppressive therapy.

Disclosures: A. Zacarias, None; J. Narvaez, None; G. Albert, None; M. Ricse, None; P. Estrada, None; M. Pestaina, None; C. Mora, None; J. Rodriguez Moreno, None; X. Fulladosa, None; M. Rubio Rivas, None; J. M. Nolla, None.
age 50. Our objective was to examine whether advanced age influences the type of histological lesions and prognosis of lupus nephritis.

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not treat pediatric populations. Patients were registered in a specific database. Patients with lupus nephritis confirmed by renal biopsy and follow-up time of at least two years (n = 79) were selected for analysis. Patients were divided into two groups according to age over 50 (n = 50) and under 50 (n = 49).

Results: In the 79 patients (64 women), mean age at the time of diagnosis of nephritis was 45 years (range 17-80) and mean time since onset of SLE was 15.3 months (range 0-456). In 81% (64/79) of cases, renal disease was present at the time of diagnosis or during the first year of follow-up. The mean SLEDAI score was 15 ± 5.6. The main results of the comparative study between age groups are shown in the following table:

<table>
<thead>
<tr>
<th>Age ≤ 50 years (N = 49)</th>
<th>Age &gt; 50 years (N = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>11/38</td>
<td>42/66</td>
</tr>
<tr>
<td>Evolution course of SLE in months (median)</td>
<td>2 (0-230)</td>
<td>1.5 (0-456)</td>
</tr>
<tr>
<td>Lupus nephritis Class II</td>
<td>7 (14%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Lupus nephritis Class III</td>
<td>10 (20%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Lupus nephritis Class IV-S</td>
<td>12 (24.5%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Lupus nephritis Class IV-G</td>
<td>13 (26.5%)</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Lupus nephritis Class V</td>
<td>7 (14%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Activity Index (mean ± SD)</td>
<td>7.8 ± 4.5</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>Chronicity Index (mean ± SD)</td>
<td>1.5 ± 1.5</td>
<td>1.3 ± 1.9</td>
</tr>
<tr>
<td>Responders/ non responders</td>
<td>40 (82%)/9 (18%)</td>
<td>24 (80%)/6 (20%)</td>
</tr>
<tr>
<td>Development of renal insufficiency</td>
<td>7 (14.3%)</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

No significant differences were observed between age groups in either the type of renal injury or prognosis. With regard to treatment, no differences were observed in the percentage of patients who were given hydroxychloroquine, corticosteroids or immunosuppressants, but the use of statins (p = 0.030) and ACE inhibitors (p = 0.033) was higher in the over 50 group.

Conclusion: Advanced age does not determine the type of histological lesion, nor does it appear to be a poorer prognostic factor in lupus nephritis.

Disclosure: E. Armengol None; J. Narvaez None; H. Borrell None; S. Heredia None; M. Ríce None; E. Benavent None; A. Roset None; C. Gomez Vaquero None; J. Torras None; F. Mitjavila None; J. M. Nolla None.

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Background/Purpose: Thrombotic microangiopathy (TMA) is characterized by microvascular occlusion, systemic or infrarenal platelet aggregation and mechanical injury to erythrocytes. It is a pathological endpoint that results from a disruption of the normal platelet-endothelial interface. TMA is one of the renal vascular lesions which can be found in systemic lupus erythematosus (SLE). The prevalence of renal TMA in SLE varies broadly between studies (8.1–24.3%), and there has been controversy regarding its prognostic significance. We aimed at identifying novel risk factors for renal TMA in SLE patients.

Methods: A retrospective, single-center study was performed. Renal biopsies from 243 SLE patients between 2008 and January 2014 were studied. We included patients with renal TMA (n = 30) and controls (n = 49) adjusted by glomerulonephritis class, glomerular filtration rate (GFR), activity and chronicity indexes, and follow-up time. The variables that were measured included: autoantibody profile; hypertension, disease activity, SLEDAI, C3 and C4 levels, leukocyte and lymphocyte count, treatment and GFR at the time of the biopsy; GFR, SLEDAI and treatment during follow-up. Differences between groups were analyzed by Student t test or Mann-Whitney U test. Association between variables was assessed by OR (95% CI). Multivariate analysis was performed by binary logistic regression model.

Results: Twenty-three patients with renal TMA and 21 controls were included. TMA prevalence was 9.8%. 90.9% of subjects were female; mean age was 26.04 years in the TMA group and 27.9 years in controls. Mean follow-up was 45.56 ± 14.39 months. At the time of the biopsy, GFR (ml/min/1.73m²) was 33.6 ± 8.33 in the TMA group and 37.91 ± 7.5 in controls; 56% of patients in the first group and 42.8% in the second required dialysis at that time. Two patients in the TMA group were diagnosed with thrombotic thrombocytopenic purpura (TTP); none of the others had clinical features suggestive of systemic TMA. Lymphopenia, platelet count, higher mean arterial pressure (MAP) and anti-Ro/SSA antibodies were associated with TMA. There was no association with APL syndrome or antibody positivity. There were no differences in SLEDAI score, GFR, end-stage renal disease (ESRD) or mortality between both groups throughout the follow-up period. At the end of follow-up, ESRD rates were 43.4% in the TMA group, and 42.8% in controls. After multivariate analysis, variables that remained significantly associated with renal TMA were: lymphopenia < 1000 cells/µL (OR 10.75, 95% CI 1.34–85.86, p = 0.025), anti-Ro/SSA antibodies (OR 9.007, 1.49–54.11 95% CI, p = 0.016), and MAP (OR 0.97, 95% CI 0.995–0.994, p = 0.009).

Conclusion: Lymphopenia and anti-Ro/SSA positivity were independent risk factors for renal TMA in SLE patients. This association could be related to their potential role in endothelial dysfunction and damage. Outcomes were worse for patients with both same GFR and biopsy characteristics, regardless of the presence of TMA.

Disclosure: A. Barrera-Vargas None; R. Rosado-Canto None; J. Meryao-Chalico None; J. Alcocer-Varela None; D. Gómez-Martin None.

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The Clinical Relevance of a Repeat Biopsy in Lupus Nephritis (LN) Flares. Milagros Ricse1, Javier Navaréz2, Gloria Albel3, Paula Estrada4, Sergi Heredia5, Andrea Zacarias6, Helena Borrell7, Eulalia Armengol8, Xavier Mulladas9, Joan Torras8, Olga Capdevila10, Francesca Mitjavila11 and Joan Miguel Nolla12. Hospital Universitario de Bellvitge, Barcelona, Spain, Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Renal biopsy is the gold standard for assessing renal activity and hence guiding treatment. Whether a repeat renal biopsy is helpful during flares of LN remains unclear. In the present study, we retrospectively reviewed LN patients who had more than one renal biopsy, in the hope of finding the clinical advantage of repeat biopsy.

Methods: The sample comprised 243 patients with systemic lupus erythematosus (SLE) treated between 1980 and 2013 at a tertiary university hospital that does not treat pediatric populations. The patients were registered in a specific database. From a total of 126 patients with LN, we selected those who underwent 2 renal biopsies for analysis. Renal biopsies were evaluated according to the WHO classification or the ISN/RPS classification (in use since 2004).

Results: We identified 28 SLE patients with LN for whom it was possible to compare reference and repeat biopsies. In total, 56 renal biopsies were considered. Overall, in 14 patients (50%), paired biopsies showed changes in the pathological pattern. Table 1 shows the pathological classification on repeat biopsy:

<table>
<thead>
<tr>
<th>Reference biopsy</th>
<th>Repeat biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II Mesangial LN</td>
<td>1 switched to Class I</td>
</tr>
<tr>
<td>N = 9</td>
<td>2 no shift in pathological class</td>
</tr>
<tr>
<td>Class III Focal LN</td>
<td>6 switched to higher grade nephritis (Class IV: 3 cases: Class V: 3 cases)</td>
</tr>
<tr>
<td>N = 4</td>
<td>2 no shift in pathological class</td>
</tr>
<tr>
<td>Class IV Diffuse LN</td>
<td>2 switched to higher grade nephritis (Class IV: 1 case: Class V: 1 case)</td>
</tr>
<tr>
<td>N = 13</td>
<td>9 no shift in pathological class</td>
</tr>
<tr>
<td>Class V Membranous LN</td>
<td>1 switched to Class IV</td>
</tr>
<tr>
<td>N = 2</td>
<td>1 no shift in pathological class</td>
</tr>
</tbody>
</table>

In the subgroup of patients with Class II mesangial LN, the repeat biopsy showed a transformation to a higher grade of nephritis (Class IV or V) in 67% of the cases.
In contrast, in most patients (65%) with proliferative classes (III and IV), there was no shift in histological class on repeat biopsy. Of the 2 patients with Class V membranous LN, only 1 changed to a proliferative class. Clinically significant class switches during LN flares were more frequent in patients with non-proliferative lesions (Classes II and V) than those with proliferative lesions (classes III and IV) in their reference biopsy (p < 0.05).

The mean relapsing activity index on first biopsy was 8.85 (SD: 4.43) and on repeat biopsy it was 7.26 (SD: 3.64) (p = 0.315). The mean chronicity index for the first biopsy was 1.95 (SD: 2.53) and for the repeat biopsy it was 2.52 (SD: 2.39) (p < 0.001).

The pathological transition could not be predicted by any clinical characteristics. A few the repeat biopsy, 10 (36%) of patients had a change of treatment regimen: 8 received an increase in immunosuppression; while in 2 cases immunosuppressive therapy was decreased or stopped.

Conclusion: Pathological conversion was highly prevalent (50%) in patients with LN. Overall, 66% of cases with class II mesangial LN in a reference biopsy showed transformation to a higher grade of nephritis (class IV or V) on repeat biopsy, so early repeat biopsy is advisable for this subgroup of patients. In contrast, in most patients (65%) with proliferative Classes (III and IV) in a reference biopsy, there was no shift in histological class on repeat biopsy. Repeat biopsy might be helpful in guiding treatment, both to identify those patients for whom it is necessary to intensify immunosuppressive therapy, and to avoid unnecessary increased immunosuppressive therapy in others.

Disclosure: M. Rice, None; J. Narvaez, None; G. Albert, None; P. Estrada, None; S. Heredia, None; A. Zacarias, None; H. Borrelli, None; E. Armengol, None; X. Fulladosa, None; J. Torras, None; O. Capdevila, None; F. Mitjavila, None; J. M. Nolla, None.

1660

A Systematic Review and Network Meta-Analysis of Cyclophosphamide and Mycophenolate Mofetil in Lupus Nephritis

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Background/Purpose: Patients consider common side effects of medications prominently in treatment decision-making. To our knowledge, with the exception of a Cochrane review that analyzed data up to April 2012, limited or no information exists on comparisons of common, non-fatal side effects of immunosuppressive medications used for the treatment of lupus nephritis. Our objective was to perform an up to date systematic review and network meta-analysis (NMA) to compare harms/safety of cyclophosphamide (CYC) and mycophenolate mofetil (MMF) for the treatment of lupus nephritis.

Methods: Cochrane and ACR librarians performed an updated search for immunosuppressive medications for lupus nephritis up to September 2013 updated data from the systematic review that formed the basis of the 2012 ACR lupus nephritis treatment recommendations and the published Cochrane Review. We abstracted safety data related to the following harms/ adverse events (AEs): alopecia, nausea, ovarian failure, endocrine AEs, cytopenia and leucopenia. Bayesian network meta-analyses (NMA) were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using Markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

Results: Compared to MMF, CYC was associated with higher risk of alopecia by almost 4-fold, leucopenia by 3-fold and ovarian failure by 6-fold (Table 1). The higher risk of cytopenia with CYC almost reached statistical significance (Table 1). The risk of nausea and endocrine side effects did not differ significantly between CYC and MMF. Risk differences between CYC and MMF are provided in Table 1.

Conclusion: Our systematic review and meta-analysis identified several important differences between the harms of CYC and MMF in patients with lupus nephritis. These findings provide clinicians and patients with the magnitude of differences in these common side effects and can help patients with treatment decision-making.

Table 1: Comparison of cyclophosphamide (CYC) vs. mycophenolate mofetil (MMF)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia, CYC vs. MMF</td>
<td>3.69 (1.37, 9.86)</td>
<td>2.21 (0.76, 6.90)</td>
</tr>
<tr>
<td>Nausea, MMF vs. CYC</td>
<td>0.37 (0.14, 1.10)</td>
<td>-0.04 (-0.29, 0.19)</td>
</tr>
<tr>
<td>Endocrine AEs*, CYC vs. MMF</td>
<td>1.52 (0.70, 3.42)</td>
<td>0.08 (-0.38, 0.54)</td>
</tr>
<tr>
<td>Cytopenia, CYC vs. MMF</td>
<td>1.62 (0.99, 2.67)</td>
<td>0.21 (-0.12, 0.54)</td>
</tr>
<tr>
<td>Leucopenia, CYC vs. MMF</td>
<td>2.82 (1.63, 4.64)</td>
<td>0.46 (0.23, 0.70)</td>
</tr>
</tbody>
</table>

Peto’s odds ratio (95% CI)

Ovarian failure, CYC vs. MMF | 6.36 (2.59, 15.63)

*Diabetes and hyperglycemia; significant odds ratios are in bold

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5, A. Kottb, None; A. Hossain, None; G. A. Wells, Novartis, Bristol-Myers Squibb, and Abbott, 2, Bristol-Myers Squibb, 2, speaker honorariums from Abbott; 8, He is a member of the executive of OMERACT and of the Scientific Committee for the Ontario Biologics Research Initiative, 9.

1661


Background/Purpose: Lupus nephritis (LN) is the major cause of morbidity and mortality in patients with systemic lupus erythematosus. The role of repeat kidney biopsies (RB) to guide treatment or to predict outcome has been controversial. In this retrospective study we focused on histological characteristics of RBs and aimed to identify any clinical variables useful to predict histological changes.

Methods: In a large single-centre cohort of 257 patients from 1988–2014 with biopsy proven LN, 56 (23%) had two or more biopsies (a total of 68 RBs). LN classes based on glomerular pathology were defined according to the ISN/RPS classification. Clinical and laboratory data were obtained from electronic records of patients.

Results: The median time between initial and RB was 33 months [IQR, 15–84]. Caucasians (n = 8) had a lower RB rate of 16% compared to blacks (n = 37, 33%; p = 0.010). Indication for RB was worsening proteinuria (n = 38, 71%; of which 23 had associated rising creatinine, 61%, rise in serum creatinine alone (n = 6, 11%) and lack of treatment response (n = 15, 17%) defined as <50 reduction in proteinuria. At time of RB, 25 (78%) had raised dsDNA, 33 (73%) had low complements. LN class transition occurred in 31 (48%), most commonly from class II or V to III or IV (n = 11, 36%). 6 RB (8.6%) showed inactive lesions either due to FSGS or advanced sclerosing LN. 42 (65%) had a change in their treatment regime. Immunosuppression was more likely to be escalated in case of a class switch (87% vs. 38%, p = 0.002). The histological transition could not be predicted by any serological or biochemical variables.

Conclusion: Over a 1/3 of our LN patients showed histological transition to a more aggressive class, based on which the majority (87%) had treatment escalation. Histological transition could not be predicted by clinical values. Hence, we conclude that RB remains an important tool to guide management of selected patients with LN, in particular those with initial class II or V who flare.

Disclosure: A. Pakozdi, None; R. Rajakariar, None; M. Sheaff, None; D. Pyne, None.

1662


Background/Purpose: The current guidelines from both the American College of Rheumatology and the American Society of Nephrology suggest initiating induction therapy for Class III and Class IV lupus nephritis with cyclophosphamide or mycophenolate mofetil and then starting maintenance therapy, generally mycophenolate mofetil or azathioprine. However, the duration of maintenance therapy is not specified in the guidelines. Many patients with lupus nephritis take these maintenance medications indefinitely.

Methods: We reviewed the charts of lupus nephritis patients in a rheumatology office practice whose biopsies showed Class III or Class IV lupus nephritis. All had been treated with mycophenolate mofetil or cyclophosphamide.
phosphamide and then switched to maintenance therapy. We describe the course of 6 patients who stopped their immunosuppressive maintenance therapy and 2 patients who never began maintenance immunosuppressive treatment.

Results: 6 patients stopped their maintenance immunosuppressive therapy for Class III or Class IV lupus nephritis. One patient with class III and one patient with class IV lupus nephritis never started it. All are still doing well without a renal or systemic disease flare up. The reasons these patients stopped the maintenance therapy included fertility and pregnancy concerns, doubt that continuing maintenance medicine was necessary, and lack of compliance.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Renal Class</th>
<th>Maintenance Drug</th>
<th>Length on Maintenance Medication</th>
<th>Current time off Maintenance Medication</th>
<th>Current Outcome of Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>31</td>
<td>III</td>
<td>M ycophenolate Mofetil</td>
<td>16 months</td>
<td>2 1/2 years</td>
<td>Remission</td>
</tr>
<tr>
<td>F</td>
<td>45</td>
<td>III</td>
<td>M ycophenolate Mofetil</td>
<td>4 months</td>
<td>4 months</td>
<td>Remission</td>
</tr>
<tr>
<td>F</td>
<td>31</td>
<td>III</td>
<td>M ycophenolate Mofetil</td>
<td>18 months</td>
<td>3 years</td>
<td>Remission</td>
</tr>
<tr>
<td>F</td>
<td>37</td>
<td>III</td>
<td>No Maintenance</td>
<td>2 years</td>
<td>M ildly active</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>IV</td>
<td>No Maintenance</td>
<td>6 months</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>III</td>
<td>Azathioprine</td>
<td>1 year</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>III</td>
<td>M ycophenolate Mofetil</td>
<td>2 years</td>
<td>1 year</td>
<td>Remission</td>
</tr>
<tr>
<td>F</td>
<td>31</td>
<td>IV</td>
<td>Azathioprine</td>
<td>1 1/2 years</td>
<td>6 months</td>
<td>Remission</td>
</tr>
</tbody>
</table>

Conclusion: Previous studies have shown that patients with class III and IV lupus nephritis, who go into remission with induction therapy, with normalization of creatinine and a significant reduction of proteinuria, are likely to remain remission. It is unknown whether they need indefinite maintenance therapy. The lupus patients described here were able to discontinue maintenance immunosuppressive therapy, or never began it, and are doing well without relapse of their nephritis. We did not find any Class III or IV lupus nephritis patients who flared after discontinuing immunosuppressive treatment in this small sample.

This study suggests that the duration of treatment with maintenance immunosuppressive therapy should be evaluated and guidelines amended to address the duration of maintenance medication based on patient responses to induction treatment.

Disclosure: R. S. Katz, None; L. Kwan, None.

1664

Background/Purpose: Lupus nephritis (LN) is a major complication of systemic lupus erythematosus (SLE) and prevalence is estimated to be 50–60%. Recently, variable responses to induction regimes have been observed in different ethnic groups with Hispanics and Blacks tending to respond better to M ycophenolate Mofetil (MMF) than CYC in Asians and Blacks, but not in Caucasians. Up to date, 20 patients (25%) have developed end-stage kidney disease with the highest rate in Blacks (n=13, 37%). Severe infections tended to be more common in patients treated with CYC than MMF (n=7, 15% vs. n=2, 8%; p=0.642). CYC caused gonadal toxicity in 6 patients (14%).

Conclusion: Current ACR guidelines (2) recommend using MMF rather than CYC for LN class III/IV induction therapy in African Americans and Hispanics. Our retrospective study provides supportive evidence that MMF tends to achieve higher remission rates in Blacks, and is at least as effective as CYC in Caucasians and Asians from the Indian Subcontinent, with fewer adverse events.

1. Isenberg D. Rheumatol 2010;49:128-140
2. Hahn BH, Arthritis Care Res 2012;64(6):797-808

Disclosure: A. Pakozdi, None; R. Rajakariar, None; M. Sheaff, None; D. Pyne, None.

1665
Novel Risk Factors for Systemic Lupus Erythematosus (SLE) Flares in Patients with End-Stage Renal Disease: Is SLE in Patients with End-Stage Renal Disease a “sleeping beauty”? Jorge Alcocer-Varela1, Mariana Quinlan2,1, Javier Meryo-Chicalco1, Ana Barrera-Vargas3,1 and Diana Gomez-Martín1,2. 1Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico, 2Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, Mexico City, Mexico.

Background/ Purpose: Renal involvement in systemic lupus erythematosus (SLE) is frequent, and a high percentage of patients (~15%) develop end-stage renal disease (ESRD) even with optimal treatment. It is widely supposed that ESRD in these patients leads to an indefinite exacerbation period. Currently, information about SLE activity in patients with renal replacement therapy is quite scant. The aim of this study was to identify risk factors for SLE flares in patients with ESRD.

Methods: A retrospective, case-control study was performed in a tertiary care center in Mexico City from 1993 to 2014. Cases (n=50) were patients with SLE diagnosis (at least 4 American College of Rheumatology criteria) who had any extra-renal flare (any increase in systemic lupus erythematosus activity index - SLEDAI- score that required the modification of immunosuppressive treatment) after at least three months of renal replacement therapy (RRT). Controls (n=70) were patients matched by sex, but without any flares, studied during the same period of time as cases (~3 months). An association between variables was calculated by X2 test and OR (95% CI). Multivariate analysis was performed by logistic regression. p values less than 0.05 were considered statistically significant.

Results: There was a higher percentage of men in the case group (24 vs 8%, p=0.029). At the time of the SLE flare, patients had required dialysis for a mean period of 23.1±3.6 months. There was no difference in the time period between SLE diagnosis and the beginning of dialysis in both groups (p=0.06). Variables previous to the exacerbation which had significant differences in the univariate analysis are showed in Table 1. V ariables that remained significant after multivariate analysis were: history of fever secondary to SLE [OR 5.20 95%CI 3.02-10.40, p=0.046], history of hemolagic activity [OR 4.02 95%CI 3.02-15.79, p=0.046], low C4 levels prior to the flare [OR 19.62 95%CI 3.72-103.3 p<0.001], anti-cardiolipin IgM positivity [OR 4.32 95%CI 1.07-17.43, p=0.040], presence of lupus anticoagulant [OR 9.38 95%CI 1.26-69.79, p=0.029], age at the beginning of renal replacement therapy [OR 0.92 95%CI 0.88-1.00, p=0.024], and showed a trend in Asians (n=6, 75% vs. n=7, 41%, respectively; p=0.114). In contrast, in Caucasians, CR rate was similar in both treatment arms at 6 months (n=5, 56% in CYC vs. n=3, 50% in MMF, p=0.833). At month 24, there was a non-statistical trend for greater response to MMF than CYC in Asians and Blacks, but not in Caucasians. Up to date, 20 patients (25%) have developed end-stage kidney disease with the highest rate in Blacks (n=13, 37%). Severe infections tended to be more common in patients treated with CYC than MMF (n=7, 15% vs. n=2, 8%; p=0.642). CYC caused gonadal toxicity in 6 patients (14%).

Conclusion: Current ACR guidelines (2) recommend using MMF rather than CYC for LN class III/IV induction therapy in African Americans and Hispanics. Our retrospective study provides supportive evidence that MMF tends to achieve higher remission rates in Blacks, and is at least as effective as CYC in Caucasians and Asians from the Indian Subcontinent, with fewer adverse events.

1. Isenberg D. Rheumatol 2010;49:128-140
2. Hahn BH, Arthritis Care Res 2012;64(6):797-808

Disclosure: A. Pakozdi, None; R. Rajakariar, None; M. Sheaff, None; D. Pyne, None.


Table 1. Variables associated with development of (univariate analysis)

<table>
<thead>
<tr>
<th>Prior to exacerbation</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
</table>

**Hematologic**
- Serositis: 10.2 2.20–47.90 0.001
- Hemolytic anemia: 6.76 1.41–32.36 0.007
- Persistent thrombocytopenia (<150,000/ul): 3.16 1.03–9.68 0.037
- Persistent leukopenia (<3,000/ul): 10.28 2.00–47.90 0.001
- Persistent lymphopenia (<1,000/ul): 2.97 1.30–6.98 0.009

**Serositis**
- 2.57 1.12–5.89 0.024

**Previous Serology**
- Lupus anticoagulant: 6.76 1.41–32.36 0.007
- Anticardiolipin IgM: 2.95 1.14–7.64 <0.003
- Low C4 levels: 4.93 1.98–12.26 <0.001

**Previous Treatment (Three months)**
- Azathioprine: 13.82 1.71–111.72 0.002
- Low C4 levels: 4.93 1.98–12.26 <0.001

Table 2. Mean change (from pre-biopsy) in cholesterol and systolic blood pressure by average daily dose of prednisone in the year following biopsy

<table>
<thead>
<tr>
<th>Average Daily Prednisone Dose</th>
<th>Sample Size</th>
<th>Mean change in Cholesterol</th>
<th>Mean change in systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 mg/d</td>
<td>27</td>
<td>−2.3</td>
<td>−2.5</td>
</tr>
<tr>
<td>10–19 mg/d</td>
<td>28</td>
<td>−12.3</td>
<td>−5.7</td>
</tr>
<tr>
<td>20 mg/d</td>
<td>21</td>
<td>−25.2</td>
<td>−0.4</td>
</tr>
</tbody>
</table>

**Conclusion:** Prednisone dose in Class III-IV lupus nephritis has been reduced in recent years, with no deleterious effect on urine protein (in fact there has been improved control of urine dipstick protein). The effect of prednisone on traditional risk factors was surprising. Patients receiving more than 20 mg/day of prednisone had a major increase in serum cholesterol. However, in those receiving 10–19 mg/d prednisone, there was a surprising decrease in both cholesterol and systolic blood pressure.

**Disclosure:** T. Bichile, None; L. S. Magder, None; M. Petri, None.

1P-value for differences between years with respect to mean daily dose of prednisone, adjusting for baseline dipstick equals 0.047.

2P-value for difference in mean urine dipstick score by year, adjusting for baseline dipstick score equals 0.046.
class III, IV or V in immunosuppressant naïve patients with lupus nephritis by using 5 criteria including BMS, ACR, LUNAR, ALMS, and ACCESS. 

Methods: This is a retrospective study on 21 SLE patients who had begun mycophenolate mofetil shortly after a biopsy-confirmed diagnosis of lupus nephritis. They consisted of 18 females, 3 males, 9 African Americans, 8 Caucasians, and 4 other ethnicities. Ages ranged from 18 to 70 with a mean age of 37 (SD = 15). There were 5 patients with class III, 9 with class IV, 4 with class III-V, 1 with class IV-V, and 2 with class V lupus nephritis. At baseline, 76% had positive anti-dsDNA, 67% had low C3, 57% had low C4 and 71% had albumin below 3.5. The initial dose of mycophenolate mofetil was 1000mg twice daily. If no improvement, it was increased to 1500mg twice daily after one month. The baseline urine protein to creatinine ratio ranged between 0.635 to 11.91grams with only 1 patient being below 1 gram at baseline. Patients were on a renal sparing regimen (52%) and hydroxychloroquine (86%). Depending on the response index, complete response was defined as reaching a urine protein to creatinine ratio of < 0.2-0.5 grams, improvement in creatinine or estimated glomerular filtration rate of 10-25%, normalization of urinalysis and tapering dose of steroids.

Results: 52% of SLE patients reached 0.5 grams of proteinuria within 51 days of starting mycophenolate mofetil (95% confidence interval 29%-74%), 77% reached 0.5 grams or less within 260 days (95% confidence interval 57%-97%). The probability of response at 90 and 180 days is shown in the table for each response index.

<table>
<thead>
<tr>
<th>Response Definition</th>
<th>Probability of response within 90 days</th>
<th>Probability of response within 180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>ACR</td>
<td>23%</td>
<td>58%</td>
</tr>
<tr>
<td>LUNAR/ALMS/ACCESS</td>
<td>24%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Conclusion: This study demonstrates that the majority of previously naïve immunosuppressant patients can reach a complete response within 6 months after initiation of mycophenolate mofetil. Furthermore, the estimate of long term response was highest in the ACR criteria.

Disclosure: H. Timlin, None; M. Petri, None; L. S. Magder, None.

1668

Identifying Patient Perceptions of Medication Decision Making Barriers in Minorities with Lupus Nephritis. Jasvinder A Singh1, Hayanu Qu2, Jinoos Yazdany1, W. Winn Chatham3, Maria Dall’era4 and Ricahrd Shewchuk1. 1University of Alabama and VAMedical Center, Birmingham, AL; 2University of Alabama at Birmingham, Birmingham, AL; 3University of California, San Francisco, San Francisco, CA; 4University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Studies suggest that adherence to medications for lupus nephritis is low. However, there are limited data available on the barriers that patients with lupus nephritis, encounter in their decisional processes involving immunosuppressive medications. Our objective was to identify a comprehensive array of patient-reported barriers (issues) and the relative difficulty these presented for racial/ethnic minority patients with lupus nephritis in their medication adherence decision-making process.

Methods: Barriers involved in the medication decision-making process were queried and then prioritized using a voting procedure during 8 Nominal Group Technique (NGT) meetings that were convened with participants who received treatment for lupus nephritis clinics at University of Alabama at Birmingham (UAB) and University of California at San Francisco (UCSF). The participants were asked "What sorts of things make it hard for people to decide to take the medicines that doctors prescribe for treating their lupus kidney disease?" We aggregated the prioritized responses from each NGT meeting by combining the same or very similar responses from different groups. NGT and its robustness as a patient-centered approach helped us generate objective, semi-quantitative information regarding factors that influence the decision making process in patients with lupus nephritis. An improved understanding of patient-perceived barriers to medication use will help us design interventions and educational materials for patients with lupus nephritis (e.g., decision aid).

Disclosure: J. A. Singh, Takeda, savient, 2, takeda, savient, regeneron, allergan, 5; H. Qu, None; J. Yazdany, None; W. W. Chatham, None; M. Dall’era, None; R. Shewchuk, None.

1669

Validation of a Machine Learning Lupus Nephritis Decision Support Tool to Predict Complete Response to Therapy. Bethany Wolf1, John Christian Spanihour2, John Arthur3, M ichael J aneck3, M ichel e Petri4, A dran K ian3 and Jim Oates5. 1Medical University of South Carolina, Charleston, SC; 2Johns Hopkins University School of Medicine, Baltimore, MD, 3Johns Hopkins University, Baltimore, MD.

Background/Purpose: The American College of Rheumatology treatment guidelines for lupus nephritis (LN) recommend that induction therapy be changed when response to therapy has not occurred within six months. Response is not defined, and renal fibrosis can occur while waiting for this endpoint. Therefore, an early treatment decision support tool is needed. The goal of this project was to create and validate such a tool.

Methods: 140 patients with active LN were recruited from patients treated with the Lupus Nephritis Decision Support Tool (LNDST) and were randomized to either receive induction therapy or to receive one year of follow-up. The researcher used a randomization scheme with a 1:1 ratio of patients to treatment groups.

Results: Patients were randomized to treatment (n = 99) and assessed both at initial therapy (n = 41) sets stratifying for LN (n = 18) and LN (n = 32). The primary outcome measure was complete response (CR) to therapy. The LNDST predicted the performance reported in Table 1 for both models, but the novel biomarker panel had superior specificity for cutpoints giving equal sensitivity.

Validation of performance for random forest models of complete response to therapy. Reported as median model from 1000 different training and validation sets. The resulting test of the LNDST demonstrated the clinically meaningful performance reported in Table 1 for both models, but the novel biomarker panel had superior specificity for cutpoints giving equal sensitivity.
1670

Characterization of Patients with Lupus Nephritis Included in a Large Cohort from the Spanish Society of Rheumatology Registry of Patients with Systemic Lupus Erythematosus.

Methods: A retrospective cohort analysis of patients with LN included in the Spanish Society of Rheumatology (S3R) Registry. The S3R Registry includes all patients with LN registered in Spain from 2006 to 2016. The following data were recorded: sex, age at diagnosis, ethnic origin, LN histological type, proteinuria, hematuria, leukocyturia, cellular casts, and creatinine clearance. The following outcomes were recorded: time to renal events, response to treatment, recurrence, and mortality. The following renal outcomes were analyzed: development of ESRD and/or the need for dialysis or renal transplantation, recurrence, and mortality.

Results: A total of 2,576 patients with LN were included in the S3R Registry. The most common histological type was proliferative (34%), followed by membranous (21%) and mixed proliferative/membranous (19%). The most common renal manifestations were proteinuria (95%), hematuria (85%), and leukocyturia (65%). Cellular casts were present in 59% of patients. The median age at diagnosis was 33 years (range, 4-85 years). The median follow-up time was 9 years (range, 0-34 years). The cumulative incidence of ESRD was 13% at 10 years. The cumulative incidence of recurrence was 58% at 10 years. The cumulative incidence of mortality was 22% at 10 years.

Conclusion: The S3R Registry is a valuable resource for the characterization of patients with LN in Spain. The results suggest that LN is a highly prevalent disease with a high incidence of renal events and mortality.
defined as proteinuria < 0.5g/day, whilst partial remission (PR) was defined as >50% reduction in baseline proteinuria achieving <2g/day. We defined proteinuric flares as proteinuria >1g/day in patients with CR, and doubling of proteinuria in cases of PR.

**Results:** 104 (87%) of 119 SLE patients with biopsy proven LN achieved either CR (n=84, 81%) or PR (n=20, 19%). 34 (33%) had at least one flare (27 had preceding CR and 7 had PR); among those 8 had >2 flares (19%), 21 patients (64%) had class 3 or 4 LN, 7 (21%) class 5 LN, 4 (12%) class 2 LN and 1 (3%) focal segmental glomerulosclerosis. The median time between remission and relapse was 29 months (IQR, 16–66) in CR, and 13 months (IQR, 3–32) in PR (p = 0.008). The maintenance immunosuppressive drug at time of flare was Mycophenolate Mofetil (MMF, n=11, 31%) or Azathioprine (AZA, n=10, 32%). 15 (48%) had Angiotensin blockers (ATB), and 22 (71%) were on low dose Corticosteroids (CS) (10mg/day).

Patients with disease after the flare did not go into remission. 5 patients (15%) reached stage 5 chronic kidney disease after the flare. 26–42 responses/meeting). 36% of all responses were endorsed (IQR, 3–32) in PR (p = 0.001). The introduction of facilitate influencing the medication decision-making was present if listed among the ACR classification criteria (ACR-LN), while patients with ACR-LN had significantly worse scores on Summary HRQOL and non-HRQOL. The average percentage of patients with ACR-LN, worse HRQOL and non-HRQOL than patients with inactive LN.

**Conclusion:** A general consistency of factors perceived to facilitate medication decision making by lupus nephritis patients can be identified across ethnic groups. Patient-identified facilitators of lupus medication adherence can inform the design of effective educational materials for patients with lupus nephritis.

**Disclosure:** R. Shewchuk None, H. Qu None, W. W. Chatham None, J. Yazdany None, D. D’Alra None, J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5.

**1673**

**Disease Specific Quality of Life in Patients with Lupus Nephritis: Chi Chiu Mok1, Sergio Tolozza2, Bena Goker2, Ann E. Clarke3, S. Navarra4, Daniel J. Wallace5, Michael H. Weisman6 and M enaaki Halljolly7, 8,**

Tuen Mun Hospital, Hong Kong, Hong Kong, 1Hospital San Juan Bautista, San Fernando del Valle de Catamarca, Argentina, 2Gazi University, School of Medicine, Ankara, Turkey, 3University of California, Calgary, AB, 4University of Santo Tomas Hospital, Manila, Philippines, 5Cedars-Sinai/ David Geffen School of Medicine at UCLA, Los Angeles, CA, 6Cedars-Sinai Medical Center, Los Angeles, CA, 7Rush University Medical Center, Chicago, IL.

**Background/Purpose:** Low medication adherence in lupus nephritis puts patients at risk for poor outcomes, but to our knowledge, relatively little is known about what patients perceive as facilitative factors in medication decisional processes. Our objective was to comprehensively identify factors that racial/ethnic minority patients with lupus perceive as facilitating decisional processes to take their lupus medications as prescribed.

**Methods:** 104 SLE patients with lupus nephritis (LN) participated in 8 NGT meetings: 1) University of Alabama at Birmingham, Birmingham, AL, 2) University of California, San Francisco, San Francisco, CA, 3) University of Alberta and VA Medical Center, Birmingham, AL.

**Setting:** 8 NGT meetings (NGT) were conducted to identify facilitators and barriers to medication adherence in lupus nephritis patients. NGT meetings were conducted at four sites (Birmingham, AL; San Francisco, CA; Manila, Philippines; Los Angeles, CA) and were led by expert facilitators with expertise in lupus nephritis.

**Participants:** 104 SLE patients with lupus nephritis participated in 8 NGT meetings: 1) University of Alabama at Birmingham, Birmingham, AL; 2) University of California, San Francisco, CA; 3) University of Alberta and VA Medical Center, Birmingham, AL.

**Desires-Goals 63.0 (28.8) 65.2 (27.4) 0.003 64.6 (27.5) 74.5 (24.7) 0.008**

**Summary HRQOL 6.7 (3.8) 7.2 (3.9) 0.02 7.4 (3.4) 8.7 (3.3) 0.001**

**Summary Non-HRQOL 6.8 (3.2) 7.3 (3.7) 0.05 7.1 (4.0) 9.3 (3.9) 0.01**

**Results:** 1259 SLE patients; ninety-four percent were women and their mean (SD) age was 41.7 (13.5) yrs. Five-hundred and thirty-nine SLE patients at risk for poor outcomes, but to our knowledge, relatively little is known about what patients perceive as facilitative factors in medication decisional processes. Our objective was to comprehensively identify factors that racial/ethnic minority patients with lupus perceive as facilitating decisional processes to take their lupus medications as prescribed.

**Background/Purpose:** Little is known about patient reported outcomes (PRO) in lupus nephritis (LN), and no studies using a disease targeted PRO tool have been undertaken thus far. Herein, we describe quality of life (QOL) among patients with LN using a valid and reliable disease targeted PRO measure (LupusPRO).

**Methods:** Cross sectional data obtained from patients with systemic lupus erythematosus who participated in a disease specific evaluation of LupusPRO from various countries were compared between those 1) with and without LN and 2) with active and inactive-LN. Data compared included demographic, disease characteristics, and LupusPRO constructs. Presence of LN was present if listed among the ACR classification criteria (ACR-LN), while presence of active LN was based on presence of urinary casts, hematuria, proteinuria or pyuria in the disease activity assessment (SELENA-SLEDAI) performed at the time of the study visit. LupusPRO has Health related QOL (HRQOL) and non-HRQOL constructs. HRQOL domains include lupus symptoms, cognition, medication, procreation, physical health, emotional health, pain-vitality and body image. Non-HRQOL domains include desires-goals, social support, coping and satisfaction with care. Non-parametric tests were used to make comparisons, and p values ≤ 0.05 were considered significant.

**Results:** There were 1,259 SLE patients; ninety-four percent were women and their mean (SD) age was 41.7 (13.5) yrs. Five-hundred and thirty-nine had ACR-LN. These patients were younger, had greater disease activity (PGA, Total SELENA-SLEDAI) and damage (SLICC/ACR) than those without LN. Summary HRQOL and non-HRQOL scores were similar in both groups; however, those with ACR-LN had significantly worse scores on medications and procreation domains, while those without ACR-LN had worse scores on Pain-Vitality domains (Table 1).

129/540 ACR-LN patients had active LN. Patients with active LN were younger, had significantly greater disease activity (PGA, Total SELENA-SLEDAI), worse HRQOL and non-HRQOL than patients with inactive LN.
Specific domains scores adversely affected among active LN patients were lupus symptoms, medications, recreation, emotional health, body image and desires-goals (Table 1). Satisfaction with care was significantly higher among patients with active LN as compared to inactive LN patients.

Conclusion: LN adversely affects several specific QOL domains and physicians need to be aware of these concerns.

Disclosures: C. C. Mok, None; S. Toloza, None; B. Goker, None; A. E. Clarke, None; S. Navarra, Pfizer, GSK; B. D. J. Wallace, None; M. H. Weisman, None; M. J. Ojly, None.

ACR/ARHP Poster Session B
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Clinical Aspects and Therapeutics: Systemic Sclerosis, Diagnostic and Therapeutic Aspects
Monday, November 17, 2014, 8:30 AM – 4:00 PM

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Long-Term Efficacy of Rituximab in Systemic Sclerosis. Javier Narvaez1, Juan Jose Algebre Castillo2, Ivan Castelvi3, Susana Herrera4, Maria Molina5, Maria Molina6, Diego Castillo7, Isabel de la Mora Barrio1, Montserrat Villarino1, A. M. Martinez Ferrer, E. Desamparados Ybarba, A. Garcia R, Valles Pascual8, Josep Maria Llobet3, Francisca Gil Labore3 and Joan Miquel Nolla1.

1Hospital Universitari de Bellvitge. Barcelona. Spain. Barcelona, Spain. 2Hospital Universitario Dr Peset, Valencia, Spain. 3Hospital de Sant Pau, Barcelona, Spain. 4Hospital Universitario de Bellvitge, Barcelona, Barcelona, Spain.

Background/Purpose: It has been proved in several studies with a small number of patients that Rituximab (RTX) can prevent worsening of interstitial lung disease (ILD) and improve skin fibrosis in patients with Systemic Sclerosis (SSc). Recently, a multicentre case-control study of the EUSTAR cohort has confirmed these favorable results (Narvaez J et al. Ann Rheum Dis 2014 Jan 17 [Epub ahead of print]). Moreover, RTX may be effective on calcinosis. However, little is known about its long-term effect. Our objective was to assess the efficacy of RTX on skin involvement, ILD and calcinosis in series of patients with refractory SSC.

Methods: Patients with refractory SSC treated with RTX (off label use) were recruited from 3 hospitals. At baseline, the following data were collected: gender, age, type and duration of the SSC, clinical features, modified Rodnan skin score (mRSS), HRCT, pulmonary function tests (PFTs), walking test, sPAP (measured by echo), previous and present treatments, and indication and dosage of RTX. Throughout the follow up, clinical changes, as well as changes in HRCT and PFTs, were registered. We also recorded the changes in the dosage of corticosteroids, cycles, duration of treatment, and withdrawals. The package SPSS 17.0 was used for descriptive statistics, and quantitative variables were compared using the t-test for paired samples.

Results: Thirty SSc patients treated with RTX were included in the analysis. The majority were women (86.7%), with a mean age of 54 years, and a mean of 9.4 years of evolution of the disease. Subtypes: DSSc 50%, LSSc 37%, and Overlap syndromes 13.3%. The baseline mean mRSS was 15. Clinical features: ILD 80% (NSIP 67%), calcinosis 37%, pulmonary hypertension 10%, joint disease 49%. The baseline mean FVC, DLCO and TLC values were 70%, 47% and 73%, respectively.

The indication for RTX was: ILD (73.4%), arthritis (36.6%), calcinosis (33.3%) and severe skin involvement (19.7%). The most used previous treatments were cyclophosphamide(50%) and mycophenolate (46.6%). RTX was always used in a RA dosage, mainly in monotherapy (46.7%), or in association with mycophenolate (40%). When data were collected, patients had received a mean of 1.7 cycles (1–5) of RTX, with a dosing interval which ranged from 6 to 15 months, and a mean of 12.8 months (1–43) of treatment. The mean mRSS was significantly reduced at follow-up (17.2 ± 10.9 vs. 14.9 ± 8.3; p = 0.012), without significant changes of the HRCT (76.9%) and PFTs. ILD and calcinosis improvements were also significant (p = 0.002 and 0.019, respectively). The dose of corticosteroids was significantly reduced (10.1 ± 8.8 vs. 5.3 ± 2.9 mg; p = 0.003). Two patients with severe ILD died despite RTX, and there were 3 withdrawals for various reasons.

Conclusion: RTX is an effective long-term therapy in refractory SSC which can improve skin fibrosis, arthritis and calcinosis, and also prevent deterioration of ILD (stabilization of lung function).

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Background/Purpose: Fingertip digital ulcers (DUs) are a rather frequent and invalidating complication in the course of systemic sclerosis (SSc), often showing a very slow or null tendency to heal, and causing intense local pain. Furthermore, most of the commonly used systemic and local therapeutic procedures have demonstrated to be scarcely or totally inadequate to induce a rapid healing in the SSc-related DUs. Recently stem cell therapy has emerged as a new approach to accelerate wound healing, and some case reports have been published where local or regional transfer of bone marrow stem cells (BMSC) was effective in improving or healing SSc-related ischemic lesions. A derived-stem cells ASCs are considered another source of multipotent stem cells potentially able to induce angiogenesis and tissue repair. In the present study we have tentatively treated long lasting and poorly responsive to traditional therapy SSc-related DUs by the implantation of autologous adipose-tissue derived cells (ATDCs) fraction, that it know to contains both the ASCs and the stromal/vascular cell (SV) component.

Methods: Fifteen patients with SSC having a long lasting DU in only one fingertip, unresponsive to intensive systemic and local treatment, were enrolled into the study. The grafting procedure consisted in the injection, at the basis of the corresponding finger, of 0.5–1 ml of ATDCs fraction, separated by centrifugation of adipose tissue collected through liposuction from subcutaneous abdominal fat. Time to healing after the procedure was the primary end point of the study, while reduction of pain intensity (measured by visual analogue scale), and of analgesic consumption represented secondary end point. Furthermore, the after therapy variation of the number of capillaries, observed in the nailfold video-capillaroscopy (NVC) exam, and of the resistivity in the digit arteries, measured by high resolution echo-color doppler were also taken into account.

Results: A rather quick healing of the DUs was reached in all of the enrolled patients (mean time to healing 4.23 weeks; range 3–8 weeks). A significant reduction of pain intensity was observed after few weeks (p<0.001), while the number of capillaries was significantly increased at second (3 months) and third (6 months) NVC examination (p<0.0001 in both cases, with respect to the basal examination). Finally, a significant after treatment reduction of digit artery resistivity was also recorded (p<0.0001).

Conclusion: Even with the limitations related to the small number of patients included, and to the open-label design of the study, the strongly favourable outcome we observed suggests that the local grafting with ATDC, containing both ASCs and SV fraction, could represent a promising option for the treatment of SSc-related DUs unresponsive to more consolidated therapies.

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Physical Therapy for Systemic Sclerosis: Systematic Review and Meta-analysis. Madhavi Peddi1, Maria A. Lopez-Olivo, Prashanth Peddi1, Gisela Espinosa Cuervo1 and Maria E. Suarez-Almazor2.

1The University of Texas, Texas, TX. 2The University of Texas, MD Anderson Cancer Center, Houston, TX. 3Instituto Mexicano del Seguro Social, Mexico City, Mexico.

Background/Purpose: Physical therapy and rehabilitation are often recommended to improve function in patients with systemic sclerosis (SSc), but a systematic review of the evidence supporting these interventions has not

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been performed. We conducted a systematic review to evaluate the efficacy of physical therapy alone or in combination with exercise in patients with SSC.

Methods: We searched electronic databases (MEDLINE, EMBASE, the Cochrane Collaboration library, and Web of Science) up to April, 2013. The reference lists from reviews were also searched. Two independent reviewers selected controlled trials (randomized or not) evaluating the efficacy of any physical therapy modality either alone or in combination with exercise in patients with SSC. Data was appraised and collected independently by two reviewers. Outcomes of interest were: health-related quality of life, and hand mobility (measured by Health Assessment Questionnaire). Short Form-36 items, and Hand Mobility in Scleroderma, respectively. M eta-analysis was performed when data was available for 2 or more studies with the same outcome.

Results: Six studies with 221 patients were included. Five were randomized controlled trials and one was a controlled clinical trial. None of the studies were blinded; therefore, the risk of performance bias was judged to be high. All studies were conducted at single centers in an outpatient setting. The weighted mean age of patients assigned to the treatment group was 57.6 years and 55.9 years for the control group. Disease duration was 90.0 years and 8.7 years, respectively. There were substantial variations in the interventions and duration of physical therapy across trials. Therapy modalities included connective tissue massage, Anul Lymphatic drainage, and M. C. Mennell joint manipulation, among others. Patients treated with any modality of physical therapy had higher scores in functional status (mean difference, MD, −0.33; 95% CI, −0.46, −0.19), physical component of health-related quality of life (MD 3.3; 95% CI 1.1, 5.5) and hand mobility (MD −0.22; 95% CI −0.37, −0.06) at 2 to 12 weeks compared with standard of care. However, this improvement was not sustained for hand mobility, 12 weeks after stopping treatment (at 24 weeks) (MD −0.22; 95% CI −0.37, −0.06). No differences were observed by type of therapy modality.

Conclusion: Rehabilitation in patients with SSC improves functional status, ability to perform physical activities, and hand mobility 2 to 12 weeks after therapy. However, loss of improvement in hand mobility at 24 weeks suggests continuation of therapy is important to preserve the benefits of physical therapy.

Disclosure: M. Peddi, None; M. A. Lopez-Olivo, None; P. Peddi, None; G. Espinosa Cuervo, None; M. E. Suarez-Almazor, None.

Association of Gastrointestinal Symptoms with Immunosuppressant Use in the Prospective Registry of Early Systemic Sclerosis Cohort.

Tracy M. Frech1, Maureen Murtough2, Ami A. Shah1, Jessica K. Gordon3, Victoria K. Shankumag4, Robyn T. Domsic5, Monique Hinchcliff6, Faye N. Hant7, Sheriv S. Steen8, F. M. A. Lopez-Olivo9, G. Espinosa Cuervo2, M. E. Suarez-Almazor2. 1VA PuMed, Salt Lake, UT, 2University of Utah School of Medicine, SLC, UT, 3Johns Hopkins University School of Medicine, Baltimore, MD, 4Hospital for Special Surgery, New York, NY, 5The George Washington University, Washington, DC, 6University of Pittsburgh, Pittsburgh, PA, 7Northwestern University Feinberg School of Medicine, Chicago, IL, 8Medical Univ of South Carolina, 9University of Texas Health Science Center at Houston, Houston, TX, 10Georgetown University Medical Center, Washington, DC, 11University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: The Prospective Registry of Early Systemic Sclerosis (PRESS) is a multicenter incident cohort study of patients with early diffuse cutaneous systemic sclerosis (dcSSc; < 2 years duration). Gastrointestinal tract (GIT) symptoms are common in this patient population. The goal of this study was to analyze whether immunosuppressant choice differentially impacts GIT symptoms in early dcSSc.

Methods: There are currently 71 patients enrolled in the PRESS study at various centers in the United States. Data is collected longitudinally using REDCap, an NIH funded database including demographics, disease characteristics, physical exam data, and patient reported outcomes. PRESS patients who had both a complete gastrointestinal tract questionnaire (SCTC UCLA GIT 2.0) and immunosuppressant regimen recorded were included in this analysis. Statistical analysis was performed using SAS version 9.4. Fisher’s exact was to examine associations between two categorical variables and unpaired t-test or Wilcoxon rank sum was used for continuous variables. Significance was assigned at p < 0.05.

Results: A total of 37 PRESS patients had the presence or absence of an immunosuppressant at the baseline visit and a complete GIT 2.0 recorded. In this subgroup of PRESS patients, the most common immunosuppressant used was mycophenolate mofetil (n=17) followed by methotrexate (n=5) and cyclophosphamide (n=3). The mean age of this patient population was 52 years (12.8) and 24 were women. The average BMI was 25.2 (17.8–40.5). Fifteen patients reported > 5 kg of weight loss over the past year, 5 of those patients had > 20 kg of weight loss. In these 15 patients with weight loss there were significantly worse scores for total GIT 2.0 (p =0.03), soilage (p =0.01), social function (p =0.05) and emotional well-being (p =0.04).

There were no significant differences in the GIT 2.0 total and component scores between different immunosuppressive regimes (Table 1). No PRESS patients reported a complete absence of gastrointestinal tract symptoms.

Conclusion: Gastrointestinal symptoms captured by GIT 2.0 are common in early dcSSc. In patients with weight loss, scores for soilage, social, and emotional well-being are significant aspects of GIT involvement. In the PRESS cohort specific immunosuppressant exposure was not a strong driver of GIT symptoms, however, further longitudinal study in this patient population is planned.

Table 1: PRESS patient immunosuppressant use and gastrointestinal symptoms captured as components of GIT 2.0 (mean, standard deviation)

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>GIT 2.0 Total</th>
<th>GIT 2.0 Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Y = 3 N = 3</td>
<td>Y = 17 N = 17</td>
</tr>
<tr>
<td>M. A. Lopez-Olivo</td>
<td>0.94 0.58</td>
<td>0.73 0.75</td>
</tr>
<tr>
<td>Mertotredate</td>
<td>N = 34</td>
<td>N = 20</td>
</tr>
<tr>
<td>Reflux</td>
<td>0.5–1.38</td>
<td>0–2.0</td>
</tr>
<tr>
<td>Boating</td>
<td>0.74</td>
<td>0.88–2.25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.25 0.29</td>
<td>0.43 0.61</td>
</tr>
<tr>
<td>Social Function</td>
<td>0.30 0.42</td>
<td>0.6 0.24</td>
</tr>
<tr>
<td>Soil</td>
<td>0.50 0.06</td>
<td>0.15 0.4</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.23 0.24</td>
<td>0.59 0.64</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.5 0.36</td>
<td>1.13 1.47</td>
</tr>
<tr>
<td>Total GIT 2.0</td>
<td>5.38 2.2</td>
<td>1.79 2.64</td>
</tr>
</tbody>
</table>

Disclosure: T. M. Frech, None; M. Murtaugh, None; A. A. Shah, None; J. K. Gordon, None; V. K. Shankumag, None; R. T. Domsic, None; M. Hinchcliff, Gilead Science, 9; F. N. Hant, None; S. Assasi, None; V. D. Steen, Actelion Pharmaceuticals US, 8; United Therapeutics, 3; Gilead Science, 8; Roche Pharmaceuticals, 2; Sanofi-Aventis Pharmaceutical, 2.

1677

Initiation with an Endothelin Receptor Antagonist Is Associated with Worse Outcomes in Patients with Systemic Sclerosis and Pulmonary Arterial Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Cohort. Matthew R. Lammi, Reley Ann Sakekko, Stephen C. M. A. Lopez-Olivo, Robyn T. Domsic, Christine M. Bojanowski, Virginia D. Shanmugam, Daniel E. Furst, and Pharo Investigators. LSU Scleroderma and Lupus Center, 1LSU School of Medicine, New Orleans, LA, 2University of Utah School of Medicine, SLC, UT, 3University of Pittsburgh, Pittsburgh, PA, 4University of Washington, 5Medical University of South Carolina, 6University of Texas Health Science Center at Houston, Houston, TX, 7Georgetown University Medical Center, Washington, DC, 8University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: The PHAROS registry is a multicenter prospective observational study enrolling SSC patients with incident pulmonary hypertension. Patients with group I PAH, 6 months of initial therapy with either an endothelin-receptor antagonist (ERA), phosphodiesterase-5 inhibitor (PDE5), or a combination of ERA/PDE5 were included. Patients treated initially with prostacyclins were excluded. The starting point for all analyses was the date of therapy initiation. Outcomes were survival and TPCW, defined as the first occurrence of death, PAH-related hospitalization, lung transplant, initiation of parenteral prostacyclin, or worsening symptoms.

Results: Ninety-eight patients (initial ERA = 24, initial ERA/PDE5 = 59, initial ERA/PDE5 = 15) were included; no significant differences in baseline variables existed. TPCW was significantly worse in patients initially started on ERA compared to PDE5 or ERA/PDE5 (p =0.0001, Fig 1). Baseline factors

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Pulmonary arterial hypertension (PAH) is a leading cause of mortality in systemic sclerosis (SSc). A through medications have improved their prognosis, optimal therapy remains undefined. The goal of this study was to compare time to clinical worsening (TTCW) and survival based on initial oral PAH therapy.

Methods: Using data from the PHAROS registry (a multicenter prospective observational study enrolling SSC patients with incident pulmonary hypertension), patients with group I PAH, 6 months of initial therapy with either an endothelin-receptor antagonist (ERA), phosphodiesterase-5 inhibitor (PDE5), or a combination of ERA/PDE5 were included. Patients treated initially with prostacyclins were excluded. The starting point for all analyses was the date of therapy initiation. Outcomes were survival and TPCW, defined as the first occurrence of death, PAH-related hospitalization, lung transplant, initiation of parenteral prostacyclin, or worsening symptoms.

Results: Ninety-eight patients (initial ERA = 24, initial ERA/PDE5 = 59, initial ERA/PDE5 = 15) were included; no significant differences in baseline variables existed. TPCW was significantly worse in patients initially started on ERA compared to PDE5 or ERA/PDE5 (p =0.0001, Fig 1). Baseline factors
independently associated with shorter TTCW were initial ERA (HR 0.38, p=0.009), lower DLCO (HR 0.69 per 10% change, p=0.04), and higher PVR (HR 1.10 per Wood unit change, p=0.007). Three year survival was significantly worse in the initial ERA group (52.9%) compared to the PDE5 (91.5%) or ERA/PDE5 group (92.9%, p=0.004, Fig 2). The only baseline factor independently associated with risk for death in this cohort was initial ERA therapy (HR 0.22, p=0.004).

Conclusion: Compared to PDE5 or combination ERA/PDE5, initial therapy with an ERA in SSC-PAH patients was associated with a significantly worse TTCW and survival, even after adjustment for commonly accepted prognostic factors. Although these findings may be the result of unmeasured imbalances between groups, it is plausible that known ERA side effects such as fluid retention may have led to clinical worsening. Further study into the optimal initial oral therapy in patients with SSC-PAH is needed.

Results: Of 39 patients, 30 completed 6 months of treatment and were included in the analysis. At 6 month, although there was no statistically significant difference in change in FVC (% predicted) from baseline between the 2 groups, patients receiving Tadalafil had shown an improvement in mean (+SE) FVC of 1.82±2.08 whereas patients in placebo group had no change in mean FVC. Out of secondary outcome measures, the only significant difference between the 2 groups was found in patient global assessment scores which was significantly improved in Tadalafil group (p=0.05). There was a trend for improvement in TLC, breathing score in visual analogue scale (VAS) and physician global assessment score favoring Tadalafil although the difference between the 2 groups were not significant (p>0.05). There was no significant difference in adverse events between both groups.

Conclusion: Treatment with 6 month oral Tadalafil (20 mg alternate days) in patients with scleroderma-related ILD resulted in improvement in patient global assessment score. There was a trend for improvement in lung function, physician global assessment and VAS breathing scores. A larger multicentric study with sufficient power and high dose of Tadalafil may determine the efficacy of Tadalafil in ILD.

Table: Change in outcome measures from Baseline to 6 month in Tadalafil vs placebo group

<table>
<thead>
<tr>
<th>Characteristics Baseline</th>
<th>Value at 6 month</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil Group (n 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (%Predicted)</td>
<td>49.18 ± 3.81</td>
<td>51.5 ± 4.06</td>
</tr>
<tr>
<td>TLC (%Predicted)</td>
<td>75.70 ± 5.18</td>
<td>78.50 ± 7.42</td>
</tr>
<tr>
<td>DLCO (%Predicted)</td>
<td>36.30 ± 3.51</td>
<td>35.8 ± 4.95</td>
</tr>
<tr>
<td>Mahler Dyspnoea score</td>
<td>Base line</td>
<td>7.0 ± 2.58</td>
</tr>
<tr>
<td>Transfational Dyspnoea score</td>
<td>2.47 ± 0.77</td>
<td></td>
</tr>
<tr>
<td>VAS Breathing(mm)</td>
<td>54.12 ± 9.15</td>
<td>24.71 ± 6.99</td>
</tr>
<tr>
<td>Physician global</td>
<td>60.12 ± 5.14</td>
<td>33.41 ± 3.22</td>
</tr>
<tr>
<td>Patient global</td>
<td>73.41 ± 5.88</td>
<td>31.35 ± 5.83</td>
</tr>
<tr>
<td>SF36 (physical)</td>
<td>37.2 ± 1.69</td>
<td>45.04 ± 1.71</td>
</tr>
<tr>
<td>SF36 (M ental)</td>
<td>37.02 ± 2.85</td>
<td>45.88 ± 2.88</td>
</tr>
<tr>
<td>Skin thickness score</td>
<td>17.71 ± 2.11</td>
<td>15.94 ± 2.71</td>
</tr>
<tr>
<td>6 min walk test (meters)</td>
<td>426.69 ± 34.08</td>
<td>472.65 ± 22.83</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>31.71 ± 2.67</td>
<td>29.59 ± 2.47</td>
</tr>
<tr>
<td>Placebo Group (n 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (%Predicted)</td>
<td>57.46 ± 2.37</td>
<td>57.46 ± 3.05</td>
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<td>TLC (%Predicted)</td>
<td>78 ± 3.92</td>
<td>75.29 ± 4.71</td>
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<tr>
<td>DLCO (%Predicted)</td>
<td>45.57 ± 3.92</td>
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<td>Transfational Dyspnoea score</td>
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<td>VAS Breathing(mm)</td>
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<td>Physician global</td>
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<td>32.62 ± 8.77</td>
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<td>Patient global</td>
<td>49.07 ± 7.51</td>
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<td>SF36 (physical)</td>
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<td>46.69 ± 2.65</td>
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<tr>
<td>SF36 (M enal)</td>
<td>39.83 ± 3.42</td>
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<td>Skin thickness score</td>
<td>20.23 ± 2.21</td>
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<td>6 min walk test (meters)</td>
<td>419.23 ± 25.37</td>
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<td>RVSP (mm Hg)</td>
<td>28.62 ± 2.12</td>
<td>27.77 ± 2.97</td>
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Plus-minus values are means±SD. *p<0.05 for comparison with placebo group. #Paired data for DLCO and TLC were available and analyzed for only 10 and 7 patients in Tadalafil and placebo group respectively.

Disclosure: J. Parida, None; A. Nath, None; Z. Neyaz, None; V. Agarwal, None.

1680
An Indirect Comparisons Analysis of Medications Used for Treatment of Raynaud’s Phenomenon...
The histopathology specimen of the explanted heart revealed myocardial fibrosis compatible with SSc primary cardiac involvement in all patients. Infectious complications occurred in 4 patients, 2 patients had ischemic lesions and 1 patient died from an unexplained graft failure. Median intensive care unit stay after the surgery was 22 days. During a median follow-up of 2.8 years, 4 patients had at least one acute cellular rejection, mainly of mild grade. Mild heart allograft vasculopathy occurred after a median of 2 years in 3 of 4 patients in whom coronary arteries were explored.

Conclusion: Symptomatic cardiac involvement in SSc has a bad prognosis. Heart transplantation is a relatively safe life-saving procedure in carefully chosen SSc patients with primary cardiac involvement manifesting with progressive dysfunction and/or arrhythmic complications.

Reference:
J. Martsens E. Transplantation. 2012

Table 1: Patients' characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVEF (%)</th>
<th>LV filling pressures</th>
<th>BV dysfunction</th>
<th>MRI - Catecholamine enhancement</th>
<th>nPAP (mmHg)</th>
<th>RAP (mmHg)</th>
<th>wedge pressure (mmHg)</th>
<th>PVR (Wood units)</th>
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<td>Yes</td>
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<td>5</td>
<td>56</td>
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<td>T2 &amp; B-ventricular</td>
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Table 2: Cardiac structural and hemodynamic values before transplantation

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<td>3.21</td>
<td>3.2</td>
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Disclosure: A. Ilicic, None; E. Chateus, None; E. Epailly, None; H. Kremer, None; J. Sibilia, None; J. Gottenberg, None; S. Pattier, None; E. Flecher, None; C. Goeminne, None; T. Martin, None.

Background/Purpose: There is no specific treatment for primary cardiac involvement in SSc. Even if heart transplantation is an option, only 1 case has been reported. The aim of the study was to collect data of patients with SSc and a primary cardiac involvement requiring a heart transplantation in order to establish the clinical course and expected outcomes for this procedure.

Methods: Retrospective chart review of patients with SSc and a primary cardiac involvement requiring a heart graft in one of the major transplantation centers in France.

Results: A national survey allowed us to identify 6 patients fulfilling ACR/EULAR 2013 classification criteria for SSc. They had a history of primary cardiac involvement with an unequivocal indication for heart transplantation. 4/6 patients were women, 50% had lcSSc and 1 patient had an overlap with RA (Table 1). The median age at SSc diagnosis was 28 years and time to cardiac dysfunction diagnosis was 2.5 years. All patients had at least another systemic involvement, mostly gastrointestinal and/or musculoskeletal. Immunosuppressive treatment excluding corticosteroids has been prescribed to 3 patients.

In the year before transplantation, all patients were classified NYHA functional capacity III or IV and 5 of them required at least 1 hospitalisation. Median time from cardiac dysfunction diagnosis to transplantation was 4 years. The leading indication was heart failure requiring intravenous vaso-pressors except for 1 patient who was transplanted for recurrent ventricular arrhythmia. Cardiac pre-transplantation structural, functional and hemodynamic data are presented in Table 2.
Results: 17 and 49 patients were treated with MMF or AZA for a mean of 3.7±1.4 and 3.8±3.1 years, respectively, with 66% of both groups previously treated with cyclophosphamide. Patients were treated with an average MMF dose of 1.57g/day and AZA of 100mg/day.

Mean age at commencement was 54.6±9.3 years for MMF and 52.9±12.9 years for AZA (p=0.23). Patients in both groups were predominantly female and Caucasian with long-standing disease (10.9±3.7 years for MMF vs. 12.7±7.3 years for AZA, p=0.28). Disease was diffuse in 65% of patients on MMF and 51% on AZA.

Median absolute FVC at T-1 for MMF treatment was 2.5L declining to 2.3L at T0 (p=0.02). At T1 and T2, FVC was stable at 2.1L (p=0.63) and 2.1L (p=0.93). Median absolute diffusion capacity (DLCO) also demonstrated decline prior to treatment (12.2 to 9.8, p=0.03), with stability at T1 (10.4, p=0.83) and T2 (11.9, p=0.04). Stability or improvement was seen at T1 in 12/15 and T2 in 9/11 cases. Comparable efficacy was achieved with AZA (16/19 cases were stable or improved at T1 and 14/19 at T2).

A diverse events leading to discontinuation were less common in the MMF group (2/17 vs. 13/49). Gastrointestinal complications were the main cause for discontinuation in both groups.

Conclusion: In patients with SSC-ILD with declining pulmonary function, MMF treatment was associated with stability in FVC and DLCO comparable to AZA, and was better tolerated, suggesting a potentially superior role as maintenance therapy.

Disclosure: C. Owen, None; G. Ngian, None; K. Elford, None; O. Moona, None; M. Nikpour, None; W. Stevens, None; S. Proustman, None; J. Roddy, None; J. Zochling, None; C. Hill, None; P. Nash, None; A. Sturgess, None; J. Sahhar, None.

1683 Botulinum Toxin-a for the Treatment of Severe Raynaud Phenomenon

Lucia Ruiz Gutiérrez1, Ana Pérez Gómez2, Nurya Valdeolivas Casillas1, Henry Moron Cruz1, Eduardo Cuende Quintana1, Ana Sánchez Atrio2, Ana Turrón Nietves1, Atusa Mvosa3, Cristina Bojohge Hara2, Fernando Albarran Hernandez1, Maria Liz Romero Bogado1, Susana Medina Montalvo1 and Melchor Alvarez de Mon1. 1Hospital Principe de Asturias, 2.1Hospital Principe de Asturias, Madrid, Spain, 3Hospital Principe de Asturias, Dermatology Department, Alcalá de Henares, Madrid, Spain.

Background/Purpose: Raynaud’s phenomenon (RP) is characterized by transient episodes of vasoconstriction of the arteries and arterioles of the extremities in response to cold or emotional stimuli. Depending on the severity of the vascular insult, it can cause superficial ulceration or deep-tissue necrosis. Pharmacological treatments aim to enhance blood flow but their efficacy is not uniform.

Methods: We present a series of 7 patients with Raynaud’s phenomenon with bad response to conventional pharmacological therapy that have been treated with local botulinum neurotoxin-A. Patients’ characteristics are summarized in table 1. Exclusion criteria included botulinum toxin allergy, recent skin ulceration or necrosis, or severe hand deformity.

A cumulative total dose of 30–60 units of botulinum toxin was injected into the palmar aspect of the hand. Prior to infiltration, obstructive pathology was ruled out by Doppler ultrasound; also, a nailfold capillaroscopy test was performed before and after the infiltration. Variables such as the number of episodes per day, pain during the episodes, recuperation time, finger color and presence of digital ulceration or necrosis had been studied baseline, 30 minutes, one week and one month after the infiltration.

Results: 30 minutes after infiltration, three patients felt no improvement, two assessed slight improvement and two very important improvement. At the patients’ one-week and thirty-days follow-up visits two patients did not perceive any change and four experienced great amelioration. Patients that did not register any change where those with fewer subjective clinical complaints and normal Doppler ultrasound and capillaroscopy tests.

The variable with the most remarkable response was pain, with important pain decrease in all of the cases. Three patients presented digit ulcers at baseline visit; ulceration healing was noted in all of them, two of them one week after the infiltration and the other one, one month after.

Three patients reported mild “weakeness” after being injected and one reported slight thenar-eminence pain that lasted a few days. None of the patients suffered any systemic complications related to the toxin.

Conclusion: Botulinum toxin-A is a safe and effective therapeutic option for patients with severe Raynaud’s phenomenon that have failed to conventional treatment.

Table 1

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>SEX</th>
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<th>PREVIOUS MANAGEMENT</th>
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Disclosure: L. Ruiz Gutiérrez, None; A. Pérez Gómez, None; N. Valdeolivas Casillas, None; H. Moron Cruz, None; E. Cuende Quintana, None; A. Sánchez Atrio, None; A. Turrón Nietves, None; A. Mvosa, None; C. Bojohge Hara, None; F. Albarran Hernandez, None; M. L. Romero Bogado, None; S. Medina Montalvo, None; M. Alvarez de Mon, None.
Effects of Mycophenolate Mofetil on Pulmonary Lung Function in Interstitial Lung Disease of Systemic Sclerosis. Michael Pham and W Leroy Griffing. Mayo Clinic Arizona, Scottsdale, AZ.

Background/Purpose: Interstitial lung disease remains a primary driver of morbidity and mortality in patients suffering from systemic sclerosis. Cyclophosphamide currently is the treatment with the most data and experience; however, toxicity and poor tolerance often limit its clinically modest usefulness. Mycophenolate mofetil (MMF) has received growing interest as an alternative agent. In this study, effects of MMF on pulmonary lung function in systemic sclerosis-associated interstitial lung disease were examined.

Methods: Twenty patient cases were retrospectively reviewed having met the American College of Rheumatology’s criteria for systemic sclerosis. Interstitial lung disease was defined and characterized by high-resolution chest tomography. Cases were included if treatment was greater than 1 gram per day dosing of MMF for at least 6 months. Pulmonary function test results were collected prior to and following treatment initiation at 6 month intervals for a total 30-month monitoring time span.

Results: Six-to-twelve months prior to MMF initiation, mean predicted forced vital capacity (%FVC) was 74% ± 15.9% (mean ± SD) and declined to 71.3% ± 16.8% at treatment baseline. Following MMF initiation, the mean %FVC remained stable at 70.7% ± 12.9% and 71.2% ± 14.2% at the 6-to-12 and 12-to-18 month follow-up interval period, respectively. Mean rate of change in %FVC or %FVC velocity was −0.25% ± 0.93% per month prior to MMF treatment. Following MMF treatment, rates of decline reversed and %FVC velocity was +0.18% ± 0.62% per month at the 6-to-12 month follow-up interval – a statistically significant improvement (p=0.005). Mean predicted diffusion capacity of carbon monoxide (%DLCO) was 54.3% ± 14.4% prior to treatment. After MMF treatment, %DLCO improved to 56.1% ± 15.2% by the 6-to-12 month follow-up interval and to 57.4% ± 19.0% by the 12-to-18 month follow-up interval. These results are summarized in Figure 1 below.

Conclusion: We report trends of stability with %FVC and trends of improvement with %DLCO over an 18-month period following MMF treatment. Our findings suggest mycophenolate mofetil is a promising alternative treatment for interstitial lung disease of systemic sclerosis. However, these observations were not statistically significant and further emphasize the need for a higher powered randomized clinical trial.

Disclosure: M. Pham, None. W. L. Griffing, None.

1686

DECT energy computed tomography for the evaluation of calcinosis in systemic sclerosis. Vivien Hsu, Mark Bramwit and Naomi Schlesinger. RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, Robert Wood Johnson University Hospital, New Brunswick, NJ, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ.

Background/Purpose: To better characterize the soft tissue details of systemic sclerosis-related (SSc) calcinosis of the hands using dual-energy computer tomography (DECT). DECT is an imaging modality used similarly to study monosodium urate (MSU) deposition in gout (1).

Methods: Fourteen patients with symmetrical hand SSc-calcinosis had DECT imaging and their clinical characteristics reviewed.

Results: Eight of 14 patients had diffuse SSc and 6 also had rheumatoid arthritis (RA). Herein are 3 DECT images: Image 1: a caucasian male with lifelong calcinosis due to diffuse sclerodema, whose painful deposits drain intermittently. Image 2: a caucasian female with limited SSc and RA for 15 years, whose calcinosis was found by imaging. Image 3: an African-American female with diffuse sclerodema and RA for 10 years. Her calcinosis caused painful wrist swelling, but despite surgery, continues to accumulate.

On DECT imaging, calcinosis was most commonly found in the subcutaneous (SQ) fat pads of the fingertips and along tendon sheaths and muscle groups. Acro-osteolysis was present in most (93%) patients, 7 (50%) with calcinosis nearby. No MSU was identified. Our cohort also had pulmonary fibrosis (79%), ischemic digital ulcers (71%) and bowel (43%) complications.

Conclusion: SSc-calcinosis affects diffuse and limited SSc. We found DECT imaging better defined the soft tissue details and was useful in the evaluation of SSc-calcinosis.

References:

Image 1: 3D image shows acro-osteolysis of the 2nd and 3rd digits, extensive calcification in the SQ fat (volar) of the second digit (arrow), punctate deposits in the fat pad of thumb, lateral to the scaphoid bone, and between several MCP joints.
Background/Purpose: Systemic sclerosis (SSc) is associated with an increased prevalence of cardiac involvement despite often being clinically silent. Cardiac involvement is a major factor in decreasing SSc survival rates because it is associated with a 70% 5-year mortality rate. Cardiac magnetic resonance imaging (CMR) is useful in SSc since it focuses on late gadolinium enhancement (LGE) abnormalities, ventricular morphology, and function. Our study aimed to comprehensively analyze CMR and investigate the association between CMR findings and brain natriuretic peptide (BNP) in SSc patients (pts) without cardiac symptoms.

Methods: Consecutive female pts with SSc without cardiac symptoms as well as healthy female controls were enrolled. SSc pts and control subjects with no history or clinical findings of systemic and pulmonary hypertension determined by echocardiography, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia underwent non-contrast or contrast CMR on a 1.5T scanner. Left ventricular (LV) function was measured using two-dimensional echocardiography. LV mass (LVM) and LVM index (LVM I) determined by the LVM/body surface area. LGE was obtained on contrast-enhanced black blood T2-WI. Serum BNP concentrations were measured simultaneously in all participants.

Results: We compared 35 SSc pts (mean age, 55.9 ± 7.1 years) 19 with diffuse type and 16 with limited type—20 healthy controls (mean age, 56.9 ± 3.1 years). There were no significant differences in characteristics such as age, gender, and cardiovascular risk factors, between SSc and control group. Compared with the control group, the SSc group had a significantly higher EDV with tendency toward a high LVM I. There was no difference in EF between the control and SSc groups. SSc with LGE was detected in 16 of 35 pts (46%). The mean finding observed in 9 of these 16 (56%) pts was a linear pattern without coronary stenosis. A patchy nodular enhancement pattern was observed in 7 pts (44%). LVM I and mass/EDV were significantly higher in the LGE (+) group than in the LGE (−) group (P < 0.001, P = 0.003, respectively). T2-WI imaging showed myocardial inflammation in 6 of 35 pts (17%). The mean BNP level of the SSc group was significantly higher than that of the control group (P = 0.04). The mean BNP level of the SSc with LGE group was significantly higher than that of the SSc without LGE group (P = 0.023). BNP level was significantly correlated with LVM I and EF in the SSc group (P = 0.04, P = 0.05, respectively).

S743
After adjustment for age, disease duration, and BNP, the SSc with LEG group did not have a modified association with LVMI.

**Conclusion:** SSc patients without cardiac symptoms have a high prevalence of cardiac abnormalities. SSc patients with LEG had abnormal morphology associated with LVMI and serum BNP even with a normal EF. Further studies are needed to determine whether CMR abnormalities affect disease activity (DA) in SSc with LEG.

**Disclosures:** K. Sugiyama, None; H. Kobayashi, None; Y. Kobayashi, None; Y. Nagasawa, None; N. Ikumi, None; T. Nozaki, None; H. Inomata, None; H. Shiraiwa, None; H. Karasawa, None; N. Kitamura, None; M. Iwata, None; Y. Matsukawa, None; M. Takei, None.

## 1689

**Microhaemorrhages and Giant Capillaries in Nailfold Videocapillaroscopy Are Able to Accurately Predict Disease Activity Level in Systemic Sclerosis.**

Domenico Sambataro, Nicolaeta Del Papa, Gianluca Sambataro, Wanda Maglione, Eleonora Zaccara and Claudio Vitali.

**Background/Purpose:** Systemic Sclerosis (SSc) is a connective tissue disease characterized by Raynaud’s phenomenon, skin fibrosis and involvement of internal organs such as lung, heart, bowel, and kidney. The microvascular involvement is considered hallmark of disease. Nailfold Videocapillaroscopy (NVC) is a simple method able to identify the disease-related microvascular alterations in an easily accessible capillary bed and is commonly used for diagnosis and patients’ sub-setting.

Aim of this study is to evaluate whether the number of microhaemorrhages (MHE), micro-thrombosis (MT), giant capillaries (GC), and normal or dilated capillaries (Cs) in NVC could predict disease activity (DA) in SSc.

**Methods:** One hundred and seven patients (57 with limited cutaneous and 50 with diffuse cutaneous SSc, 10 males) meeting the 2013 ACR/EULAR classification criteria, were selected for this study. The European Scleroderma Study Group (ESSG) index was taken as gold standard for DA assessment. Score ≥3.5 and = 3 were considered as indicative of highly and moderate DA, respectively. NVC was performed on 8 fingers (second to fifth of both hands) in the middle of nailfold taking 4 consecutive fields of 1 millimeter with a 200× magnification lens. The following NVC features were considered: total number of MHE/MT aligned in the same row on the cuticle (here called NEMO score); total number of GC (GC score); mean number of Cs observed in all NCV fields (Cs score).

Non-parametric tests were used to compare the NVC scores with the variables here taken into account. Receiver operating characteristic (ROC) curves were constructed by plotting sensitivity and specificity values of NVC scores in correctly classifying patient having or not an active disease phase. Logistic regression model was also tested to assess the contribution of the NVC scores in predicting the presence of DA.

**Results:** NEMO and GC scores were positively correlated with ESSG index (R = 0.65, p < 0.0001, and R = 0.47, p < 0.0001, respectively), whilst Cs score showed a negative correlation with that DA index (R = -0.30, p < 0.001).

The area under the curve (AUC) of receiver operating characteristic (ROC) plots, obtained by NEMO score sensitivity and specificity values in classifying patients with ESSG index ≥3.5, was significantly higher than the corresponding AUC derived from either GC or Cs scores (p < 0.001 and p < 0.0001, respectively). A modified score, defined by the presence of given number of MHE/MT and GC, had a good performance in classifying active patients (ESSG index ≥ 3, sensitivity 95.1%, specificity 84.8%, accuracy 88.7%).

**Conclusion:** This newly proposed NCV scoring system, here named mNEMO score, seems to be a valid tool to predict DA level in SSc. In addition, it appears also feasible since it can be derived simply during an outpatient visit and in a rather short time.

It is, of course, evident that a patient with a positive mNEMO score should be addressed to a more careful clinical, instrumental, and serological evaluation to confirm the suspicion and define a more precise clinical profile.

**Disclosures:** D. Sambataro, None; N. Del Papa, None; G. Sambataro, None; W. Maglione, None; E. Zaccara, None; C. Vitali, None.

## 1690

**Improvement of Digital Ulcerative Disease in Patients with Systemic Sclerosis Is Associated with Better Functional Prognosis.**


**Background/Purpose:** Ischemic digital ulcers (DU) represent a major complication of systemic sclerosis (SSc) leading to hand disability. We investigated the impact of controlling the ulcerative disease on hand disability and quality of life in SSc patients following one year of bosentan treatment.

**Methods:** ECLIPSE is a 2-year prospective, observational study. Patients with SSc who experienced at least one DU in previous year and received bosentan to prevent occurrence of new DU were included between October 2009 and March 2011. Demographical and clinical data were collected at inclusion and at 1 year, as well as disability scores (Chon hand function scale (CHFS), health assessment questionnaire disability index (HAQ-DI)), pain score (Visual Analog Scale), and quality of life (SF-36). A controlled ulcerative disease was defined by healing of all DU present at inclusion and the absence of new ulcer between inclusion and one-year follow-up. Data are presented as means ± standard deviations.

**Results:** Follow-up data were available at one year for 120 patients out of the 190 included patients. Patients’ characteristics were similar to those of the overall cohort. Mean age at inclusion and at SSc diagnosis were 54 ± 15 and 44 ± 15 years, respectively. SSc was diffuse in 42% of the cases. At inclusion, patients had been receiving bosentan for 15.6 ± 22,1 months. During the one-year follow-up, 46 (38%) patients experienced an episode of new DU and the incidence of the event was 0.6 event/patient-year [95% confidence interval: 0.44-0.81]. Nevertheless, the proportion of patients with at least one DU decreased from 61% to 22% and the number of DU per patient decreased from 1.4 ± 1.8 to 0.6 ± 1.6 (p < 0.0001). In parallel disability scores decreased from 29.4 ± 20.1 to 25.0 ± 20.2 (p = 0.005) on the CHFS and from 0.96 ± 0.68 to 0.68 ± 0.73 (p = 0.04) for the HAQ-DI; the pain score decreased from 4.3 ± 3.1 to 2.9 ± 2.8 (p = 0.0001). Improvements in the physical and mental components of the SF-36 were not significant except for bodily pain (p = 0.04) and mental health (p = 0.01).

Patients with a controlled ulcerative disease (n = 58) significantly improved CHFS (p = 0.04), HAQ-DI (p = 0.04), and physical component of the SF-36 (p = 0.05) compared with patients with an uncontrolled disease (n = 62).

During the one-year follow-up, 21 (17%) patients discontinued bosentan for an adverse event including 5 patients presenting elevated aminotransferases

**Conclusion:** In patients with SSc receiving bosentan, a controlled ulcerative disease is associated with a significant attenuation of disability.

**Disclosures:** P. Carpentier, None; C. Lok-Charles, None; P. Clerson, None; V. Gressin, None; E. Huchel, None; A. Berzene, None; E. Diet, None; A. Kifas, None; Vu Kien, None; P. Jego, None; C. Agard, None; A. B. Duval Modeste, None; A. Sparsa, None; E. Puzenat, None; M. A. Richard, None; L. Mouton, None.

## 1691

**Systemic Sclerosis Patients with Pulmonary Hypertension Have a Lower Change in End Tidal Carbon Dioxide Following Three Minutes of Step Exercise Than Systemic Sclerosis Patients without Pulmonary Hypertension: A Cross-Sectional Study.**


**Background/Purpose:** Systemic Sclerosis Patients with Pulmonary Hypertension have a lower change in End Tidal Carbon Dioxide Following Three Minutes of Step Exercise Than Systemic Sclerosis Patients without Pulmonary Hypertension: A Cross-Sectional Study.

**Methods:** Thirty Sscl patients (17 PP and 13 non PP) were included in this cross-sectional study. Exercise was tolerated by all participants. Two minute control TCO2 was followed by three minutes of steady step exercise at 40% of the maximal stage achieved by the patient on a bicycle ergometer. TCO2 was then measured for the next three minutes.

**Results:** The mean TCO2 at rest, at 0 and 1 minute of exercise were not different between the PP and non PP patients. During the 3 minutes of exercise, the mean (± SD) TCO2 was 11.8 ± 2.5 in PP and 17.5 ± 4.6 in non PP (p = 0.001) and 4.0 ± 1.0 in PP and 7.6 ± 1.5 in non PP (p = 0.002) after 1 and 3 minutes, respectively.

**Conclusion:** Systemic Sclerosis Patients with Pulmonary Hypertension have a lower change in End Tidal Carbon Dioxide Following Three Minutes of Step Exercise Than Systemic Sclerosis Patients without Pulmonary Hypertension: A Cross-Sectional Study.

**Disclosures:** E. Puzenat, None; A. B. Duval, None; A. Sparsa, None; E. Puzenat, None; M. A. Richard, None; L. Mouton, None.
**Background/Purpose:** Pulmonary hypertension (PH) is a leading cause of death in patients with systemic sclerosis (SSc). Transthoracic echocardiography and pulmonary function testing are standard noninvasive screening methods for PH. However, both are limited in their ability to distinguish between SSc patients with and without PH. The gold standard diagnostic test for PH is right heart catheterization (RHC), which although accurate, is expensive, invasive, and has associated risks. Finding an accurate, noninvasive technique to screen for PH in the SSc population is an important unmet need.

The submaximal heart and pulmonary evaluation (step test) is a standardized, noninvasive, submaximal stress test that consists of a 5.5 inch high step that patients step up and down on for 3 minutes. During the test, end tidal carbon dioxide, which is positively correlated with cardiac output and pulmonary blood flow and inversely correlated with the minute ventilation to carbon dioxide production ratio ($V_{CO2}$) and reflects the severity of PH, is monitored. Our primary aim was to determine whether SSc patients with PH would have a lower change in end tidal carbon dioxide ($\Delta V_{ETCO2}$) from rest to end-exercise on the step test than SSc patients without PH. Our secondary aim was to determine whether SSc patients with PH would have a higher $V_{ETCO2}$ than those without PH. We also examined differences in validated self-report questionnaires and biomarkers between SSc patients with and without PH. We hypothesized that SSc patients with PH would have a lower $\Delta V_{ETCO2}$ and higher $V_{ETCO2}$ than SSc patients without PH.

**Methods:** This is a cross-sectional study of 27 patients with limited or diffuse cutaneous SSc who underwent an RHC within 24 months of study entry. All patients were administered the step test between May 2012 and August 2013. $\Delta V_{ETCO2}$ and $V_{ETCO2}$ were compared between patients with and without PH, defined as a mean pulmonary artery pressure $\geq$ 25 mmHg on RHC. Differences in self-report data and biomarkers were also compared between groups. Statistical analysis was performed using Kruskal-Wallis, chi square, and Fisher exact tests, as appropriate.

**Results:** See Table 1 for patient characteristics. SSc patients with PH had a statistically significantly lower median $\Delta V_{ETCO2}$ than SSc patients without PH ($-2.1$ [$-5.1$ to $-0.7$] vs. $1.2$ [$0.7$ to $5.4$, p = 0.035] and a statistically significantly higher median $V_{ETCO2}$ ($53.4$ [39-64.1] vs. $36.4$ [31.9-41.1], p = 0.035) than SSc patients without PH. There were no statistically significant differences in self-report data or biomarkers between groups (Table 1).

**Conclusion:** $\Delta V_{ETCO2}$ and $V_{ETCO2}$ as measured by the step test are statistically significantly different between SSc patients with and without PH. Neither traditional self-report outcome measures nor biomarkers differed between groups. Further prospective studies are needed to evaluate the step test as a screening tool for PH in the SSc population.

### Table 1: Patient Characteristics, Self-Report Questionnaire Scores, and Biomarker Levels

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>PH (N = 18)</th>
<th>No PH (N = 9)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age - yr</td>
<td>61.9 (52.9-69.2)</td>
<td>65.7 (56.4-70.3)</td>
<td>0.64</td>
</tr>
<tr>
<td>Female sex</td>
<td>13 (72%)</td>
<td>5 (56%)</td>
<td>0.39</td>
</tr>
<tr>
<td>White race</td>
<td>13 (72%)</td>
<td>7 (78%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Limited cutaneous SSc</td>
<td>13 (72%)</td>
<td>6 (67%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>17.5 (6.4-26.1)</td>
<td>11.5 (4.02-19.4)</td>
<td>0.22</td>
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<tr>
<td>Interleukin-6 pg/mL</td>
<td>4.46 (3.37-10.54)</td>
<td>5.45 (3.19-6.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypoxia-inducible factor 1a - units</td>
<td>23.62 (22.98-23.80)</td>
<td>23.29 (22.93-23.53)</td>
<td>0.40</td>
</tr>
<tr>
<td>Vascular endothelial growth factor - pg/mL</td>
<td>346.4 (260.1-472.2)</td>
<td>265.2 (228.9-468.2)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**Conclusion:** $\Delta V_{ETCO2}$ and $V_{ETCO2}$ as measured by the step test are statistically significantly different between SSc patients with and without PH. Neither traditional self-report outcome measures nor biomarkers differed between groups. Further prospective studies are needed to evaluate the step test as a screening tool for PH in the SSc population.
Table: Clinical phenotypes stratified for systemic sclerosis specific autoantibodies and nailfold capillaroscopy pattern (anti-ScI-70 + patients and anti-RNP + patients with an early pattern were left out because of low numbers, n = 3 and n = 0, respectively).

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Early n = 12</th>
<th>ACA + Active n = 3</th>
<th>Active n = 9</th>
<th>Late n = 27</th>
<th>Late n = 18</th>
<th>Active n = 22</th>
<th>Active n = 18</th>
<th>Late n = 9</th>
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<tr>
<td>Age in years, mean (SD)</td>
<td>59 (15)</td>
<td>52 (14)</td>
<td>62 (12)</td>
<td>54 (14)</td>
<td>55 (13)</td>
<td>46 (7)</td>
<td>46 (14)</td>
<td></td>
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<tr>
<td>Female, n (%)</td>
<td>11 (92)</td>
<td>9 (75)</td>
<td>22 (22)</td>
<td>22 (22)</td>
<td>22 (22)</td>
<td>11 (61)</td>
<td>11 (61)</td>
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<tr>
<td>Skin</td>
<td></td>
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<tr>
<td>SSc, type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>lcSSc</td>
<td>9 (75)</td>
<td>6 (50)</td>
<td>18 (22)</td>
<td>8 (44)</td>
<td>17 (94)</td>
<td>7 (39)</td>
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<tr>
<td>dcSSc</td>
<td>3 (25)</td>
<td>2 (14)</td>
<td>6 (8)</td>
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<td>1 (6)</td>
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<tr>
<td>mRSS, median (IQR)</td>
<td>2 (0.5–4)</td>
<td>2 (0.5–4)</td>
<td>2 (0.5–4)</td>
<td>2 (0.5–4)</td>
<td>2 (0.5–4)</td>
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<tr>
<td>Intercostal nerve weakness</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (8)</td>
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<td>1 (8)</td>
<td>1 (8)</td>
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<tr>
<td>DLCO % if predicted, mean (SD)</td>
<td>73 (10)</td>
<td>75 (12)</td>
<td>61 (13)</td>
<td>64 (77)</td>
<td>57 (14)</td>
<td>60 (12)</td>
<td>49 (19)</td>
<td></td>
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<tr>
<td>DLCO % if predicted, median (IQR)</td>
<td>20 (8)</td>
<td>17 (10)</td>
<td>15 (8)</td>
<td>16 (10)</td>
<td>15 (8)</td>
<td>5 (3)</td>
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<tr>
<td>eGFR, median (IQR)</td>
<td>89 (66–108)</td>
<td>63 (61–113)</td>
<td>91 (70–160)</td>
<td>88 (66–106)</td>
<td>53 (42–99)</td>
<td>88 (66–99)</td>
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<tr>
<td>NT-proBNP, median (IQR)</td>
<td>60 (47–99)</td>
<td>60 (48–99)</td>
<td>59 (37–99)</td>
<td>60 (48–99)</td>
<td>60 (56–99)</td>
<td>59 (47–99)</td>
<td>60 (48–99)</td>
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<td>Vascular</td>
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<tr>
<td>Digital ulnar SC, n (%)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (8)</td>
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<tr>
<td>Polytrop SC, n (%)</td>
<td>0</td>
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<td>Heart</td>
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<tr>
<td>NT-proBNP, median (IQR)</td>
<td>64 (61–108)</td>
<td>64 (61–108)</td>
<td>64 (61–108)</td>
<td>64 (61–108)</td>
<td>54 (47–108)</td>
<td>64 (61–108)</td>
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<td>Perfusion index, n (%)</td>
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<td>Inter-rater Agreement</td>
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<tr>
<td>Inter-rater Agreement</td>
<td>0.64 (p &lt; 0.05)</td>
<td>0.64 (p &lt; 0.05)</td>
<td>0.64 (p &lt; 0.05)</td>
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</table>

**Method:** Baseline characteristics and one year follow up results from patients with diffuse cutaneous SSc (dcSSc) or limited (cutaneous) SSc (lcSSc) referred to the multidisciplinary health-care program were evaluated. Progressive disease was defined as: SSc-related decrease, decrease of ≥10% of forced vital capacity (FVC), decrease of ≥15% of diffusion capacity for carbon monoxide (DLCO), decrease of ≥10% of body weight, decrease of ≥30% of estimated glomerular filtration rate, increase of ≥30% of hsCRP, and C-reactive protein (hsCRP). Progressive disease was defined as: SSc-related decrease, decrease of ≥10% of forced vital capacity (FVC), decrease of ≥15% of diffusion capacity for carbon monoxide (DLCO), decrease of ≥10% of body weight, decrease of ≥30% of estimated glomerular filtration rate, increase of ≥30% of hsCRP, and C-reactive protein (hsCRP). Progressive disease was defined as: SSc-related decrease, decrease of ≥10% of forced vital capacity (FVC), decrease of ≥15% of diffusion capacity for carbon monoxide (DLCO), decrease of ≥10% of body weight, decrease of ≥30% of estimated glomerular filtration rate, increase of ≥30% of hsCRP, and C-reactive protein (hsCRP).

**Results:** Between April 2009 and January 2014 303 SSc patients were referred to the health-care program, of which 164 underwent re-evaluation after one year (mean 13.5, range 10–23 months). Sixty-six patients (38% of 172) had progressive disease, including 8 patients who died 18 months after first evaluation. Progressive disease was found in 27 (33%) patients with dcSSc, 32 (50%) with lcSSc, and seven (26%) with lcSSc. The mean time of skin involvement, mRSS and disease duration could not independently discriminate progressive patients. Multivariable analysis showed that friction rubs and proximal muscular weakness were most significantly associated with progressive disease, additional to type of SSc, age, gender, disease duration, autoantibody profile and use of immunosuppressive therapy. The multivariable model showed fair discrimination (AUROC 0.738 [95% CI 0.630–0.840]).

**Conclusion:** Thirty-eight percent of SSc patients showed progressive disease after one year follow-up, with highest frequency of progression among patients with lcSSc. The strongest predictors of progressive disease were friction rubs and proximal muscular weakness; pattern of skin involvement and disease duration were not independently discriminative. These observations underline the relevance of strict follow-up in all SSc patients as well as the need for more effective treatment strategies.
Background/Purpose: Objective method to evaluate the skin involvement in the patients with scleroderma has not been definitely established. We have developed Vesmeter, a computer-linked device to simultaneously quantify the skin characteristics such as viscosity, elasticity and softness, and have reported its usefulness to evaluate the skin characteristics of patients with scleroderma. Here, we validated Vesmeter as a diagnostic tool of scleroderma.

Methods: Using Vesmeter, we evaluated the skin characteristics of patients with scleroderma and healthy volunteers. 17 points of the body were evaluated, like modified Rodnan’s skin score. First, we compared the skin characteristics of scleroderma patients with that of healthy volunteers matched by age and sex. Second, we conducted bivariate Receiver Operating Characteristic (ROC) analyses to examine which points and parameters are useful to diagnose scleroderma. Third, using whole data of healthy volunteers, we conducted logistic regression and ROC analysis to validate Vesmeter as a diagnostic tool of scleroderma.

Results: 39 patients with scleroderma and 413 healthy volunteers were included. Among the healthy volunteers, 78 people were selected at random, matching age and sex with patients as the control group for the first and second analyses. Regarding the background of the 2 groups, body weight of patients was lighter than controls. As the result of the comparison of skin characteristics, patients’ skin were statistically harder and showed higher elasticity than control on both fingers, left hand, both forearms (Figure 1), both lower legs, and both feet. Viscosity of patients’ skin were also statistically higher than control on both fingers, both hands, both forearms, face, chest, right femur, and right foot. As the result of bivariate ROC analyses, moderate accuracy to distinguish patients from control was recognized by softness of both fingers and both forearms, elasticity of right finger and both forearm, and viscosity of left finger, right hand, both forearms, and face. Based on this result, age, body weight, softness of both fingers and right forearm, elasticity of left forearm, and viscosity of face, left finger, right hand, and both forearms were selected variables for the next logistic regression and ROC analysis using whole data of 413 healthy volunteers. (One of softness and elasticity was used because of the multi-collinearity). This ROC analysis resulted in high accuracy (AUC = 0.92514, Sensitivity = 0.7949, Specificity = 0.9562) to diagnose scleroderma (Figure 2).

Conclusion: Vesmeter showed high accuracy to diagnose scleroderma.
Peripheral Blood Eosinophil Counts Increase in Patients with Systemic Sclerosis and Associated with Its Disease Severity. Tamao Nakashita1, Shinji M otomiya2, Katsutoshi Ano3 and Akihiro Dibatake4. 1Kameda Medical Center, Kamogawa city, Japan, 2Juntendo University, Tokyo, Japan, 3Kameda Medical Center, Kamogawa city, Japan.

Background/Purpose: Increased levels of serum pro-fibrotic cytokines such as IL-4 and IL-13 and plasma CXCL4 have been previously reported in patients with systemic sclerosis (SSc). These pro-fibrotic cytokines also play an important role for differentiation and migration of eosinophils and eosinophils themselves release pro-fibrotic cytokines such as IL-11 and TGF-beta. Accordingly, we hypothesized that eosinophils might contribute, at least partly, to fibrogenic process of SSC.

Methods: We retrospectively reviewed the peripheral blood eosinophil counts (PB-EOS) in 70 untreated patients with SSc (diffuse 14, limited 56) and compared with those in other major connective tissue diseases including 175 RA patients with RA, 10 with lupus erythematosus (LE), 19 with primary Raynaud’s phenomenon (P-R), 20 with SLE and 8 with mixed connective tissue disease (MCTD). The diagnosis was made according to the criteria of ACR, except that criteria used for MCTD was that by Japan Ministry of Health, Labor and Welfare. All the patients were not on treatment by glucocorticoid and/or immunosuppressant. We also evaluated the association with disease severity of SSc, that is, the grade of interstitial lung disease (ILD) and skin sclerosis. The severity of ILD was graded into 4, grades 0 to grade 3, according to the extent of ILD on chest CT by the method of Gochucho et al. (A.Rch Intern Med 2008). Chest CT images were graded by 2 independent respirologists. The skin sclerosis was evaluated by modified Rodnain’s skin score (mRS).

Results: The mean of coefficient of variance of PB-EOS in 8 patients was 0.32, suggesting that PB-EOS are considerably stable. The order of mean PB-EOS was as follows: diffuse-SSc (mean 32±11 mcl) > limited-SSc (210 ± PM/DM (164) > RA (154) > pSS (128) > MCTD = SLE = LE (57) > indicates significantly different). ILD was observed in 39 % (27/70) of SSc patients, and the numbers of SSc patients with grade 0/1/2/3 were 43/15/9/3, respectively. PB-EOS positively correlated with ILD grade in SSc (rs = 0.26, p < 0.02), but not in RA (rs = 0.02) and other diseases. M-Rodnan SS also correlated with PB-EOS (rs = 0.35, p = 0.003) and ILD severity (p = 0.0001).

Conclusion: It was suggested that eosinophils contribute, at least in part, to fibrogenic process in SSc and anti-eosinophil strategy might become a treatment option when such drugs become available. It is also suggested that the mechanism of ILD is somewhat different between SSc and RA. Authors have no COI.
identified in SSc (Table). In contrast, there were consistent negative correlations between PMP (but not EMP) levels and digital perfusion at both baseline and following cold challenge in primary RP (Table).

**Conclusion:** This is the first study to explore the relationship between circulating MP levels and peripheral microvascular dysfunction in primary RP and SSc. Higher EMPs were associated with a history of DU/DP in SSc. Higher EMP and PMP levels, however, were associated with higher digital perfusion following local cold challenge in SSc. In contrast, higher PMP levels were associated with lower digital perfusion in primary RP. There was no association between EMP levels and digital perfusion in primary RP. Additional work is needed to explore factors leading to MP generation and their contribution to peripheral microvascular dysfunction in primary RP and SSc. MPs may have the potential to act as biomarkers of peripheral microvascular dysfunction/damage in primary RP and SSc.

**Table**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
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<tr>
<td>SSc EMP</td>
<td>Spearman’s rho</td>
<td>0.05</td>
<td>0.42</td>
<td>0.42</td>
<td>0.46</td>
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<tr>
<td>p value</td>
<td>0.621</td>
<td>0.044</td>
<td>0.043</td>
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<tr>
<td>PM EMP</td>
<td>Spearman’s rho</td>
<td>0.377</td>
<td>0.047</td>
<td>0.009</td>
<td>0.006</td>
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<tr>
<td>p value</td>
<td>0.19</td>
<td>0.42</td>
<td>0.52</td>
<td>0.54</td>
<td>0.84</td>
</tr>
<tr>
<td>Primary RP EMP</td>
<td>Spearman’s rho</td>
<td>-0.34</td>
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<td>-0.39</td>
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<tr>
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<td>0.64</td>
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<tr>
<td>PM Primary RP EMP</td>
<td>Spearman’s rho</td>
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<td>-0.33</td>
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<tr>
<td>p value</td>
<td>0.0415</td>
<td>0.023</td>
<td>0.003</td>
<td>0.006</td>
<td>0.057</td>
</tr>
</tbody>
</table>

**Disclosure:** J. D. Pauling, None; D. Moreno-Martínez, None; F. Wilkinson, None; B. Parker, None; J. A. Shipley, None; D. Hart, None; N. J. McHugh, None; Y. Alexander, None.

**1700 Laser Speckle Contrast Analysis in the Follow-up of Digital Ulcers in Systemic Sclerosis Patients.** Barbara Ruaro, Alberto Sulli, Teresa Canavale, Marco Amedeo Cimmino, Carmen Pizzorni, Sabrina Paolino and Maurizio Cutolo. Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy.

**Background/Purpose:** Typical clinical aspects of systemic sclerosis (SSc) include microvascular damage and reduction of peripheral blood perfusion, resulting in increased incidence of digital ulcers (DUs) (1-2). Several studies report different methods to assess the severity of DUs but, to the best of our knowledge, ulcer blood perfusion was not assessed (3-5). This study investigates blood perfusion (BP) of DUs by laser speckle contrast analysis (LASCRA), a non-contact technique, during treatment for ten days with local medications (6).

**Methods:** During their regular planned follow-up and systemic treatment, twenty SSc patients with DUs of recent onset (mean age 63±12 years, mean disease duration 7±6 years) were enrolled after informed consent. Local BP was studied in all patients by LASCRA before starting local treatment (T0), both at the level of the dorsal and palmar aspect of the hands (6). Subsequently, regions of interest (ROIs) were created at the level of the fingertips, periangual, ulcer and periangular areas and the perfusion values were reported as perfusion units (PU) (6). Hydrocolloid dressing was daily applied on ulcer area (7). After 10 days of treatment (T1) LASCRA was repeated. Visual analogic scale for DU pain (VAS-pain) (score 0-10) was administered to patients before and after the treatment. The patients marked on the line from 0 ("no pain") to 10 ("worst imaginable pain") the intensity of DU pain that they felt (8). Statistical analysis was performed by non-parametric tests.

**Results:** A statistically significant increase of BP was observed from T0 to T1 in the ROIs created at the level of the ulcer area (due to granulation tissue) (median 37 vs 57 PU, p<0.0001), as well as a significant decrease of BP was observed in the periangular area (due to decreased inflammatory reaction) (median 108 vs 90 PU, p<0.0001). A positive correlation was observed between fingertip BP and periangular BP at both T0 (r=0.66, p=0.02) and T1 (r=0.44, p=0.05). There was a statistically significant decrease of VAS-pain scale during the ten days of treatment (median 9 vs 8, p=0.001).

**Conclusion:** LASCA seems to offer a quantifiable and safe method to evaluate local blood perfusion changes of the DU area during local treatment, and it most likely represents a reliable technique to monitor DU evolution in SSc patients.

**References:**

**Disclosure:** None.

**1701 Short-Term Effects of Iloprost on Micro-Vessels Hemodynamics in Systemic Sclerosis Patients Evaluated By Laser Doppler Flowmetry.** L. Iannone, C. Rotondo, M. Ariangela Nivuori, E. Praino, L. Coladonato, M. Michele Covelli and G. Lapadula. Rheumatology Unit, Bari, Italy.

**Background/Purpose:** Iloprost is a milestone in the treatment of Raynaud’s Phenomenon (RP). However, it has transient hemodynamic effects due to a very short half-life, thereby a treatment protocol has been never validated and the interval time between infusions is empirical. We aimed at evaluating the short and medium term effects of Iloprost on blood flow, assessed by Laser Doppler (LD), in patients with RP associated to Systemic Sclerosis (SSc).

**Methods:** 19 SSc patients, aged 55.9±16 (mean±SD) years with disease duration of 9.3±6 years, have undergone Iloprost infusions (50 µg at 1.5 ng/kg/min) for 3 consecutive days. The LD flowmetry (Perflux System 5000, Perimed) was performed at baseline and after heating test (heat stimulus of 44 degree centigrade), and ischemic/occlusive test (200 mm/Hg pressure applied by air-bracelet on brachial artery for 3 min) before illoprost (T0), at the end of 3 consecutive days of treatment (T1), at 24h(T2) and at 7 days(T3) after last administration of Iloprost. During occlusive test, LD evaluated the micro-vessels flux at rest (RF), flux at pick (PF), the percentage variation between RF and PF (RF/PF %), and recovering and hyperemic times before and after occlusion. During heating test, LD evaluated percentage variation between perfusion units before and after heating test (pre-postPU%var). Comparisons between times were assessed by repeated measures ANOVA. Significance was set at p<0.05. During the study no variation of the baseline therapy was allowed.

**Results:** We observed a prompt improvement, even though transient, of LD parameters following Iloprost infusion. A statistically significant difference (p<0.05) (Tab.1) was found for RF/PF %, showing a time decreasing improvement. In particular the percentage difference comparing to T0 was: -10.26% at T1, -7.4% at T2, -7.8% at T3. For percentage variation between perfusion units before and after heating test (pre-postPU%var) a decreasing trend were observed, in particular the variation among times comparing to baseline is: +0.54 % at T1, -18.71% at T2, -19.37 % at T3.

**Table**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10</th>
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<tr>
<td>SSc</td>
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<tr>
<td>p value</td>
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<tr>
<td>p value</td>
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<tr>
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<td>-0.33</td>
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<td>p value</td>
<td>0.0415</td>
<td>0.023</td>
<td>0.003</td>
<td>0.006</td>
<td>0.057</td>
</tr>
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**Disclosure:** B. Ruaro, None; A. Sulli, None; T. Canavale, None; M. A. Cimmino, None; C. Pizzorni, None; S. Paolino, None; M. Cutolo, None.


**Background/Purpose:** Systemic Sclerosis (SSc) is an autoimmune disease characterized by collagen deposition and vascular changes of the skin...
**Method:** A hundred patients who met the American College of Rheumatology classification criteria for systemic sclerosis were included in the study. Demographics and clinical data on skin, internal organ involvement and history of malignancy were recorded.

**Results:** 70 anti-PMSCl positive patients were identified (3.1% of cohort), with frequent lung, renal and muscular involvement as described previously (table 1). 48 patients (66.8%) had antibodies targeting both PM/ScI 75 and 100; 6 (8.6%) PM/ScI 75 only and 16 (22.8%) PM/ScI 100 antibody only. There was a significant association between positivity for anti-PM/ScI 100 alone and malignancy (p = 0.037) when compared to presence of both reactivities or reactivity to PM/ScI75 alone. 13 patients (18.6%) had developed a malignancy, 4 of these had onset within 36 months from SSc diagnosis and all were positive for anti-PM/ScI 100, combined with anti-PM/ScI75 in 7/13 (53.8%). The study population standardized incidence ratio (SIR) for cancer was 2.14 (CI 95%: 1.55–2.74), with higher values showed for male gender (SIR 3.10, CI 95%: 1.55–4.65) than female gender (SIR 1.95, CI 95%: 1.31–2.61). 7/13 were adenocarcinoma, mainly breast, 4/13 squamous cell and the remainder haematological malignancy.

**Conclusion:** The association of malignancy with PM/ScI reactivity in SSc is of interest in the context of recent studies describing a potential pathogenic role of anti-RNA polymerase III antibodies with malignant disease in SSc. This cohort is otherwise representative of others in terms of demographics and clinical characteristics and underlines the importance of close surveillance for concurrent malignancy in all SSc disease subphenotypes.

### Table 1. Prevalence of clinical, instrumental and laboratory features in the study population

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total PM/ScI population (n=70, 100%)</th>
<th>PM-ScI Patients with Cancer (n=13, 18.6%)</th>
<th>SIR Cancer VS non cancer population</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>58±4 (14.0)</td>
<td>60±9 (10.3)</td>
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<tr>
<td>Female Sex</td>
<td>56</td>
<td>9 (69.2%)</td>
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<tr>
<td>Age at first diagnosis</td>
<td>44±1 (14.5)</td>
<td>46±3 (9.9)</td>
<td>0.365</td>
<td></td>
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<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>32 (45.7%)</td>
<td>10 (76.9%)</td>
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<tr>
<td>Anticoagulant therapy</td>
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<tr>
<td>Digital Ulcers</td>
<td>14 (20.0%)</td>
<td>4 (28.6%)</td>
<td>0.041</td>
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<tr>
<td>OR 0.629 (0.03–12.022)</td>
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<tr>
<td>Anticoagulant therapy</td>
<td>13 (18.6%)</td>
<td>4 (28.6%)</td>
<td>0.041</td>
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<tr>
<td>Malignancy</td>
<td>7 (10.0%)</td>
<td>0 (23.1%)</td>
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<tr>
<td>OR 0.99 (0.36–2.68)</td>
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<tr>
<td>Distal Pulmonary Hypertension</td>
<td>7 (10.0%)</td>
<td>0 (23.1%)</td>
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</tr>
<tr>
<td>Myositis Sympathetic</td>
<td>43 (61.4%)</td>
<td>5 (76.9%)</td>
<td>0.454</td>
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### Table 2. Association of positive antiphospholipid and antithrombin-2-glycoprotein I antibody testing with clinical features in SSc patients

<table>
<thead>
<tr>
<th>Anticardiolipin antibody (95% confidence intervals)</th>
<th>Antibody (95% confidence intervals)</th>
<th>Digital Ulcers (95% confidence intervals)</th>
<th>Interstitial Lung Disease (95% confidence intervals)</th>
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<tbody>
<tr>
<td>OR 0.844 (0.257–3.041)</td>
<td>OR 0.829 (0.382–30.8)</td>
<td>OR 0.522 (0.522–3.688)</td>
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<tr>
<td>0.844 (0.257–3.041)</td>
<td>0.829 (0.382–30.8)</td>
<td>0.522 (0.522–3.688)</td>
<td>0.522 (0.522–3.688)</td>
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</tbody>
</table>

**Table 1.** Association of positive anti-cardiolipin and anti-beta-2-glycoprotein I antibody testing with clinical features in SSc patients.

**Conclusion:** Our study showed a positive association with aCL antibodies and interstitial lung disease in patients with systemic sclerosis. This use of aCL antibodies as a biomarker of pulmonary disease in SSc should be further explored.

**1703**

**An Association of Anti-PM/ScI Antibody Reactivity with Risk of Malignancy in Scleroderma.** Cosimo Bruní, Ana Lages, Hiteh Patel, Jennifer Harvey, Voon H. Ong, Marco A. Mucić-Cerinic, Emma C. Derrett-Smith and Christopher P Denton. 1University of Florence, Florence, Italy, 2Affiliati servizio di Medicina Interna, Hospital De Braga, Braga, Portugal, 3Department of Clinical Immunology, Royal Free Hospital, London, United Kingdom, 4UCL Medical School Royal Free Campus, London, United Kingdom.

**Association of anti-PM/ScI antibody with risk of malignancy in scleroderma.**

2. Department of Rheumatology, AOI Careggi, Firenze (Italy)
3. Affiliati servizio di Medicina Interna, Hospital De Braga, Braga (Portugal)
4. Department of Clinical Immunology, Royal Free Hospital, London (UK)
5. UCL Medical School Royal Free Campus, London (UK)

**Background/Purpose:** Anti-PM/ScI antibodies are heterogeneous autoantibodies in scleroderma (SSc) directed mainly against 75kDa and 100kDa human exosome components, associated with overlap syndromes. Published data suggest that up to 12.5% of SSc patients carry this seropositivity with associations with myositis, mild skin involvement, pulmonary fibrosis, articular involvement and calcinosis and a lower prevalence of pulmonary arterial hypertension and gastrointestinal involvement. In this study, we characterised the clinical and detailed serological phenotype of anti-PM/ScI positive SSc patients from a single centre cohort of 2200 patients and identified a cohort within this group with increased risk of malignancy.

**Methods:** Anti-PM/ScI positive SSc patients identified by indirect immunofluorescence pattern and confirmed on counter-immunoelectrophoresis were enrolled in the study. Demographics and clinical data on skin, internal organ involvement and history of malignancy were recorded.

**Results:** 70 anti-PM/ScI positive patients were identified (3.1% of cohort), with frequent lung, renal and muscular involvement as described previously (table 1). 48 patients (66.8%) had antibodies targeting both PM/ScI 75 and 100; 6 (8.6%) PM/ScI 75 only and 16 (22.8%) PM/ScI 100 antibody only. There was a significant association between positivity for anti-PM/ScI 100 alone and malignancy (p = 0.037) when compared to presence of both reactivities or reactivity to PM/ScI75 alone. 13 patients (18.6%) had developed a malignancy, 4 of these had onset within 36 months from SSc diagnosis and all were positive for anti-PM/ScI 100, combined with anti-PM/ScI75 in 7/13 (53.8%). The study population standardized incidence ratio (SIR) for cancer was 2.14 (CI 95%: 1.55–2.74), with higher values showed for male gender (SIR 3.10, CI 95%: 1.55–4.65) than female gender (SIR 1.95, CI 95%: 1.31–2.61). 7/13 were adenocarcinoma, mainly breast, 4/13 squamous cell and the remainder haematological malignancy.

**Conclusion:** The association of malignancy with PM/ScI reactivity in SSc is of interest in the context of recent studies describing a potential pathogenic role of anti-RNA polymerase III antibodies with malignant disease in SSc. This cohort is otherwise representative of others in terms of demographics and clinical characteristics and underlines the importance of close surveillance for concurrent malignancy in all SSc disease subphenotypes.
was performed using qPCR. Analysis of CD44\(^{\text{CD24}^\text{low}}\) expression in epithelial cells was measured using flow cytometry. The production of superoxide by mitochondria in fibroblasts was visualized by flow cytometry using the MitoSOX™ Red reagent. Hydrogen peroxide production by fibroblasts was measured by AmplexRed.

**Results:** After CXCL4 treatment, both, endothelial and epithelial cells acquired fibroblast-like, mesenchymal appearances, and showed upregulation of mesenchymal markers (such as N-cadherin, vimentin, and αSMA). Moreover, epithelial cells exposure to CXCL4 resulted in the acquisition of the CD44\(^{\text{CD24}^\text{low}}\) antigen phenotype, which is associated with induction of an EMT (epithelial-mesenchymal transition). In human dermal fibroblasts, CXCL4 increased expression of collagen type I, and suppressed transcription factor Fli-1. Additionally, the levels of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, were increased upon stimulation with CXCL4.

**Conclusion:** Our results suggest that CXCL4 can directly promote the fibrotic process, by transtion of fully differentiated epithelial and endothelial cells into activated myofibroblasts, a process called epithelial/endothelial mesenchymal transition (EMT/EndoMT). Moreover, CXCL4 might indirectly drive fibrosis by inhibition of Fli-1 and induction of collagen type I expression in fibroblasts. Further, CXCL4 increases ROS production in fibroblasts, which additionally stimulate synthesis and deposition of extracellular matrix (ECM) and promote fibrosis. In accordance with high level of CXCL4 in the circulation and skin of SSC patients, we demonstrate novel mechanisms in which CXCL4 could contribute to SSC phenotype.

**Reference:**

**Disclosure:** W. Marut, None; A. J. Affandi, None; A. Limper, None; T. R. D. J. Radstake, None.

1705

The Lectin Pathway of Complement – a Potential Role in the Pathogenesis and Disease Manifestations of Systemic Sclerosis, Michael Osthoff\(^*,\) Gene-Siew Ngian\(^*,\) Melinda Dean\(^*,\) Mandana Nikpour\(^*,\) Wendy Stevens\(^*,\) Susanna Proudman\(^*,\) Damon Eisen\(^*\) and Joanne Sahhar\(^*\). 1The University of Melbourne, Melbourne, Australia, 2Royal Melbourne Hospital, Parkville, Australia, 3Australian Red Cross Blood Service, Brisbane, Australia, 4University of Melbourne, Fitzroy, Australia, 5St. Vincent’s Hospital, Fitzroy, Australia, 6Royal Adelaide Hospital, Adelaide, Australia, 7Monash Health, Melbourne, Australia.

**Background/Purpose:** Repetitive episodes of ischemia and reperfusion (I/R) are a cardinal feature of the pathogenesis of systemic sclerosis (SSc), which precedes tissue fibrosis. The complement system is a key mediator of tissue damage after I/R, primarily by activation of the lectin pathway. This study investigated whether serum levels and polymorphisms of mannose-binding lectin (MBL) and ficolin-2 (FCN2), two pattern recognition receptors of the lectin pathway, are associated with the predisposition to, and clinical features of SSc.

**Methods:** A case-control study was undertaken involving 90 patients with SSc according to the American College of Rheumatology (1990) or the LeRoy and Medsger criteria (1990) from a single SSc outpatient clinic and 90 age- and sex-matched blood donors. MBL and FCN2 levels and polymorphisms were measured in both groups, and in cases correlated with clinical data.

**Results:** MBL levels and genotypes were equally distributed in cases and controls while there were some significant differences in FCN2 polymorphisms. Median MBL levels were higher in SSc cases with diffuse disease compared to controls (2.6 vs. 1.0 μg/ml, p < 0.001).

In cases, higher MBL levels were associated with the presence of clinical findings associated with vascular dysfunction and local tissue damage (digital ulcers, calcinosis and pitting). Moreover, MBL levels were associated with fibrotic disease manifestations as evidenced by the presence of diffuse disease (median 2.6 vs. 0.8 μg/ml, p = 0.002), the modified Rodnan skin score (r = 0.39, p < 0.001), and interstitial lung disease as measured by forced vital capacity (r = 0.33, p = 0.001). Importantly, MBL levels also correlated with the SSC Health Assessment Questionnaire scores (r = 0.33, p = 0.002). Results for FCN2 levels were less striking. Phenotypic MBL results were largely confirmed by analysis of MBL polymorphisms. MBL levels were not associated with the presence of autoantibodies or hypocomplementemia.

**Conclusion:** Overall, predisposition to SSc was not influenced by the lectin pathway of complement in our matched case-control study. However, our preliminary data suggest that MBL, and to a lesser extent FCN2 may modulate disease manifestations of SSc, particularly in diffuse cutaneous disease.

**Acknowledgments:** Kathleen Elford, Scleroderma Nurse for her assistance in collection of data and samples. SSc patients were recruited from Monash Health as part of the Australian Scleroderma Cohort Study (ASCs), a longitudinal, prospective study of SSc patients.

1706

Prevention of SU5416-Induced Pulmonary Hypertension in a TGFβ Dependent Genetic Mouse Model of Scleroderma Using the Endothelin Receptor Antagonist Machtentan, Emmina C. Derrett-Smith\(^*,\) Vincent Sobanski\(^*,\) Sarah Trinder\(^*,\) Adrian J Gillbane\(^*,\) Marc Iglarz\(^*,\) David J. A Ibrahim\(^*,\) Alan M. Holmes\(^*\) and Christopher P Denton\(^*\). 1UCL Medical School Royal Free Campus, London, United Kingdom, 2UCL Medical School, London, United Kingdom, 3Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, 4UCL, London, United Kingdom.

**Background/Purpose:** Pulmonary arterial hypertension (PAH) is an important complication of systemic sclerosis (SSc) that occurs in around 10% of cases. We have previously shown that a TGFβ dependent transgenic mouse strain (TßRII\(\Delta\kappa\)-fib) is susceptible to organ based pathology relevant to SSc and that pulmonary endothelial injury is associated with development of PH with perturbed VEGF, BMP and endothelin signalling. In this study, we have prevented the development of PH in this mouse strain using macitentan, a potent endothelin receptor antagonist recently licensed to treat PAH in connective tissue disease based upon a significant effect on morbidity and mortality in PAH.

**Methods:** SU5416, a VEGF receptor inhibitor, was administered to all TßRII\(\Delta\kappa\)-fib transgenic (TG) mice and littermate wildtype (WT) animals to induce endothelial injury with subsequent endoluminal proliferation and PH in
transgenic mice only. Mice were treated with either 50mg/kg macitentan daily by oral gavage or vehicle alone (n=8 each group). The development of PH in each group was assessed by histology and immunohistochemistry of vessel architecture, in vivo haemodynamic studies and RV mass index measurements.

Results: Compared with WT littermates, after SU5416, all TG mice developed a prominent perivascular chronic inflammatory infiltrate and smooth muscle layer hypertrophy, as previously described. RV mass index was elevated in TG animals receiving vehicle compared to other groups (TG vehicle 0.29±0.007, TG macitentan 0.24±0.007, p=0.05). The increase in RV systolic pressure in TG animals treated with SU5416 was also abrogated by macitentan (figure 1) without any significant change in systemic arterial blood pressure in any group. Explanted TG lung fibroblasts showed an increase in proliferation and migration with upregulation of VEGF and TGFbeta signalling and downregulation of endothelin receptor A compared with WT littermates. There was oblitative pulmonary arteriolar occlusion in 21% of vessels in TG mice treated with vehicle. In contrast, no vessels in WT mice or TG mice treated with macitentan developed this histological change.

Conclusion: Macitentan prevents the development of histological and haemodynamic PH in this mouse model of SSC. These findings support a pivotal role for perturbed endothelin activity in a model that is induced by altered TGFbeta signalling and triggered by experimental VEGF inhibition. It underpins the value of this model as a platform for experimental therapeutic studies as well as providing insight into pathogenic mechanisms of disease.


Disclosure: E. C. Derrath-Smith, None; V. Sabanski, None; S. Trinder, None; A. J. Gilbane, None; M. Iglarz, None; A. M. Holmes, None; C. P. Denton, Actelion Pharmaceuticals Ltd, 2, Actelion Pharmaceuticals Ltd, 5.

1707
High Oxidative Stress in Fibrotic and Non-Fibrotic Skin of Patients with Systemic Sclerosis. Khalli I, Bourji1, Alain Meyer2, Emmanuel Chatelus2, Erika Pigatto3, Francois Singh2, Bernard Geny2, Leonardo Punzi2, Jacques-Eric Gottenberg2, Franco Cozzi2 and Jean Sibilia2. 1University Hospital of Padova, Padova, Italy, 2University Hospital of Strasbourg, Strasbourg, France.

Background/Purpose: Systemic Sclerosis (SSc) is a chronic multisystemic connective tissue disease characterized by progressive fibrosis affecting skin and internal organs. Despite serious efforts to unveil pathogenic mechanisms of SSc, they are still unclear. High levels of Reactive Oxygen Species (ROS) in affected skin have been shown, but the role of oxidative stress remains controversial (1, 2, 3). In this study we assessed ROS levels in non-fibrotic (NS) and fibrotic (FS) skin of patients with SSc and we compare them with those obtained from healthy controls (CS).

Patients and Methods: We enrolled 9 SSc patients fulfilling the EULAR/ACR classification criteria (4) and 7 healthy controls. Patients were 4 men and 5 women with mean age of 46±10 yrs. Controls were matched by sex and age. All patients were affected by diffuse cutaneous form of SSc and the ANA pattern anti-Scl70. Mean disease duration was 7.5±5 yrs. Skin involvement was evaluated by modified Rodnan Skin Score (mRSS). Skin samples (4mm punch biopsy) were taken from fibrotic skin (FS) and non-fibrotic skin (NS) of patients and from healthy controls (CS) as well. To detect ROS, specimens were analyzed immediately after sampling by electron paramagnetic resonance spectroscopy (ESR).

Results: ROS levels (expressed as median and range, unit of measurement was AU/mg) were 118.6×10^3 (52.4×10^2–225.7×10^3) in FS, 89.6×10^3 (34.8×10^2–163.1×10^3) in NS and 36.8×10^3 (17×10^3–65.1×10^3) in CS. ROS levels in Fibrotic (FS) and Non-fibrotic (NS) skin of SSc patients were significantly higher than in Healthy Control (CS) (p=0.002 and p=0.009, respectively). Although ROS levels in FS were raised in comparison to NS, this difference was not statistically significant (p=0.24). ROS levels of FS were correlated with DLCO (r=−0.59, p=0.09), VC (r=−0.75, p=0.02) and ESR (r=0.70, p=0.03). All other clinical and laboratory parameters showed no significant correlation.

Conclusion: Our results confirm the presence of high oxidative stress either in non-fibrotic skin (NS) or in fibrotic skin (FS) of SSc patients, but with higher tendency in the latter. Raised ROS levels in non-fibrotic skin (NS) of SSc patients might hint of early involvement in skin fibrogenesis. However, a longitudinal prospective study is necessary for such proof.

References:

Disclosure: K. I. Bourji, None; A. Meyer, None; E. Chatelus, None; E. Pigatto, None; F. Singh, None; B. Geny, None; L. Punzi, None; J. E. Gottenberg, None; F. Cozzi, None; J. Sibilia, None.

1708
The Pathogenic Role of Immune Complexes Containing Sclerodermaspecific Autoantibodies in the Inductor Phase of the Disease. Cecilia B. Chighizola1, Elena Raachi2, Laura Cesana2, Silvana Zeni4, Maria Orietta Borghi3 and Pier Luigi Meroni4. 1Istituto Aulogico Italiano, University of Milan, Cusano Milanino, Italy, 2Istituto Aulogico Italiano, Milan, Italy, 3Division of Rheumatology, Istituto G. Pini, Milan, Italy, 4Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune condition characterized by excessive tissue fibrosis, microvascular alterations and immune dysfunction with the production of peculiar autoantibodies. These autoantibodies are highly specific for SSc diagnosis, and provide the most reliable tool to predict disease subset and the pattern of internal organ involvement. Despite such diagnostic and prognostic role, no evidence supporting the pathogenic potential of these autoantibodies has to date been raised. Therefore the aim of this study is to evaluate for the first time the pathogenicity of immune complexes (IC) from scleroderma patients in the inductor phase of the disease, using skin fibroblasts from healthy controls as cellular in vitro model.

Methods: Fibroblasts have been isolated from skin biopsies obtained from healthy controls and then cultured in adequate conditions. IC have been purified from sera of scleroderma patients bearing different autoantibody specificities (antibodies against centromeric proteins [ACA], DNA topoisomerase I [ATA], RNA polymerase [ARA] and Th/To [anti-Th/To]) or of healthy controls using polyethylen glycol precipitation. Cell cultures have been incubated with pathologic and control IC and with cell activating agonists as TLR3 [Poly(I:C)] and TLR4 (LPS) ligands. Several parameters of fibroblast activation have been assessed in the different experimental conditions. In particular, mRNA levels of type I interferons (IFN-alpha and IFN-beta) have been investigated by real-time PCR; ICAM-1 expression has been evaluated by cell-ELISA and the secretion of IL-6 and IL-8 in culture supernatants has been measured by commercial ELISA kits. Furthermore, the involvement of intracellular signaling pathways culminating with the activation of p38 MAPK, NFKB and JNK has been assessed by Western Blotting.

Results: Stimulation of normal skin fibroblasts with pathologic IC induced a significant increase in the gene expression levels of both IFN-alpha and IFN-beta; similar results have been observed in the presence of TLR agonists but not of control IC. In addition, the expression of ICAM-1 and the secretion of IL-6 and IL-8 were up-regulated by Poly(I:C) LPS and IC from scleroderma patients but not from healthy controls. Further, pathologic IC induced the activation of p38 MAPK, NFKB and JNK.

Conclusion: Our data provide the first demonstration of the pathogenic role of IC isolated from scleroderma patients with different autoantibody specificities in the inductor phase of SSc. Indeed, pathologic IC can interact with normal skin fibroblasts, inducing a pro-inflammatory phenotype mediated by p38 MAPK, NFKB and JNK. These evidences fit well with the diagnostic and prognostic role of sclerodermaspecific autoantibodies, providing novel insights into SSc pathogenesis and potentially leading to new treatment strategies.

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Background/Purpose: Currently, there are no approved treatments in the United States for Raynaud’s Phenomenon (RP). Prostanoids, i.e., prostacyclin (PGI2) and Alprostadil (PGE1); may be used to treat severe cases but have limited applicability for outpatient use due to intravenous administration. RayVa®or Alprostadil topical cream is being developed to treat the symptoms associated with Raynaud’s Phenomenon (RP) secondary to scleroderma. In an ongoing Phase 2a study, topical administration of RayVa® to affected individuals is being assessed for changes in blood flow and temperature relative to treatment.

This nonclinical study was conducted to demonstrate hemodynamics after local delivery utilizing Laser Doppler Imaging (LDI) and assessing varying dose levels of the alprostadil cream relative to placebo in non-human primates (NHP).

Methods: NHP were anesthetized and baseline blood flow recorded with LDI. Following baseline measurements, the animal’s hands were placed in an ice-water bath for 2 minutes followed by application of placebo cream on one hand and topical alprostadil cream on the other hand. Both hands were imaged every 15 minutes from the end of the application until baseline blood flow was reached for a maximum of two hours.

The topical alprostadil cream consisted of 0.42% alprostadil and 2.5% DDAIP-HCl, administered at two alprostadil dose levels: 300 and 1000 micrograms. The placebo cream contained no alprostadil and 2.5% DDAIP-HCl.

Results: Alprostadil topical cream did not elicit clinical abnormalities in the majority of animals over the study duration. After cold-challenge, administration of the topical alprostadil cream induced a dose-responsive, statistically significant increase (p<0.05) in hemodynamic parameters relative to the placebo cream over the assessment period. The time-to-peak response was reached within 15 minutes after application and post-cold-challenge. The statistically significant increase in the hemodynamic response to the alprostadil cream was at least one hour in duration.

Conclusion: Topical alprostadil cream (RayVa®) induces a dose-responsive increase in hemodynamics relative to placebo utilizing LDI in NHP. Local application of the vasodilator may be a beneficial treatment for patients with restricted blood flow to distal extremities, as seen in Raynaud’s Phenomenon. The observed hemodynamic changes support the RayVa® dose and determine the vascular injury and organ involvement in systemic sclerosis (SSc).

Disclosure: S. Meier-Davis, None; S. Debar, None.

1710

Endothelin-1 Is a Downstream Mediator of Profibrotic Effects by Transforming Growth Factor-β1 in Systemic Sclerosis Skin Fibroblasts.
Tomoki Higuchi1, Yasushi Kawaguchi3, Akiko Tachimoto2, Yoko Otani2, Yasuhiro Katsumata2, Takahisa Gono1, Masanori Hanaoka2, Yuko Okamoto1, None; H. Kawasaki3, None; H. Yamanaka1, None.

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by excess collagen deposition, vascular changes and production of autoantibodies that affects multiple organs. Transforming growth factor-β1 (TGF-β1), that promotes collagen synthesis, extracellular matrix (ECM) remodeling and myofibroblast differentiation, is thought to play a key role in the pathogenesis of SSc. The vasoconstrictive peptide endothelin-1 (ET-1) is also known as potent fibrotic factors. ET-1 binds to two distinct subtype of G protein coupled receptors, ET receptor A (ETRA) and ET receptor B (ETRB). The fibrotic functions of each ET receptor has been unclear partly because the distribution and expression of ET receptors differs according to the disease situations, the respective organs or the cell types. The aim of our study was to examine the effects of TGF-β1 on the fibrogenic phenotype of SSc skin fibroblasts through ET-1 production and to clarify how the signal transduction through TGF-β1 is associated with upregulation of ET-1.

Methods: Human SSc skin fibroblasts (SSc fibroblasts) were obtained from 5 SSc patients. Recombinant TGF-β1, recombinant ET-1, SIS as an inhibitor of Smad3 phosphorylation, SP600125 as an inhibitor of c-JUN N-terminal kinase (JNK), BQ123 as a selective ETRA antagonist, BQ788 as a selective ETRB antagonist and bosantan as a dual ETRA/ETRB receptor antagonist were used in this study. SSc fibroblasts were incubated with TGF-β1 in the presence of SIS or SP600125. In addition, the effects of BQ123, BQ788 or bosantan were explored. The expression of ET-1, CTGF and type I collagen was evaluated using ELISA and real time RT-PCR. ETRA and ETRB expressions were assessed by immunohistochemistry and fluorescence activated cell sorting (FACS) analysis.

Results: Both ETRA and ETRB were expressed in SSc fibroblasts as detected by immunohistochemistry. TGF-β1 increased ET-1 in the levels of mRNA and protein and this increase in ET-1 was suppressed by either either SIS or SP600125. Upregulation of COL1A1 and CTGF by TGF-β1 were reduced by either ETRA or ETRB antagonist, and the effects were enhanced by dual ETRA/ETRB antagonist.

Conclusion: We herein revealed that TGF-β1 produced ET-1 through both SIS and JNK cascade and dual ETRA/ETRB antagonist contributed to diminishing COL1A1 and CTGF mRNA in fibroblasts. These findings suggest that the fibrogenic effects by TGF-β1 may in part be explained by the autocrine stimulation of ET-1. The dual ETRA/ETRB might be a novel therapeutic strategy for the SSc skin fibrosis.

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1711

The Relationship Between Vascular Biomarkers and Disease Characteristics in Systemic Sclerosis: Elevated MCP-1 Is Associated with Predominantly Fibrotic Manifestations. Yasemin Yalcinkaya1, Suzan Cinar1, Sevil Kamal1, Lale Ocal1, Gunmur Deniz2 and Murat Inanc3, None; Istanbul University, Istanbul, Turkey, 2Division of Rheumatology, Department of Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey.

Background/Purpose: To determine the relationship between vascular biomarkers reflecting the vascular injury and organ involvement in systemic sclerosis (SSc).

Methods: Seventy-two SSc patients (66 female) fulfilling 2013 ACR/EULAR Criteria were evaluated. Serum samples of patients were collected for flow-cytometric analysis of CD40L, tPA, MCP-1, sE-selectin, IL-8, IL-6, VEGF, and sCD40L. MCP-1 levels were measured in 58 SSc patients and 20 healthy controls. Results were compared with Pearson chi-square / Fischer’s and Mann Withney tests.

Results: The mean age of the patients was 44.9 and disease duration from the appearance of first non-Raynaud symptom was 3.2±2.4 years. Of the patients 23 (32%) had diffuse and 49 (68%) limited cutaneous involvement, 15 (21%) were anti-centromere (+) and 34 (47%) were anti-Scl70 (+). In SSc patients, levels of tPA (p=0.02), MCP-1 (p=0.001), sE-selectin (p=0.008), TGF-β1 (p=0.001) were significantly higher, sP-selectin (p=0.011) and IL-8 (p=0.001) were lower than healthy controls (table-1).

Table 1: Vascular Biomarkers in Healthy Controls and Systemic Sclerosis

<table>
<thead>
<tr>
<th>Biomarker Levels</th>
<th>Healthy Controls (n=20)</th>
<th>Systemic Sclerosis (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>scD40L (pg/ml)</td>
<td>24620±13051</td>
<td>27847±33154</td>
</tr>
<tr>
<td>tPA (pg/ml)</td>
<td>2415±1279</td>
<td>4036±6961*</td>
</tr>
<tr>
<td>MCP-1 (pg/ml)</td>
<td>907±300</td>
<td>1302±550**</td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>205±78</td>
<td>269±106**</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>49±73*</td>
<td>22±80</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>0</td>
<td>0.6±2.8</td>
</tr>
<tr>
<td>VEGF (pg/ml)</td>
<td>704±363</td>
<td>776±591</td>
</tr>
<tr>
<td>sP-selectin (ng/ml)</td>
<td>364±137*</td>
<td>287±86**</td>
</tr>
<tr>
<td>sCD40L (pg/ml)</td>
<td>24±785</td>
<td>827±592**</td>
</tr>
<tr>
<td>VCM (pg/ml)</td>
<td>3231±1435</td>
<td>3945±1754</td>
</tr>
</tbody>
</table>

*p<0.05. **p<0.01 When healthy controls and systemic scleroderma patients were compared with Mann Whitney test

Levels of MCP-1 was elevated in patients with dcSSc, flexion contractures, FVC<80%, DLCO<80%, pulmonary fibrosis and high acute phase response (p=0.002, p=0.005, p=0.045, p=0.005, p=0.036, p=0.006, respectively), TGF-β1 in patients under immunosuppressives (p=0.001), sE-selectin in patients with high acute phase response (p=0.028), scD40L in patients with smoking habitus (p=0.032) and iCSc (p=0.011) (table-2).

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Monday, November 17
Table 2: Vascular Biomarkers between disease characteristics of Systemic Sclerosis Patients

<table>
<thead>
<tr>
<th>MCP-1</th>
<th>sC4d</th>
<th>sE-selectin</th>
<th>TGF-β1</th>
<th>TGF-β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/ml</td>
<td>ng/ml</td>
<td>ng/ml</td>
<td>ng/ml</td>
<td>ng/ml</td>
</tr>
</tbody>
</table>

Skin Involvement - diffuse
| + (n = 23) | 1581 ± 579 | 2156 ± 784 | 1240 ± 784 | 987 ± 784 |
| deltoid | 1581 ± 579 | 2156 ± 784 | 1240 ± 784 | 987 ± 784 |

Skin Involvement - limited
| + (n = 49) | 1169 ± 487 | 1321 ± 487 | 1022 ± 487 | 844 ± 487 |
| + (n = 49) | 1169 ± 487 | 1321 ± 487 | 1022 ± 487 | 844 ± 487 |

Fibrosis Contractions
| + (n = 12) | 1737 ± 644 | 1957 ± 644 | 1321 ± 644 | 844 ± 644 |
| - (n = 60) | 2111 ± 487 | 2357 ± 487 | 1787 ± 487 | 1022 ± 487 |

Low D/D C (> 0.3)
| + (n = 28) | 1581 ± 579 | 2156 ± 784 | 1240 ± 784 | 987 ± 784 |
| + (n = 14) | 1169 ± 487 | 1321 ± 487 | 1022 ± 487 | 844 ± 487 |

Low D/D C (< 0.3)
| + (n = 14) | 1169 ± 487 | 1321 ± 487 | 1022 ± 487 | 844 ± 487 |
| + (n = 14) | 1169 ± 487 | 1321 ± 487 | 1022 ± 487 | 844 ± 487 |

Monocytic Angiotensin and Endothelin Receptor Imbalance Determines Surrogate Marker for Fibrotic Disease Activity. Treatment and smoking may have an effect on cytokine profiles. Vascular biomarkers can be used to characterize the disease activity level.

**Conclusion:** Receptor expression might reflect systemic activation of the angiotensin and endothelin system in SSC. Since patients with lung fibrosis and high mRSS showed a reduced ET<sub>α</sub>/ET<sub>β</sub> ratio, imbalance of ATR and ETR may influence effects of aab in SSC and could serve as a marker for disease complications. High ATR/AT<sub>2R</sub> and low ET<sub>α</sub>/ET<sub>β</sub> ratios on monocytes correspond to higher secretion of CCL18 suggesting a link between receptor expression and monofunctional activity.

**Disclosures:** J. Rademacher, None; J. Guenther, None; A. Kil, Actelion Pharmaceuticals US, 2, E. Siegert, None; G. Riemekasten, Actelion Pharmaceuticals US, 2, CellTrend, 5.

1713

Increased Number of CD206<sup>+</sup> Cells in Peripheral Blood and Skin of Systemic Sclerosis Patients.

**Purpose:** To investigate the presence and number of CD206<sup>+</sup> cells in peripheral blood and skin of systemic sclerosis patients.

**Methods:** CD206<sup>+</sup> cells in peripheral blood and skin of systemic sclerosis patients were assessed by flow cytometry.

**Results:** Increased number of CD206<sup>+</sup> cells was observed in peripheral blood and skin of systemic sclerosis patients compared to healthy controls.

**Conclusion:** Increased number of CD206<sup>+</sup> cells in peripheral blood and skin of systemic sclerosis patients suggests a potential role in the disease process.
Background/Purpose: IL-6 is a key mediator in activation of extracellular matrix (ECM) in scleroderma (SSc) fibroblasts and via its interplay with chemokines may modulate mononuclear cell recruitment and fibrosis. We have explored the role of IL6 in macrophage differentiation in SSc and its regulation of fibrotic response.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from patients with early stage diffuse cutaneous SSc (dcSSc) (n=12) and healthy controls (n=6) via Ficoll gradient centrifugation. Dermal fibroblasts were cultured from skin biopsies from healthy controls (n=4) and dcSSc (n=4). Flow cytometry was used to quantify M2 macrophages in PBMCs defined by CD68+/CD163+ cells. A magnetic-activated cell sorting (MACS) based protocol was used to select CD14+ cells. CD14+ Cells were stimulated for 6 days with M-CSF before further stimulation with M-CSF alone or IL6/2% FBS. Flow cytometry was then used to determine the effect of IL-6 trans-signalling on macrophage polarisation. Control and SSc fibroblasts were stimulated with conditioned media(CM) from cultured M2 macrophages. Western blot analysis for Collagen type-I (Col-1) and alpha smooth muscle actin (aSMA) was used to assess ECM protein levels induced by CM and the effect of CM on fibroblast contractile response was evaluated with collagen gel contraction assays.

Results: PBMCs were isolated from healthy controls (n=6) mean age (35 ± 13.8 months), and dcSSc patients (n=12), mean age (42.2 ± 15.6 years) and disease duration (34.2 ± 15.6 months). Flow cytometry of PBMCs demonstrated significantly higher proportion of circulating M2 macrophages (mean ± SEM %) in dcSSc patients compared to healthy controls (9.3 ± 0.3% vs 1.4 ± 1.2% p=0.0087) respectively. There was no significant difference in the total number of CD68+ macrophages between the two groups. Stimulation of isolated macrophages with IL6/2% FBS polarised the M2 macrophage population by (4-fold, p<0.02) and (1.6-fold, p<0.04) in control and SSc macrophages respectively. Cultured fibroblasts treated with CM generated from SSc M2 macrophages led to increased synthesis of ECM proteins aSMA (3-fold, p<0.04) and Col-I (3.2-fold, p<0.04) compared with control macrophages in the presence of control fibroblasts. CM from SSc M2 macrophages induced contraction of control fibroblasts leading to (4mm ± 0.3% p<0.05) reduction in collagen gel diameter compared to control CM.

Conclusion: Our data indicate that M2 macrophage phenotype in early stage scleroderma may partly be polarised by IL-6 trans-signalling. This supports the critical role of distinct macrophage subpopulation in regulation of key fibrotic markers, myofibroblastic differentiation and contractile response in SSc. Elucidating these pathways may lead to better understanding of macrophage biology in disease pathogenesis and the potential for targeted specific subpopulation as emerging therapeutics in SSc.

Disclosure: R. Alade, None; 9, S. Xu, None; K. Khan, None; A. Tam, None; C. P. Denton, Actelion Pharmaceuticals US, S; V. H. Ong, Actelion Pharmaceuticals US, B.
classified in diffuse cutaneous (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) based on the extent of their skin involvement. They were evaluated to determine presence and severity of organ involvement (Medsger's severity scale). Peripheral venous blood was obtained to test for ANA, SSc-associated antibodies and sequence-based MHC class I and II typing. We included 234 healthy, ethnically matched individuals as controls. Admixtree estimations and principal component analysis (PCA) were performed. IRB approval was obtained for this study, which was performed according to the Helsinki Declaration. Informed consent was obtained from all participants. Differences were evaluated using Student's t-test, X², Fisher exact test and Bonferroni when appropriate, p values <0.05 were considered significant.

Results: We found female predominance (98% vs 84%; p = 0.004) and longer disease duration in lcSSC patients (13 vs 8 years; p = 0.001); higher proportion of interstitial lung disease (44% vs 24%, p = 0.01) and gastrointestinal involvement (73 vs 57%, p = 0.03) in dcSSC patients. Anti-topoisomerase I antibody predominated in dcSSC patients (p = 0.0009) and antitriantmorerne (ACA) in lcSSC patients (p = 0.005). HLA allele analysis showed increased frequency of HLA-B*08:04:01 in SSC (gene frequency (gf) 4%) and in dcSSC patients (p = 0.004) when compared to controls (p = 0.6%, OR 0.1, 95% CI 0.3-2.3; and p = 0.008, OR 7.1, 95% CI 25-31, respectively); increased frequency of HLA-DRB1*11:04 in dcSSC patients (p = 0.009, OR 0.4, 95% CI 0.2-0.7, respectively). Antibody analysis revealed association of HLA-DRB1*08:02 and HLA-DQB1*0302 was negatively associated to the presence of this genes in lcSSC patients (13% vs 24% in dcSSC). Susceptibility, influence clinical presentation and autoantibody profile. Genetic admixture shows different components in dcSSC and lcSSC subsets and in controls.

Conclusion: MHC Class I and II genes contribute to Systemic Sclerosis susceptibility, influence clinical presentation and autoantibody profile. Genetic admixture shows different components in dcSSC and lcSSC subsets and in controls.

Disclosure: T. S. Rodriguez-Reyna, None; J. Zuniga, None; J. Granados, None; P. Mercado Velazquez, None; C. Nunez Alvarez, None; N. Yu, None; S. Alosco, None; A. Cruz Lagunas, None; E. Yunis, None.

1717
Endothelial to Mesenchymal Transition Contributes to the Development of Pulmonary Vasculopathy in Systemic Sclerosis PAH: Robert Good1, Adrian Gilbane2, Sarah Trinder2, David Abraham3, Christopher Denton4 and Alan M. Holmes2, 1UCL, LONDON, United Kingdom, 2UCL, London, United Kingdom, 3UCL Medical School, London, United Kingdom.

Background/Purpose: Vascular complications in Scleroderma (SSc) patients are associated with high mortality, particularly in patients who develop pulmonary arterial hypertension (SSc-PAH). Vascular complications, thought to arise from initial activation and dysfunction of the endothelium can lead to: elevated vascular leak, inflammation, mesenchymal hypertrophy by activation of resident smooth muscle cells and fibroblasts, and neointima formation. Recent studies suggest that as well as resident mesenchymal cells, endothelial cells can undergo endothelial-mesenchymal transition (EndoMT), and acquire a mesenchymal phenotype which may contribute to the expansion of the mesenchymal cell population. We sought to determine the prevalence of EndoMT in SSc-PAH patients and pre-clinical models of PAH, and assess the cellular effects on pulmonary artery endothelial cells (PAECs) functions.

Methods: Using lung tissue from SSC-PAH patients (n = 3), healthy control (HC) donors (n = 3), and from the hypoxia/SU5416 pre-clinical murine model of PAH (n = 5), EndoMT was determined by immunofluorescence based on co-expression of vWF and αSMA. EndoMT was induced in human PAECs (n = 3) in vitro by TNFα [5ng/ml], IL-1β [0.1ng/ml]; and TGFβ [5ng/ml] in combination. Morphological changes were assessed by light microscopy and phalloidin staining. Western blotting and immuno-fluorescence was used to quantify: CD31, vWF, occludin, VE-cadherin, αSMA, calponin and collagen type I expression. Conditioned media was collected from PAECs, PAECs following treatment to initiate EndoMT and SSC-PAH and HC fibroblasts; levels of inflammatory secretion was quantified by MSD arrays.

The capacity of homogenous EndoMT monolayers (n = 6) and mixed cultures of 1:10 EndoMT:PAECs (n = 6) cells to form exclusion barriers was assessed using trans-well permeability FITC-albumin assays.

Results: Co-localisation of vWF and αSMA was observed in ≤5% of pulmonary arteries from SSC-PAH patients and hypoxia/SU5416 mice. PAECs treated with TNFα, IL-1β and TGFβ exhibited significant changes in expression, morphology, loss of endothelial markers and elevated expression of mesenchymal markers by day 6. There was a significant (P <0.05) increase in secretion of pro-inflammatory chemokines by EndoMT cells compared to PAECs including IL-6 [254.4 ± 95.8 to ≤12.6 ± 6.6 pg/ml] and IL-8 [602.7 ± 36.4 to ≤28.5 ± 6.5 pg/ml]. EndoMT cells alone or in mixed 1:10 ratio cultures with PAECs, exhibited a significant (P <0.01) 5-fold increase in permeability compared to PAECs alone. Consistent with this, EndoMT cells co-cultured with PAECs in a ratio of 1:10 led to 2.5-fold significant (P <0.05) increase in permeability.

Conclusion: The co-localisation of vWF and αSMA present in the pulmonary arteries of SSC-PAH patients and pre-clinical models of PAH, is indicative of EndoMT. We demonstrate EndoMT leads to a loss of normal PAEC morphology and an enhanced secretion of pro-inflammatory chemokines. Furthermore EndoMT cells failed to form integral biological barriers and contributed to enhanced permeability of PAEC barriers. Collectively our data suggests that EndoMT may contribute to the loss of normal endothelial function and the development of SSc-PAH.

Disclosure: R. Good, None; A. Gilbane, None; S. Trinder, None; D. Abraham, None; C. Denton, None; A. M. Holmes, None.

1718
B Cell Subsets Homeostasis and Functional Properties Are Altered in a Murine Model of Systemic Sclerosis: Sébastien Sangés1, Niloufar Kaviani2, Carine Hauspie3, Carole Nicco3, Thomas Guerrier1, Virginie Dubut-Lefèvre1, Guillaume Lefèvre4, Alexandra Foresede5, Vincent Sobanski5, Christelle Faveeuw6, Myriam Labalette6, Frédéric Batteux2, David Launay2 and Sylvain Dubucquoi1, 1Université Lille Nord de France, Faculté de Médecine Henri Waremberg, Lille, Lille, France, 2Université Paris Descartes, EA 1833, Hôpital Cochin, AP-HP, Paris, Paris, France, 3Institut d’Immunologie, Centre de Biologie-Pathologie-Genèque, CHRU Lille, Lille, France, 4Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, 5EA 2686, Lille, Lille, France, 6Institut National de la Santé et de la Recherche Médicale Unité 547, Institut Pasteur de Lille, Institut Fédératif de Recherche 142, Université de Lille Nord de France, Lille, France.

Background/Purpose: Systemic sclerosis (SSc) is a multi-organ fibrotic disease associated with auto-immune abnormalities. Several clinical and experimental observations suggest that B cells are involved in the inflammatory and fibrotic processes responsible for the disease; but their exact role has yet to be precisely explored. In this work, we assessed the B cell homeostasis modifications in a murine model of SSc (HOCl mouse), both at a phenotypic and functional level, during the course of the disease.

Methods: Overall, 48 Balb/c mice underwent daily subcutaneous injection of hypochlorous acid (HOCl) or PBS, and were then sacrificed at day 21 (early, inflammatory stage) or day 42 (late, fibrotic stage) from the beginning of the protocol (n = 12 in each of the 4 groups). Mouse spleens were retrieved and immediately dissected. The distribution of the splenic leucocyte populations (B cells, T CD4 and CD8 cells, macrophages) and B cell subsets (transitional, follicular, marginal zone, B1 and regulatory B cells) was analyzed by flow cytometry. The functional properties of B cells were evaluated by MACS- or FACS-sorting the different subsets, and measuring the secretion levels of 20 cytokines in culture supernatants, after stimulation by LPS and CD40L for 48h.

Results: The phenotypic analysis showed a B cell expansion in the HOCl mice at both stages of the disease. This expansion concerns mainly the transitional and B1a cells at the early stage; and mostly the mature forms (follicular and marginal zone) and B1b cells at the later stage. The regulatory CD5+ CD1d+ B cells were also shown to expand at both times of the disease, but more importantly during the inflammatory stage.

At a functional level, the large screening of B cell secretion capacities identified 2 cytokines that were differently produced within the 4 groups: IL-6 and MIP1α. Those 2 cytokines that display pro-inflammatory and pro-fibrotic properties, were produced in more important levels in the supernatant of B cells culture from HOCl mice, at both stages of the disease. Within the B cell compartment, IL-6 was mainly secreted by the marginal zone (MZ) subset. Due to its potential regulatory effects, a special focus was also given...
on IL-10 secretion. Levels of IL-10 in the supernatant of B cells appeared similar in the 4 groups.

**Conclusion:** To our knowledge, this study is the first to find evidence of B cell homeostasis alterations in murine model of SSc. It further implies a potential implication of B cells in the pathogenesis of this disease, either by secretion of cytokines (like IL-6 and MIP-1α) or by expansion of pathogenic subsets (such as marginal zone B cells). The exact role of the regulatory B cell subset, that may exert beneficial properties, needs further studying, as the expansion of the CD5+ CD19+ B cells in HCOL mice seems inconsistent with the similar secretion of IL-10 in the 4 groups. Nevertheless, in light of those results, the B cell appears to be a relevant target for therapy in SSc.

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**1719**

**Periostin May Promote Production of Extracellular Matrix by Modulating TGF-β Signaling in Human Skin Fibroblasts.** Yuki Yamauchi1, Noriko Koomitsu2, Kazuhiro Arima2, Kenji Izuhashi2 and M Ichiko Aihara2.

1Yokohama City University Graduate School of Medicine, Yokohama, Japan, 2Saga Medical School, Saga, Japan.

**Background/Purpose:** Systemic sclerosis (SSc) results in significant morbidity and mortality due to organ fibrosis characterized by increased deposition of extracellular matrix (ECM). Periostin is one of the matricellular proteins, a class of ECM-related molecules defined by their ability to modulate cell–matrix interactions. Recent studies revealed that periostin serves as a critical regulator of wound healing, epithelial mesenchymal transition, and fibrosis. We previously reported elevated serum periostin levels in SSc patients which correlated with severity of skin sclerosis. However, the pathogenic role of periostin in fibrosis has not been well elucidated. In this study, we further examined the role of periostin in transforming growth factor-β (TGF-β) signaling mediating fibrosis.

**Methods:** Periostin levels in skin and lung primary fibroblasts obtained from SSc patients were first determined. To enhance the function of periostin, we overexpressed periostin in human skin fibroblasts and examined protein levels of ECM proteins, α-smooth muscle actin (α-SMA), matrix metalloproteinases (MMPs) in the presence or absence of TGF-β by immunoblotting. Interaction of periostin with TGF-β receptors (TGF-βR1, TGF-βRII) was assessed by immunoprecipitation assay. Furthermore, effects of periostin to Smad proteins following TGF-β stimulation were also evaluated.

**Results:** Periostin was strongly expressed in skin and lung primary fibroblasts obtained from SSc patients compared with healthy subjects. Although single stimulation of recombinant periostin (rP) did not increase ECM protein levels, rP-treated fibroblasts and periostin overexpressed fibroblasts produced significant ECM proteins in the presence of TGF-β compared to respective control fibroblasts stimulated with TGF-β alone. Overexpression of periostin enhanced the induction of α-SMA in the presence of TGF-β and increased expression of MMP-1, which is reported to associate TGF-β activation. In addition, phosphorylation of Smad 2/3 by TGF-β was not affected by periostin, but a level of Smad 7, a TGF-β inducible inhibitor of TGF-β signaling, was reduced in periostin expressed fibroblasts stimulated with TGF-β.

**Conclusion:** Periostin may contribute to fibrosis by enhancing TGF-β signaling via TGF-β activation and Smad 7 inhibition, which leads to further ECM deposition and periostin generation. Periostin may be a therapeutical target molecule mediating fibrosis.

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**1720**

**GATA6 Deficiency Activates UPR Pathways in Endothelial Cells during the Development of Pulmonary Arterial Hypertension.** Rong Han1, Rosanne Van Deuren1, Stefania Lenna1, Izabela Chrobak1, Timothy Radstake2, Carol Feghali-Bostwick3, and Maria Trojanowska1.

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**Background/Purpose:** Pulmonary arterial hypertension (PAH) is a severe lung complication of systemic sclerosis (SSc), and accounts for a large proportion of SSc-related deaths. As a manifestation of the SSc vasculopathy in pulmonary arteries, PAH is characterized by endothelial dysfunction, inflammation, and vascular wall remodeling. The transcription factor GATA6 is produced at high level in the normal pulmonary vasculature, including endothelial cells and smooth muscle cells, but its level is markedly reduced in both SSc-PAH and idiopathic PAH (IPAH) lungs. Furthermore, genetically modified mice that lack Gata6 in endothelial cells develop PAH spontaneously, suggesting that downregulation of GATA6 is an early and key event that leads to endothelial dysfunction and the development of PAH (Ghatnekar et al, 2013). Given that various stimuli induce endothelial dysfunction through the unfolded protein response (UPR) and autophagy pathways, we aim to test the hypothesis that GATA6 deficiency induces ER stress and autophagy in endothelial cells during the process of PAH development.

**Methods:** Sections of lung specimens from SSc-PAH patients were stained for BiP and CHOP, two major players of UPR pathways, by immunohistochemistry. The level of these two proteins were similarly tested in the lungs of two mouse models of PAH: chronic hypoxia-induced, and endothelial conditional knockout of GATA6 (GATA6 CKO). Expression of UPR and autophagy pathway genes in the lungs of these mouse models was measured by quantitative RT-PCR. GATA6 expression was blocked by siRNA in human pulmonary endothelial cells (HPEACs) cultured in vitro and the expression of UPR pathway genes was measured by quantitative RT-PCR. BiP and CHOP protein levels were also determined by western.

**Results:** BiP and CHOP levels were low in lung sections from healthy human subjects, but increased dramatically in the lungs of patients with SSc-PAH. Similarly, these two proteins were more abundant in the lungs from the two mouse models of PAH than in the lungs of wild-type mice. Specifically, BiP and CHOP were found in endothelial cells and macrophages in both human and mouse PAH lungs. In addition to BiP and CHOP, other UPR pathway genes such as PERK, ATF6, and XBP1, and autophagy markers LC3β, ATG3, ATG5, and ATG12 were also upregulated in murine lung by chronic hypoxia or loss of GATA6 from endothelial cells, but hypoxia treatment of GATA6 CKO mice did not have any additive effect on the expression of these genes. Consistent with the above in vivo data, deleting GATA6 in HPAECs with siRNA increased ATF4 mRNA level and BiP and CHOP protein levels in vitro.

**Conclusion:** GATA6 deficiency disrupts endothelial homeostasis and triggers a stress response, including the activation of UPR and autophagy pathways. Chronic activation of these pathways in endothelial cells contributes to the development of PAH.

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**1721**

**Investigating the SFC/c-Kit Pathway in Scleroderma Fibrosis.** Bahja Ahmed Abdi, Oseme Etomi, Xu Shiwen, David Abraham, Christopher Denton and Richard J Stratton. UCL Medical School, London, United Kingdom.

**Background/Purpose:** Stem cell factor (SCF) is a potential driving factor in the development of systemic sclerosis (SSc) and a possible therapeutic target. SCF is a cytokine which acts via c-kit, a tyrosine kinase receptor, present on the surface of progenitor cells, mast cells and melanocytes. This relationship with mast cells potentially drives pruritus, an under-reported but significant problem in SSc, which can be the first clinical presentation. The activity of the greatly altered pigmentation seen in SSc may also reflect altered SCF/c-kit signalling affecting melanocytes. Previous work from our laboratory has demonstrated increased levels of SCF and c-kit in SSc fibroblasts compared to healthy controls. Our aim was to measure the activity of SFC/c-kit pathway in Scleroderma fibrosis.

**Methods:** Blister fluid, tissue and plasma samples were harvested from healthy controls (HC) and SSc patients. The SCF and c-kit protein levels in SSc and HC lung fibroblasts were determined by western blotting. SCF (soluble and membrane bound) and c-kit gene expression was measured using quantitative PCR (qPCR) from control and SSc lung fibroblasts and epidermal sheet. The levels of SFC and c-kit in SSc and HC were assessed by ELISA. The expression of CD117 positive lung fibroblasts was analysed by FACS.

**Results:** The soluble SCF mRNA expression was enhanced in SSc lung fibroblast samples by qPCR compared to healthy controls (soluble transcript: 23 versus 10 copy number respectively p=0.008 and membrane bound: 11 versus 0.7 p=NS). C-kit was expressed at low levels in both SSc and HC.
fibroblasts (0.31 versus 0.28 copy number, p = NS). We then used a slow radiometric assay to measure levels of c-KIT mRNA in SSc lung fibroblasts compared to controls with a density of 2.25 and 0.76 respectively (p = 0.009) while the level of c-KIT protein expression was low in both SSc and control fibroblasts (0.16 vs 0.25) p=NS. Furthermore, measuring the epidermal sheet for c-KIT gene expression in SSc and HC showed that the soluble SSc isoform had 357 and 366 copy number respectively, while the membrane bound isoform showed a higher expression of 106 for SSc and 124 for HC. Using ELISA, SSc specimens had higher levels of SCF in both SSc patients (1572pg/ml) than the HC group (1245pg/ml) p = 0.04, as were the plasma c-KIT levels (13ng/ml versus 16ng/ml) respectively p = 0.028. Levels of SCF in conditioned media of cultured lung fibroblasts were higher in SSc (150ng/ml) vs HC (130ng/ml) p = 0.002 but lower in blister fluid 1233pg/ml vs 1414 pg/ml respectively. C-KIT was undetectable in conditioned media and blister fluid. A subpopulation of CD117 positive cells was found in both SSc and HC lung fibroblasts (1.26% SSc cells, 2.3% HC).

Conclusion: We demonstrated that the full length soluble SCF mRNA is found at higher levels in the epidermis and in the lung fibroblasts of SSc subject and that SSc appears at slightly higher levels in SSc fibroblast conditioned media. However, when measured in plasma or blister fluid SCF was lower or unaltered in SSc when compared to controls. Cultured fibroblasts were heterogeneous and only a minority were positive for c-KIT. If SCF is important in SSc pathogenesis then it might be acting locally on a small subpopulation of c-KIT positive cells.

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1722

TLR4 and TLR7 Are Required for Gadolinium Based Contrast Agent Induction of Dermal and Pulmonary Fibrosis in an Adenine-Induced Model of Chronic Renal Failure. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Nephrogenic Systemic Fibrosis (NSF) is a generalized progressive fibrotic disorder that occurs in some patients with renal insufficiency exposed to various gadolinium based contrast agents (GdBCA). TLR4 and TLR7 signaling has been reported to be necessary for the in vitro establishment of a profibrotic phenotype by the GdBCA Omniscan in normal human macrophages. In this study, we examined the role of TLR4 and TLR7 in the development of NSF-like lesions in vivo in mice with renal failure induced by a high adenine diet following exposure to GdBCA or by intratracheal instillation.

Methods: Chronic renal failure was induced in normal mice and in TLR4 and TLR7 knockout (TLR4 KO) and (TLR7 KO) mice by ad libitum feeding of a standard rodent diet supplemented with 3% adenine for 30 days. Two weekly doses of either the GdBCA Omniscan (100 μL of a 0.5 M solution, corresponding to a 0.05 mmol/kg dose) or an equal volume of normal saline were administered by intratracheal instillation to mice with either normal renal function or with adenine diet-induced chronic renal failure. Mice were sacrificed 56 days after the final instillation and tissues were isolated for histopathology studies showed monoclonal cell infiltration and severe peribronchial fibrosis and moderate diffuse interstitial fibrosis in lungs isolated from adenine-fed control (C57BL/6J) mice instilled with Omniscan. In contrast, lungs from adenine-fed TLR4 KO or TLR7 KO mice maintained normal lung histology. Mice of all three strains with normal renal function instilled with Omniscan and mice with either normal or ablated renal function instilled with saline also demonstrated no fibrosis. Hydroxyproline content was increased ~3 fold in the lungs of Omniscan-instilled wild type mice with adenine diet-induced renal failure. In contrast, the lungs of Omniscan-instilled TLR4 KO and TLR7 KO mice with or without renal failure had normal hydroxyproline levels.

Conclusion: The present study demonstrates for the first time in vivo that the ability of Omniscan to induce significant tissue fibrosis and increased collagen deposition in mice with adenine induced renal failure exposed to the gadolinium contrast agent Omniscan requires signaling through TLR4 and TLR7. These results indicate that targeting of TLR signaling could be a valuable strategy to prevent or treat NSF and other TLR-mediated chemically-induced fibrotic disorders.

1723

Identification of the Microbiome As a Potential Trigger of Systemic Sclerosis By Metagenomic RNA-Sequencing of Skin Biopsies. Michael Johnson1, Zhenghui Li2, Michelle Dimon3, Tamara A. Wood4, Robert Lafyatis5, Sarah Arron6 and Michael Whitfield7. 1Giesel School of Medicine at Dartmouth, Hanover, NH, 2University of California, San Francisco, San Francisco, CA, 3Boston University, Boston, MA

Background/Purpose: Systemic sclerosis (SSc) is a rare and poorly understood systemic autoimmune disease that results in skin fibrosis and severe internal organ involvement. There is a limited understanding of its pathophysiology and there are little data to indicate what may trigger the disease. Previous studies have suggested a variety of bacterial and viral pathogens as a trigger of systemic sclerosis (SSc), though neither a definitive pathogen nor a mechanism of pathogenesis has been established. Here we used RNA-seq to identify differences in the skin microbiome associated with SSc to test the hypothesis that an environmental microbiome component may be more strongly associated with SSc skin.

Methods: RNA-seq was performed on eight patients with early diffuse SSc and four controls, to a depth of 200 million reads per patient. All patients were diagnosed with diffuse systemic sclerosis (dSSc) and were not on immunosuppressive therapy at the time of biopsy. Each patient was assigned to their respective intrinsic gene expression subset: five patients mapped to the inflammatory subset, and three patients to the fibroproliferative subset; one patient classified in the inflammatory subset exhibited both inflammatory and fibroproliferative gene expression. RNA-seq data were analyzed using Integrated Metagenomic Analysis (iMSA) to quantify non-human sequence reads in each sample, and compared to the NCBI taxonomic database to identify significantly enriched pathogens between groups. Differences in immune reactivity of SSc and healthy controls were confirmed by Western blot and mass spectrometry using fungal lysates probed with human sera.

Results: Little difference in viral and bacterial read counts were found between SSc patients and healthy controls. However, a significant difference in the fungal mycobionoms of SSc and controls was evident for the read counts of Rhodotorula glutinis. Within SSc, the highest read counts were consistently found in patients classified in the inflammatory intrinsic subset (p = 0.02 vs. controls). Lower R. glutinis read counts were found in three fibroproliferative patients (p = 0.15 vs. controls); virtually no R. glutinis or other Rhodotorula sequence reads were present in controls. We were able to assemble the D1–D2 hypervariable region of the 28S ribosomal RNA (rRNA) of R. glutinis from each of the SSc samples. We observe differences in immune reactivity to R. glutinis between SSc and healthy controls as determined by Western blot and mass spectrometry to autoantibody-bound proteins. Validation and extension of these results are being performed by fungal internal Transcribed Spacer (ITS) sequencing from SSc and control biopsies.

Conclusion: These results suggest the microbiome, and R. glutinis specifically, may be a trigger or potential modifier of the inflammatory response in SSc. We found R. glutinis to be most significantly associated with the inflammatory subset of SSc, extending our prior work. A genomic and temporal differences in the abundance of this pathogen in the context of host genetics may be associated with differences in clinical presentation and molecular phenotypes.

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1724

Loss of IRF5 Ameliorates Tissue Fibrosis in a Murine Model of Systemic Sclerosis. Ryosuke Saigusa1, Yoshihide A. Sano1, Takashi Taniguchi1, Y. Ichimiya2, Takahiro Takahashi3, Tetsuo Toyama4, A. Yonii5, Y. Shi6, Tatsuya Taniguchi2 and Shinichi Sabo7. 1University of Tokyo Graduate School of Medicine, Tokyo, Japan, 2Institute of Industrial Science, University of Tokyo, Tokyo, Japan

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease with clinical manifestations that result from fibrosis development, immune activation and vascular injuries. A genome-wide association study showed the involvement of genetic variants in the development of SSc. In particular, a single nucleotide polymorphism within the promotor region of interferon regulatory factor 5 (IRF5) was associated with an increase in SSc. This polymorphism results in a decrease in steady-state IRF5 transcript levels,
accompanied with longer survival and milder interstitial lung disease. In this study, we explore the function of IRF5 in the development of SSc utilizing a bleomycin (BLM)-induced SSc mouse model in mice deficient in IRF5 (Irf5−/− mice).

Methods: Wild-type (WT) and Irf5−/− mice were induced to develop SSc following BLM treatment. Dermal thickness and fibrosis were measured by histological analyses. The quantity of the collagen-specific amino acid hydroxyproline was also measured. Immunohistochemistry and quantitative reverse transcription-PCR were conducted to evaluate the degree of inflammation and the expression of cytokines, growth factors, chemokines, and cell adhesion molecules.

Results: Dermal and pulmonary fibrosis in BLM-treated Irf5−/− mice was attenuated as compared to WT mice. Consistent with this, inflammatory cell infiltration induced by BLM treatment was suppressed in the mutant mice. Further, IRF5 deficiency modulated the expression of cell adhesion molecules toward the induction of TGF-β1-skewed inflammation by BLM treatment, as represented by the lower expression of intercellular adhesion molecule-1 and glycosylation-dependent cell adhesion molecule-1 in the skin lesion and lung of Irf5−/− mice than in those of wild type mice. Finally, matrix metalloproteinase 13 mRNA and protein expression was higher in the skin and lung of the BLM-treated Irf5−/− mice.

Conclusion: With BLM treatment, Irf5−/− mice exhibited attenuated tissue fibrosis due to the alterations to fibroblasts, immune cells and cell adhesion molecules, indicating a pivotal contribution of IRF5 to pathological tissue fibrosis. As such, our results experimentally lend support to the notion that reduced IRF5 transcripts as a result of a nucleotide polymorphism in the IRF5 promoter region accounts for the attenuation of SSc manifestations.

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1725 The SYK Inhibitor Fostamatinib Limits Tissue Damage and Fibrosis in a Bleomycin-Induced Scleroderma Mouse Model. Omer Nuri Pamuk1, Guray Can2, Suleyman Ayvaz2, Turan Kara1, Gulsum Pamuk2, Selim Demirtas1 and George C. Tsokos2, 1Trakya University Medical Faculty, Edirne, Turkey, 2Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: The possible anti-fibrotic effects of various kinase inhibitors has been studied before in SSc. Spleen tyrosine kinase (Syk) is a protein tyrosine kinase which activates intracellular signal transduction pathways and has been claimed to be involved in the pathogenesis of systemic autoimmune diseases. We investigated the ability of a small drug Syk inhibitor, fostamatinib, to protect mice from bleomycin-induced SSc.

Methods: Four study groups of Balb/c mice were included in this study: control, bleomycin (administered subcutaneously to BALB/c mice for 21 days), bleomycin and fostamatinib (mice fed with chow containing a Syk inhibitor for 21 days) and fostamatinib alone groups. Skin and lung tissue specimens were obtained and evaluated histologically.

Results: Mice treated with bleomycin alone had significantly more skin thickness (416.1 ± 61.1) compared to control (260.1 ± 10.1) and fostamatinib (254.3 ± 7.9) treated mice (p < 0.001). Mice subjected to bleomycin and fed with fostamatinib-containing chow generated more (312.3 ± 4.4) dermal thickness than control and fostamatinib-treated mice (p values < 0.001) but, significantly less when compared to mice treated with bleomycin alone (p < 0.001). Alveolar hemorrhage, edema, damage and leukocyte scores in the lungs of mice treated with bleomycin were significantly higher than control mice compared to control or fostermatinib alone-treated mice (p values < 0.001). At the end of the 21-day bleomycin administration, there was apparent prominent fibrosis which was reduced significantly in the group of mice which received in parallel fostamatinib. Following fostamatinib treatment, Syk, phospho-Syk, and TGF-β expression decreased in both skin and lung tissues.

Conclusion: The Syk inhibitor fostamatinib prevented bleomycin-induced fibrosis and inflammation in the skin and the lung. The anti-fibrotic effect of fostamatinib is linked to reduced Syk phosphorylation and TGF-β expression. The Syk pathway appears as a potential molecular target for therapeutic intervention in SSc.

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1726 Therapeutic Efficacy of Mesenchymal Stem Cells in Diffuse Murine Hypocholesterolemic-Induced Systemic Sclerosis. Alexandre Maria1, Claire Bony1, Karine Toupet2, Christian Jorgensen3, Philippe Gulpain4 and Daniele Noél5. 1Inserm, Montpellier, France, 2Clinical Immunology and Osteoarticular Diseases, Therapeutic Unit, CHU Lapeyronie, Montpellier, France, 3Department of Internal Medicine, Montpellier, France, 4UM1, Montpellier, France.

Background/Purpose: Systemic sclerosis (SSc) is a rare intractable disease with unmet medical need and fibrosis-related mortality. Absence of efficient treatments has prompted to develop novel therapeutic strategies. Observations in mouse models of systemic sclerosis (mSSc) suggest that MSCs are one of the most attractive options. Herein we provide the first preclinical study using MSCs in the relevant hypocholesterolemic (HOCI)-induced murine model of diffuse SSc, recapitulating the main features of the disease: multisclerotic, vasculopathy, and autoimmunity.

Methods: Balb/c mice underwent six weeks of daily intradermal injections of HOCI leading to SSc-HOCI phenotype. Different doses of syngenic bone marrow-derived MSCs (2.5 × 106; 5 × 105; 105) were transfused in the tail vein of the mice, either the day before disease induction, or at day 21. Skin thickness was measured weekly, and samples of skin and lung were taken at euthanasia (d42) to assess by rt-qPCR the expression of collagens I and III, TGF-β, alpha-smooth actin muscle (α-SMA), MMP-1 and -9, Tissue Inhibitor of MMP (TIMP1), Hepatocyte Growth Factor (HGF), VEGFA, IL-1β, TNF-α, IL-6, IL-10, Superoxide Dismutase (SOD2), and Heme Oxygenase (HMOX1). An anti-scl70 antibodies levels were measured in sera.

Results: We first compared the effects of different doses of MSCs (2.5 × 106; 5 × 105 and 105) infused the day before disease induction, on clinical and biological parameters. When considering skin thickness in time, we observed a slower progression in MSC-treated mice, with the best results obtained with the lowest dose of 2.5 × 105 MSCs. At euthanasia, a lower expression of fibrotic markers (collagens I and III, TGF-β, α-SMA) was observed in both skin and lung of treated mice, consistent with histological improvement and inversely proportional to the injected dose. Importantly, sera from treated mice exhibited lower levels of anti-scl70 autoantibodies and enhanced antioxidant capacity, confirming the systemic effect of MSCs. Of interest, MSC administration was also efficient when infused at d21 while disease is known to be established. We further provide evidence at a molecular level that in skin and lung tissues, MSCs exerted an anti-fibrotic role by normalizing extracellular matrix remodeling parameters (MMP-1 and -9, TIMPs, HGF, VEGFA), as well as reducing pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-10) and increasing antioxidant defenses (SOD2, HMOX1).

Conclusion: In conclusion, this preclinical study is the first to demonstrate the therapeutic efficacy of MSCs in SSc, acting through the modulation of inflammation, tissue remodeling and antioxidant defenses. The benefits observed in a curative approach are particularly promising in sight of clinical perspectives.

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Background/Purpose: The enzyme poly(ADP-ribose) polymerase-1 (PARP-1) transfers negatively charged ADP-ribose units from the donor NAD onto various substrate proteins either as mono- or oligomeric moieties or as linear or branched poly (ADP-ribose) (PAR) chains. These modifications can have pronounced regulatory effects on the half-life or the enzymatic activity of target proteins. Recent studies demonstrated that PARP-1 can poly(ADP-ribosyl)ate (PARylate) members of the Smad family of transcription factors. However, the role of PARP1 in the pathogenesis of SSc has not been investigated.

Methods: The expression of PARP1 in human skin and in experimental fibrosis was determined by qPCR and immunohistochemistry. TGF-β signalling was analysed by Smad reporter assays and target gene analysis after 1 mM selective PARP-1 inhibitor 3-Aminobenzamide (3AB). Bleomycin-induced skin fibrosis and Tsk-1 mice were used to

Disclosure: A. Maria 1, Claire Bony 1, Karine Toupet 2, Christian Jorgensen 3, Philippe Gulpain 4, Daniele Noél 5.
evaluate the effect of PARP deficiency and PARP inhibition (10mg/kg/d 3AB) in vivo.

Results: Decreased expression of PARP1 was detected by immunohistochemistry in skin sections of SSC patients, particularly in fibroblasts. Inhibition of PARylation by 3AB augmented the stimulatory effects of TGFβ on fibroblasts in vitro. PARP1 inhibition increased Smad dependent transcription in reporter assays and promoted the transcription of TGFβ/Smad target genes. Treatment with 3AB also stimulated the collagen release and fostered the expression of contractile proteins and increased expression of α-smooth muscle actin (α-SMA) and enhanced formation of stress fiber formation compared to fibroblasts stimulated with TGFβ alone. Inhibition of PARylation also exacerbated experimental fibrosis in vivo. Treatment with 3AB induced a more secrete fibrotic response to bleomycin with increased dermal thickening by up to 103% (p < 0.0001), hydroxyproline contents and myofibroblast counts compared to control mice (p = 0.0001 and p = 0.0593). Inhibition of PARylation also strongly exacerbated fibrosis in Tsuk-L mice. Meanwhile, after bleomycin injection, dermal thickening, hydroxyproline contents and myofibroblast counts of PARP1 knockout mice were increased by 85% (p = 0.0046), 67% (p = 0.0098) and 56% (p = 0.0043) compared to wild-type mice.

Conclusion: We demonstrate that PARP1 negative regulates canonical TGFβ signaling. The down-regulation of PARP1 in SSC fibroblasts may thus directly contribute to hyperactive TGFβ signaling and to persistent fibroblast activation in SSC.


1728 Bromodomain Inhibitor JQ1 Modulates Collagen Processing and Aminolates Bleomycin Induced Dermal Fibrosis in Mice. Sarah Trinder1, Mary Tarriela2, Adrian Gilbane1, Robert Good3, Xu Shi-Wen3, David Abraham3 and Alan M. Holmes1, UCL, London, United Kingdom, 1Centre for Rheumatology and Connective Tissue Diseases, London, United Kingdom, 2UCL, London, United Kingdom, 3University of California, San Francisco, United States of America.

Background/Purpose: Scleroderma (SSc) is a complex pro-inflammatory scarring disease, characterised by elevated deposition of extracellular matrix (ECM) proteins, in particular collagen type I. The disease is heterogeneous affecting both the skin and visceral organs including kidney, lung and heart. The SSc fibroblast is a key cell which promotes a pro-inflammatory and fibrotic microenvironment that can lead to the loss of normal tissue architecture and organ function. The mechanisms that contribute to the formation and persistence of the SSc dermal fibroblast remain unclear. We have previously shown the epigenetic bromodomain and extra-terminal domain-containing proteins (Brd) which bind to acetylated histone residues, play a significant role in pulmonary fibrosis. Here we seek to explore the contribution of Brd proteins in the development of dermal fibrosis using a specific inhibitor of Brd proteins (Brd 2, 3, 4 and T), JQ1.

Methods: We investigated the dose-response of JQ1 on SSC and healthy control (HC) donor (n = 3) dermal fibroblasts. We assessed the effects on collagen deposition and processing using the Scar-in-a-Jar in vitro fibrosis assay, by western blot and immuno-fluorescence microscopy for collagen type I (n = 4). To determine the effect of JQ1 in a pre-clinical model of skin fibrosis, female C57BL/6 mice were given three weekly subcutaneous injections of 100μl sterile saline (n = 6) or 0.1U/ml bleomycin (n = 6) for 14 days and treated with 12mg/kg/day JQ1 (n = 6) or vehicle (n = 6). After 14 days histological analysis for fibrogenic proteins and ECM was performed on skin, and pro-fibrotic markers including SMA, and collagen expression in skin (n = 5). Furthermore, secretions of the inflammatory marker, IL-6, was significantly attenuated (p < 0.05).

Conclusion: We have assessed the functional effects of the Brd inhibitor, JQ1, on SSC dermal fibroblasts and the development of dermal fibrosis in a pre-clinical model of dermal fibrosis. We demonstrate that JQ1 markedly attenuated the excessive deposition and processing of collagen type I by SSC fibroblasts. In keeping with Brd proteins playing a pivotal role in the development and progression of dermal fibrosis, JQ1 significantly inhibited ECM deposition in vivo. Our data suggests a key role for Brd proteins in the persistence of the SSc dermal fibroblast phenotype.

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1729 Adenosine A2A Receptor (A2AR) Promotes Collagen Type 3 Expression Via β-Catenin Activation. Miguel Perez-Aso1,2, Bruce N. Cronstein1, 1New York University, New York City, NY, 2NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: A2AR stimulation promotes collagen 1 and 3 (Col1 and Col3) synthesis, principal mediators of fibrosis and scarring. We have recently demonstrated that the A2AR is a fine-tune modulator of collagen balance that signals via PKA/EPAC2/AKT but is independent of Smad2/3 signaling. Wnt signaling is an important player in the progression of fibrosis, and other recent studies have suggested that cAMP and Wnt pathways converge.

Methods: Primary human dermal fibroblasts (<5 passages) were stimulated by the A2AR-selective agent CGS21680 (1μM) and β-catenin, dephosphorylated β-catenin and β-catenin phospho-Ser552 levels were determined in cytosolic and nuclear fractions by Western Blot. Nuclear translocation of β-catenin was determined by confocal microscopy. β-catenin was knocked down by transfection with specific siRNA or scrambled-siRNA and protein levels determined by Western Blot.

Results: Stimulation of A2AR rapidly (15 min) increases cellular β-catenin levels to 169 ± 13% of control (N = 3, P < 0.01). Similarly CGS21680 stimulates de-phosphorylation of β-catenin (188 ± 27% of control; N = 5, P < 0.05) and promotes β-catenin phosphorylation at Ser 552 (239 ± 15% of control; N = 5, P < 0.001), the site of β-catenin activation by AKT. Furthermore, CGS21680 stimulates translocation of β-catenin to the nucleus confirmed by confocal microscopy. The A2A K. We next knocked down β-catenin (54 ± 5% decrease in β-catenin siRNA vs scramble siRNA; N = 10, P < 0.001) and determined the effect of A2A R stimulation on collagen production. A2A R-stimulated increases in Col1 scramble-siRNA transfected cells (63 ± 22% increase, N = 7) which were unaffected by β-catenin knockdown (53 ± 17% increase, N = 7). In contrast, β-catenin knockdown abrogates A2AR-stimulated increments in Col3 synthesis by 73% (β-catenin siRNA 66 ± 14% increase of Col3 vs β-catenin siRNA 18 ± 16% increase of Col3; P < 0.05, N = 8).

Conclusion: Our results strongly indicate that A2AR stimulation activates both canonical and non-canonical Wnt pathways for increased Col3 synthesis, leading to dermal fibrosis and excessive scarring.

Disclosure M. Perez-Aso. None; B. N. Cronstein, Canfite Pharma, 1, AstraZeneca, 2, Celgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Research Foundation, 6, ACR, 6, Arthritis Foundation, 6.
Methods: A systematic and undirected approach was undertaken to screen for autoantibodies in human serum samples of 100 individuals with SSc and related overlap syndromes using 7000 recombinant protein targets. Active and passive control groups comprised healthy controls and serum samples of other systemic autoimmune diseases including systemic lupus erythematosus (SLE), and early rheumatoid arthritis (RA). The frequency of autoantibodies for a particular antigen was determined by applying the mean value of the signal intensity of the healthy control cohort plus 2 standard deviations (SD) as a cut-off. Then, the frequency of 116 candidate antigens in 1100 healthy controls and 90 SSc samples was assessed using a connective tissue disease array. Afterwards, ELISAs were developed for 7 antigens with high frequency in SSc or higher frequency in SSc subtypes. The performance of ELISAs was assessed in comparison with the Luminox multiplex system in additional 150 SSc samples.

Results: Sera of 100 SSc patients with limited or diffuse SSc or overlap syndromes were tested for established and novel autoantigens. 30% of SSc patients were previously tested negative for ACA and anti-Scl70. The frequency of established and novel autoantibodies in the test cohort ranged from 40% to 10% in descending order: CENPB: 40%, Scl70: 36%, TRIM21 (Ro52): 27%, antigen 1: 28%, antigen 2: 27%, antigen 3: 17%, antigen 4: 15%, antigen 5: 13%, antigen 6: 11% and antigen 7: 4%. While autoantibodies to antigens 1-4 were more frequently observed in limited SSc, autoantibodies to 5-7 were more abundant in diffuse SSc. Autoantibody reactivity above the cut-off level was identified in 50% of the previously negative-tested SSc patients. ELISA and Luminex showed good qualitative agreement. The encoding for these proteins were found being enriched in pathways of histone modifications and chromatin remodeling suggesting their involvement in epigenetic processes.

Conclusion: An alternative combination of Luminox bead-arrays for high-throughput autoantibody profiling and complementary ELISA development provides an alternative route to discover and verify novel SSc-associated autoantibodies. By measuring 7 antigens the number of autoantibody positive SSc patients increased from 68% to 84%.

Disclosure: H. D. Zucht, None; P. Buddle, None; P. Schulz-Knappe, Protagen AG, 3; N. Hunzelmann, None; K. Conrad, None; P. D. M. Schneider, None.

1731
Translocation of IGFBP-5 to the Nucleus and Its Interaction with Nucleolin Do Not Dictate Its Fibrotic Effects. Yunyun Su and Carol Feghali-Bostwick. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Insulin-like growth factor binding protein (IGFBP-5) is one of six IGFBPs. IGFBP-5 is the most conserved member of the family, and is increased in many chronic diseases and malignancies. IGFBP-5 induced fibrotic activity in vivo is mainly due to its nuclear translocation in human fibroblasts, and a fibrotic phenotype. We previously reported that IGFBP-5 is a pro-fibrotic factor that induces extracellular matrix (ECM) production and deposition. IGFBP-5 promoted a fibrotic phenotype in vitro in primary human fibroblasts, in vivo in mouse lung and skin, and ex vivo in human skin. Since IGFBP-5 contains a nuclear localization signal (NLS) that facilitates its nuclear translocation, we sought to understand the role of nuclear translocation on the fibrotic activity of IGFBP-5 and identify IGFBP-5 binding partners relevant for its nuclear compartmentalization.

Methods: We generated functional wild type IGFBP-5 and IGFBP-5 with a mutated NLS. A bration of nuclear translocation in the NLS mutant was confirmed using immunofluorescence and immunoblotting of nuclear and cytoplasmic cellular extracts. The fibrotic activity of wild type and NLS-mutant IGFBP-5 was examined in vitro in primary human fibroblasts and ex vivo in human skin. We identified IGFBP-5 binding partners using immunoprecipitation and Mass Spectrometry. Binding of IGFBP-5 to its partners was validated using co-immunoprecipitation and immunoblotting. We examined the effect of the partner on IGFBP-5 localization and function via sequence-specific silencing in primary human fibroblasts.

Results: Our results show that IGFBP-5-induced ECM production in vitro in primary human fibroblasts is independent of its nuclear translocation as the NLS-mutant IGFBP-5 retained fibrotic activity. The NLS-mutant IGFBP-5 also induced fibrosis ex vivo in human skin maintained in organ culture, thus confirming and extending the in vitro findings. Nucleolin, a nuclear protein that can serve as a nuclear receptor, was identified as an IGFBP-5 binding partner. Silencing nucleolin in primary human fibroblasts reduced IGFBP-5 translocation to the nucleus but did not block the ability of IGFBP-5 to induce ECM production and a fibrotic phenotype.

Conclusion: IGFBP-5 transport to nucleus requires an intact NLS and nucleolin. However, nuclear translocation is not necessary for IGFBP-5 fibrotic activity. Our data provide further insights into the mechanism mediating the fibrotic activity of IGFBP-5 and the role of nuclear compartmentalization in IGFBP-5-induced fibrosis.

Disclosure: Y. Su, None; C. Feghali-Bostwick, None.

1732
Attenuation of Sclerodermatous Graft Versus Host Disease (sclGVHD) in IL4RA Receptor-Deficient Mice. Kalia Urso, Kelly Tsang, Robert Lafayatis and Antonios O. Aliprantis. Brigham and Women’s Hospital, Boston, MA; Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; Boston University School of Medicine, Boston, MA.

Background/Purpose: Scleroderma is a rare autoimmune disease characterized by the accumulation of fibrotic tissue in multiple organs including the skin, gut and lungs. To date, the cause of this disease has not been identified and specific treatments are unavailable. SclGVHD in mice recapitulates many scleroderma manifestations and can be used to determine potential therapeutic pathways. Previously, we identified activation of the Interleukin-13 (IL-13) cytokine pathway in the skin of both murine sclGVHD and a subset of scleroderma patients characterized by an "inflammatory" gene expression signature. We also showed that host mice lacking IL4RA, a functional subunit of IL-13 and IL-4 receptors, are protected from the cutaneous manifestations of sclGVHD. The purpose of this study is to define the mechanism that protects IL4RA-deficient mice from sclGVHD.

Methods: Spleenocytes from BALB/c Rag2-/- or BALB/c Rag2-/- Il4ra-/- hosts were transferred to recipient mice, thus inducing sLN fibrosis. Seven days after cell transfer the skin was processed for histopathology and scored blindly for inflammation. Subcutaneous lymph-nodes (sLNs) were isolated, collagenase digested and analyzed by flow cytometry. SLN cells were also stimulated in vitro for 5h with LPS, PMA and ionomycin to analyze IL-10 production by intracellular cytokine staining. mRNA was extracted from skin and sLN and subjected to qRT-PCR. Student's t-tests, with n=10-13 per group, were used to determine statistical significance.

Results: One week after cell transfer IL4RA-deficient mice lost significantly less weight than control sclGVHD mice (8.4± 4.2% of baseline body weight vs. 16.28± 3.68%, p<0.0001) and displayed less skin inflammation as assessed by histopathologic score (1.50 ± 0.53 for BALB/c Rag2-/- and 0.80 ± 0.42 for BALB/c Rag2-/-Il4ra-/-, p=0.0042). Despite reduced skin inflammation, the sLNs of BALB/c Rag2-/-Il4ra-/- mice showed significantly higher cellularity (8.7 ± 2.33 x10^5 vs. 3.09 ± 1.23 x10^5, p<0.0001), with elevated numbers of T cells, B cells and myeloid CD11b+ Ly6C+ cells compared to BALB/c Rag2-/- controls. Cells from these populations also produced more IL10 than those isolated from control mice when stimulated ex vivo. In addition, among the CD4+ T-cells, Il4ra-deficient hosts had a significantly higher frequency of Foxp3+ regulatory T-cells (3.92± 1.95 vs. 6.82± 4.10, p=0.0008). qRT-PCR analysis also revealed elevated Il10 transcripts in the sLNs of BALB/c Rag2-/-Il4ra-/- hosts (p=0.0008). In contrast, no differences were observed in transcript levels of chemokines important for the homing of immune cells to sLNs, including cc19 and cxc13.

Conclusion: IL4RA promotes sclGVHD early in the disease course by promoting infiltration of immune cells into the skin and suppressing the expansion of regulatory T-cells and IL-10 expression. Surprisingly, the sLNs of mutant mice contained more adaptive and innate immune cells. A tional data are needed to understand if this accumulation of cells in sLN of IL4RA-deficient mice is due to a defect in the pathways that control apoptosis, proliferation or the migration of activated cells from the sLN to the skin.

Disclosure: K. Urso, None; K. Tsang, None; R. Lafayatis, None; A. O. Aliprantis, None.

ACR/ARHP Poster Session B
T cell Biology in Rheumatoid Arthritis and Other Arthritis.

1733
Background/Purpose: A accumulating evidence indicates the relevance of intestinal microbiota in shaping the immune response and supports its contribution to the development of autoimmune diseases. Prebiotic non-digestible oligosaccharides are known to selectively support growth of commensal Blifidobacteria and Lactobacilli and adjust the microbiota composition. The aim of this study was to assess the efficacy of microbiota modulation using non-digestible oligosaccharides as a therapeutic approach for T cell-dependent autoimmune arthritis.

Methods: IL-1Ra deficient mice spontaneously developing an autoimmune T cell- and interleukin (IL)-17-dependent arthritis were used for this study. We previously showed that spontaneous arthritis in IL-1Ra−/− mice depends on the presence of commensal microbiota, since germ-free mice develop less severe disease. To examine the feasibility of microbiota modulation as a therapeutic approach during established disease, IL-1Ra−/− mice which had already developed arthritis under conventional microbial status were orally fed a prebiotic diet containing 2.5% or 5% short-chain galacto- and long-chain fructooligosaccharides (scGoslcFos; 9:1). Disease progression was monitored and intestinal and systemic T cell differentiation was studied.

Results: Oral treatment of arthritic IL-1Ra−/− mice with scGoslcFos significantly suppressed the progression of arthritis. Furthermore, dual-energy X-ray absorptiometry scanning revealed that a prebiotic diet containing scGoslcFos significantly improved bone mineral density and tended to increase bone mineral content in arthritic IL-1Ra−/− mice.

Gene expression of T-bet and ROR-γ, the Th1 and Th17-related transcription factors, in lymph nodes draining the arthritic joints was significantly reduced in the group receiving the scGoslcFos diet. Flow cytometry analysis of the lymph nodes showed no effect on the percentages of Th1, Th17 and regulatory T cells (Tregs). However, the percentage of CD3+CD4+ IL-4 producing cells tended to be increased in the scGoslcFos treated group.

Interestingly, small intestine lamina propria of mice receiving scGoslcFos diet contained increased percentages of CD3+CD4+ FoxP3+ regulatory T cells. In addition, intestinal gene expression of the Treg-related transcription factor FoxP3 as well as anti-inflammatory cytokine IL-10 were increased with scGoslcFos. Accordingly, small intestine lamina propria lymphocytes of mice receiving the 5% scGoslcFos diet produced significant higher levels of IL-10 upon ex vivo stimulation with PMA and ionomycin. Production of IL-4 and IFN-γ also tended to be increased, while production of TNFα, IL-6 and IL-17 was not affected by the prebiotic diet.

Conclusion: Our data suggest that scGoslcFos suppresses arthritis progression, potentially through induction of anti-inflammatory cytokines such as IL-10 and IL-4. Suppression of disease progression using dietary intervention with prebiotic scGoslcFos may be applicable as a therapeutic approach to suppress autoimmune arthritis.

Disclosures: R. Rogier None; T. Eerdeven None; A. Hartog None; B. Walgreen None; L. van den Bersselaar None; M. M. Helsen None; P. Vos None; J. Garseen None; L. Wilhelmsson None; W. B. van den Berg None; M. I. Koenders None; S. Abdollahi-Roodsaz None.

1734

IL-22 Plays a Significant Role in the Initiation and Augmentation of Th17-Dependent Experimental Arthritis.

Debbie M. Roeleveld1, Renoud Marijnissen1, Rebecca Rogier2, Birgitte Walgreen1, Monique M. Helsen1, L. van den Bersselaar1, B. Walgreen1, M. M. Helsen1, L. van den Bersselaar1, S. Abdollahi-Roodsaz None; W. B. van den Berg None; M. I. Koenders None.

Background/Purpose: Type II collagen (CII) has been suggested as a possible autoantigen in RA, since autoimmunity to CII is commonly detected in patients with RA. Also a RA-like disease, collagen-induced arthritis (CIA) can be induced in rodents expressing H-2aQ and H-2aR MHC class II haplotypes after immunization with heterologous CII. Autoreactive T cells in both RA and CIA recognize the same immunodominant CII epitope 259–273, which binds both CIA-associated mouse H-2aQ and human RA-associated HLA-DRB1 MHC class II molecules. CIA-reactive T cells from RA patients predominantly recognize the immunodominant CII 259–273 epitope when it is glycosylated at positions 264 and 270. Glycosylation of the lysine side chain at position 264 is of particular importance for CIA development as well as for tolerance induction to CII. It has been previously shown in our laboratory that administration of soluble MHC class II molecules in complex with the glycosylated CII peptide 259–273 (GalOK264/Aq) can prevent CIA development and ameliorate a chronic relapsing disease, which can be relevant for patients with RA. However, the exact mechanism of tolerance induction by GalOK264/Aq complexes remains to be elucidated.

Methods: We established Vβ12-transgenic mouse model, which have galactosylated CII epitope specific T cells and the corresponding clonotypic antibody to track them unambiguously. By immune-phenotyping of galactosylated CII epitope specific T cells we investigated the role of CII-reactive T cells in tolerance induced by vaccination with GalOK264/Aq complexes. Vβ12- tg mice were immunized with rat CII emulsified in CFA. 100 mg of GalOK264/Aq complexes or PBS were injected intravenously day 3 post-immunization. Day 10 post-immunization T cells from draining (inguinal) lymph nodes were either directly analyzed by FACs or restimulated in vitro with galactosylated CII peptide and the numbers of cytokine-expressing T cells were determined by FACs or ELISPOT and cytokine concentrations in cell culture supernatants were evaluated by ELISA.

Results: Injection of Vβ12 transgenic mice with GalOK264/Aq complexes leads to reduction in number of the galactosylated CII-specific T cells. Also the proportion of T cells expressing CD69, an early activation marker, within galactosylated CII specific T cell population was reduced in vaccinated mice compared to PBS controls. Further phenotypic analysis of galactosylated CII-specific T cells revealed that vaccination with GalOK264/Aq of Vβ12 transgenic mice leads to an increased expression of the co-inhibitory molecules such as PD-1 and LAG3.
Furthermore, administration of Aq/gal-K264 complexes significantly attenuates Th1 and Th17 responses in galactosylated CII specific T cells both in and V G2-transgenic- and B6 N mice.

Conclusion: Thus, vaccination with GalOK264/Aq complexes skewes the CII specific T cell responses from activation and differentiation into effecter cells toward antigen specific immune tolerance phenotype.

Disclosures: V. Urbanoviciute, None; C. Ge, None; B. Xu, None; S. van den Berg, None; B. Dzhambazov, None; J. Bäcklund, None; R. Holmdahl, None.

1736

Immune Related Adverse Events Associated with Anti-CTLA-4 Antibodies: Systematic Review and Meta-Analysis. 

A. Bertrand, M. Kostine, Thomas Barnetche and Thierry Schaeverbeke. Bordeaux University Hospital, Bordeaux, France.

Background/Purpose: CTLA-4 is a costimulatory molecule that downregulates T-cell activation and promotes an immunotolerance, well known by rheumatologist since the use of Abatacept. Targeting CTLA-4 is a recent strategic approach in cancer control: blocking CTLA-4 enhances an antitumor immunity by promoting T-cell activation and cytotoxic T-lymphocytes proliferation. This induction of a tolerance break against the tumor may be responsible for immune related adverse events (irAEs) in most responder patients, some of which concerning rheumatologists.

Objective: To assess the incidence and nature of irAEs in oncologic treatment with anti-CTLA-4 antibodies (Ipilimumab and Tremelimumab).

Methods: A systematic search of literature up to February 2014 was performed in MEDLINE, EMBASE and Cochrane databases to identify relevant articles. Reading and data extraction were performed independently by two readers. Pooled incidence was calculated using R software with the package meta. Heterogeneity was quantified using I².

Results: The literature search identified 491 articles and a manual search retrieved 4 other articles. Finally, 121 articles were full-text reviewed and 80 finally included in the study. 1265 patients from clinical trials were included for meta-analysis.

Anti-CTLA-4 antibodies were mainly given for melanoma, and in few studies for renal cell carcinoma, mesothelioma and pancreatic, gastric, oesophageal, colorectal, prostatic and bladder cancer. Described irAEs consisted of skin lesions such as rash, pruritus and vitteligo, colitis, and less frequently inflammatory hepatitis, hypophysitis, oesophagal, colorectal, prostatic and bladder cancer.

The overall incidence of high-grade irAEs was 24% (CI95%: 18%–30%). The overall incidence of high-grade irAEs was 24% (CI95%: 18%–30%). The risk of developing irAEs was dependent of dosage with incidence of irAEs of (36–104) vs. 115 (109–125), p = 0.001. TCR diversity was also reduced in CD28⁻/⁻ Tregs as compared to CD28⁺/⁺ Tregs and CD28⁻/⁻ Tregs to TNF-α led to a downregulation of CD28 and thus to the CD28⁻/⁻ FoxP3⁺ phenotype.

Conclusions: We discovered a novel T cell subset which combines both senescent as well as regulatory properties. This subset favors the pro-inflammatory milieu and shows altered phenotype and function compared to normal (non-senescent) Tregs.

Disclosures: J. Fessler, None; C. Schwarz, None; A. C. Fijcan, None; R. Husic, None; E. Höller, None; A. Lackner, None; W. B. Graninger, None; C. Dejaco, Pfizer, MSD, 2. Pfister, MSD, Roche, UCB, BMS, AbbVie, 8.

1737

Altered Phenotype and Function of Senescent Regulatory T Cells in Rheumatoid Arthritis. 

Johannes Fessler, Christine Schwarz, Anja C. Fijcan, Rusmir Husic, Evelyne Höller, Angelika Lackner, Winfried B. Graninger and Christian Dejaco. Medical University Graz, Graz, Austria.

Background:Immunosenescence accompanied by accumulation of senescent T cells is a hallmark feature in the pathogenesis of rheumatoid arthritis (RA). Here we characterize a novel senescent regulatory T cell (Tregs, CD4⁺/CD28⁻/FoxP3⁺) subset in RA patients.

Methods: Prospective, cross-sectional study on 35 patients with RA (mean age 58.3±9.5, 71.4% female, SDAI 8.15 ±12.1) and 25 healthy controls [HC, mean age 55.6 (±6.7), 60% female]. We used flow cytometry to determine the prevalence of senescent CD4⁺/CD28⁻/FoxP3⁺ T cells and to characterize their phenotype, proliferation, cytokine production and apoptosis. T cell receptor diversity was determined by RT-PCR. In vitro generation of senescent Tregs was performed in cell culture experiments using magnetic bead isolated CD4⁺/CD25⁺CD127⁺/-Tregs and stimulation with anti-CD3/CD28 beads, interferon (IFN) and TNF-α for 14 days.

Results: Two percent (±2.8) of CD4⁺ T cells were CD28⁻/FoxP3⁺ in RA patients whereas this subset was almost absent in HC [0.6 (±0.8), p < 0.001]. The number of CD4⁺/CD28⁻/FoxP3⁺ Tregs was comparable in both groups [28.6 (±18.5) vs. 32.7 (±18), p = 0.480]. In vitro assays showed that exposure of CD4⁺/CD28⁻/FoxP3⁺ Tregs to TNF-α led to a downregulation of CD28 and thus to the CD28⁻/FoxP3⁺ phenotype.

Conclusions: In RA patients we discovered a novel T-cell subset which combines both senescent as well as regulatory properties. This subset favors the pro-inflammatory milieu and shows altered phenotype and function compared to normal (non-senescent) Tregs.

Disclosures: J. Fessler, None; C. Schwarz, None; A. C. Fijcan, None; R. Husic, None; E. Höller, None; A. Lackner, None; W. B. Graninger, None; C. Dejaco, Pfizer, MSD, 2. Pfister, MSD, Roche, UCB, BMS, AbbVie, 8.
CCR6+ T cell subpopulations were distinguished by differential expression of CXCR3 and CCR4. All four CCR6+ subpopulations shared Th17 cell characteristics such as ROR-γt and CCL20 expression, but IL-17A, IL-17F, IL-22 and IFN-γ expression differed greatly between these subpopulations. However, even the population with lowest expression of these cytokines showed high pathological potential as shown by stimulating IL-1α, IL-6, IL-8, COX-2 and MMP-3 expression upon co-culture with RASF. Indeed, despite dissimilar Th17 and Th1 characteristics between the CCR6+ sub-populations, all four showed highly increased pathological potential in co-culture compared to naive and T-helper-1 cells.

Conclusion: ACAP + and ACAP- patients can be distinguished by the distribution of Thg and CCR6+ T helper cell subpopulations. These CCR6+ subpopulations exhibit dissimilar T-helper-17 and T-helper-1 characteristics, but all possess high pathological potential, including the population that has low IL-17A/F and IL-22 expression. These findings indicate a prominent role of CCR6+ T helper cells in the pathogenesis of ACAP + patients with early RA and may contribute to the worse disease outcome in ACAP + patients.

Disclosure: S. M. J. Paulissen, None; J. P. van Hamburg, None; N. Davelaar, None; H. Vroman, None; J. M. Hazes, None; P. H. P. de Jong, None; E. Lubberts, None.

1739

Immunomodulatory Properties of CD271+ and CD271- Synovial Mesenchymal Cells. Alicia Ustategui1, Manuel J. Del Rey2, Regina Fare6, Gabriel Criado1, Vanessa M. Miranda1, Juan D. Cañete2 and Jose L. Pablos1.

1Instituto de Investigación Hospital 12 de Octubre (I-I2), Madrid, Spain; 2Hospital Clinic de Barcelona, Barcelona, Spain.

Background/Purpose: Mesenchymal stem cells (MSC) have been isolated from synovium and represent a fraction of synovial fibroblast (SF) cultures. CD271+ is considered a MSC surface marker that is also present in a small fraction of primary cultures of SF. Bone marrow or synovial derived CD271+ cells have shown increased chondrogenic potential but their immunosuppressive properties have not been analyzed. We have analyzed the immunosuppressive potential of CD271+ compared to CD271- SF cultures from human osteoarthritic synovial tissues.

Methods: Osteoarthritic synovial membranes were obtained at knee joint replacement surgery (n=9). CD271+/− separation was carried out by magnetic sorting of passage 0 SF cultures and confirmed by flow cytometry. Multipotent differentiation capability of SF to adipocytes, chondroblasts and osteoblasts was studied using standard in vitro tissue culture-differentiating conditions and staining with oil red, alcalgin blue or alizarin red, respectively. Immunomodulatory properties of CD271+− sorted cells were analyzed in co-cultures with T lymphocytes obtained from healthy donors (ratio 1:10), stimulated with anti-CD3/CD28 beads. T-cell proliferation was measured by CellVue dye dilution as detected by flow cytometry. T-cell cytokine production (IL-2, IL-10, IL-17 and IFN-γ) in supernatants was quantified by ELISA.

Results: Primary passage 0 OA SF cultures contained (11.27±7.25%) CD271+ cells. After sorting, both CD271+ and CD271- SF cultures contained multipotential MSC capacity to differentiate to adipocytes, chondroblasts and osteoblasts in specific differentiation media. Both types of cells significantly inhibited the proliferation of anti-CD3/CD28 stimulated T cells and there were no quantitative differences between CD271+ and CD271- cells (70.46±13.15% respectively compared to single T-cell parallel cultures where proliferation was set to 100%). Co-culture of SF and T lymphocytes induced a significant increase in IL-2, IL-10, IL-17 and IFN-γ production by T cells that was similar in CD271+ and CD271- cells.

Conclusion: These data confirm that SF cultures contain a CD271+ cell fraction. Both CD271+ and CD271- SF cultures showed multipotential and immunomodulatory properties previously described as characteristic of MSC. T-cell anti-proliferative effect and non-specific up-regulation of T-cell cytokine production were similar in CD271+ and CD271- SF cultures.

Disclosure: A. Ustategui, None; M. J. Del Rey, None; R. Fare, None; G. Criado, None; V. Miranda, None; J. D. Cañete, None; J. L. Pablos, None.

1740

Predicting the Evolution of Inflammatory Arthritis in ACPA-Positive Individuals: Can T-Cell Subsets Model Help? Laura Hunt1, Agata Burska2, Elizabeth M.A. Hensor1, Jackie L. Nam2, Frederique Ponchel1 and Paul Emery2.

1NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom; 2NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

Background/Purpose: ACPA+ individuals with non-specific musculoskeletal symptoms are at high risk of developing rheumatoid arthritis (RA). We previously demonstrated dys-regulation of T-cell subsets with loss of naive and regulatory T-cells (Treg) in early RA. The aim of the current study is to demonstrate the predictive value of T-cell subset analysis for progression towards inflammatory arthritis (IA) onset in ACPA+ individuals.

Methods: 82 ACPA+ individuals without clinical synovitis at recruitment were followed. 120 healthy controls provided a reference group. T-cell subset analyses were performed using 6-colour flow-cytometry for naive T-cells (CD4+CD45RB+BHI CD45RA−), Treg (CD4+CD25hi FSexp+CD127low) and inflammatory related cells (IRC: CD4+CD25-RB+BHI CD45RA+). We calculated one-sided 95% reference ranges for each subset (age-related for naive and Treg) and classified values as normal or abnormal accordingly. Using Cox proportional hazards regression we created a risk score; each subset’s coefficient rounded to nearest 0.5, multiplied by 2, then a total score for each person was calculated. Risk categories were then derived based on the proportions of patients progressing at each score level.

Results: In this cohort 40/82 (49%) developed IA within a median follow-up of 6.4 months (range 1-52 months). Cox regression analysis (Table 1) allowed categorisation into moderate and high risk. Within the high risk group 78% (18/23) progressed to IA in a median of 8 months compared to 37% (22/59) within the moderate group (Table 2; Figure 1).

Conclusion: T-cell dys-regulation in ACPA+ individuals with non-specific musculoskeletal pain may be useful in predicting progression to IA. Further modelling will be needed to quantify the clinical utility of T-cell subsets in predicting progression to IA.

Table 1: Sensitivity and specificity of T-cell subset frequencies for progression to IA; results of multivariable Cox regression and risk scores for each subset

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>&lt;LLN for age</td>
<td>81.3 (69.4, 91.7)</td>
<td>2.5 (1.5, 4.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>IRC</td>
<td>&lt;LLN for age</td>
<td>85.7 (77.9, 96.2)</td>
<td>2.4 (1.2, 4.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Treg</td>
<td>&lt;LLN for age</td>
<td>88.7 (80.8, 94.4)</td>
<td>1.6 (0.8, 3.2)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Table 2: Proportions of people progressing to IA according to T-cell risk score; risk categories derived

<table>
<thead>
<tr>
<th>T-cell risk score</th>
<th>% progressed to IA (n/N)</th>
<th>Risk category</th>
<th>Median (95% CI) months to IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31% (10/32)</td>
<td>Moderate</td>
<td>50 (41, 58)</td>
</tr>
<tr>
<td>1</td>
<td>44% (12/27)</td>
<td>High</td>
<td>8 (1, 16)</td>
</tr>
<tr>
<td>2</td>
<td>73% (11/15)</td>
<td>High</td>
<td>8 (1, 16)</td>
</tr>
<tr>
<td>3</td>
<td>86% (6/7)</td>
<td>High</td>
<td>8 (1, 16)</td>
</tr>
<tr>
<td>4</td>
<td>100% (1/1)</td>
<td>High</td>
<td>8 (1, 16)</td>
</tr>
</tbody>
</table>

Figure 1: Kaplan-Meier survival plot showing cumulative survival for people at moderate or high risk of progression to IA.

Disclosure: L. Hunt, None; A. Burska, None; E. M. A. Hensor, None; J. L. Nam, None; F. Ponchel, None; P. Emery, None.
Anti-TNFα Treatment Increases IL-17A+ and IL-22+ T Cells in Spondyloarthropathy Regardless of Concomitant Gut Inflammation. Thomas Andersene,1 René Østgård2, Bent Deleuran4, Malene Hvïd2 and Hennig Glørup2.1Aarhus University, Aarhus, Denmark, 2Aarhus University Hospital, Aarhus, Denmark, 3Regional Hospital of Silkeborg, Silkeborg, Denmark.

Background/Purpose: The pro-inflammatory Th17 associated cytokines IL-17A and IL-22 have been proposed as important mediators of the inflammation seen in spondyloarthropathy (SpA) and inflammatory bowel disease (IBD). A strong link between the development of SpA and IBD has been established, with Th17 cells as presumed pivotal players in the co-development of these inflammatory diseases. The aim of this study was to investigate differences in Th17 expression between SpA patients with subclinical gut inflamation, and SpA patients without gut inflammation. Further, changes in Th17 levels with anti-TNFα therapy was investigated.

Methods: Thirty SpA patients with high (>100 mg/kg, n=15) and with normal (<50 mg/kg, n=15) faecal calprotectin (fCal), and 14 healthy controls (HC) were included in this study. Patients with known psoriasis or IBD at the time of enrollment were excluded. All patients were eligible for anti-TNFα therapy. Th17 cells were determined by flow cytometry and assessed for the expression of the Th17 defining chemokine receptor 6 (CCR6) and the gut-homing integrin complex α4β7.

Results: Since no differences in the two groups were observed, they were merged into one for the analysis of the Th17 defining chemokine receptor 6 (CCR6) and the gut-homing integrin complex αf4β7. Similar percentages of IL-17A, IL-22 and CCR6 expressing CD45RO T cells were observed. No difference in the gut homing potential of the IL-17A and IL-22 expressing T cells in either of the SpA groups evaluated as C3+ + CD4+ + CD45RO+ lymphocytes double positive for αf4α4 and β7β7 was observed.

Conclusion: Anti-TNFα therapy improved clinical disease activity of the SpA patients substantially. Surprisingly, underlying inflammatory activity, in the form of Th17/22 cells persisted, even 1 year after initiation of anti-TNFα therapy. The exact reasons for this finding could be involved in the on-going disease progression seen in SpA patients even with clinically low, and well-controlled disease activity.


1742
Depletion of Reactive Oxygen Species Biases T Cells to Proinflammatory Cytokine Production in Rheumatoid Arthritis. Zhen Yang1, Eric L. Matteson2, Jorg J. Goronzy2 and Comedal M. Weyand2.1Stanford University School of Medicine, Stanford, CA, 2Stanford, Stanford, CA.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, genetically associated with polymorphisms in HLA class II molecules. CD4 cells produce proinflammatory cytokines and orchestrate multiple disease-relevant functions in the infected joint. How threshold settings in intracellular signaling cascades in such CD4 T cells affect arthritogenic functions is insufficiently understood. Intracellular reactive oxygen species (ROS) are classically considered harmful as they can cause oxidative stress. However, they also have critical cytoprotective functions by modulating cellular signal transduction. Intracellular ROS derive from mitochondria as a byproduct of metabolic activity. Cells possess a complex machinery for ROS removal, with the principal cellular reductant NADPH deriving from the pentose phosphate pathway (PPP), where glucose-6-phosphate dehydrogenase (G6PD) functions as the rate-limiting enzyme.

Methods: Naive CD4 T cells from patients with seropositive RA and age-matched controls were isolated and their T cell receptors were cross-linked. The following parameters were measured in resting and poststimulation T cells: ROS production, cell cycle progression and apoptotic susceptibility; commitment to the Th1, Th17, Th2 and Treg lineage. Expression of G6PD transcripts was quantified by RT-PCR.

Results: Intracellular ROS in RA T cells were consistently decreased below 70% of those in controls (p=0.01). The ROS loss in RA T cells was associated with faster cell cycle progression (p<0.001), increased apoptotic susceptibility (p<0.01) and premature conversion of the naïve to memory phenotype (p=0.05). Treating T cells with the ROS scavenger Tempol could mimic this differentiation defect. RA T cells were prone to differentiate into IFN-γ and IL-17-producing cells, whereas the frequencies of IL-4-producing and FoxP3-expressing cells were indistinguishable in RA and control cells. RA T cells had a reduced mitochondrial mass and their intracellular NADPH concentrations were increased (p<0.04). Further evidence for a more active PPP in RA T cells came from increased expression of PPP (p<0.03). The reduction of mitochondrial mass was reproduced in synovial tissue biopsies, where HLA-DRB1*04+ patients expressed significantly reduced mitochondrial DNA (p=0.05).

Conclusion: Intracellular ROS levels in RA T cells are reduced, imposing reductive stress. ROS loss may result from reduced mitochondrial mass, but also from enhanced production of the reductant NADPH. ROS depletion fundamentally shifts the functional behavior of human T cells, enhancing their cell cycle progression and swaying their differentiation towards proinflammatory Th1 and Th17 cells. The data delineate a mechanistic connection between intracellular redox imbalance and athritogenic T cell functions, with the prospective of therapeutically influencing such T cell defects via restoration of ROS production.

Disclosure: Z. Yang, None; E. L. Matteson, None; J. J. Goronzy, None; C. M. Weyand, None.

1743
Antigen-Specificity Regulates Peripheral Homeostasis of Regulatory T Cells. Laura Su1 and Mark Davis2.1University of Pennsylvania, Philadelphia, PA, 2Stanford, Stanford, CA.

Background/Purpose: One key mechanism of peripheral tolerance involves regulatory T cells (Tregs). Tregs are best known for the expression of the transcription factor Foxp3 that drives many Treg-specific gene expressions. Defects in Foxp3 expression result in severe autoimmunity, but a high numbers of Tregs can also be pathologic and contributes to the evasion of tumor surveillance. Thus, the appropriate balance between regulatory and effector T cells is essential to maintain self-tolerance while preserving effective immunity. How antigen-recognition impacts Treg homeostasis is not known. The goal of this study is to characterize the peripheral Treg repertoire in healthy people in order to establish the foundation for evaluating Treg homeostatic dysregulation in rheumatoid arthritis and other autoimmune diseases.

Methods: Antigen-specific T cells were identified directly ex vivo using peptide-HLA (pMHC) tetramers. We selected self-peptides from gp100, citrullinated fibrinogen (cit-Fib), or preproinsulin (PPins) for their relevance in vitiligo, rheumatoid arthritis, and type I diabetes. Three foreign antigens from the influenza virus (HA, PB1, and PA) were selected for comparison. Tetramer staining was performed using blood from de-identified healthy blood donors, followed by staining for CD25, CD45RO, Foxp3, and Ki67 expression. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry. We also compared the frequency of antigen-specific Foxp3+ cells in adult blood versus the cord blood.

Results: We show vastly different Foxp3 expression between self-antigen-specific T cells versus flu-reactive T cells. On average, 10% of autoreactive-specific T cells express Foxp3, whereas less than 3% of flu-reactive T cells specific for HA are Foxp3+. This difference is likely due to antigen exposure, because many more HA-specific T cells express Foxp3 in cells from the cord blood. Moreover, the robustness of the T cell response also determines Foxp3 expression. We examined
three distinct flu-reactive T cell populations and found that the frequency of Foxp3+ cells is highest in the least abundant PA-specific T cells, followed by PB1-specific T cells, and lowest in the most highly expanded and memory dominant HA-specific T cells. In contrast, antigen exposure increases Treg frequency in self-reactive T cell populations, and this correlates with an increase in cellular proliferation.

**Conclusion:** These data demonstrate that peripheral homeostasis between Tregs and conventional T cells are regulated by antigen-specificity. Contextual differences in ligand exposures alter this balance and this has significant implications for autoimmunity.

**Disclosure:** L. Su, None; M. Davis, None.

### 1744

**CD4+ T Cell Subpopulations in Blood and Synovial Fluid Defined By Differential Expression of Integrins.** Deepak A. Rao1, Adam Chicoine2, Peter A. Nigrovic1, Soumya Raychaudhuri3, Michael B. Brenner4 and ACR Authors 2014. 1Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA, 3Brigham and Women’s Hospital/Harvard University, Cambridge, MA, 4M ancher Academic Health Sciences Centre, Manchester, United Kingdom, 5Brigham & Women’s Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** CD4+ T cells are important mediators of inflammation in rheumatoid arthritis; however, the specific CD4+ T cell populations most important in driving disease pathology remain unclear. CD4+ T cells are often divided into subsets based on effector functions (e.g. Th1, Th2, Th17). Here we describe an alternative strategy of defining T cell subpopulations in blood and synovial fluid based on differential expression of integrins and other migratory receptors that help cells localize to specific target tissues. Blockade of integrin-dependent migration is already employed clinically; therefore, understanding patterns of migratory receptor expression that allow infiltration into the joint and other target organs is of significant interest.

**Methods:** We developed multiparametric flow cytometry panels to characterize expression of integrins and other migratory receptors on blood and synovial fluid CD4+ T cells. Dimensional reduction was performed using Spanning tree Progression of Density normalized Events (SPADE) to identify CD4+ T cell subpopulations that express specific combinations of migratory receptors.

**Results:** More than half of circulating memory CD4+ T cells coordinately express α3, α5, and α6 integrins. α4 integrin is expressed on ~25-50% of circulating memory CD4+ T cells, but in a distinct pattern such that memory CD4+ T cells can be divided into 3 groups based on the differential expression of α4 and α6 integrin ([α4+α6−, α4−α6+, α4+α6+]). Both central memory and effector memory CD4+ T cell subsets contain these populations, while naive T cells lack significant expression of either α chain. Interestingly, both CD4+CD25+CD127− regulatory T cells and CD4+ CLA+ “skin-homing” cells fall predominantly within the α4-α6+ population. Both α4−α6+ and α4+α6+ cells co-express β1, while α4+α6− cells co-express β7 rather than β1, α4β7+ cells constitute ~10-20% of circulating memory CD4+ T cells; however, these cells are not present in inflammatory synovial fluid, in which almost all CD4+ T cells express β3. Small populations of circulating memory CD4+ cells also express α1, α2, αβ, and αε integrins and CD146, with certain subsets substantially enriched in synovial fluid. SPADE analyses allowed for visual demonstration of cell subpopulations defined by migratory receptor expression.

**Conclusion:** Differential integrin expression identifies CD4+ T subpopulations in a manner non-redundant with traditional methods of classifying T cells. Specific integrin-defined memory CD4+ T subpopulations are enriched in synovial fluid compared to blood, suggesting that certain integrins, in particular β3 integrins, may promote CD4+ T localization to the joint. Further characterization of integrin-defined T cell subpopulations can that infiltrate the joint may lend new insights into mechanisms of synovial inflammation.

**Disclosure:** D. A. Rao, None; A. Chicoine, None; P. A. Nigrovic, None; S. Raychaudhuri, None; M. B. Brenner, None.

### 1745

**Memory Stem T Cells Are Selectively Enriched in Patients with Rheumatoid Arthritis.** Enky Hayashi, A. Chicoine, M. B. Brenner, A. Pieters, J. B. van der Heijden, F. Ciceri, I. Boi, S. Raychaudhuri, A. P. Nigrovic, and ACR Authors. 1Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA, 3Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 4M ancher Academic Health Sciences Centre, Manchester, United Kingdom, 5Brigham & Women’s Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** T cell memory is a multifaceted and encompasses multiple subsets with divergent properties. In addition to central memory (TSCM) and effector memory (TEM) cells, the spectrum of immunological memory has been recently extended with the identification of memory stem T cells (TSCM). Gene expression profiling, corroborated by in vitro and in vivo experimental results, posits TSCM upstream TEM and TCM in T-cell ontogeny (Gattinoni, Nat Med 2011; Cier, Blood 2013). While self-renewing TSCM would be highly desirable if bearing protective specificities, this very same cell subpopulation may also represent a foe when considering T-cell mediated pathologies. We hypothesized that, in these clinically relevant contexts, TSCM may represent a reservoir of long-lived T cells with undesired and detrimental specificities responsible for disease perpetuation.

**Methods:** We characterized TSCM dynamics in 15 patients with active rheumatoid arthritis (RA) and upon treatment with etanercept (median time from anti-TNF treatment onset: 3 months). T cell subset composition and function was evaluated by multiparametric flow cytometry.

**Results:** We found that TSCM cells, defined as γδ+γδ+γδ+CD4+CD62L−CD27−CD95−, are significantly more represented in terms of frequencies and absolute counts in patients with active RA as compared to age- and sex-matched healthy controls. Of notice, the extent of TSCM expansion correlated with disease severity (quantified by DAS28 score), suggesting an active role of TSCM in disease pathophysiology. Functionally, expanded CD4+ TSCM displayed a preferential IFNγ polarization, known to have a fundamental pathogenic role in rheumatic synovitis, and thus further corroborating TSCM lymphocytes as a potential novel player in RA pathogenesis and perpetuation. Importantly, TNF-a neutralization, upon etanercept administration, efficiently reduced the frequency and number of circulating TSCM and restored T-cell homeostasis in responder patients. Prior to etanercept treatment, TSCM lymphocytes expressed TNFR2 to significantly higher levels compared to the other T-cell subsets both in CD4+ and CD8 T compartments, suggesting that TNF-a might act as a costimulatory signal for TSCM lymphocytes in the context of RA. Finally, ongoing experiments will elucidate whether TSCM accumulation is due to the selective expansion of arthritogenic clones through the characterization of the TCR repertoire and antigen-specificities of TSCM cells from RA patients.

**Conclusion:** Understanding the dynamic and quantitative aspects of TSCM lymphocyte behavior in RA will have profound implications for devising strategies to counteract T-cell dysfunction in RA patients.

**Disclosure:** N. Cieri, None; G. Oliveira, None; R. Greco, None; M. Baldini, None; E. Baldwin, None; F. Ciceri, None; C. Bonini, None.

### 1746

**Involvement of IL-17-Producing MAIT Cells in the Pathogenesis of Rheumatoid Arthritis.** Enky Hayashi, A. Chicoine, M. B. Brenner, A. Pieters, J. B. van der Heijden, F. Ciceri, I. Boi, S. Raychaudhuri, A. P. Nigrovic, and ACR Authors. 1Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA, 3Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** Mucosal-associated invariant T (MAIT) cells are a subset of innate-like lymphocytes which are restricted by the MHC-related molecule-1 (MR1) and express a semi-invariant TCR αβ chain-7.2-J chain. MAIT cells constitute about 5–10% of αβ T cells in peripheral blood and intestine, suggesting that MAIT cells may play important roles in human autoimmune diseases. In this study, we aimed to investigate whether MAIT cells are involved in the pathogenesis of rheumatoid arthritis (RA).

**Methods:** Peripheral blood mononuclear cells (PBMC) of RA patients and
age- and sex- matched healthy subjects were separated by Lymphoprep. PBMC were stained with anti-human monoclonal antibodies against CD3, γδTCR, Vα7.2 TCR, and CD161, and MAIT cells were identified as CD3γδTCR Vα7.2TCR CD161high cells by FACS. The expression of HLA-DR and CCR9 on MAIT cells and other T cell subsets were also assessed. PBMC (2 × 10⁶ cells per well in 96-well culture plates) were stimulated with phorbol-myristate-acetate (50ng/ml) and ionomycin (500ng/ml) for 3 hours. Brefeldin A was added in the last 2 hours of culture. After surface staining, cells were permeabilized by using BD Cytofix/Cytoperm Fixation/Permeabilization Solution Kit and intracellular cytokine staining for IL-17A, IFNγ, TNFα and IL-6 was performed. Cells were analyzed on FACS LSR Fortessa with FlowJo software.

**Results:** The percentages of MAIT cells were decreased in RA patients compared with healthy controls. The reduction in MAIT cell frequency was more enhanced in RA patients with active disease. There was a tendency of increased expression on MAIT cells from patients with lower MAIT cell frequencies. MAIT cells produced IL-17A, IFNγ, TNFα and IL-6 upon stimulation, and the frequency of IL-17A-producing MAIT cells was inversely correlated with that of MAIT cells in RA. However, there was no correlation with the frequencies of IFNγ, TNFα or IL-6-producing cells and that of MAIT cells. We also found the negative correlations in the frequency of a gut-homing chemokine receptor CCR9-positive MAIT cells with that of MAIT cells in RA.

**Conclusion:** We demonstrated that the frequency of MAIT cells was reduced in RA. The elevated expression of HLA-DR and IL-17 production by MAIT cells indicated the activated state of remaining MAIT cells in RA. The increase of CCR9-positive MAIT cells indicates the recruitment of gut MAIT cells to the peripheral blood in RA.

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### 1749 WITHDRAWN

#### 1748

**CCR6 CD4+ Cells Are Counterparts of Follicular T-Cells Supporting Autoantibody Production in Rheumatoid Arthritis.** Karl ME Andersson1, Dan Hu2, Ron Cialic2, Nicola Cavallini3, Vijay K. Kuchroo4, Malin Erlandsson5, Howard Lee Weiner2 and Maria Bokarewa2. 1University of Gothenburg, Gothenburg, Sweden, 2Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, 3University of Göteborg, Göteborg, Sweden, 4Brigham and Women’s Hospital, Boston, MA, 5University of Göteborg, Göteborg, Sweden.

**Background/Purpose:** CCR6 has been associated with rheumatoid arthritis (RA) in genome-wide association studies. CCR6 expression characterizes Th17 cells recruited to inflamed joints of RA patients. The purpose of this study was to characterize gene transcription in the peripheral lymphocytes in RA patients.

**Methods:** CCR6+ CD4+ cells were isolated from peripheral blood lymphocytes of 14 RA patients and 6 healthy controls by magnetic beads. The isolated cells consisted of 85% CCR6+ CCRX3+ cells and had a viability of 94%. Cells were stimulated with PMA/ionomycin for 4h, supernatants were collected for cytokine analysis and cell pellets were used for gene expression analysis using nCounter Analysis System (NanoString Technologies).

**Results:** Transcription analysis showed that 140 genes had significant (p<0.05) 1.5-folds difference between CCR6+ CD4+ cells of RA patients and healthy controls. As expected, RA patients CCR6+ CD4+ cells were also CCRX5+ CCRX3+. Despite the intense immunosuppression with methotrexate and TNF-inhibitors, RA lymphocytes had had higher transcription of Th17 cytokines (IL17F, IL17A, IL22). Also Th17 (Rorc) and Th1 (Tbx21 and Egr-2) differentiation genes were enhanced, while other genes regulating cytokines (IL17F, IL17A, IL22). Also Th17 (Rorc) and Th1 (Tbx21 and Egr-2) differentiation genes were enhanced, while other genes regulating cytokines (IL17F, IL17A, IL22) were repressed. Genes controlling the CCR6+ CD4+ cells was dampened by low IL27R, low STAT signal (reduced STAT1, STAT3, STAT4) and low transcriptional regulator AHR, suggesting that the gp130 activation occurs on a cell populations different from the studied, e.g. B-cells.

**Conclusion:** This study demonstrates that CCR6+ CD4+ T cells of RA patients have features of proliferative, proinflammatory and IL17 producing cells controlled through TGFβ and IL23 mediated signalling. CCR6+ CD4+ T cells are a source of CXCR5+ Th17 cells efficient producers of IL21 cytokine presumably stimulating autoantibody production in RA patients.

**Disclosure K. M. Anderson, None; D. Hu, None; R. Cialic, None; N. Cavallini, None; V. K. Kuchroo, None; M. Erlandsson, None; H. L. Weiner, None; M. Bokarewa, None.**

### 1749

**Molecular Mechanisms Underlying 1,25(OH)D3-Mediated Suppression of Th17 Cell Activity.** Wendy Dankers1, Jan Piet van Hamburg2, Wida Razawy3, Nadine Daveelaer2, Anne-Marie Mus2, Patrick Asmañdijaja4, Johannes van Leeuwen5, Edgar Colin6 and Erik Lubberts7. 1Erasmus MC, University Medical Center, Rotterdam, Netherlands, 2ZGT, Almeio, Netherlands.

**Background/ Purpose:** Vitamin D has suppressive effects on autoimmune diseases, such as rheumatoid arthritis (RA). Within these diseases, Th17 cells play a crucial role in the processes underlying chronic inflammation. Currently, Th17 cells are of high interest in the development of novel therapeutic strategies such as the development of antibodies against IL-17A or specific small molecule inhibitors of RORγt, the Th17 cell associated transcription factor.

Previously we have shown that the active vitamin D metabolite 1,25(OH)2D3 is capable of directly inhibiting the polarization and pathogenic activity of Th17 cells. However the molecular mechanisms underlying this modulation of Th17 cell activity by vitamin D are currently unclear.

**Methods:** Therefore CD4+ CD45RO+ (memory) and CCR6+ memory T-helper cells were sorted from peripheral blood of patients with early RA and healthy volunteers. They were cultured under the presence or absence of 1,25(OH)2D3. The expression of cytokines and transcription factors of interest was analyzed using microarray based gene expression profiling, flow cytometry, ELISA and/or RT-PCR.

**Results:** In the presence of 1,25(OH)2D3, the pro-inflammatory cytokines IL-17A, IL-17F and IL-22 were inhibited. Also the expression of Th17 signature genes like RORγt and IL-23R was reduced. On the other hand we find an increase in IL-4 and IL-10 expression.

Interestingly neutralization of IL-4 partly reversed the effect of 1,25(OH)2D3 on the inhibition of IL-17A, IL22 and RORγt expression. In addition, the inhibition of IL-17F by 1,25(OH)2D3 was almost completely absent when IL-4 was blocked.

In contrast to IL-4, IL-10 neutralization had limited effects in these cultures.

Because the effect of 1,25(OH)2D3 is only partially dependent on IL-4, we examined factors that could play a role independent of IL-4. Gene expression profiling revealed that two transcription factors that are known to play a role in Th17 differentiation, EOMES and IRF8, were upregulated by 1,25(OH)2D3. The expression of cytokines and transcription factors of interest was analyzed using microarray based gene expression profiling, flow cytometry, ELISA and/or RT-PCR.

**Conclusion:** From these findings, we conclude that 1,25(OH)2D3 is a direct modulator of Th17 cell activity. This modulation is partly dependent on up regulation of IL-4. IL-4 independent mechanisms may include the down-regulation of RORγt expression via up regulation of IF8 and EOMES.

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### 1750

**The Effect of a Pro-Inflammatory Milieu on Tregaluzumab (BT-061)-Induced Regulatory T-Cell Activity.** Jan Kubach1, Faiza Rharboua2, Martin Koening2, Jörg Schüttrumpf2, Silke Aigner2, Benjamin Däkken2 and Helmut Jonuleit2. 1University of Mainz Medical Center, Mainz, Germany, 2Biotest AG, Dreieich, Germany.

Monday, November 17

S767
**Background/Purpose:** Regulatory T cells (Tregs) are essential for maintaining normal immune homeostasis. We have previously reported that tregalizumab is a humanized, non-depleting, CD4 agonistic antibody that selectively activates Tregs. The specific functionality of tregalizumab may originate from the recognition of a unique epitope on domain 2 of CD4 that is not recognized by other anti-CD4 monoclonal antibodies. Tregalizumab is in clinical development for the treatment of rheumatoid arthritis (RA). Currently, a Phase Ib/II trial -TREAT 2b- is in progress to further evaluate the efficacy and safety of tregalizumab and define the optimal dose in combination with methotrexate (MTX) in adults with RA and an inadequate response to MTX.

Recent data have shown that pro-inflammatory cytokines may have a profound negative effect on the suppressive properties of Tregs or on the responsiveness of effector cells to suppression. Serum cytokine levels for RA patients have been reported in the range of: IL-1β: 0–0.269 ng/mL; IL-6: 0–0.138 ng/mL; TNF-α: 0.001–2.952 ng/mL (Myever et al., 2010). Therefore, we performed in vitro studies to investigate the effects of pro-inflammatory cytokines on the ability of tregalizumab to activate Treg suppressive activity.

**Methods:** Allogenic effecter T cells (Teffs) isolated from healthy volunteers were co-cultured with freshly isolated Tregs and APCs from a different blood donor (mixed lymphocyte reaction, MLR) in the presence of different concentrations of cytokines as previously described by Trinschek et al. (2013). Cell proliferation was measured by incorporation of radioactive thymidine. Suppression was derived by the ratio of the radioactive count obtained in the co-culture in presence of Treg versus no Treg. At least 3 independent experiments were performed at different days using cells isolated from different blood donors.

**Results:** In the absence of cytokine, activation of Tregs with tregalizumab resulted in strong suppression of Teff proliferation, on average at least 50% reduction of cell proliferation was measured with tregalizumab at 1 μg/mL. In presence of pro-inflammatory cytokines, little effects were observed. At the concentrations tested, corresponding to levels rarely measured in plasma from RA patients (up to 2000 ng/mL of IL-1β and 500 ng/mL of IL-6), neither IL-1β nor IL-6 inhibited tregalizumab-induced suppression of Teff proliferation. In case of TNF-α, only the highest concentrations tested (50 and 100 ng/mL) had a marginal effect on tregalizumab-suppressed induction.

**Conclusion:** In this in vitro study, activation of Tregs by tregalizumab and the suppression of Teffs was not notably inhibited by pro-inflammatory cytokines, only moderately by TNF-α at very high concentration. This result gives further insights into the potential of tregalizumab to activate Tregs in the presence of systemic levels of pro-inflammatory cytokines that are elevated in autoimmune diseases such as RA. Further in vitro investigations are in progress to determine if the observed moderate effect of TNF-α is the result of a reduction of Treg suppressive activity or an increased Teff-resistance to Treg suppression. In similar experimental conditions, effects of MTX or prednisolone will also be assessed.

**Disclosure:** J. Kubach, None; F. Rharbaoui, Biotest AG, 3; M. Koenig, Biotest AG, 3; J. Schüttrumpf, Biotest AG, 3; S. Aigner, Biotest AG, 3; B. Dälken, Biotest AG, 3; H. Jonuleit, Biotest AG, 2; Self, 9.

### 1751

**CD4 Apteramer-ROR-γt shRNA Chimera Inhibits IL-17 Synthesis By Human CD4+ T cells.** Cong-Qiu Chu1, Pingfang Song1, Yuan K. Chou1, Xiaowei Zhang2, Roberto Meza-Romo2, Kento Y. Yomogida3, Biotest AG, 3; Si Aigner, Biotest AG, 3; B. Dälken, Biotest AG, 3; H. Jonuleit, Biotest AG, 2; Self, 9.

**Background/Purpose:** RNA interfering (RNAi)-mediated gene silencing holds great promise for manipulating T cells to study basic T cell biology and to develop potential T cell targeted therapeutics. However, efficient delivery of small interfering RNA (siRNA) specifically into primary T cells is a major hurdle to the widespread use of RNAi technology. We explored the use of single-stranded oligonucleotide aptamers as vehicle to deliver small hairpin RNA (shRNA) to target T cells.

**Methods:** An RNA aptamer specifically binds to CD4 was previously designed and tested. An ssDNA aptamer against CD30 was able to inhibit IL-17A expression in vitro. CD4-AshR-ROR-γt chimera has the potential to be developed as a novel class of therapeutic agents to treat Th17 mediated inflammatory diseases.

**Disclosure:** C. Q. Chu, None; P. Song, None; Y. K. Chou, None; X. Zhang, None; R. Meza-Romo, None; K. Y. Yomogida, None; G. Bendeck, None.

### 1752

**CD30 As a Target of Aaptamers and Delivery Portal for Aaptamer-shRNA to Block Th17 Cells.** Cong-Qiu Chu1, Pingfang Song1, Yuan K. Chou1 and Shao Tao2. 1Oregon Health & Science Univ, Portland, OR, 2Oregon Health & Science University, Portland, OR.

**Background/Purpose:** Aaptamers are single-stranded 20-100 nucleotides (RNA or DNA) that bind to molecular targets with high affinity and specificity due to their stable three dimensional shapes and were referred as "chemical antibodies". Aaptamers are being investigated and developed as therapeutic agents and carriers for cell type specific delivery of drugs including small interfering RNA (siRNA). CD30 is expressed by activated Th17 cells and plays a critical role in Th17 cell differentiation.

**Methods:** Single stranded DNA (ssDNA) or RNA CD30 aptamers were synthesized. A chimera of RNA CD30 aptamer-small hairpin RNA (shRNA) against retinoic acid related orphan receptor (ROR)-γt (CD4-AshR-ROR-γt) was generated in vitro from a cDNA template by in vitro T7 RNA transcription. Human PBMC were stimulated with anti-CD3 and CD28 and polarized towards Th17 differentiation. CD30 aptamers or CD30-AshR-ROR-γt chimera was incubated with the stimulated PBMC. ELISA and intracellular cytokine staining were used to quantify IL-17A production and Th17 cells.

**Results:** An ssDNA aptamer against CD30 was able to inhibit IL-17A production by anti-CD3/CD28 stimulated PBMCs in a dose dependent manner. The inhibitory effect of ssDNA CD30 aptamer was comparable to that by anti-CD30 antibody. CD30 RNA aptamer alone had a lesser inhibitory effect on IL-17A production but could enhance the effect of ssDNA CD30 aptamer. CD30-AshR-ROR-γt chimera was internalized by activated but not resting CD4+ T cells. Compared with a CD30-AshR-scramble sequence, CD30-AshR-ROR-γt inhibited 60-70% of IL-17A production and IL-17A producing CD4+ T cells.

**Conclusion:** CD30 Aaptamers showed significant inhibitory effects on IL-17A production by human PBMCs. In addition being a target by CD30 aptamers, CD30 expressed by activated CD4+ T cells can serve as a portal for aptamer mediated delivery of RNAi to target T cell genes.

**Disclosure:** C. Q. Chu, None; P. Song, None; Y. K. Chou, None; S. Tao, None.

### 1753

**Human T-Cells Express RANKL In Response to Combination of ZAP-70, Calcineurin and Voltage-Gated K+ Channel Signaling Following Co-Ligation of the Adhesion Molecule CD2 and the T-Cell Receptor Complex.** Bohdan P. Harvey and Zehra Kaymakcalan. Abt IvBioscience Center, Worcester, MA.

**Background/Purpose:** Human T lymphocytes promote osteolysis in rheumatic diseases through the production of the osteoclastogenic cytokine RANKL. We have previously demonstrated that RANKL secretion is
mediated by the simultaneous engagement of the lymphocyte function-associated antigen 2 (CD2) and T-cell receptor (TCR/CD3). However, the cell signaling events involved in its expression and release from T-cells are poorly understood. By using a variety of signaling mutants of Jurkat as well as chemical inhibitors to cell signaling factors, we sought to elucidate the role of the TCR signaling complex and that of ion channel-mediated signaling cascades in the induction of RANKL by CD2.

**Methods:** The human T-cell line Jurkat and several signaling mutant derivatives were exposed to various combinations of bead-bound anti-CD3, CD2 and CD28 antibodies. Total soluble RANKL was determined by osteoprotegrin capture sandwich ELISA. A Jurkat clone with a stably integrated NFAT-luciferase reporter (NFAT-Luc) was used to assess the signaling events leading to NFAT activation, a known regulator of RANKL expression, in response to cross-linking of CD3, CD2 and CD28 for 4 hrs. Prior to being exposed to the bead-bound antibodies, these cells were treated with a panel of chemical inhibitors to a variety of signaling factors including kinases (PI3K, CaMKII, AKT and PKC), phosphatase (calcineurin), calmodulin (CaM), calcium (TRPC3) and potassium ion channels (Kv1.1, 1.2 and 1.5) at broad concentration ranges. Cytotoxicity was evaluated by CellTiter-Fluo®.

**Results:** Similar to primary human T lymphocytes, Jurkat cells secreted RANKL only in response to cross-linking of both CD2 and CD3. This process was dependent on ZAP70 signaling but was independent of the following components associated with TCR signaling: beta-chain of the TCR, CD45, and PLCgamma. Cross-linking of CD3 and CD28 failed to induce RANKL secretion in wild-type cells even though high levels of IL-2 were generated. A 2-fold higher level of NFAT-Luc activation was observed with CD2/CD3 co-ligation as compared to CD28/CD3 and from the panel of inhibitors, chlorpromazine HCl, an inhibitor of both calmodulin and K+ channel signaling, was more effective at blocking NFAT-Luc activation by CD2/CD3 co-ligation than that of CD28/CD3, suggesting that these signaling cascades contribute to RANKL expression regulated by NFAT in response to CD2. Adaptor inhibitors to either calcium or potassium signaling cascades (FK 506, a calcineurin inhibitor, and 4-aminopyridine, a Kv1.1 & 1.2 inhibitor, respectively) also blocked CD2/CD3-induced activation of the NFAT reporter without cytotoxicity; however, inhibition was not restricted to CD2 since CD28/CD3-induced signaling was also affected.

**Conclusion:** Our results demonstrate that T-cells secrete RANKL in a ZAP70-dependent manner and only require the co-ligation of CD3 and CD2 in the absence of the co-stimulatory receptor CD28. Furthermore, calcineurin and voltage-gated K+ channel signaling cascades were shown to induce the activation of NFAT in response to CD2/CD3 co-ligation, suggesting that these pathways may contribute to the expression RANKL in the inflamed RA synovium by T-cells.

**Disclosure:** B. P. Harvey, AbbVie Inc, 3; A. AbbVie Inc, 1; Z. Kaymakcalan, AbbVie Inc, 3; AbbVie Inc, 1.

**ACR/ARHP Poster Session B**
**Vasculitis**

**Monday, November 17, 2014, 8:30 AM - 4:00 PM**

**1754**

**Peripheral CD5+ B-cells in ANCA-Associated Vasculitis.** Sebastian Unizony1, Noha Lim5, Vincent Carey4, Deborah J. Phippard2, Nadia Tchao2, Eli M. Miloslavsky2, Peter A. Merckel, Paul Monach, William St. Clair2, Robert F. Spiera7, Adam Asare2, Philip Seo8, Carol A. Langford9, Gary S. Hoffman4, Cees Kallenberg10, Ulrich Specks11 and John H. Stone1. 1Massachusetts General Hospital, Boston, MA, 2Immune Tolerance Network, Bethesda, MD, 3Brigham and Women’s Hospital, Boston, MA, 4Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, 5Boston University, Boston, MA, 6Duke University, Durham, NC, 7Hospital for Special Surgery, New York, NY, 8Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, 9Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, 10Cleveland Clinic Foundation, Cleveland, OH, 11University of Groningen, Groningen, Netherlands, 12Mayo Clinic, Rochester, MN.

**Background/Purpose:** We explored the utility of peripheral CD19+ CD5+ B-cells (CD5+ B-cells) as biomarkers in ANCA-associated vasculitis (AAV).

**Methods:** CD5+ B-cells were measured longitudinally by flow cytometry in patients randomized to rituximab (RTX, n = 99) or CYC followed by AZA (CYC/AZA, n = 98) for the treatment of AAV (RAVE trial). Number of CD5+ B cells/mL and %CD5+ B-cells within the total population of CD19+ B-cells were determined. Outcomes assessed were disease activity, induction treatment failure, disease severity, relapse, and in the RTX arm, relapse-free survival according to %CD5+ B-cells at B-cell repletion (10-68 CD19+ B-cells/mL) and reconstitution (≤ 69 CD19+ B-cells/mL) using %CD5+ B-cells as dichotomous (≥30% and ≤30%) and categorical predictor. Repeated measure ANOVA, Wilcoxon, Fisher’s, logrank and Cox PH tests were used.

**Results:** Median CD5+ B-cell numbers and %CD5+ B-cells were comparable between groups at baseline. After an initial decline, CD5+ B-cell numbers increased in the RTX arm, but remained low in the CYC/AZA cohort. In both groups, %CD5+ B-cells decreased during remission induction and declined thereafter (Fig 1). %CD5+ B-cells correlated inversely with disease activity in RTX-treated patients (baseline 12%, remission 28% and relapse 23%; p < 0.05), but not in CYC/AZA-treated patients (Fig 2). No significant association was observed between CD5+ B-cells and induction failure or disease severity. Disease relapses were not preceded consistently by declines in %CD5+ B-cells. Once B-cells returned in the RTX arm, %CD5+ B-cells did not predict time to flares (Fig 3). The hazard ratio (HR) for relapse in patients with >30% CD5+ B-cells (versus ≤30%) at B-cell repletion was 1.14 (95% CI 0.49–2.64; P = 0.75). The HR for relapse in patients with >30% CD5+ B-cells (versus ≤30%) at B-cell reconstitution, was 0.9 (95% CI 0.31–2.55; P = 0.84). Division of patients by quantities of %CD5+ B-cells upon B-cell repopulation failed to show any trend in time to relapse following the order of the strata.

**Conclusion:** In patients with AAV treated with CYC or RTX CD5+ B-cells do not predict treatment response, relapse or disease severity.
Background/Purpose: ANCA vasculitis is characterized by the presence of autoantibodies directed against MPO, PR3 and other neutrophil proteins. Binding of these autoantibodies to activated neutrophils is thought to be an important driver of the pathology underlying this disease. To date, investigation of serum biomarkers in this patient population have been limited. A more comprehensive approach to defining the biomarker profile would aid in our understanding of the mechanisms underlying the disease, may point to novel therapeutic targets, and would aid in the definition of biomarkers to monitor disease activity and therapeutic response.

Methods: ANCA vasculitis (n=46) and healthy control (n=30) donor serum samples were obtained from commercial sources. Vasculitis samples were derived from patients with positive c-ANCA or p-ANCA patterns by immunofluorescence analysis. Anti-PR3 and anti-MPO autoantibody levels were measured by ELISA to assess autoantibody status of the vasculitis samples. Proteomic profiling was performed using SOMAscan™ and multiplexed analysis on the Luminex® platform.

Results: Measurement of anti-MPO and anti-PR3 antibodies in the ANCA vasculitis sera indicated that approximately one-third of the samples had detectable levels of one or the other of these most common autoantibodies. Multiplexed proteomic analysis of control and vasculitis serum samples revealed elevated TNF-α, GM-CSF, IL-7, eotaxin, MCP-1, CXCL1, sCD40L, IL-21, growth factors such as VEGF, EGF, and FGF-2 (see Table). Increased levels for these analytes were observed with both conventional Luminex® multiplex assay and with the SOMA scan™ analysis that measures levels of more than 1,200 protein analytes. No clear difference in levels of these biomarkers was apparent in patient samples with or without detectable antibodies against MPO or PR3. Further analysis of the SOMA scan™ data indicated a pattern of increased levels of proteins in several classes. Across vasculitis serum samples, we observed an elevation in levels of biomarkers associated with angiogenesis, select inflammatory mediators, platelet activation and markers of tissue remodeling/repair. Interestingly we also observed clear increases in the levels of several autoantigens associated with this disease - MPO, PR3, lactoferrin and moesin. This finding is consistent with heightened neutrophil activation, and in patients with autoantibodies against these proteins, may drive immune complex-mediated inflammation.

Table 1. Serum concentrations of select analytes measured by multiplex analysis (mean ± SD in pg/ml)

<table>
<thead>
<tr>
<th>Healthy control</th>
<th>ANCA vasculitis</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>sCD40L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>145 ± 141</td>
<td>7252 ± 9070</td>
<td>0.0001</td>
</tr>
<tr>
<td>EGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ± 15</td>
<td>233 ± 254</td>
<td>0.0001</td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 ± 69</td>
<td>262 ± 234</td>
<td>0.0001</td>
</tr>
<tr>
<td>CXCL1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>189 ± 181</td>
<td>919 ± 764</td>
<td>0.01</td>
</tr>
<tr>
<td>TGF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 ± 7</td>
<td>9 ± 9</td>
<td></td>
</tr>
<tr>
<td>IL-21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 ± 3</td>
<td>8 ± 15</td>
<td>0.01</td>
</tr>
<tr>
<td>Flt-3L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 ± 18</td>
<td>28 ± 60</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-17A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 ± 1</td>
<td>3 ± 4</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 ± 7</td>
<td>20 ± 16</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-12p70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ± 14</td>
<td>8 ± 26</td>
<td>0.005</td>
</tr>
<tr>
<td>MCP-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>364 ± 285</td>
<td>830 ± 396</td>
<td>0.0001</td>
</tr>
<tr>
<td>FGF-2</td>
<td></td>
<td></td>
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<tr>
<td>18 ± 28</td>
<td>40 ± 48</td>
<td>0.0001</td>
</tr>
<tr>
<td>Eotaxin</td>
<td></td>
<td></td>
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<tr>
<td>56 ± 37</td>
<td>121 ± 73</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 ± 6</td>
<td>8 ± 6</td>
<td>0.0001</td>
</tr>
<tr>
<td>MIP-1β</td>
<td></td>
<td></td>
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<tr>
<td>27 ± 32</td>
<td>48 ± 38</td>
<td>0.0001</td>
</tr>
<tr>
<td>IFN-γ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 ± 7</td>
<td>6 ± 12</td>
<td>0.0005</td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
<td></td>
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<tr>
<td>12 ± 16</td>
<td>16 ± 32</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusion: A deep analysis of the biomarker profile of ANCA vasculitis serum revealed upregulation of pathways related to angiogenesis, neutrophil and platelet activation, and tissue repair. These data provide a view more comprehensive than previously reported of the altered serum profile in ANCA vasculitis patients and highlight candidate biomarkers to track disease activity and therapeutic responses.

Disclosure: M. Parker, Medimmune, LLC, 3; D. Gold, Medimmune, LLC, 3; AstraZeneca, 1; K. Ranade, Medimmune, LLC, 3; AstraZeneca, 1; E. Grant, Medimmune, LLC, 3; AstraZeneca, 1.

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Proteomic Analysis of ANCA Vasculitis Serum Reveals Broad Neutrophil Activation, Angiogenesis, and Selective Inflammatory Pathway Activation. Melissa Parker, David Gold, Koustubh Ranade and Ethan Grant. Medimmune, LLC, Gaithersburg, MD.

RTX n = 68 (22 relapsers); CYC/AZA n = 60 (16 relapsers); x = baseline; * = remission; # = relapse.

Fig 3

A/C redetection; B/D reconstitution

1 Bunch DO. CJASN 2013

Disclosure S. Unizony, None; N. Lim, None; V. Carey, None; D. J. Phippard, None; N. Tcho, None; E. M. Milsavsky, Genentech and Biogen IDEC Inc.; S. A. Merkl, None; P. Monach, None; W. St. Clair, None; R. F. Spiera, roche-genetech, 2; A. Asare, None; P. Seo, None; C. A. Langford, Genentech and Biogen IDEC Inc.; 2; G. S. Hoffman, None; C. Kallenberg, None; U. Specks, None; J. H. Stone, Genentech and Biogen IDEC Inc.; 2; Roche Pharmaceuticals; 2, Roche Pharmaceuticals; 2, Genentech and Biogen IDEC Inc.; 5, Bristol-Myers Squibb.

Table 1. Serum concentrations of select analytes measured by multiplex analysis (mean ± SD in pg/ml)
Molecular Diagnosis Reveals a Surprising Prevalence of Limited GPA Among Patients with Orbital Inflammatory Diseases. James T. Rosenbaum1, Dongseok Choi1, Christine Harrington2, Patrick Stauffer3, David Wilson4, Seema Gupta5, Roger Dailey6, John Ng7, Eric Steele8, Patrick Yeatts9, Peter Dolman10, Valerie White11, Gerald Harris12, Craig Czyz13, Jill Foster14, Deepak Edwin15, Hind Alkatan16, Bobby Korn17, Don Kikkawa1, Dinesh Selva18, Sander Dubovy11, Chris Alabadi11, David Tse11, Michael Kazim12, Payal Patel12 and Stephen R. Planck1. 1OHSU, Portland, OR, 2Oregon Health and Science University, Portland, OR, 3Oregon Health & Science University, Portland, OR, 4Wake Forest University, Winston-Salem, NC, 5University of British Columbia, Vancouver, BC, 6Medical College of Wisconsin, Milwaukee, WI, 7Ohio State University, Columbus, OH, 8King Khaled Eye Hospital, Riyadh, Saudi Arabia, 9University of California, San Francisco, 10University of Miami, Miami, FL, 11Columbia University, New York City, NY.

Background/Purpose: Gene expression profiling provides diagnostic and therapeutic information in several malignancies, but its role in evaluating inflammatory disease is relatively untested. We hypothesized that gene expression profiling could provide diagnostic information for orbital inflammatory diseases which include thyroid eye disease (TED or T in Figure 1), sarcoidosis (S in figure), granulomatosis with polyangiitis (GPA or G in figure), or nonspecific orbital inflammation (NSOI (N in figure), previously known as pseudotumor).

Methods: Formalin-fixed orbital biopsies, 20 from healthy controls (C in Figure 1), 25 from subjects with NSOI, 25 from subjects with TED, 6 from subjects with GPA, and 7 from subjects with sarcoidosis were obtained by an international consortium, divided into discovery and validation sets, and analyzed with regard to histopathology and gene expression using microarray.

Results: Principal coordinate analysis (Figure 1), heat maps (Figure 2), and Venn diagrams showed distinct gene expression profiles for healthy controls and subjects with TED, GPA, or sarcoidosis. A statistical method called random forest based on 39 probe sets identified controls, GPA, or TED with an average accuracy of 76% (p=0.02 compared to random) while two expert pathologists had accuracies of 49% and 58% respectively (neither significant compared to random). Random forest analysis indicated that 52% of tissues from patients with nonspecific inflammation were consistent with a diagnosis of GPA.

Conclusion: Molecular diagnosis by gene expression profiling is more accurate than histopathology in differentiating forms of orbital inflammatory disease. Although NSOI is a heterogeneous collection of diseases, many patients with NSOI have a gene expression profile resembling GPA. A limited form of GPA affecting the orbit is far more common than previously realized. Molecular diagnosis should be tested for its ability to identify GPA affecting sinuses and nasal or subglottic mucosa.

Disclosure: J. T. Rosenbaum, Genentech and Biogen IDEC Inc., 2; D. Choi, None; C. Harrington, None; P. Stauffer, None; D. Wilson, None; S. Gupta, None; R. Dailey, None; J. Ng, None; E. Steele, None; P. Yeatts, None; P. Dolman, None; G. Harris, None; C. Czyz, None; J. Foster, None; D. Edward, None; H. Alkatan, None; B. Korn, None; D. Kikkawa, None; D. Selva, None; S. Dubovy, None; C. Alabadi, None; D. Tse, None; M. Kazim, None; P. Patel, None; S. R. Planck, None.

1757


Background/Purpose: At 1251 on 22 February 2011 a magnitude 6.4 earthquake struck Christchurch killing up to 185 people and causing widespread damage to buildings in the city centre and surrounds. Multiplier building collapses during the busy lunchtime period in Christchurch when the earthquake occurred will have resulted in significant environmental exposure. Prominent involvement of the upper and lower respiratory tracts suggests that inhaled antigens may have a role in pathogenesis of ANCA associated vasculitis. An increased incidence and severity of MPO positive vasculitis was observed after the Kobe earthquake in 1995. The aim of this study was to describe the incidence and characteristics of ANCA positive vasculitis before and after the 2011 Christchurch earthquake.

Methods: All ANCA tests reported by Christchurch pathology centres over a 2 year period prior to February 21 2010 (period 1) and the 2 year period after February 22 2011 (period 2) were extracted from laboratory information systems. Clinical notes from patients with positive MPO or PR3 antibodies were reviewed to confirm newly diagnosed vasculitis cases who resided within the Christchurch area. Demographic information and organ involvement was confirmed on all newly diagnosed cases and compared between periods using Fisher’s exact and independent t-tests. Total Canterbury population was obtained from Statistics New Zealand.

Results: In period 1, 2592 total ANCA requests were processed; of these 37 (1.4%) were MPO positive and 100 (3.9%) were PR3 positive. 13/37 (35%) patients were subsequently confirmed to have newly diagnosed MPO positive vasculitis and 9/100 (9%) patients were confirmed to have PR3 positive vasculitis. In period 2, 2416 total ANCA requests were processed; of these 32 (1.3%) were MPO positive and 118 (4.9%) were PR3 positive. 7/32 (21.9%) patients were confirmed to have newly diagnosed MPO positive vasculitis and 11/118 (9.3%) newly diagnosed PR3 positive vasculitis. The rate of MPO vasculitis per 100,000 population was 3.45 in period 1 and 1.93 in period 2 (RR 1.8 95%CI 0.66–5.29). The rate of PR3 vasculitis per 100,000 population was 2.39 in period 1 and 3.03 in period 2 (RR 0.79 95%CI 0.29–2.09). In the post-earthquake period those with a new diagnosis of MPO
vasculitis were significantly younger than those diagnosed in the pre-earthquake period (Table).  

**Conclusion:** In contrast to a previous study we have shown no statistically significant difference in rate of newly diagnosed MPO or PR3 positive vasculitis after a major earthquake. A longer study period post-earthquake may be required. The earlier age onset of MPO vasculitis post-earthquake is of interest and may relate to younger people being in the areas of greatest building collapse in the city center. Further information of location at the time of the earthquake will be required.

**Table 1:** Demographic and clinical characteristics pre (period 1) and post (period 2) the 2011 Christchurch earthquake

<table>
<thead>
<tr>
<th>PR3 vasculitis</th>
<th>Age years; mean (SEM)</th>
<th>% male</th>
<th>PR3 mean (SEM)</th>
<th>Renal involvement</th>
<th>Respiratory involvement</th>
<th>MPO vasculitis</th>
<th>Age years; mean (SEM)</th>
<th>% male</th>
<th>MPO mean (SEM)</th>
<th>Respiratory involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1 (n=9)</td>
<td>63.0 (5.2)</td>
<td>100%</td>
<td>1224 (550)</td>
<td>5 (55.6%)</td>
<td>6/13 (46.2%)</td>
<td>Period 1 (n=13)</td>
<td>71.3 (2.9)</td>
<td>100%</td>
<td>520 (48.0)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Period 2 (n=11)</td>
<td>68.7 (4.4)</td>
<td>63.6%</td>
<td>934.8 (360.5)</td>
<td>4 (36.4%)</td>
<td>8 (88.9%)</td>
<td>Period 2 (n=7)</td>
<td>58.4 (5.3)</td>
<td>63.6%</td>
<td>462.3 (154.6)</td>
<td>2/7 (28.6%)</td>
</tr>
<tr>
<td>p value</td>
<td>0.41</td>
<td>0.09</td>
<td>0.66</td>
<td>0.65</td>
<td>0.59</td>
<td>p value</td>
<td>0.03</td>
<td>1</td>
<td>0.59</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Disclosure:** B. McGettigan, None; R. A. Watts, None; C. Freampton, None; J. L. O’Donnell, None.

**1759**

**Analysis of Employment, Work Disability and Quality of Life of Patients with ANCA-Associated Vasculitis.** Lucy Benarous1, Benjamin Terrier2, Alice Berezne3, Bertrand Dunogué4, Hervé Laborde-Casterot5, Pascal Cohen6, Xavier Puéchal7, Nathalie Costedoat-Chalumeau8, Claire Le Jeune9, Dominique Choudat10, Luc Mouthon11 and Loïc Guillemin for the French Vasculitis Study Group12. 1Cochin Hospital, Paris, France; 2Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France; 3Hôpital Cochin, Paris, France; 4National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, Paris, France.

**Background/Purpose:** Improved therapeutic strategies for ANCA-associated vasculitis (AAV) have transformed acute and life-threatening diseases into chronic ones responsible for marked morbidity that could impact employment, work disability and quality of life (QoL). The French EXPO-VAS inquiry aimed to analyze work, handicaps and QoL of AAV patients and identify their determinants.

**Methods:** Patients with AAV seen in our department were included in a cross-sectional study assessing employment, work disability and QoL. Specific and non-specific questionnaires, including SF-36, were sent to 531 AAV patients. QoL was compared to that of the general population, patients with end-stage renal failure (ESRD), and previously reported AAV patients from the EUVAS cohort. Clinical–biological data that could affect QoL were recorded, and their determinants analyzed.

**Results:** Questionnaires were completed by 198 patients (109 women (55%), mean age 59±14 years). Diagnoses were granulomatosis with polyangiitis for 132 (67%), eosinophilic granulomatosis with polyangiitis (EGPA) for 42 (21%) and microscopic polyangiitis for 24 (12%). A mong 94 working-age (<60 years) patients, 57% had jobs, consistent with their qualifications for 81%; 77% were stably employed, with 67% working full-time. Concerning the impact of AAV, 23% of workers felt that their disease qualitatively limited the nature of their work, while 43% felt it limited the quantity of work they could do; 77% of patients did not benefit from any work adaptation; 50% thought their disease had hindered their careers and 43% that it had led to a salary reduction. 33% were not employed and not looking for work; and 9% were looking for a job. These results were comparable for the different vasculitides. QoL was significantly impaired for AAV patients compared to the general population (P<0.0001). In contrast, QoL of AAV patients was significantly better than that of ESRD patients. Finally, our AAV population’s QoL was similar to that of the EUVAS cohort, except for our patients’ physical functioning, which was better (P<0.001), and their mental health, which was more impaired (P<0.001). Physical health determinants for our population were an EGPA diagnosis, long disease duration and its neurological involvement, whereas mental health determinants were ear, nose & throat signs and cardiovascular involvement.

**Conclusion:** Our findings showed that AAV patients’ QoL was impaired compared to the general population, mainly for patients with EGPA and long-standing disease. In contrast, normal employment seemed to be preserved.

**Disclosure:** L. Benarous, None; B. Terrier, None; A. Berezne, None; B. Dunogué, None; H. Laborde-Casterot, None; P. Cohen, None; X. Puéchal, None; N. Costedoat-Chalumeau, None; C. Le Jeune, None; D. Choudat, None; L. Mouton, None; L. Guillemin for the French Vasculitis Study Group, None.

**Background/Purpose:** GPA is a rare condition of unknown etiology. Prominent involvement of the upper and lower respiratory tracts suggests that inhaled antigens may trigger systemic immunopathogenic responses. Although no definite inhaled environmental factor has been identified farming and solvent exposure have been reported to be associated with GPA in Northern hemisphere studies. A latitudinal gradient has been observed in both Northern and Southern hemispheres with higher rates of disease in those areas closest to the North and South Poles. The aim of this study was to determine any environmental risk factors for GPA in Canterbury New Zealand (latitude 41°–44°S), with a particular focus on inhaled antigens. 

**Methods:** A case-controlled study was undertaken. All GPA cases and controls were matched for age (±10 years), gender, and matched with four controls (2 osteoarthritids or fracture and 2 asthma or emphysema). A structured questionnaire to assess potential environmental agents was administered. Data was analyzed using conditional logistic regression to allow for the individual matching of cases and controls.

**Results:** 49 cases and 196 controls were recruited. 53% were male and 47.5% were New Zealand European. The mean ± SD age of the cases was 64.9 ± 12.4yrs and controls 59.5 ± 14.6yrs. In the 2 years prior to the first symptoms attributable to GPA 14.3% of cases and 18.6% of controls lived in a rural environment (p=0.48). Place of birth within New Zealand (whether North Island or South Island) had no influence on risk (p=0.7).

Any reported exposure to dust (specifically silicon and grain dust) increased the risk of GPA, OR 3.6 (1.5 – 8.3; p=0.003). GPA was associated with a higher intensity of exposure to silica (p<0.001), metals (p<0.003) and solvents (p<0.001).

Occupation as a farm worker was associated with GPA OR 3.43 (1.5 – 7.5; p=0.002). In the year prior to the first symptoms attributable to GPA cases were significantly more likely to have lived on, worked on or visited a farm than controls OR 2.7 (1.3 – 5.9; p=0.009). There was no significant relationship between exposure to crops (OR 1.7; 0.8 – 3.6; p=0.16). However exposure to livestock was associated with an increased risk (OR 2.3; 1.1 – 5.0; p=0.02), specific exposure to sheep (OR 3.6; 1.6 – 7.7; p=0.001). GPA was also associated with more time spent in the garden (Cases 22.7 ± 41 hrs/month vs. controls 13.2 ± 20 hrs/month p=0.04). Specific gardening activities were associated with increased risk including digging (OR 3.2; 1.4 – 7.0; p=0.002), mowing (OR 2.7; 1.3 – 5.8; p=0.008) and planting (OR 2.6; 1.2 – 5.5; p=0.013).

**Conclusion:** Previous studies have identified a latitudinal gradient and a peak in GPA disease onset in the winter months. We have shown activities associated with exposure to inhaled antigens, in particular those related to farming or gardening activities may increase the risk of GPA. We have replicated findings from northern hemisphere studies identifying dust and solvent exposure as well as farm exposure as risk factors for the development of GPA.
United Kingdom & Ireland Vasculitis Registry - Cross-Sectional Data on the First 1085 Patients. Jan Sznejd, Alan D. Salama, David Jayne, Azfal Chaudhry, Michael Robson, Joe Rosa, Neil Basu, Sarah Moran, Michael Venn, Peter Lanoy, Ashesh Sharma, Mark A. Little, Richard Watson and Raashid Luqmani. 1Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, 2University College London, London, United Kingdom, 3Adevenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, 4King’s College London, London, United Kingdom, 5University of Aberdeen, Aberdeen, United Kingdom, 6Cork University Hospital, Cork, United Kingdom, 7Manchester Royal Infirmary, Manchester, United Kingdom, 8Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, 9University Hospital Aintree Liverpool, Liverpool, United Kingdom, 10Trinity College Dublin, Dublin, Ireland, 11Ipswich Hospital NHS Trust, Ipswich, United Kingdom, 12Oxford NIHR M usculoskeletal Biomedical Research Unit, Oxford, United Kingdom.

Background/Purpose: Clinical care and research into systemic vasculitis is hampered by its rarity and its presentation to a wide array of medical specialties. We aimed to establish a UK and Ireland registry of patients with different forms of vasculitis (UKIVAS) in order to amalgamate our clinical experience and provide comparative outcome data on a large cohort of patients from multiple centres. This will inform research (trials, immunogenetics, epidemiology), service planning and commissioning (particularly of expensive biologic agents).

Methods: We are recruiting patients with systemic vasculitis under regular care of a variety of specialists across the UK and Ireland. We developed web-based software to enable prospective collection and central storage of anonymised clinical data with local storage of patient identifiable information. The application was designed for use by each centre as the local clinical database and audit tool.

Results: To date, we have recruited 1085 patients from 16 centres. The median age at diagnosis was 55.8 years (IQR 40.9–66.0) with similar gender distribution; almost 90% were white Caucasians; 87% were prevalent cases at the time of recruitment. The majority had one of the anti-neutrophil cytoplasm antibody (ANCA) associated vasculitides: granulomatosis with polyangiitis (GPA) (42%), microscopic polyangiitis (MPA) (25%), or eosinophilic granulomatosis with polyangiitis (EGPA) (9%); the remainder were defined as giant cell arteritis (GCA) (5.6%), unclassified ANCA associated vasculitis (4.2%), anti-glomerular basement membrane disease (2.3%), Behcet’s (2.3%), IgA vasculitis (2.3%), Takayasu’s (1.2%), polyarteritis nodosa (1%) and other types of vasculitis (<1% each). Biopsies were performed in 755 (69.6%) patients; results were positive in 466/555 (84%) GPA and MPA IVs. 54% EGPA and 52% GCA. The majority (82.1%) received oral corticosteroids and cyclophosphamide (56% overall, 68% in GPA/MPA) for induction. The most common maintenance treatment with corticosteroids was azathioprine (39.5%). The detailed characteristics of the whole cohort and the 3 largest groups are shown in Table 1.

Conclusion: We have established a web-based registry for systemic vasculitis which can be used for gathering data at a national level and potentially linked with other international databases. The clinical features and treatment regimens reflect the predominance of ANCA vasculitis with renal involvement, with relative under-representation of other types of vasculitis. The introduction of new non-renal centres, the opportunity to biobank samples and longitudinal observation of this cohort will support further development of this project and research in vasculitis. The UKIVAS registry will be a useful way of identifying patients who may wish to take part in future clinical trials.

Table 1. Selected characteristics of all vasculitis patients and the 3 largest groups recruited in UK and Ireland vasculitis (UKIVAS) registry.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number of patients</th>
<th>GPA</th>
<th>MPA</th>
<th>EGPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1085 (100)</td>
<td>453 (42)</td>
<td>269 (25)</td>
<td>99 (9)</td>
</tr>
<tr>
<td>Median age at diagnosis in years (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>1.14</td>
<td>1.00</td>
<td>1.01</td>
<td>1.11</td>
</tr>
<tr>
<td>Median duration of the disease in years (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ involvement</td>
<td>4.0 (0.9–8.9)</td>
<td>5.5 (1.9–11.5)</td>
<td>2.2 (1.0–7.1)</td>
<td>4.9 (1.5–10.2)</td>
</tr>
<tr>
<td>Kidney</td>
<td>56%</td>
<td>55%</td>
<td>86%</td>
<td>25%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>44%</td>
<td>74%</td>
<td>12%</td>
<td>67%</td>
</tr>
<tr>
<td>Mucouscatal</td>
<td>42%</td>
<td>54%</td>
<td>32%</td>
<td>80%</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>25%</td>
<td>21%</td>
<td>15%</td>
<td>34%</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>12%</td>
<td>11%</td>
<td>10%</td>
<td>34%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>9%</td>
<td>5%</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>Abdominal</td>
<td>8%</td>
<td>6%</td>
<td>3%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Conclusion: We have established a web-based registry for systemic vasculitis which can be used for gathering data at a national level and potentially linked with other international databases. The clinical features and treatment regimens reflect the predominance of ANCA vasculitis with renal involvement, with relative under-representation of other types of vasculitis. The introduction of new non-renal centres, the opportunity to biobank samples and longitudinal observation of this cohort will support further development of this project and research in vasculitis. The UKIVAS registry will be a useful way of identifying patients who may wish to take part in future clinical trials.

Table 1. Selected characteristics of all vasculitis patients and the 3 largest groups recruited in UK and Ireland vasculitis (UKIVAS) registry.
retaken) in the introductory set to 1.05 (1 in 21 cases retaken) in the advanced set, showing intra-training improvement. Median time to complete a case was 4.18 (IQR 2.50–6.67) minutes and there was a trend showing a decrease in time taken per case as the participants progressed through the cases. The average mark at completion was 92.3% (range 86.6–96.4%) for BVAS and 92% (range 88.9–95.0%) for VDI. Overall 100% completed the training and were awarded certification. 92% of participants agreed that the training should be mandatory for all doctors who treat vasculitis patients.

**Conclusion:** We have developed a web-based training package to enhance clinicians’ ability to evaluate patients with systemic vasculitis, based on assessment of BVAS and VDI. This package is easy to use, feasible and acceptable to participants to facilitate their ability to manage patients with vasculitis, although its effectiveness needs to be validated in clinical setting. Currently we are expanding the number of cases based on clinical data from observational studies to allow for randomized case selection and retakes using different clinical scenarios.

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### 1763

#### Tobacco Differentially Affects the Clinical-Biological Phenotype of ANCA-Associated Vasculitides at Diagnosis.

- **Lucas Benarous,1 Benjamin Terrier2, Bertrand Dunogué2, Pascal Cohen3, Xavier Puéchal4, Claire Le Jeune1, Luc Mouton4 and Loric Guillevin for the French Vasculitis Study Group**

*Background/Purpose:* Occupational and non-occupational exposures may play a role in the occurrence of ANCA-associated vasculitides (AAV) and affect their initial clinical-biological phenotype. Among these potential environmental exposures, tobacco use could represent a factor that could influence AAV characteristics at diagnosis. However, these effects could differ according to the type of AAV, since granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) involve different pathophysiological mechanisms.

**Methods:** AAV patients entered in the FVSG database with available information on previous and current smoking habits were analyzed. The clinical-biological phenotype at diagnosis was compared according to current tobacco use (current smokers) or not (including previous and never smokers).

**Results:** This analysis concerned 1165 patients (545 men and 620 women; mean age of 52.8±16.1 years). AAV diagnoses were: GPA for 583 (50%), MPA for 256 (22%) and EGPA for 326 (28%). Among them, 973 patients (84%) were never smokers, 116 (10%) were previous smokers and 76 (6%) were current smokers. Among GPA patients, current smokers (n=55), compared to non-current smokers (n=528) respectively, were younger (44.5±13.5 vs. 52.0±16.3, P=0.0001), more frequently men (64% vs. 48%, P=0.016) and had more frequent cutaneous involvement (50% vs. 32%, P=0.025), and tended to have more frequent arthralgias (67% vs. 54%, P=0.11) and less frequent constitutional symptoms (33 vs. 47%, P=0.08) and ear, nose & throat (ENT) involvement (73 vs. 83%, P=0.13). BVAS, PR3-ANCA–positivity and inflammatory parameters were similar for the 2 groups. Among EGPA patients, current smokers (n=15), compared to non-current smokers (n=311) respectively, were also younger (41.1±15.8 vs. 50.3±15.2, P=0.028) and had less frequent constitutional symptoms (29 vs. 62%, P=0.02), arthralgias (7 vs. 35%, P=0.04), renal involvement (0 vs. 26%, P=0.025) and MPO-ANCA–positivity (0 vs. 30%, P=0.02). BVAS and inflammatory parameters were comparable for the 2 groups. Finally, analysis of MPA patients was impossible because only 6 (2%) were current smokers.

**Conclusion:** These results suggest that tobacco use could differentially affect GPA and EGPA clinical-biological phenotypes, while no conclusion can be drawn for MPA. Moreover, they support the role of environmental exposures in AAV development and its phenotype.

**Disclosure:** L. Benarous, None; B. Terrier, None; B. Dunogué, None; P. Cohen, None; X. Puéchal, None; C. Le Jeune, None; L. Mouton, None; L. Guillevin for the French Vasculitis Study Group, None.

### 1764

#### Clinical and Other Differences Observed Between Cocaine Induced and Non-Cocaine Induced Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis.

- **Santhi Pennessa,1 N. Suzzo Emili2, Joshua Duchene3, Wilmer Sibblitt4, Arthur Bankhurst3 and Roderick Fields5**

*Background/Purpose:* To compare various factors including clinical manifestations, laboratory data and mortality in between two groups of patients with anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis: with cocaine use and without cocaine use. The goal of this study is to evaluate clinical differences and similarities between these two groups as there are no previous studies per literature review. This also may help clinicians to better understand these two disease processes and to further aid in diagnostic and management approaches.

**Methods:** A total of patients with a diagnosis of ANCA positive vasculitis between 2000 and 2012 were selected and a total 46 patients were included in this study of which 22 Patients were cocaine users (age range 26–61) and 24 patients (age range 17–80) with no history of cocaine use. Clinical manifestations, laboratory data, pertinent serology, skin biopsy and other diagnostic data were gathered and analyzed in each category. Each of
these factors was compared between the Cocaine use and non-cocaine use group.

**Results:** Cocaine-associated ANCA positive vasculitis group had higher proportion of the patients with abnormal perinuclear ANCA (pANCA) (86% vs 66.7%, \(P = 0.084\)), myeloperoxidase (MPO), (100% vs 66%), abnormal both MPO and proteinase 3 (PR3) antibodies (32% vs 4.2%, \(P = 0.015\)) compared with non-cocaine use group. This group also has higher concentrations of anti-phospholipid antibodies (50% vs 4%) compared to non-cocaine group. Skin lesions were significantly more frequent in cocaine use group (81.8% vs 33.3%, \(P = 0.0009\)) with female sex preponderance for facial lesions. Pulmonary renal involvement and complications as well as mortality (12.5% vs none) were higher in non-cocaine use group compared to cocaine associated vasculitis group.

**Conclusion:** ANCA positive vasculitis, the cocaine-associated and non-cocaine associated have their own distinctive clinical, laboratory and other diagnostic characteristics as well as complications. It is important for clinicians to be aware of these differences in order to recognize cocaine-associated ANCA positive vasculitis in high-risk populations since management and long term prognosis differ. More studies are needed to evaluate the significance of the presence of the related antibodies in pathogenesis, follow up and management of ANCA positive vasculitis with immunosuppressive therapy in long term.

Disclosure: S. Penmetsa; None. N. S. Emil; None. J. Duchene; None. W. Sibbitt, Jr.; None. A. Bankhurst; None. R. Fields; None.

**1765**

**Comparison of Clinical Characteristics of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis By the Serotype Specificity to Myeloperoxidase and Proteinase-3.** Takamasa Murosaki, Takeo Sato, Yoichiro Akiyama, Katuya Nagatani and Seiji Minota. Jichi Medical University, Tochigi, Japan.

**Background/Purpose:** To correlate the clinical characteristics of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with myeloperoxidase (MPO)-ANCA and proteinase-3 (PR3)-ANCA, and to detect clinical characteristics of AAV in Japanese patients.

**Methods:** The clinical data of AAV patients from 2005 to 2014 were retrieved retrospectively. AAV patients were divided into three subgroups: MPO single positive-AAV (MPO-AAV), PR3 single positive-AAV (PR3-AAV), and double positive AAV. The clinical diagnosis was based on the European Medicines Agency Algorithm along with pathological findings. The clinical characteristics of AAV such as age, sex, organ involvement, treatment, and prognosis were evaluated and compared between MPO and PR3-ANCA.

**Results:** Among 165 patients positive for ANCA, 77 patients were diagnosed with MPO-AAV, 13 with PR3-AAV, 4 with double positive AAV, and 71 with non-AAV. The clinical diagnosis of MPO-AAV included microscopic polyangiitis (MPA) in 55, granulomatosis with polyangiitis (GPA) in 15, and eosinophilic granulomatosis with polyangiitis (EGPA) in 8. PR3-AAV included 10 GPA, 2 MPA, and 3 EGPA. All patients with double positive AAV were diagnosed with MPA. Patients PR3-AAV were younger than those with MPO-AAV (median age 70 vs 55 years old, \(P = 0.006\)). Involvement in the eyes (46.2% vs 6.5%, \(P < 0.001\)), nose (53.8% vs 19.4%, \(P = 0.013\)), and ears (61.5% vs 23.4%, \(P = 0.009\)) was higher in PR3-AAA. There was no difference in gender ratio or involvement in other organs between MPO and PR3-AAA. In both MPO and PR3-AAA, the respiratory system was most frequently involved (83.1% vs 76.9%). The respiratory involvement in MPO and PR3-AAA included interstitial pneumonia (49.4% vs 7.7%, \(P = 0.004\)), nodular shadow (7.8% vs 53.8%, \(P < 0.001\)), alveolar hemorrhage (3.9% vs 7.7%, \(P = 0.47\)), and bronchitis (12.9% vs 0%, \(P = 0.191\)). All AAV patients except one with MPO-AAV were treated with glucocorticoid, and immunosuppressant was added as initial remission induction therapy in 20.8% and 46.2% of the patients with MPO- and PR3-AAA, respectively. In 58.4% and 23.0% of the patients with MPO- and PR3-AAA, respectively, glucocorticoid alone was sufficient for disease-activity suppression, however, in 20.8% and 30.8% of the patients with MPO- and PR3-AAA, respectively, additional immunosuppressant was required during the course. During 2 years, the relapse rate in the patients with PR3-AAA was higher than that in those with MPO-AAV (log-rank test, \(P = 0.046\)), and Cox hazard analysis revealed that PR3-ANCA showed a higher relapse rate (hazard ratio 2.54, 95% CI 0.97-6.605, \(P = 0.057\)). There was no difference in the survival between patients with MPO- and PR3-AAA (log-rank test, \(P = 0.931\)).

**Conclusion:** Unlike AAV patients in Western countries, MPO-AAV was predominant in Japan. The clinical characteristics were different between MPO and PR3-AAA. The involvement of the respiratory system was most frequent in both AAVs. In contrast to Western countries, alveolar hemorrhage was rare in Japanese, and in half of MPO-AAV patients, glucocorticoid alone was sufficient. Higher relapse rate in PR3-AAA than in MPO-AAV was similar to reports from Western countries.

Disclosure: T. Murosaki; None. T. Sato; None. Y. Akiyama; None. K. Nagatani; None. S. Minota; None.

**1766**

**Comparison of Clinicopathologically- and Serologically-Based Classification Systems for ANCA-Associated Vasculitis.** Sebastian Unizony1, Ei M. Miloslavsky2, Miguel Villarreal3, Peter A. Merker4, Paul Monach5, E. William St. Claire6, Cees Kallenberg7, David Ikle8, Robert F. Spiera9, Nadia Tchabo10, Deborah J. Phippard11, Linna Ding12, Carol A. Langford13, Philip Seo14, Gary S. Hoffman15, John H. Stone16 and Ulrich Specks17. 1Massachusetts General Hospital, Boston, MA, 2Rho, Chapel Hill, NC, 3Vasculitis Center, University of Pennsylvania, Philadelphia, PA, 4Bost University, Boston, MA, 5Duke University School of Medicine, Durham, NC, 6University of Groningen, Groningen, Netherlands, 7Hospital for Special Surgery, New York, NY, 8Immune Tolerance Network, Bethesda, MD, 9NIAID, Bethesda, MD, 10Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, 11Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, 12Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, 13Mayo Clinic, Rochester, MN.

**Background/Purpose:** Genome-wide association studies suggest that PR3-ANCA-positive ANCA-associated vasculitis (AAV) is genetically distinct from MPO-ANCA AAV. We evaluated patients enrolled in the RAVE trial according to ANCA type (PR3- versus MPO-ANCA) as opposed to disease type (granulomatosis with polyangiitis [GPA] versus microscopic polyangiitis [MPA]) to explore whether either classification predicts clinical course and response to treatment.

**Methods:** The RAVE trial randomized 197 patients to receive rituximab (RTX) or CYC followed by AZA (CYC/AZA) for remission induction. Demographics, clinical features, response to induction treatment, and disease flares were analyzed according to ANCA type and AAV diagnosis. Chi square, Fisher and Mann-Whitney tests were used for univariate analyses. Logistic regression was used for multivariate analyses.

**Results:** Demographic characteristics and baseline organ system involvement: Considerable overlap existed between AAV type and ANCA diagnosis with regard to patient demographics and clinical phenotype (Table 1). Patients with GPA and PR3 were younger, more often male, and had more constitutional, ocular and ENT manifestations compared to those with MPA and MPO. Renal disease was more common among patients with MPA and MPO.

**Response to treatment:** PR3-positive patients achieved complete remission (CR) at 6 months more frequently when treated with RTX (65%) than CYC/AZA (48%) (\(P = 0.04\)) (Table 2). Findings were consistent after adjustments for age, sex and new versus relapsing disease. No significant association between CR at 6 months and treatment allocation was seen for MPO patients. When stratified by AAV diagnosis, the proportion of patients in CR at 6 months was not significantly different between treatment arms. The difference in response to treatment was no longer seen at 12 and 18 months, by which time the effects of RTX had waned.

**Disease relapse:** A higher percentage of PR3 and GPA patients had experienced flares at 12 and 18 months than did their MPO and MPA counterparts. There were no differences in time to first flare. In addition, patients with PR3 and GPA were more likely to achieve CR at 6 months if treated with RTX than with CYC/AZA. This observation requires confirmation in future studies but supports the concept that classifying patients according to ANCA type rather than AAV diagnosis may be highly relevant to the choice of remission induction therapy. Patient demographics, clinical features, and disease relapse were similar when patients were stratified by either AAV diagnosis or ANCA type.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>MPO (n = 66)</th>
<th>ANCA type</th>
<th>PR3 (n = 131)</th>
<th>GPA (n = 48)</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59</td>
<td>49.6</td>
<td>&lt;0.01</td>
<td>61</td>
<td>50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>24 (36%)</td>
<td>76 (58%)</td>
<td>&lt;0.01</td>
<td>18 (37%)</td>
<td>80 (54%)</td>
</tr>
</tbody>
</table>

Monday, November 17
sub-Saharan and Afro-Caribbeans had less frequent fever (20 vs 51%; P < 0.05), weight loss (25 vs 51%; P < 0.05), kidney involvement (38 vs 59%; P = 0.07), cardiovascular involvement (0 vs 15%; P = 0.06) and peripheral neuropathy (45 vs 22%; P = 0.06), and their serum creatinine levels (70 vs. 175 μmol/L; P < 0.01) and B2AVS (12.3 ± 7.2 vs 19.6 ± 9.1; P < 0.01) were significantly lower. Finally, relapse-free survival tended to be shorter for sub-Saharan and Afro-Caribbeans (median survival 44.8 vs 59.8 months), without reaching the significance [HR 1.75 (0.92-4.80); P = 0.08]. Overall survival was similar for the 2 populations.

Conclusion: Our findings indicated different GPA clinical presentations in white Europeans vs sub-Saharan and Afro-Caribbeans, with blacks having more frequent severe granulomatous manifestations and less frequent constitutional symptoms, renal involvement and peripheral neuropathy. Prognoses did not differ according to geographic origin.

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1768
Cardiac Involvement in Granulomatosis with Polyangiitis: A Magnetic Resonance Imaging Study of 31 Consecutive Patients. Grégoire Pugnet1, Xavier Puichal2, Bertrand Terrier3, Hervé Gouya4, André Kahan5, Paul Legmann6, Loïc Guillemin2 and Olivier Vignaux5. 1National Referral Center for Rare Systemic A Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, 2AP-HP Cochin Hospital, Department of Radiology B, Paris, France, 3Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, 4Cochin University Hospital, Paris, France.

Background/Purpose: Cardiac manifestations in granulomatosis with polyangiitis (GPA) patients are usually considered to be rare but may be life-threatening. However specific cardiac involvement in GPA is probably underestimated during lifetime because many of these cardiac disturbances are subclinical. Contrast-enhanced magnetic resonance imaging (MRI) is a sensitive tool to detect and analyze cardiac involvement in GPA associated vasculitis. The objective of our study was to assess the prevalence and patterns of cardiac abnormalities detected by cardiac magnetic resonance imaging in patients with GPA.

Methods: Thirty-one consecutive patients with either new or relapsing GPA underwent CMRI to determine morphological, functional, perfusion at rest and delayed enhancement abnormalities.

Results: At least one abnormality on CMRI was observed in 19/31 patients (61.3%). Four patients (14.8%) had an impaired left ventricle (LV) ejection fraction with evidence of clinically cardiac failure in two of them. LV kinetic abnormalities were found in 11 patients (36.7%). M yocardial delayed contrast enhancement (DCE) was detected in 9/31 patients (29%), 6 of whom with cardiac manifestations. DCE was mainly nodular (n = 7/9). Myocardial delayed enhancement was detected in 5 of 31 patients (16.1%), and was always associated with DCE in the same territory. CMRI detected pericarditis in 7 patients (22.6%). GPA of less than 18 months duration as compared with GPA of longer duration had greater LV ejection fraction (P = 0.008) and less CMRI abnormalities (P = 0.04). DCE (P = 0.19) or LV hypokinesia (P = 0.04). Patients who presented with new-onset GPA had less CMRI abnormalities than patients who experienced a relapse (P = 0.02).

Conclusion: CMRI is an accurate technique for diagnosing heart involvement in GPA and for analyzing precisely its mechanisms including inflammatory, microvascular and fibrotic components. This unique noninvasive information may have important clinical implications in early and accurate assessment of cardiac lesions in GPA patients but also to detect cumulative non reversible damage. Moreover, it may have prognostic implications.

Disclosure: G. Pugnet, None; X. Puichal, None; B. Terrier, None; H. Gouya, None; A. Kahan, None; P. Legmann, None; L. Guillemin, None; O. Vignaux, None.

1769
Abdominal Visceral Adipose Tissue Measured by DXA As a Novel Surrogate Marker of Cardiovascular Risk in Primary Nectroizing Vasculitides. Bertrand Dunogu1, Karine Briot2, Sami Kolta3, Alexis Regent4, Pascal Cohen5, Allice Berezne4, Xavier Puichal2, Claire Le Jenne5, Luc Mouthon5, Christian Roux2, Loïc Guillemin for the French Vasculitis Study Group4 and Benjamn Terrier1. 1Hôpital Cochin, Paris, France, 2Paris Descartes University, Paris, France, 3Paris Descartes University, Cochin...
Background/Purpose: Studies have shown a strong prevalence of cardiovascular events among patients with primary necrotizing vasculitides. Recent studies indicate that visceral adipose tissue (VAT) is highly associated with insulin resistance and cardiovascular events. Dual energy X-ray absorptiometry (DXA) is a validated technique able to accurately determine cross-sectionally the mass of discreet fat deposits.

Objective: To assess the relevance of abdominal adipose tissue measurement as potential surrogate markers for cardiovascular risk in patients with primary necrotizing vasculitides.

Methods: Patients with ANCA-associated vasculitides (AAN) and polyarteritis nodosa (PAN) seen in our department were prospectively included in an ongoing cross-sectional study assessing cardio-vascular complications and other sequelae (OSTEOVAS cohort). Alongside the evaluation of usual clinical and extra-clinical features associated with increased cardiovascular risk, DXA was performed to evaluate body composition and abdominal adipose tissue (subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)).

Results: Fifty-six patients were analyzed (38 females, mean age 50 ± 18 years, mean disease duration of 85 ± 79 months). Diagnoses were granulomatosis with polyangiitis (GPA) in 33 patients, microscopic polyangiitis in 6, eosinophilic GPA in 18, and PAN in 8. Five (7.7%) patients had developed cardiocirculatory complications. The median daily dose of corticosteroid was 5 mg/day (0–80). High cardiovascular risk defined by the NCEP-ATPIII was found in 11 (16.9%) patients. Using univariate analysis, cumulated dose of corticosteroids (p=0.038), Vascular Damage Index (VDI) (p=0.008), and VAT/SAT ratio (p=0.009) were significantly associated with high cardiovascular risk. Using multivariate analysis, VAT/SAT ratio remained independently associated with high-risk status [OR 1.07 (1.01–1.12), p=0.004]. VAT/SAT ratio was also independently correlated with an increased Framingham cardiovascular risk score (p<0.01).

Among factors correlated with a higher VAT/SAT ratio, we identified male gender (p=0.0001), age (r=+0.31, p=0.014), cumulated corticosteroid dose (r=+0.26, p=0.048), VDI score (r=+0.26, p=0.048), Body Mass Index (r=+0.35, p=0.006), waist circumference (r=+0.56, p<0.0001), and elevated troponin levels at time of assessment (r=+0.36, p=0.007).

Conclusion: This is the first study showing a significant association between a high VAT/SAT ratio assessed by DXA and cardiovascular risk in patients with primary necrotizing vasculitides. A abdominal adipose tissue seems to be an accurate and independent surrogate marker of cardiovascular risk in these patients.

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1770
Increased Risk of Chronic Obstructive Pulmonary Disease in Granulomatosis with Polyangiitis: A General Population-Based Study, Neda Amir1, Mohsen Sadat Shafi2; Eric C. Sayre2; John M. Esdaille1 and J. Antonio A-vina-Zubieta1,2. 1University of British Columbia, Vancouver, BC, 2Arthritis Research Centre of Canada, Richmond, BC, 3University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC.

Background/Purpose: Chronic obstructive pulmonary disease (COPD) is increasingly recognized as an inflammatory condition. We aimed to identify the risk of newly recorded COPD among patients with incident GPA cases compared to the control population using a combination of physician billing codes and hospitalization data covering the entire province of British Columbia, Canada.

Methods: Our data includes all health professionals and hospital visits covered by the comprehensive provincial medical services plan (1990–2010) and all dispensed medication (1996–2010), for all BC residents.

We conducted a retrospective matched cohort study among new cases with GPA meeting a pre-defined criteria as follows: a) diagnosis of GPA (ICD-9-CM 446.4) in adults on at least two visits within a two-year period between 1996 and 2010 by a non-rheumatologist physician; b) diagnosis of GPA on at least one visit by a rheumatologist or from hospitalization; c) absence of a prior GPA diagnosis between January 1990 and December 1995 (to ensure incident GPA cases). Ten controls matched by birth year, sex and calendar year of follow-up were selected from the general population. Incident COPD cases were identified using a validated algorithm (first ICD-9-CM: 491, 492, 496, 493.2, or ICD-10-CM J43 or J44) from hospitals or death certificates. We estimated incidence rate ratios (IRRs) by comparing GPA cases with age-, sex- and entry-time-matched comparison cohorts. Multivariable Cox-regression models adjusting for confounders were also used. Sensitivity analyses were conducted to assess for unmeasured confounders (e.g. smoking).

Results: Among 512 patients with incident GPA, (mean age 57.7, 54% female) 34 developed COPD. This translated to a 20.25 incident rate (IR) per 1000 person-years in the GPA cohort compared to 4.10 IR / 1000 person-years in the control population. The age-, sex- and entry-time matched RR was significantly increased in the GPA cohort (See Table). The risk of developing COPD was the highest in the first 10 years following diagnosis of GPA (17 fold). The results also remained statistically significant after adjusting for the potential impact of unmeasured confounders (adjusted RRs ranging between 5.03 and 5.58 in all sensitivity analyses).

Conclusion: To our knowledge, this is the first general population-based study that shows a six-fold increase in risk of COPD in patients with GPA. The highest incidence of COPD in the first year following diagnosis supports the role of immune mediated inflammation in the pathogenesis of COPD.

Table: Risk of Incident COPD according to GPA Status

<table>
<thead>
<tr>
<th>GPA n</th>
<th>Non-GPA n</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD cases, N</td>
<td>34</td>
</tr>
<tr>
<td>Incidence Rate/1000 Person-Years</td>
<td>20.25</td>
</tr>
<tr>
<td>Age, sex- and entry-time-matched IRRs (95% CI)</td>
<td>4.94 (3.24–7.36)</td>
</tr>
<tr>
<td>&lt; 1 year of disease duration</td>
<td>16.93 (6.05–36.49)</td>
</tr>
<tr>
<td>&lt; 2 years of disease duration</td>
<td>11.21 (5.93–21.03)</td>
</tr>
<tr>
<td>&lt; 3 years of disease duration</td>
<td>7.72 (4.40–13.26)</td>
</tr>
<tr>
<td>&lt; 4 years of disease duration</td>
<td>6.77 (4.00–11.17)</td>
</tr>
<tr>
<td>&lt; 5 years of disease duration</td>
<td>5.64 (3.42–9.06)</td>
</tr>
<tr>
<td>&lt; 6 years of disease duration</td>
<td>3.95 (1.59–8.60)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)</td>
<td>5.59 (3.13–9.43)</td>
</tr>
<tr>
<td>Male</td>
<td>5.20 (2.48–10.9)</td>
</tr>
<tr>
<td>Female</td>
<td>6.22 (2.90–13.33)</td>
</tr>
</tbody>
</table>

Disclosure: N. Amir, None; M. Sadat Shafi, None; E. C. Sayre, None; J. M. Esdaille, None; J. A. A-vina-Zubieta, None.

1771
Arterial Thrombotic Events in Systemic Vasculitis. Alexander Tsoukis, Sashia Bernasky, Lawrence Joseph, David Buckeridge, Patrick Belisle and Christian A. Pineau. McGill University Health Centre, Montreal, QC, McGill University, Montreal, QC, Research Institute of the McGill University Health Centre, Montreal, QC.

Background/Purpose: To estimate the incidence rate of clinically apparent arterial thrombotic events and associated comorbidities in patients with primary systemic vasculitis.

Methods: Using large-cohort administrative data from Quebec, Canada, we identified all patients with vasculitis, including those with polyarteritis nodosa and granulomatosis with polyangiitis. Incident myocardial infarctions and cerebrovascular events after the diagnosis of vasculitis were ascertained longitudinally via billing and hospitalization data and compared to rates of a general population comparator group. The incidences of comorbidities (DMII, dyslipidemia, and hypertension) were also collected.

Results: Among the 836 patients identified with vasculitis, the myocardial infarction event rate was substantially higher in younger patients, with rates up to 268.1 events per 10,000 pt years [95% CI 67.1–1070.2] in males aged 18–45 with polyarteritis nodosa, approximately 30 times that seen in the age- and sex-matched control group. The cerebrovascular event rate was also substantially higher, particularly in adults aged 45–65 regardless of vasculitis type. All patient groups with vasculitis had elevated incidences of diabetes, dyslipidemia and hypertension compared to the general population.

Conclusion: Atherothrombotic event rates were elevated in patients identified as having primary systemic vasculitis. While incident rates of cardiovascular comorbidities were also increased, the substantial elevation in
myocardial infarctions seen in young adults suggests a disease-specific component which requires further investigation.

Disclosure: A. Tsoukas, None; S. Bernatsky, None; L. J. Joseph, None; D. Buckeridge, None; P. Belisle, None; C. A. Pineau, None.

1772

Venous Thromboembolic Events in Eosinophilic Granulomatosis with Polyangiitis (EGPA). Chiara Baldini1, Francesco Ferro2, Nicoletta Luciano3, Antonio Tavoni4, Francesca Sernissi5, Daniela Martini6, Sara L’Abbate7, M. arta Mosca8 and Stefano Bombardieri9. 1. Rheumatology Unit, Pisa, Italy, 2. Immunology Unit, Pisa, Italy, 3. Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Previous studies have documented an increased risk of venous thromboembolic events in patients with antineutrophil cytoplasmic antibodies (ANCA) associated vasculitides (AAV) as compared to healthy subjects. However, only a limited number of studies have analyzed the prevalence of thrombosis in eosinophilic granulomatosis with polyangiitis (EGPA). Aim of the study was to determine the frequency of venous thromboembolic events (VTE) in a single center cohort of patients with EGPA and to describe its relation with disease clinical manifestations and activity.

Methods: Patients diagnosed with EGPA (1990 ACR classification criteria) from 1994 to 2014 were included in the study. Data were retrospectively retrieved from patients’ charts, including gender, demographic data, cumulative clinical features, ANCA status and BVAS at the baseline. In patients with VTE (i.e. deep venous thrombosis and/or pulmonary embolism), EGPA characteristics and disease activity at the time of VTE occurrence were also collected. Categorical variables were compared using Fisher’s exact test; continuous variables were compared using Student’s t-test. A 2-tailed value of p < 0.05 was taken to indicate statistical significance.

Results: The systematic search of our database identified 89 patients, among whom 51 were included in the study. Median (IQR) age at the EGPA diagnosis was 59 (41–62.2) years and their M:F sex ratio was 1:0.4. During a median (IQR) follow-up of 72.2 (14.8–135.2) months, 6/51 (11.8%) EGPA patients presented at least one VTE. One patient presented 4 recurrent thromboses despite anticoagulant therapy; overall, then, 9 VTE were recorded. Lower-limb deep venous thromboses (DVTs) were the most common VTE manifestations, representing the 89% (8/9) of all the VTE in our series. One patient developed also a pulmonary embolism, while another presented a cardiac intra-ventricular thrombus. Six (67%) VTE occurred within 6 months before the EGPA diagnosis. The patient with recurrent thromboses presented 2 DVTs before the EGPA diagnosis and 2 further DVTs within 15 months after the EGPA diagnosis. The patient with the pulmonary embolism, developed the VTE 13 years after EGPA diagnosis concomitantly with a femoral neck fracture. According to our analysis, factors associated with the occurrence of VTE were renal involvement (p = 0.01), nephrotic range proteinuria >3 g/24 h (p = 0.03) and a FFS >1 (p = 0.03). No differences were observed when comparing ANCA status and the BVAS score at the diagnosis between the groups.

Conclusion: The results of this study confirm a higher risk of VTE in patients with EGPA. The pathogenesis of thrombosis in EGPA calls for further studies.

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1773

Otolaryngologic Lesions Are Not Rare and Closely Related with Pachymeningitis and Cranial Neuropathy in MPO-ANCA Associated Vasculitis. Takaehiro Nunokawa, Naoto Yokogawa, Kota Shimada and Shoji Sugii. Tokyo Metropolitan Tama Medical Center, Tokyo, Japan.

Background/Purpose: Recently several case reports of serous otitis media (SOM), hypertrophic pachymeningitis (HP) and cranial neuropathy (CN) have been reported in connection with MPO-ANCA associated vasculitides (MPO-AAV). However, there are few clinical studies on the lesions. Herein, we address the frequency and the characteristics of these manifestations in patients with MPO-AAV.

Methods: This retrospective study focused on consecutive patients in whom MPO-AAV was diagnosed between 2003 and 2014 at Tokyo Metropolitan Tama Medical Center. We investigated their clinical and radiological profile by reviewing the medical records.

Results: A total of 111 patients with MPO-AAV were seen at the hospital in this period. There were 19 patients (17%) with at least one of the manifestations: SOM, HP, or CN. SOM was observed in 16 cases (14%), and constituted the first manifestation of the disease in 11 cases. HP and CN were seen in eight (7%) and seven (6%) patients, respectively. Of the patients presenting with SOM, seven patients had HP and/or CN (4 with HP and CN, 2 with CN, 1 with HP). Of three HP patients unassociated with SOM, CN was detected in one. There were no patients with isolated CN. Of the 11 patients examined by M R I, six patients demonstrated intense inflammation in the epipharynx. There was a significant difference in the rate of glomerulonephritis between the patients with the manifestations and those without them (32% vs. 73%; P = 0.0006). Furthermore, none of the patients with HP exhibited glomerulonephritis.

Conclusion: SOM is not a rare manifestation in MPO-AAV and often precedes other manifestations. There is a close relationship among SOM, HP and CN. Inflammation in the epipharynx might play a role as a pre-condition for the development of SOM and HP.

Disclosure: T. Nunokawa, None; N. Yokogawa, None; K. Shimada, None; S. Sugii, None.

1774


Background/Purpose: Tracheobronchial stenosis (TBS) is noted in 12 to 23% in patients with granulomatosis with polyangiitis (GPA), and includes subglottic stenosis (SGS) and bronchial stenosis. The optimal systemic treatments and endoscopic interventions providing the best efficacy, and the best timing for such interventions, remain unclear, explaining why, in the 2010s, TBS remains a therapeutic challenge in the management of GPA patients.

Methods: To analyze the endoscopic management of TBS in GPA and to identify factors associated with the efficacy of endoscopic interventions, we conducted a French nationwide retrospective study that included 47 patients with GPA-related TBS. We also compared characteristics of GPA patients with TBS and GPA patients without TBS included in the French Vasculitis Study Group.

Results: Compared to patients without TBS, those with TBS were younger, more frequently female, and had less frequent kidney, ocular and gastrointestinal involvement and mononeuritis multiplex. 173 procedures were performed in 47 patients. Endoscopic procedures included 137 tracheal and 30 bronchial interventions, mainly endoscopic dilatation, local steroid injection and conservative laser surgery, and less frequently stenting. Per-endoscopic events were noted in only 5/173 cases (2.9%). After the first endoscopic procedure, cumulative incidence of endoscopic treatment failure was 49% at 1 year, 70% at 2 years and 80% at 5 years.

Factors significantly associated with a higher cumulative incidence of treatment failure were a shorter time from GPA diagnosis to endoscopic procedure [HR 1.16 (1.01–1.14); P = 0.01] and a bronchial stenosis [HR 1.96 (1.28–3.00); P = 0.002]. A prednisone dose ≥30 mg/day at the time of the procedure was associated with a lower cumulative incidence of treatment failure [HR 0.53 (0.31–0.89); P = 0.02]. No difference was observed according to the immunosuppressive agents used.

Conclusion: TBS represent severe and refractory manifestations with high rate of restenosis. High-dose systemic corticosteroids at the time of the procedure and increased time from GPA diagnosis to bronchoscopy inter-
vention are associated with a better event-free survival. In contrast, bronchial stenoses are associated with a higher rate of restenosis than SGS.

Disclosure: B. Terrier, None; A. Dechartres, None; C. Girard, None; S. J. ouneau, None; J. E. Kahn, None; R. Dhots, None; J. Cabanne, None; E. Lazaro, None; T. Papo, None; N. Schienitz, None; G. Le Guenco, None; L. Mouton, None; L. Guillevin for the French Vasculitis Study Group, None.


Background/Purpose: Patients with granulomatosis with polyangiitis (GPA) suffer from frequent disease relapses, with up to 50% of patients relapsing within 5 years. Several risk factors for relapse have been described, such as pretreatment ANCA titers and Staphylococcus aureus nasal carriage. However, no method to predict a relapse in individual patients is currently known. Changes in measures that reflect the pathogenic process in the patient may be useful to improve relapse prediction in these patients.

Methods: Forty-nine patients with GPA were monitored for a period of 8-16 months, with 3-7 sampling moments for each patient. At each time point peripheral blood mononuclear cells were cultured in presence of CpG oligodeoxynucleotide (ODN 1826). The activating factor and interleukin-2 for 10 days. Subsequently supernatants were analyzed for PR3-ANCA by Phada Elia, results being expressed in response units (RU), and production of total IgG was assessed by ELISA. Moreover, ANCA titers were determined by immunofluorescence. B cell phenotypes were analysed by using flow cytometry on whole blood stained for CD19, CD24, CD27 and CD38. With these markers percentages and total numbers of B cells were determined, and naïve, transitional, memory and regulatory B cells were distinguished. Median values from the last measured time point before relapse were compared to non-relapsing patients. For non-relapsing patients the average value of all time points measured was used. All patients were also scored based on their inclusion sample and subsequently analyzed for differences in disease-free survival.

Results: During follow-up 12 patients relapsed. Patients that relapsed showed higher median values of in vitro PR3-ANCA (9.1 RU vs 2.2 RU) as well as higher ANCA titers compared to the non-relapsing patients. The higher levels of PR3-ANCA IgG were not a reflection of higher total IgG production. Levels of IgG were in fact decreased in patients before relapse. Three patients relapsed directly after the inclusion sample, two of which showed >15 RU of in vitro PR3-ANCA. Of the remaining nine patients, six were positive for PR3-ANCA, and also showed an increase in this measure prior to relapse. Patients that had >2 RU of in vitro PR3-ANCA at inclusion showed lower disease-free survival, while no such difference was observed for ANCA titers. In terms of percentages of memory and regulatory B cells, both CD24hiCD38hi and CD24hiCD27+ were lower in patients prior to relapse. However, no differences in disease-free survival were observed when patients were divided based on percentage at inclusion. When analyzing the absolute numbers of B cell subsets patients with low numbers of CD27+ memory B cells at inclusion were shown to be more prone to relapse.

Conclusion: This study shows a few promising factors to assist in the prediction of relapse in GPA patients, most notably in vitro ANCA production. Finding a better predictive factor for relapse in GPA would allow for timely intervention and possibly prevention of relapse in patients. Currently 80 PR3-ANCA positive GPA patients are being monitored with this method to strengthen these data.

Disclosure: J. Land, None; W. H. Abdulrahad, None; C. A. Stegeman, None; P. Heeringa, None; A. Rutgers, None.

1776 Factors Predictive of ANCA-Associated Vasculitis Relapse in Patients Given Rituximab-Maintenance Therapy. Benjamin Terrier1, Christian Pagnoux2, Guillaume Geri2, Alexandre Karas2, Chahera Khouatra2, Olivier Aumatre3, Pascal Cohen4, Francois Maurier2, Olivier Decaux2, Helene Desmurs-Clave1, Pierre Gobert5, Thomas Queuneur2, Claire Blanchard-Delaunay2, Pascal Godmer2, Xavier Puéchal2, Luc Mouthon2, and Loïc Guillevin for the French Vasculitis Study Group6, Cochin Hospital, Paris, France; University of Toronto, Toronto, ON, Hôpital Européen Georges Pompidou, APHP, Paris, France; CHU Louis Pradel, Lyon, Lyon, France; CHU Clermont-Ferrand, France; National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, Paris, France; Department of Internal Medicine, Metz, France; Rennes University Hospital, Rennes, France, University of Lyon, Lyon, France; Centre Hospitalier d’A vignon, Avignon, France, CH V et Mentor, France, CH hôpital de Nice, Nice, France; Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France.

Background/Purpose: Rituximab (RTX) was shown to be as effective as cyclophosphamide to induce remission in patients with ANCA-associated vasculitis (AAV). The prospective MAINRITSAN trial compared RTX to azathiprine (AZA) to maintain AAV remission after a corticosteroid-and-cyclophosphamide induction regimen. Patients were randomly assigned to receive 500-mg RTX infusions on D1, D15 and 5.5 months later, then every 6 months until 18 months, or AZA for 22 months (initial dose: 2 mg/kg/d). Trial results demonstrated that RTX was superior to AZA at maintaining AAV remission during the planned 28 months of observation. Extended follow-up showed that late relapses could occur in RTX-treated patients. In this follow-up study, we analyzed these relapses occurring after RTX-maintenance therapy, aiming to identify factors predictive of them.

Methods: For the 57 patients randomized to the RTX arm, data on their relapses were recorded during the 28-month trial and extended follow-up, and factors predictive of relapse were identified with univariate and multivariate analyses.

Results: Fifty-six patients (men 64%; mean age 54±13 years) were analyzed, with median follow-up at 50 months. Fifteen (26%) patients experienced at least 1 major relapse after a median of 40 (range 8–52) months. Three relapses occurred during the 28-month trial, while 12 relapses occurred during extended follow-up. According to univariate analysis, relapse-associated factors were: granulomatosis and polyangiitis (Wegener’s) diagnosis (HR 5.39 (0.70–41.5), P=0.11), proteinase-3 (PR3)-ANCA at AAV diagnosis (HR 6.29 (0.82–48.2), P=0.08), glomerular filtration rate <60 mL/min (HR 0.43 (0.14–1.36), P=0.15), and persistent ANCA-positivity 6 months (HR 2.21 (0.80–6.12), P=0.13) and 12 months (HR 4.45 (1.60–12.4), P<0.01) after starting maintenance therapy. Multivariate analysis retained the following factors as being significantly associated with relapse: PR3-ANCA-positivity (HR 12.5 (1.47–106), P=0.02) and persistent ANCA-positivity at 12 months (HR 7.79 (2.51–24.2), P<0.01). The 50-month cumulative relapse rates were 82.5, 23.4 and 0%, respectively, for patients with PR3-ANCA and ANCA positivity at 12 months, patients with PR3-ANCA and negative ANCA at 12 months, and those with myeloperoxidase-ANCA.

Conclusion: A quarter of AAV patients who received RTX-maintenance therapy experienced late relapses during extended follow-up. Factors predictive of relapse for these patients were PR3-ANCA-positivity and persistent ANCA positivity 12 months after starting maintenance therapy. Our findings suggest that pursuing RTX-maintenance therapy in these patients could be beneficial to prevent relapses.

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1777 Staphylococcus Aureus Nasal Carriage and Relapses, Bvas, ANCA-Positivity and Cotrimoxazole Use in ANCA-Associated Vasculitis. Boun Kim Tan1, Yoann Crabol1, Jason Tasse2, Frederic Laurent2, Xavier Puechal3, Christine Vinter4 and Loïc Guillevin5. Hôpital Cochin, University Paris V Descartes, Paris, France; International Centre for Research in Infectious Diseases, Lyon, France; French Vasculitis Study Group (FVSG), Paris, France, Hôpital Cochin, Paris, France.

Background/Purpose: Staphylococcus aureus (SA) nasal carriage has been reported to be more frequent and associated with persistent ANCA-positivity and relapse in patients with granulomatosis with polyangiitis (GPA). Antibiotics, including cotrimoxazole (CTX), usually active against SA, have been shown to prevent relapses in some GPA patients. Nasal
Rituximab Versus Azathioprine for ANCA-Associated Vasculitis Maintenance Therapy: Impact in Health-Related Quality of Life. Grégory Pugnet, None; C. Pagnoux, None; A. Karras, None; C. Khouatra, None; O. Aumaitre, None; P. Cohen, None; F. Maurier, None; O. Decaux, None; J. Ninet, None; P. Gobert, None; T. Quemeneur, None; C. Blanchard-Delaunay, None; P. Godmer, None; X. Puechal, None; L. Carron, None; P. Y. Hatron, None; N. Limal, None; M. Hamidou, None; E. Daugas, None; T. Papo, None; B. Bonnotte, None; A. Mah, None; B. Terrier, None; P. Ravaud, None; L. Mouthon, None; L. Guilllemin, None.

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Background/Purpose: ANCA-associated vasculitides (AAV) are rare, potentially fatal diseases with multiorgan involvement. Evidence for use of plasmapheresis (PLEX) in patients with severe forms of AAV is limited and its long-term benefits on mortality and renal outcome are still unclear. The aim of our study was to evaluate renal outcome and mortality in clinical ground of AAV patients undergoing PLEX.

Methods: Retrospective study of patients with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) and positivity for MPO or PR3-ANCA antibodies attended at our center from 2000 to 2012. In 25 patients, PLEX was added to conventional therapy (high-dose steroids plus one or more immunosuppressants); they were compared with 25 patients treated only with conventional therapy without PLEX, matched for age (≤ 7 years), activity of disease (BVAS/GW, range ≥ 6) and glomerular filtration rate (GFR) (MDR Death range ≥ 16 ml/min) at the time of intervention. Demographic data, comorbidities, clinical and laboratory characteristics were recorded. Outcome variables were mortality, dialysis dependence and GFR at 12 months. Statistics: Descriptive statistics, Student T-test, Mann-Whitney U-test, Chi-square, Fisher exact test, McNemar’s test and Kaplan-Meier survival analysis, log-rank test, p < 0.05.

Results: Patients were mainly female (56%) and GPA (78%), mean age 47 years and BVAS/GW of 13. The only basal differences between patients with and without PLEX were more positivity for anti-PR3 (p = 0.02), more frequency of methylprednisolone pulses ever (p = 0.002) and lower accrued doses of CYP (p = 0.01) in patients with PLEX. Main indication for PLEX was glomerulonephritis (96%).

At the time of intervention more patients in the PLEX group were on rituximab (p = 0.02) and received concomitant methylprednisolone pulses (p = 0.02) compared to patients without PLEX. At 12 months, both groups showed improvement in GFR before and after intervention (18.3±13.7 and 43.2±37.4 ml/min, p = 0.001 in PLEX group; 23.5±14.5 and 39.6±25.1 ml/min, p = 0.001 in conventional therapy group), but no difference was found between groups (p = 0.85). No
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Outcomes of Triple Therapy (Plasma Exchange, Cyclophosphamide and Systemic Corticosteroid) for Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis. Joanna Ueng1, Katerina Pavenski2 and Laurence Rubin3.

Background/Purpose: Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and Churg-Strauss Syndrome (CSS) are syndromes known as ANCA-associated vasculitis (AAV). In addition to immunosuppressive therapy, plasma exchange (PLEX) may be indicated in patients with pulmonary hemorrhage and/or severe renal insufficiency. However, PLEX may be associated with serious adverse effects such as infection. The objective of this study was to characterize and examine outcomes in patients with AAV treated with PLEX, in addition to corticosteroid and cytotoxic agents, at a major referral centre for PLEX.

Methods: A retrospective chart review was performed on all patients with AAV treated with PLEX at a major referral centre for PLEX between January 1, 2002 to May 31, 2012. Patients with GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitides were included while those with incomplete 3 and 12 month follow-up were excluded. Demographic, clinical, laboratory, and radiographic data from electronic and paper medical records were collected. Acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥2.5 umol/L within 48 hours, or a ≥1.5 times increase above baseline serum creatinine within 7 days. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) (v.3). Primary outcomes were survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months from initiation of PLEX. The study was approved by the institution’s Research Ethics Board.

Results: Forty-nine patients with AAV were treated with PLEX during the study period. Outcomes are reported for 43 patients, which excludes 4 patients lost to follow up and 2 patients with 3 and 12 month follow up that occurred outside the study period. 58% were male, and the median age was 59 years (range 25–83). This was the first presentation of AAV for 60% of patients. GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitides was the primary diagnosis in 39%, 28%, 0%, 5%, and 28% of patients. Both pulmonary hemorrhage and AKI were present in 66%. The mean BVAS (v.3) score at presentation was 17.9. Triple therapy with systemic corticosteroid, cyclophosphamide, and PLEX occurred in 90%. Survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months was 88%, 28%, and 37%, respectively. Renal recovery amongst those who were dialysis-dependent at presentation was 37% and 47% at 3 months and 1 year, respectively. Infection, bleeding (non-pulmonary hemorrhage), symptomatic hypotension, and catheter-related thrombosis occurred in 44%, 20%, 5%, and 2% of patients.

Conclusion: With triple therapy, 88% of patients with AAV survived at least 1 year. Almost 50% of patients who were dialysis-dependent on presentation experienced renal recovery after 1 year. An international randomized controlled trial is currently underway to investigate the specific role of PLEX in the treatment of AAV.

Disclosure: D. Solar-Cafaggi, None; Y. Atisha-Fregoso, None; A. Hinojosa-Azaola, None.
Long-Term Follow-up of Non-HBV Polyarteritis Nodosa and Microscopic Polyangiitis with Poor-Prognosis Factors.


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Background/Purpose: To study the long-term outcomes of 65 patients with non-HBV polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA) enrolled in a prospective, randomized, open-label trial,1 with Five-Factor Score (FFS)-defined poor-prognosis factors, focusing on survival, relapses, clinical and laboratory findings, therapeutic responses and sequelae.

Methods: Patients' data were updated in 2014. The new Chapel Hill criteria were applied to classify PAN and MPA. The following definitions were used: relapses; recurrence and/or new appearance of ≥1 vasculitis manifestation(s) after remission lasting ≥3 months; failure: no clinical remission with the assigned treatment. Times to relapse and/or death were calculated from treatment onset. For survival analyses, data were censored after 90 months of follow-up.

Results: Mean±SD overall follow-up was 65.6±47.5 months, comparable for PAN and MPA patients. For the 65 patients (41 MPA and 24 PAN), mean age at diagnosis was 55.3±17.0 years, mean Birmingham Vasculitis Activity Score 2003 23.7±8.8; FFS=1, 2 or >3 for 28, 30 or 8 patients, respectively: ANCA-positivity: 2 (8.3%) PAN (1 cANCA+ and 1 pANCA+), myeloperoxidase (MPO)- and proteinase-3 (PR3)-negative; and 34 (82.9%) MPA (pANCA+, 90.6% MPO-specific). Patients received 3 methylprednisolone pulses and corticosteroids (CS) and were randomized to receive 6 or 12 intravenous cyclophosphamide (CYC) pulses. After treatment, 53/65 (81.5%, 32 MPA and 21 PAN) entered remission. Treatment was intensified for the 12 nonresponders: 4 achieved remission and 8 died before remission. After remission, 25/57 (43.9%, 18 MPA, 7 PAN) patients relapsed 29.4±27.4 months after starting treatment. The respective 3-, 5- and 7-year overall survival rates were 79.5%, 72.3% and 64.4%, with no significant difference between PAN and MPA patients (p=0.241). Overall survival tended to be shorter for patients given 6 versus 12 CYC pulses (p=0.157). The respective 1-, 3- and 5-year relapse-free-survival rates were 84%, 68.4% and 52.4%, comparable for PAN and MPA patients. The relapse-free-survival difference between patients that received 6 versus 12 CYC pulses tended to decline during follow-up and was no longer significant at 90 months (p=0.07). At the last follow-up visit, 38/65 (58.5%) patients were still alive, 12/38 (31.6%) were still taking CS and 8/38 (21.1%) an immunosuppressant (IS). The mean vasculitis damage index score for the 57 patients with ≥1 remission(s) was 2.3±1.5, with the most frequent sequelae being hypertension (50%), chronic renal failure (creatininemia >150 μmol/L) (44.6%) and neuropathy (23.2%). Notably, 7 patients, all with MPA, progressed to end-stage renal failure and required chronic dialysis; 2 of them received kidney transplants.

Conclusions: For non-HBV PAN or MPA patients with FFS ≥1 at diagnosis, overall survival at 7 years reached 64%. Relapses were frequent during long-term follow-up, even for patients who had received 12 CYC pulses at diagnosis, thereby confirming that PAN and MPA patients with FFS ≥1 at diagnosis require post-remission maintenance therapy with an IS or biototherapy.

Reference:
strongly and independently with renal function at 1 and 5-years follow up.

**Objective:** The aim of this study was to determine whether the new histopathologic classification scheme is associated to changes in renal function and renal survival in a cohort of patients with ANCA associated vasculitis (AAV) who underwent kidney biopsy in a single center.

**Methods:** We included retrospectively all patients with diagnosis of ANCA GN between January 2002 and May 2013 and had at least 1 year of follow-up. Baseline date was defined as the date of the biopsy. Renal biopsies were reviewed and classified according to the new classification. Serum creatinine, estimated glomerular filtration rate (eGFR) at time of the biopsy, death, requirement of dialysis, use of immunosuppression and plasmapheresis at follow up were recorded.

**Results:** Forty-four patients (77.2% females) were included (table 1). The mean age was 63.7 (SD: 17.5). 25 (56.8%) patients were pANCA positive, 14 (31.8%) cANCA positive, and 5 (11.3%) were ANCA negative. Four patients died during first year of follow up (1 within each biopsy category). Among surviving patients, overall mean improvement in eGFR at 1 year was 13.2-ml/min/1.73 m². Age and sex were not significantly associated with the 1-year eGFR change. There was a significant difference in the mean change in eGFR at 1 year based on the histopathologic class (table 2). Focal biopsies were associated with the highest eGFR at presentation, whereas crescentic, mixed and sclerotic were associated with lower eGFRe. Crescentic class was associated with the greatest 1-year improvement in eGFR while sclerotic class in eGFR at 1 year based on the histopathologic clas (table 2). Focal biopsies were associated with the highest eGFR at presentation, whereas crescentic, mixed and sclerotic were associated with lower eGFRe.

**Conclusion:** Our study shows association between crescentic class and improvement in eGFR and association between sclerotic class and reduction in eGFR at 1-year. These results support the use of the histopathologic classification in determining renal prognosis of patients with ANCA GN.

**TABLE 1**

<table>
<thead>
<tr>
<th>Focal</th>
<th>Crescentic</th>
<th>Mixed</th>
<th>Sclerotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>68.5 (15.4)</td>
<td>54.0 (16.9)</td>
<td>69.2 (15.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (90)</td>
<td>9 (64.2)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²), mean</td>
<td>14.9 (12-78)</td>
<td>13.6 (9-17)</td>
<td>33.4 (20-53)</td>
</tr>
<tr>
<td>Baseline eGFR category (mL/min/1.73 m²), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90</td>
<td>2 (18)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>60-69</td>
<td>3 (27)</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>30-59</td>
<td>2 (18)</td>
<td>0 (0)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>15-29</td>
<td>2 (18)</td>
<td>0 (0)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>A NCA immunofluorescence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cANCA</td>
<td>4 (36)</td>
<td>6 (43)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>pANCA</td>
<td>6 (55)</td>
<td>7 (50)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Both negative</td>
<td>1 (9)</td>
<td>1 (7)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>BVAS at diagnosis, mean (SD)</td>
<td>14.8 (5.5)</td>
<td>16.7 (3.7)</td>
<td>13.4 (5.4)</td>
</tr>
<tr>
<td>Treatments, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>8 (66)</td>
<td>14 (100)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9 (82)</td>
<td>13 (93)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1 (9)</td>
<td>5 (36)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dialysis at diagnosis, n (%)</td>
<td>1 (9)</td>
<td>4 (29)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Dialysis at 1 year, n (%)</td>
<td>0 (0)</td>
<td>1 (7.4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Histologic class</th>
<th>n</th>
<th>Basal mean eGFR (mL/min/1.73 m²), mean</th>
<th>1 year mean eGFR (mL/min/1.73 m²), mean</th>
<th>Delta mean eGFR improvement (year-basal)</th>
<th>Death within 1 year, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>11</td>
<td>46.9</td>
<td>57.1</td>
<td>5.2*</td>
<td>1 (9.0)</td>
</tr>
<tr>
<td>Crescentic</td>
<td>14</td>
<td>49.7</td>
<td>35.2*</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>15</td>
<td>33.3</td>
<td>46.7</td>
<td>12.1#</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>4</td>
<td>13.4</td>
<td>12.1</td>
<td>1.5</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

* p = 0.008; # p = 0.026.

**Disclosure:** V. Scaglioni, None; M. Scolini, None; L. J. Catoggio, None; C. F. Varela, None; G. Greloni, None; S. Christiansen, None; E. R. Soriano, None.

**Background/Purpose:** Many patients with interstitial lung disease (ILD) complicated by microscopic polyangiitis (MPA) show a UIP pattern on chest CT. The prognosis is poorer than that of ILD-free MPA. However, the details remain to be clarified.

**Methods:** Of patients with MPA who were admitted to our hospital between 2003 and 2013 based on the EMEA classification in 2007, the subjects were MPO-ANCA-positive patients with ILD on HRCT. Using the clinical data and fibrosis score on HRCT (2), we examined prognostic factors.

**Results:** There were 42 patients with MPA-ILD, consisting of 20 males and 22 females, with a median age (interquartile range) of 73 years (range: 69–76 years). The MPO-ANCA, KL-6, Aa-D-DO2, %FVC, %DLco/VA, and RV/TLC values at the start of treatment were 189 (52–459) EU, 46.4 (261–615) mL/min, 25.7 (12–34), 83.3 (69–95), 81.4 (45–71), and 41.1 (33–50), respectively. Concerning HRCT images, 30 patients showed a UIP pattern, and 12 showed a non-UIP pattern. PSL was administered to 41 patients. In 37, it was combined with immunosuppressive drugs (CY was used in 16). In 8, apheresis was performed. In 37 patients, the MPO-ANCA level was maintained below the detection limit.

**Conclusion:** Treatment for MPA-ILD was continued, and the prognosis was more favorable than previously reported. Marked fibrosis and CPFE at the start of treatment were considered to be prognostic factors for lung disease-associated death. Immunosuppressive therapy early after onset may improve the prognosis of MPA-ILD.

**Disclosure:** T. Shoda, None; T. Takeuchi, None; T. Ishida, None; H. Shiba, None; Y. Fujiki, None; D. Wakura, None; S. Yoshida, None; T. Kotani, None; S. Makino, None; T. Hanafusa, None.

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**Survival of Microscopic Polyangiitis (MPA) Patients with and without Pulmonary Fibrosis (PF).** Lina María Saldarriaga Rivera, Natelly Reyes Ruiz and Luis F. Flores-Suarez. Instituto Nacional de Enfermedades Respiratorias, Mexico City, M exico.

**Background/Purpose:** Pulmonary fibrosis (PF) occurs in up to 30% of patients with microscopic polyangiitis (MPA). Data suggest PF implies a higher mortality. We examined the survival of our MPA patients according to the presence or absence of PF.

**Methods:** Retrospective analysis of all MPA patients present in a single respiratory referral centre from 2003-present. All patients were defined according to the ChiCC 2012 Nomenclature. Univariate analysis was used to establish proportions with means ± SD and medians calculated; bivariate analysis was used to compare groups. Student’s t test for continuous variables and X² test with Yates correction for categorical variables. Kaplan-Meier analysis was done for survival. Significance was established when p < 0.05.

**Results:** From 37 MPA patients (35 MPO-ANCA positive, 2 PR-3-ANA positive), the majority were females (67.5%); 15/37 (40.5%) had PF with microscopic polyangiitis (MPA). Data suggest PF implies a higher mortality. We examined the survival of our MPA patients according to the presence or absence of PF.

**Disclosures:** T. Shoda, None; T. Takeuchi, None; T. Ishida, None; H. Shiba, None; Y. Fujiki, None; D. Wakura, None; S. Yoshida, None; T. Kotani, None; S. Makino, None; T. Hanafusa, None.

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tory failure (6.7% vs. 36.7%) and lymphopenia (0 vs. 22.7%) were less frequent (all significant). Lung hemorrhage was more frequent in those without PF (68.2% vs 33.3%, p=0.08). No other significant differences in clinical or paraclinical variables were seen, being similar at disease onset in both groups. There were 6 deaths, 5 with and 1 without PF; 1 lost to follow-up patient without PF was censored as death for survival analysis. By 41 months, there is a trend for a better cumulative survival in patients without PF (88 vs 70%) (graph), irrespective of PF being present at onset or during disease evolution.

Conclusion: While we acknowledge the limitations of this study (sample size, need of longer follow-up), it suggests that patients with MPA and PF have a worse outcome than those without PF, even when patients without PF presented with more severe manifestations (respiratory failure, lung hemorrhage, renal symptoms). Interestingly the majority of these patients had PF antedating other MPA manifestations, probably due to referral bias. The influence of this mode of presentation and other factors in outcome is subject to further evaluation.

Disclosure: L. M. Saldarriaga Rivera, None; N. Ruiz, None; L. F. Flores-Suarez, None.

Vasculitis As Underlying Cause of Death in the United States: 1999 - 2010

Background/Purpose: Current data on mortality rates of primary vasculitides are inadequately associated with a dreadful prognosis, are limited. Therefore, we aimed to estimate the mortality rates of the main primary vasculitides disorders using the most current publicly available mortality data in the USA.

Methods: To obtain mortality rates of vasculitides as the underlying cause of death, we used the CDC Wonder Underlying Cause of Death database and its query system, which contains data from 1999 to 2010. We used the following ICD-10 codes for the queries: D61.0 (Allergic purpura for Henoch-Schönlein purpura, D89.1 (Cryoglobulinemia), M30.0 (Polyarteritis nodosa), M30.1 (Polyarteritis with lung involvement [Churg-Strauss]) for eosinophilic granulomatosis with polyangiitis, M30.3 (Mucocutaneous lymph node syndrome [Kawasaki]), M31.0 (Hypersensitivity angitis) for Goodpasture’s syndrome, M31.3 (Wegener’s granulomatosis) for granulomatosis with polyangiitis (GPA), M31.4 (Aortic arch syndrome [Takayasu]), M31.5 (Giant cell arteritis [GCA] with polymyalgia rheumatica [PM R]) and M31.6 (Other giant cell arteritis) for GCA, M31.7 (Microscopic polyangiitis), and M35.2 (Behcet’s disease). Results were obtained by year, gender, and race. To obtain age-adjusted mortality rates we used year 2000 U.S. standard population.

Mortality rates are given as number of deaths per million. Mantel-Haenszel chi-square was used to analyze trends.

Results: During the twelve-year period, vasculitis was the underlying cause of death of 7,888 patients. Age-adjusted mortality rate was 2.22 per million (95% CI: 2.17–2.27). There were more deaths in females (4,412) than in males (3,476), but the age-adjusted mortality rate was higher in males than in females (2.28 vs 2.16 per million). Age-adjusted mortality rate was clearly higher in Whites (2.34, 2.28–2.39) than in Black/African American populations (1.16, 1.08–1.31). Regarding disease-specific mortality, GPA counted for 51.2% of all vasculitis deaths. Interestingly, there were no deaths for GCA with PMR. Year 2000 showed the highest mortality (2.58, 2.40–2.77), whereas the lowest level was seen in 2008 (1.79, 1.64–1.94). Since 1999, there has been a significant trend to the decrease (p<0.0001).

Conclusion: The most current public data indicates that mortality by vasculitis remains very low, which is clearly related to the low incidence of these disorders. Age-adjusted mortality rate was higher in males than in White, which can be explained by the fact that GPA, which is more frequent in males and White, is responsible for half of the overall number of deaths. There is a clear trend to a progressive decrease of the mortality rates by primary vasculitis over the 12-year period of the study. Recent introduction of biological treatments, less toxic therapeutic regimens, such as shortening cyclophosphamide treatment, earlier diagnosis as a result of higher awareness and improved diagnostic tools may have contributed to this decrease in mortality rates. Our findings should be taken with caution until quality studies to determine the reliability of the data about these rare diseases available in national databases are performed.

Disclosure: A. Rodriguez-Pla, None; P. A. Monach, None; J. Rosello-Urgell, None.

HLA-DRB1*01 Is Associated with Henoch-Shönlein Purpura in the Spanish Population

Background/Purpose: Henoch-Schönlein purpura (HSP) is essentially a childhood disease, being the most common type of vasculitis in children and an infrequent condition in adults. An increased familial occurrence supports a genetic predisposition for this vasculitis. In this context, the role of the HLA (human leukocyte antigen) region in the HSP pathogenesis has previously been studied. However, data reported so far on the potential association of HSP with HLA-DRB1 alleles are scarce and they were generally the result of small series of HSP patients with often contradictory results. To further investigate whether HLA-DRB1 alleles are implicated in the susceptibility and severity of HSP, we performed a study that encompassed the largest series of HSP patients ever assessed for genetic studies in Caucasian individuals.

Methods: Our study population included 279 Spanish patients diagnosed with HSP and 335 sex and ethnic matched controls. HSP patients fulfilling the American College of Rheumatology (Arthritis Rheum 1990; 33: 1114–21) and the Michel et al (J Rheumatol 1992; 19: 721–8) classification criteria were recruited from Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario La Princesa (Madrid), Hospital Universitario San Cecilio (Granada) and Hospital Universitario Virgen del Rocío, Seville, Spain. HLA typing was performed with the sequence specific primers (SSP-PCR) method following standard protocols.

Results: Of the 138 HLA-DRB1 alleles identified, the most frequent was HLA-DRB1*04 (46.2%), followed by HLA-DRB1*01 (27.5%) and HLA-DRB1*15 (12.7%) in HSP patients. In controls, the most frequent was HLA-DRB1*04 (38.4%), followed by HLA-DRB1*01 (27.6%) and HLA-DRB1*15 (12.7%). The frequency of HLA-DRB1*01 was significantly increased in HSP patients compared to controls (OR: 1.44, 95% CI: 1.02–2.05) and the frequency of HLA-DRB1*04 was significantly decreased in HSP patients compared to controls (OR: 0.60, 95% CI: 0.40–0.90). These results were confirmed by the unconditional logistic regression analysis. Additionally, the frequency of HLA-DRB1*15 was significantly increased in HSP patients compared to controls (OR: 1.66, 95% CI: 1.12–2.47). These results were confirmed by the unconditional logistic regression analysis.

Conclusion: HLA-DRB1*01 is associated with HSP in the Spanish population. Further studies are warranted to address the functional significance of these observations.
Universitario de Basurto (Bilbao). HLA-DRB1 phenotypes were determined using PCR-SSOP Luminex.

Results: After adjusting the results for multiple testing corrections, we disclosed a statistically significant increased frequency of HLA-DRB1*01 in HSP patients compared to controls (p<0.001, OR = 3.98 [95% CI: 2.68–5.95]). In contrast, a significantly decreased frequency of HLA-DRB1*03 was observed in HSP patients compared to controls (p<0.001, OR = 0.18 [95% CI: 0.085–0.37]). When patients were stratified according to the presence of nephritis or gastrointestinal manifestations, we disclosed that although no specific HLA-DRB1 association with nephritis was observed, HLA-DRB1*07 was significantly reduced in the group of HSP patients who experienced gastrointestinal manifestations (p=0.0011, OR = 0.36 [95% CI: 0.19–0.71]) even after adjusting the results for multiple testing correction (p=0.012).

Conclusion: Our study supports an association of HSP with HLA-DRB1*01. In contrast, a protective effect against the development of HSP was observed in individuals carrying the HLA-DRB1*03 allele. HLA-DRB1*07 exerts a protective effect against the development of gastrointestinal manifestations in patients with HSP.

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Association of HLA-B*41 with Hench-Schönlein Purpura in Spanish Individuals Irrespective of the HLA-DRB1 Status. Fernanda Genre1, Raquel López-Mejías2, Belén Sevilla Pérez3, Santos Castañeda4, Norberto Ortego-Centeno5, Javier Llorca2, Begoña Ubilla2, Trinitario Pina Murcia6, Vanessa Calvo-Río7, Ana Márquez8, Luis Sala-Icardo9, Jose A. Miranda-Filloy10, Marta Conde-Jaldoñ11, Lourdes Ortiz-Fernández12, Juan María Blanco-Madrigal13, Eva Galindez-Agirregoikoa14, Francisca González-Escribano15, Javier Martín16, Ricardo Blanco17 and MA González-Gay.18

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Are EULAR/Printo/Pres Classification Criteria Appropriate for Classification of IgA Vasculitis in Adults? Alajosa Hocevar2, Zipa Rota3, Vesna Juric4, Joze Pizem5, Sasa Cunic6, Alenka Vizjak7 and Matija Tomsic8. 1University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, 2University Medical Centre Ljubljana, Ljubljana, Slovenia, 3University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, 4BioRx.si, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: In 2010 EULAR/PRINTO/PRES proposed new classification criteria for pediatric IgA vasculitis (IgAV). In pediatric population these criteria have a higher diagnostic sensitivity than the 1990 American College of Rheumatology (ACR) criteria, while they have thus far not been evaluated in adults. Our main objective was to compare the diagnostic sensitivity of the EULAR/PRINTO/PRES and ACR classification criteria in adult IgAV.

Methods: Adult IgA V cases fulfilling the 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides definition of IgA V at a secondary/tertiary rheumatology referral center were critically reviewed in partially retrospective (from January 1, 2010 to December 31, 2012) and partially prospective (from January 1, 2013 to April 30, 2014) manner and we assessed whether these patients also fulfilled either the ACR or EULAR/PRINTO/Pres criteria. Biopsy samples were retrieved from the archive and were reevaluated by two pathologists.

Results: Between January 1, 2010 and April 30, 2014 (52 months observation period) 100 consecutive new adult IgAV cases fulfilling the CHCC Nomenclature of Vasculitides definition of IgA V were identified. There were 60 males and 40 females. Median age was 63.2 years (range 18–92, interquartile range (IQR) 40.1–77.2). 4/100 patients were ≤ 20 years old at disease presentation. The mean symptom duration was 14 days (range 1–150). Purpura was present in all cases, necrotic in 46/100 and bullous in 11/100 cases. Joints (arthralgia or arthritis) involved in 49/100, gastro-intestinal tract in 38/100, and kidneys in 58/100 patients. General symptoms were present in 18/100 cases. In all patients IgA deposition in vessel walls was documented on direct immunofluorescence staining. Leucocytoclastic vasculitis was observed in 97/100 cases. Granulocytes in vessel wall were found in 85/100 cases. The diagnostic sensitivity of the EULAR/PRINTO/Pres classification criteria was 100 %, and 90 % for the ACR classification criteria (Figure 1).
Background/Purpose: In our population IgA vasculitis (IgAV) has an annual incidence rate of 5.1 cases per 10^5 adults increasing with patients’ age which makes it by no means uncommon contrary to common belief. Little data is available in the literature about the clinical picture and prognosis of adult IgAV. A valuable data is most often limited to adult IgAV cases with kidney disease. Our aim was to determine short-term outcomes in an unselected adult IgAV population diagnosed at a single secondary/tertiary rheumatology center.

Methods: We performed an electronic and paper chart review of all adult IgAV cases, diagnosed in our center between January 1, 2010 and December 31, 2013. A descriptive statisticial methods and post hoc tests were used describe our cohort (e.g. Mann-Whitney test, Fisher exact test).

Results: During the observation period 96 new adult IgAV cases were identified. Clinical characteristics at presentation are shown in Table 1. Disease severity was higher in males (median BVAS3 13 vs. 9, p = 0.027), and in patients with generalized purpura in contrast to purpura limited to lower limbs (median BVAS3 14 vs. 9, p = 0.014). Treatment of IgAV consisted of systemic glucocorticoids (oral 67/96; additional i.v. metil prednisolone pulses 13/96), intravenous cyclophosphamide (9/96), hyperimmune gammaglobulins (4/96), plasma exchange (2/96) and mycophenolate mofetil (1/96). During acute phase of the disease 9/96 patients died. Two deaths were attributed to vasculitis (intractable GI hemorrhage in the first, and alveolar hemorrhage in the second patient), while one succumbed following generalized CMV infection and heart failure attributable to immunosuppressive treatment. 18/93 (19.4%) survivors were lost to follow up. The remaining 75/93 (80.6%) patients were followed for a median of 8.4 (IQR 4.8-19.2) months. IgAV relapsed in 13/75 cases (one, two and three times in 8/75, 4/75 and 1/75 cases, respectively). 8/13 (62.7%) patients had a single organ, and 5/13 a multi-organ relapse. Skin was involved in 11, joints in 3, GI tract in 2, and kidney in 2 cases. At last visit renal function abnormalities were present in 13/68 patients. 13/68 had microhamaturia (1+; 2+; 3+ in 6, 3 and 4 cases, respectively); 4/68 had mild proteinuria and 1 patient had proteinuria >1 g per day. Renal function remained stable in 67/68, and worsened in 1/68 case. 7/75 (9.3%) patients died during follow up (cause of death: infection 2; cardiovascular disease 4; unknown 1). In 2/68 survivors malignancy was diagnosed (1 hematologic; 1 teratoma).

Table 1. Clinical characteristics of IgAV patients at presentation and at last follow-up

<table>
<thead>
<tr>
<th>Clinical characteristic of IgAV</th>
<th>at presentation N=96</th>
<th>at last follow-up visit N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>% male</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Age (median; IQR)</td>
<td>63.4 (40.8-77.3)</td>
<td>/</td>
</tr>
<tr>
<td>Purpura (%)</td>
<td>96 (100)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>necrotic (%)</td>
<td>43 (44.8)</td>
<td>0</td>
</tr>
<tr>
<td>Joint involvement (%)</td>
<td>44 (45.8%)</td>
<td>0</td>
</tr>
<tr>
<td>arthralgia (%)</td>
<td>21 (42.7)</td>
<td>0</td>
</tr>
<tr>
<td>arthritis (%)</td>
<td>41 (21.9)</td>
<td>0</td>
</tr>
<tr>
<td>GI tract involvement (%)</td>
<td>38 (36.4)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Kidney involvement (%)</td>
<td>56 (58.3)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>nephritic or nephrotic syndrome (%)</td>
<td>10 (10.4)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>BVAS3 (median; IQR)</td>
<td>12 (6-17)</td>
<td>3 (1-3)*</td>
</tr>
</tbody>
</table>

*patients in remission not included

Legend: GI gastrointestinal tract

Conclusion: Our findings suggest that even in short-term IgAV might not be as benign as perceived thus far. From our data it is impossible to conclude whether this is due to the nature of the IgAV or due to the fact that IgAV seems to be more common in older adults, who also have more comorbidities.

Disclosure A. Hocevar, None; Z. Rotar, None; J. Ostrovrsnik, None; M. Tomsic, None.

1791

Applicability of the 2006 European League Against Rheumatism (EULAR) Criteria for the Classification of Henoch-Schönlein Purpura. An Analysis Based on 766 Patients with Cutaneous Vasculitis. M ontserrat Santos-Gomez1, Francisco Ortiz Sanjuan1, Jose L. Hernandez2, Marcos A. Gonzalez-Lopez2, Ricardo Blanco3, Javier Loricera3, Vanessa Calvo-Rio1, Trinitario Pina Murcia2, Carmen Gonzalez-Vela3, Marina Lacalle1,1 Javier Rueda-Gotor1, Lino Alvarez4, Lourdes Riano-Zarabal5 and Miguel A. Gonzalez-Gay3. 1Hospital Universitario Marques de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, 2Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander. Spain.
Background/Purpose: The European League Against Rheumatism (EULAR) proposed in 2006 a new classification criteria for Henoch-Schönlein Purpura (HSP). We aimed to establish the applicability of these criteria in patients with primary cutaneous vasculitis (CV). We also compared these criteria with previously established classification criteria for HSP.

Methods: A series of 766 (346 women/420 men; mean age 34 years) consecutive unselected patients with CV was assessed. Of them, 124 with secondary CV or with CV associated to other well defined entities were excluded. The 2006 EULAR criteria were also used for comparisons: a) the 1990 American College of Rheumatology (Arthritis Rheum 1990; 33: 1114–21), and b) the ACR-modified criteria proposed by Michel et al. in 1992 (J Rheumatol 1992; 19: 721–8).

Results: 451 (70.2%) of 642 patients were classified as having HSP according to the EULAR-2006 criteria, 405 (63.1%) using the ACR-1990 criteria, and 392 (61.1%) by the Michel-1992 criteria. However, only 336 patients (52.3%) met at the same time the EULAR-2006 and the ACR-1990 criteria, and only 229 patients (35.7%) fulfilled both the EULAR-2006 and Michel et al criteria. Noteworthy, only 276 (43%) patients met the three sets of criteria. Children fulfilled all the sets of criteria more commonly than adults (215 [66.6%] of 323 versus 61 [19%] of 319 respectively; p < 0.0001).

Conclusion: Aiming to our results, the EULAR-2006 criteria show a poor concordance with previous sets of classification criteria for HSP.

Disclosure: M. Sants-Gómez, None; F. Ortiz Sanjuan, None; J. L. Hernández, None; M. A. González-López, None; R. Blanco, None; J. Loricer, None; V. Calvo-Rio, None; T. Pina Murcia, None; C. Gonzalez-Vela, None; M. Lacalle, None; J. Rueda-Gotor, None; L. Alvarez, None; L. Riano-Zarrabetia, None; M. A. González-Gay, None.

1792
Clinical-Biological and Pathological Spectrum and Outcome of IgA Vasculitis in Adults. Alexandre Audemard1, Evangeline Pillebout2, Patrice Cacoub3, Noémie Jourde-Chiche4, Zahir Amoura2, Noémie Le Gouellec5, Francois Maurier6, Boris Bienvenu7, Geoffrey Urbanski8, Sébastien Sanges9, Aurélie Hummel10, Alain Derouz11, Loïc Rafay12, Luc Mouthe12, Luc Guéguin for the French Vasculitis Study Group13, Éric Thervet14 and Benjamin Terrier15.1Centre Hospitalier Universitaire de Caen, Caen, France, 2Saint Louis, Paris, France, 3Groupe Hospitalier Pitié Salpêtrière, Service de Médecine Interne, DHU 128, Paris, France, 4CHU, Marseille, France, 5Pitié-Salpêtrière Hospital (A-PH), Paris, France, 6Internal Medicine, Lille, France, 7Department of Internal Medicine, Montpellier, France, 8CHU Coët Quinic, CHU Lille, France, 9Necker Hospital, Paris, France, 10CHU Grenoble, Grenoble, France, 11Internal Medicine, Bordeaux, France, 12National Reference Center for Rare Systemic Autoimmune Diseases, hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, 13Hôpital Européen Georges Pompidou, APHP, PARIS, France, 14Cochin Hospital, Paris, France.

Background/Purpose: IgA vasculitis is an immune-complex small-vessel vasculitis that mainly affects children and, more rarely, adults, in whom it seems to be more severe, because of gastrointestinal and renal involvement. Data on therapeutic management are lacking. The IGAVAS study was designed to describe IgA-vasculitis presentation and evaluate treatment efficacy. Here, we characterize its presentation and outcome.

Methods: Retrospective, single-center cohort study in patients with IgA vasculitis (according to ACR criteria), who were insufficiently controlled with CS and other immunosuppressant therapies (AZA, MTX, MMF). Patients were treated with Peg-IFN-alpha2b (3.9 million units per week) for induction and maintenance of remission. Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0. After achieving remission, time to first relapse and total occurrence of relapses were recorded. Patients received lung-functioning tests before treatment and at time of remission. A diverse events were recorded.

Results: 25 patients, age of 50 ± 9.5 years were evaluated for induction of remission and in 21 patients IFN was continued for maintenance of remission. Five-factor-score (FFS) at initiation of treatment was 0 in 18 (72%) and 1 in 7 (28%) in patients. Mean BVAS at initiation of treatment was 8.3 ± 2.2. Previous therapies were CYC (N = 4), AZA (N = 4), Omalizumab (N = MTX (N = 1), MMF (N = 1), MMF (N = 1), MMF (N = 1). Treatment was discontinued in 18 of 25 (72%) patients and 7 (28%) were still on IFN after a mean time of treatment of 31 (2131) months. Of 25 patients, 21 (84%) achieved remission and mean time to remission was 5 (312) months. CS were tapered from 18.75 (5–50) mg per day to 5 (0–30) mg per day at time of remission (p < 0.0001).

Conclusion: IFN is effective in both induction of remission and maintenance of remission while depression is the main side effect that limits therapy. As IFN showed good effect on CS-tapering and on asthma in particular, it can be considered as an alternate treatment in EGPA patients without life- or organ-threatening manifestations.

Disclosure: B. Seeliger, None; M. Foerster, None; A. Meoer, None; J. Happe, None; C. Kroegel, None; T. Neumann, None.

1793
Efficacy and Safety of IFN-Alpha in Induction and Maintenance of Remission in Patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA). Single-Center Observational Study. Benjamin terrier1, Martin Foerster1, Anne Meoer2, Janet Happe3, Claus Kroegel1 and Thomas Maurer2.1) University Hospital Internal Medicine I, Jena, Germany, 2) University Hospital Internal Medicine III, Jena, Germany.

Background/Purpose: To evaluate the efficiency and safety of IFN-alfa in induction and maintenance of remission in patients with EGPA and to describe its effects on lung function tests and corticosteroid (CS) tapering.

Methods: A retrospective, single-center cohort study in patients with EGPA (according to ACR criteria), who were insufficiently controlled with CS and other immunosuppressant therapies (AZA, MTX, MMF). Patients were treated with Peg-IFN-alpha2b (3.9 μg per week) for induction and maintenance of remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0. After achieving remission, time to first relapse and total occurrence of relapses were recorded. Patients received lung-functioning tests before treatment and at time of remission. A diverse events were recorded.

Results: 25 patients, age of 50 ± 9.5 years were evaluated for induction of remission and in 21 patients IFN was continued for maintenance of remission. Five-factor-score (FFS) at initiation of treatment was 0 in 18 (72%) and 1 in 7 (28%) in patients. Mean BVAS at initiation of treatment was 8.3 ± 2.2. Previous therapies were CYC (N = 4), AZA (N = 4), Omalizumab (N = MTX (N = 1), MMF (N = 1), MMF (N = 1). Treatment was discontinued in 18 of 25 (72%) patients and 7 (28%) were still on IFN after a mean time of treatment of 31 (2131) months. Of 25 patients, 21 (84%) achieved remission and mean time to remission was 5 (312) months. CS were tapered from 18.75 (5–50) mg per day to 5 (0–30) mg per day at time of remission (p < 0.0001).

Conclusion: IFN is effective in both induction of remission and maintenance of remission while depression is the main side effect that limits therapy. As IFN showed good effect on CS-tapering and on asthma in particular, it can be considered as an alternate treatment in EGPA patients without life- or organ-threatening manifestations.

Disclosure: A. Audemard, None; E. Pillebout, None; P. Cacoub, A. Zoneca, B. Boehringer Ingelheim, Gilead, Glaxo Smith Kline, Jansen, Merck Sharp Dohme, Roche, Servier, Vifor, N. J. Jourde-Chiche, None; Z. Amoura, None; F. Maurier, None; B. Bienvenu, None; G. Urbanski, None; S. Sanges, None; A. Hummel, None; A. Derouz, None; L. Raffray, None; L. Mouton, None; L. Guéguin for the French Vasculitis Study Group, None; É. Thervet, None; B. Terrier, None.

S787
ACR Plenary Session II: Discovery 2014
Monday, November 17, 2014, 11:00 AM – 12:30 PM

1794
The Sting Pathway Regulates Bone Remodeling in a Model of Autoimmune Disease. Rebecca Baum1, Jason M. Organ2, David B. Burr3, Ann M. Marshak-Rothstein4, Katharine A. Fitzgerald4 and Ellen M. Gravallese5.

1. University of Massachusetts Medical School, Worcester, MA; 2. Indiana University School of Medicine, Indianapolis, IN; 3. Indiana University School of Medicine, Indianapolis, IN, 4. UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Cytosolic DNA sensors detect viral and bacterial DNA, inducing inflammatory cytokines and type I IFNs via the adaptor stimulator of interferon genes (STING) to clear infection. The STING pathway also responds to endogenous DNA from dying cells and contributes to autoimmune disease. We have identified a potentially important role for cytosolic DNA sensor pathways in bone by studying a mouse that develops inflammatory polyarthritis and arthritic erosions in the setting of DNA accrual. In this model, DNA accumulates in macrophages due to deletion of the lysosomal endonuclease DNaseI and is detected by cytosolic sensors that signal through STING. Type I IFNs in DNaseI−/− mice lead to aemia-related embryonic lethality; thus co-deletion of the type I IFN receptor is required (DNaseI/IFN-IR double deficient, (DKO) mouse). We investigated the impact of DNA and of the STING pathway in bone in this model of autoimmune disease.

Methods: STING−/− mice were intercrossed with DKO mice to generate STING/DNaseI/IFN-IR triple knock out (TKO) mice. uCT was performed on TKO, DKO, and control femurs from 6-16 month-old mice. Mesenchymal colony forming unit (CFU) assays were used to determine the number of osteoblast precursor cells in bone. uCT was performed on femurs from 6 month-old STING−/− and littermate controls. Finally, RNA from wild type (WT) osteoblasts was analyzed for the expression of cytosolic DNA sensors. To determine the potential for osteoblasts to respond directly to DNA, MC3T3 osteoblast-lineage cells were transfected with poly(dA:dT) and RNA was analyzed by qPCR.

Results: Inflammatory cytokines in the DKO model would be expected to induce bone loss in the axial skeleton, as well as articular erosions. Paradoxically, we found that bone accumulates in long bones, with significant replacement of the marrow cavity by 16 months. CFU assays demonstrate increased osteoblast precursor numbers and osteoid is also significantly increased in DKO compared to controls (13,881 vs. 424 μm², p=0.02). Surprisingly, ectopic bone forms in DKO spleens, a site of DNA accumulation in macrophages. We thus sought to define the contribution of cytosolic DNA sensor pathways to bone accrual. STING deficiency almost completely abrogates both arthritis and bone accrual in the spleen and long bones of DKO mice (BV/TV: Het = 0.44%, DKO = 114.7%, TKO = 1.99%, p=0.02 compared to DKO). STING also contributes to bone homeostasis in independent of DSAl deficiency, as revealed by uCT performed on femurs from STING−/− and littermate controls (BV/TV: STING−/− = 1.39%, WT = 0.62%, p=0.011). Furthermore, cytosolic DNA sensors are expressed in osteoblasts and expression of several sensors is increased in osteoblasts upon transfection with a DNA ligand.

Conclusion: The STING pathway plays a role in bone remodeling in situations of DNA accrual as well as in bone homeostasis. Cytosolic DNA sensors are expressed in differentiating osteoblasts and expression is upregulated by DNA. These findings have relevance to SLE and other autoimmune diseases in which DNA plays a pathogenic role. Discovery of new pathways linking bone and the immune system may identify new targets for the treatment of bone loss in inflammatory autoimmune diseases.

Disclosure: R. Baum, None; J. M. Organ, None; D. B. Burr, None; A. Marshak-Rothstein, None; K. A. Fitzgerald, None; E. M. Gravallese, AbbVie, 2, Eli Lilly and Company, 2.

1795
Denosumab Restores Cortical Bone Loss at the Distal Radius Associated with Aging and Reduces Wrist Fracture Risk. Analyses from the Denosumab Restores Cortical Bone Loss at the Distal Radius Associated with Aging and Reduces Wrist Fracture Risk. Analyses from the Extension of Denosumab Pivotal Fracture Trial. JP Bilezikian1, CL Benhamou2, CJF Lin3, JP Brown4, NS Daizadeh5, PR Ebeling6, A Fahrleitner-Pammer7, E Franek7, N Gilchrist8, PD Miller9, JA Simon10, I Valtair11, CAF Zerbin12 and C Libanati13, 1College of Physicians and Surgeons, Columbia University, New York, NY, 2CHR d’Orléans, Orléans, France, 3Amgen Inc., Thousand Oaks, CA, 4CHU de Quebec Research Centre and Laval University, Quebec City, QC, 5onash University, Clayton, Australia, 6Medical University, Graz, Austria, 7Medical Research Center, Polish Academy of Sciences, Warsaw, Poland, 8The Princess Margaret Hospital, Christchurch, New Zealand, 9Colorado Center for Bone Research, Lakewood, CO, 10George Washington University, Washington, DC, 11Center for Clinical and Basic Research, Tallinn, Estonia, 12Centro Paulista de Investigação Clínica, São Paulo, Brazil.

Background/Purpose: Cortical bone loss is a major determinant of increased fracture risk. Denosumab (DMAb) has been shown to increase BMD at sites of cortical bone, including the radius, a skeletal site not responsive to most osteoporosis treatments. Here, we evaluated changes over time in radius BMD and wrist fracture incidence during 3 years of placebo (Pbo) and up to 5 subsequent years of DMAb therapy in FREEDOM and its Extension (EXT).

Methods: We evaluated 2207 women who received Pbo during FREEDOM (3 years) and enrolled in the EXT to receive DMAb 60 mg Q6M (cross-over group); all women received daily calcium and vitamin D. A subset of these women (n=115) participated in a distal radius DXA substudy and were evaluated at baseline and during FREEDOM and EXT. Analysis of mean percentage changes in BMD over time from FREEDOM and EXT baselines consisted of a repeated measure model. Wrist fracture rates (per 100 subject-years), rate ratios, and 95% CI were computed.

Results: At FREEDOM baseline, the mean (SD) 1/3 radius T-score was -2.53 (1.18). During FREEDOM, daily calcium and vitamin D alone was associated with a progressive and significant loss of BMD at the 1/3 radius (-1.2%); however, during EXT, DMAb halted and reversed bone loss (Figure). With 5 years of DMAb treatment, a significant gain in BMD (1.5% at EXT Yr 5) was observed, compared with EXT baseline. The wrist fracture rate during the Pbo period in FREEDOM was 1.02 (0.80-1.29) per 100 subject-years. During the first 3 years of EXT, BMD recovered to the original baseline levels in response to DMAb and the wrist fracture rate remained comparable to the FREEDOM Pbo rate (Table); with 2 additional years of DMAb treatment, BMD increased further and the wrist fracture rate declined to levels significantly lower than the FREEDOM Pbo rate (rate ratio = 0.57, 95% CI = 0.34-0.95; p=0.03).

Conclusion: In untreated women with postmenopausal osteoporosis, cortical bone density at the radius declined significantly. DMAb treatment for 3 years fully reversed this bone loss, and 2 additional years of treatment resulted in further BMD gains that translated to significantly lower wrist fracture rates, highlighting the clinical importance of reversing cortical bone loss.

Disclosure: J. M. Organ, 2, Eli Lilly and Company; A. Marshak-Rothstein, None; K. A. Fitzgerald, None; E. M. Gravallese, AbbVie, Eli Lilly and Company.

Table 1. Wrist Fracture Rates During FREEDOM and Through Extension Year 5 (N = 2207 Cross-over subjects)

<table>
<thead>
<tr>
<th>FREEDOM (Yr 1–5)</th>
<th>EXTENSION (Yr 6–7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (Calcium + Vitamin D)</td>
<td>Denosumab 60 mg Q6M</td>
</tr>
</tbody>
</table>

Denosumab exposure NA 67 58 19
Wrist fracture, n 1.02 (0.80–1.29) 0.96 (0.74–1.25) 0.58 (0.37–0.90)

*Fracture rate (95% CI) per 100 subject-years.

S788
Autotaxin Is Highly Expressed in Systemic Sclerosis (SSc) Skin, Mediates Fibrosis Via IL-6, and Is a Target for SSC Therapy, Flavia V. Castelino1,2, Leaya M. George1, Gretchen Bain2, Lance Goulet2, Robert Lafyatis3 and Andrew M. Tager1. 1Massachusetts General Hospital, Boston, MA, 2PharmAkea Pharmaceuticals, San Diego, CA, 3Boston University School of Medicine, Boston, MA.

Background/Purpose: Autotaxin (ATX) is an enzyme present in biological fluids that is responsible for the production of the lipid mediator, lysophosphatidic acid (LPA). We previously implicated LPA and its receptor, LPA1 in SSc pathogenesis. Here we studied the role of ATX in SSc dermal lysophosphatidic acid (LPA). We previously implicated LPA and its receptor, logical fluids that is responsible for the production of the lipid mediator, ATX inhibition with PAT-048 (20mg/kg oral gavage daily) was assessed in the model. PAT-048 was administered concurrently with BLM or PBS for 28 days, or initiated at 7 or 14 days after BLM. ATX inhibition with PAT-048 (20mg/kg oral gavage daily) abrogated LPA-induced ATX expression, suggesting an autocrine loop for ATX/LPA/IL-6 signaling. Both ATX and IL-6 are cytokine implicated in SSc, in mediating ATX-induced fibrosis. Additionally, healthy and SSc dermal fibroblasts were stimulated with BLM or PBS for 28 days, or initiated at 7 or 14 days after BLM. ATX expression, compared to healthy fibroblasts. Furthermore, ATX expression increased in SSc skin compared to healthy controls, and LPA-induced IL-6 expression is increased in SSc fibroblasts, further supporting an ATX/LPA/IL-6 autocrine loop in SSc. Targeting ATX may thus be an effective new therapeutic strategy for SSC fibrosis.

Methods: We performed a retrospective cohort study of adults who underwent double or single LTx in the United States between May 4, 2005 (the date of implementation of the lung allocation score) and September 14, 2012. Data were provided by the United Network for Organ Sharing, a non-profit organization that records data on all solid organ transplants performed in the U.S. Subjects were included if they were at least 18 years of age at the time of LTx; had a diagnosis of SSc, ILD, or PAH; and were transplanted at a center that has performed at least 1 LTx for SSc. Subjects were excluded if they had received a heart-lung transplant; if they received a LTx from a living donor; or if they had missing data on survival time. We included patients with systemic sclerosis (SSc) who have developed end-stage lung disease due to interstitial lung disease and/or pulmonary hypertension. However, many transplant programs are hesitant to offer lung transplantation (LTx) to those with SSc due to concerns about extra-pulmonary involvement that might affect short- and long-term survival. However, survival data for lung transplantation in SSc are sparse. The primary aim of this study was to determine whether adults with SSc have higher 1-year mortality rates after LTx compared to those with interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH) not due to SSc. We hypothesized that adults with SSc would have higher 1-year mortality rates after LTx than those with ILD or PAH not due to SSc.

Results: A total of 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 with ILD (Table 1). The 1-year unadjusted mortality rate following LTx per 100 person-years was 21.4 among adults with SSc, 19.0 among adults with PAH, and 17.8 among adults with ILD. A diagnosis of SSc was associated with a statistically significant increase in the 1-year mortality rate compared to a diagnosis of ILD (HR 1.48, 95% CI 1.01-2.17). However, a diagnosis of SSc was not associated with a relative increase in the 1-year mortality rate compared to a diagnosis of PAH (HR 0.85, 95% CI 0.50-1.44). Conclusion: Adults with SSc had a 48% increased risk of death at 1 year following LTx compared to adults with ILD, but no increase in risk of death at 1 year compared to adults with PAH. Rather than denying SSc patients LTx because of their SSc diagnosis, variables need to be identified that will enable risk stratification of these patients prior to LTx, with particular attention to modifiable risk factors.

Table 1: Recipient Characteristics and Covariates

<table>
<thead>
<tr>
<th>Recipient Characteristics</th>
<th>SSC N = 229</th>
<th>PH N = 201</th>
<th>ILD N = 3333</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53 (44-59)</td>
<td>46 (34-57)</td>
<td>62 (56-66)</td>
</tr>
<tr>
<td>Female sex</td>
<td>135 (58.9%)</td>
<td>126 (62.6%)</td>
<td>941 (28.23%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>162 (70.7%)</td>
<td>161 (80.10%)</td>
<td>2782 (83.47%)</td>
</tr>
<tr>
<td>Black</td>
<td>38 (14.59%)</td>
<td>37 (18.46%)</td>
<td>2199 (65.97%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (10.92%)</td>
<td>27 (13.86%)</td>
<td>621 (18.73%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (1.31%)</td>
<td>5 (2.49%)</td>
<td>67 (2.03%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.44%)</td>
<td>0 (0.00%)</td>
<td>24 (0.72%)</td>
</tr>
<tr>
<td>LAS score</td>
<td>44.31 (18.03-52.48)</td>
<td>36.90 (33.93-46.00)</td>
<td>41.36 (29.42-58.10)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.97 (10.29)</td>
<td>169.59 (9.62)</td>
<td>172.28 (9.56)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.10 (4.21)</td>
<td>24.93 (4.36)</td>
<td>27.16 (3.99)</td>
</tr>
<tr>
<td>Stenosis use</td>
<td>117 (52.00%)</td>
<td>145 (72.00%)</td>
<td>1741 (53.75%)</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mmHg</td>
<td>48 (37.66)</td>
<td>83 (68.98)</td>
<td>39 (32.48)</td>
</tr>
</tbody>
</table>


Background/Purpose: Lung transplantation is a potentially life-saving treatment for patients with systemic sclerosis (SSc) who have developed end-stage lung disease due to interstitial lung disease and/or pulmonary hypertension. However, many transplant programs are hesitant to offer lung transplantation (LTx) to those with SSc due to concerns about extra-pulmonary involvement that might affect short- and long-term survival. However, survival data for lung transplantation in SSc are sparse. The primary aim of this study was to determine whether adults with SSc have higher 1-year mortality rates after LTx than those with ILD or PAH not due to SSc.

Methods: We performed a retrospective cohort study of adults who underwent double or single LTx in the United States between May 4, 2005 (the date of implementation of the lung allocation score) and September 14, 2012. Data were provided by the United Network for Organ Sharing, a non-profit organization that records data on all solid organ transplants performed in the U.S. Subjects were included if they were at least 18 years of age at the time of LTx; had a diagnosis of SSc, ILD, or PAH; and were transplanted at a center that has performed at least 1 LTx for SSc. Subjects were excluded if they had received a heart-lung transplant; if they received a LTx from a living donor; or if they had missing data on survival time. We used modified Cox regression models where survival time was the dependent variable, adjusting for recipient, donor, and procedural factors (Table 1). We used multiple imputation to account for missing covariate data.

Results: A total of 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 with ILD (Table 1). The 1-year unadjusted mortality rate following LTx per 100 person-years was 21.4 among adults with SSc, 19.0 among adults with PAH, and 17.8 among adults with ILD. A diagnosis of SSc was associated with a statistically significant increase in the 1-year mortality rate compared to a diagnosis of ILD (HR 1.48, 95% CI 1.01-2.17). However, a diagnosis of SSc was not associated with a relative increase in the 1-year mortality rate compared to a diagnosis of PAH (HR 0.85, 95% CI 0.50-1.44).

Conclusion: Adults with SSc had a 48% increased risk of death at 1 year following LTx compared to adults with ILD, but no increase in risk of death at 1 year compared to adults with PAH. Rather than denying SSc patients LTx because of their SSc diagnosis, variables need to be identified that will enable risk stratification of these patients prior to LTx, with particular attention to modifiable risk factors.
Forced vital capacity, %predicted 44 (36–60) 73 (60–87) 45 (36–57.5)
N = 225 N = 200 N = 225
Creatinine, mg/dL 0.8 (0.7–1.0) 1.0 (0.8–1.2) 0.8 (0.7–1.0)
N = 225 N = 197 N = 330
Extracellular membrane oxygenation 11 (4.0%) 5 (2.4%) 14 (6.96%)
N = 225 N = 31 (10.50%)
Mechanical ventilation 23 (10.04%) 6 (2.99%) 232 (6.96%)
N = 225 N = 16 (4.6) N = 330
Oxygen requirement, L/min 5 (3–6) 6 (4–6) 5 (3–6)
N = 228 N = 200 N = 330
Covariates adjusted for in Cox regression models
Recipient factors
Age Sex Race/Ethnicity AAS score Height BMI Steroid use
Mechanical ventilation
Procedural factors
Ischemic time Single vs. bilateral transplant Transplant center Distance from donor hospital to transplant center
Recipient donor sex mismatch CMV mismatch (D+/R–)
* Data presented as mean (SD), median (IQR), or frequency (percentage)
** AAS = angulation score; PaO2 = arterial oxygen tension; FI O2 = fraction of inspired oxygen; CMV = cytomegalovirus; D+/R– = donor positive; R– = recipient negative; HLA = human leukocyte antigen

Disclosure E. J. Bernstein, None; E. R. Peterson, None; J. M. Bathon, None; D. J. Lederer, None

1799
Elevated Indoleamine-2,3-Dioxygenase (IDO) Activity and Kynurinene-3-Monoxygenase (KMO) Expression in Interferon Positive Primary Sjögren's Syndrome Patients Is Associated With Increased CD25s FoxP3s Regulatory T-Cells: A Skew Towards Neuropsychiatric Disease or an Autoimmune Rescue?
Naomi L. Maria,1 Cornelis G. van Helden-Meeuwsen,2 Zana Brkić,3 Sandra M. J. Paulissen,1 Virgil A. Dalm1, Paul L. van Daele,1 P. Martin van Hagen1, Sinead M. Gilbey1, Andrew Harkin1, Henmo A. Drexahe,1 Erik Lubberts2 and Marjan A. Versnel1,2 Erasmus Medical Center, Immunology, Rotterdam, Netherlands, 2Erasmus Medical Center, Rheumatology, Rotterdam, Netherlands, 3Trinity College Institute of Neuroscience, Neuropsychopharmacology, Dublin, Ireland.

Background/Purpose: The role of indoleamine-2,3-dioxygenase (IDO) in suppression of effector T-cell function and promotion of regulatory T-cell (Treg) differentiation has been described. IDO - the rate-limiting enzyme in tryptophan (TRP) catabolism - is driven in part by type I and type II IFNs. Systemic overactivation of IFN-signaling is evident in Primary Sjögren's syndrome (pSS), and could shift the delicate regulatory balance towards a more auto-reactive state in these patients. Interestingly aberrant systemic TRP catabolism, resulting in a shift from neuroprotective towards neurotoxic downstream metabolites, has been associated with mood disturbances as well as neurobehavioural consequences, and possibly contributes to symptoms of fatigue and depression in pSS. Here we investigate the role of IDO and downstream TRP catabolism in pSS and hypothesize an increase in Tregs, in concordance with increased IDO-activity in IFN-positive pSS patients.

Methods: A cohort of 20 Healthy controls (HC), 18 IFNnegative and 21 IFNpositive pSS patients, diagnosed according to the 2002 American-European criteria, CD4+CD45RO−helper (Th) memory cell populations defined by chemokine receptor expression: CD25sFoxP3+ Tregs, CCR6−CCR4+CXCR3+CCR10−Th17, CCR6−CCR4+CXCR3+CCR10−Th12, CCR6−CCR4+CXCR3+CCR10+Th2-cells were analyzed by flow cytometry in peripheral blood mononuclear cells (PBMCs). Analysis of TRP and Kynurenine (KYN) were performed simultaneously in serum using HPLC. CD14 monocyte mRNA-expression of IDO, and downstream enzymes was assessed using real-time quantitative PCR, to investigate the direction of downstream TRP catabolism in pSS.

Results: Activity of IDO (p = 0.0054) - as determined by measuring levels of the KYN/TRP-ratio in sera - and CD25sFoxP3+ Tregs (p = 0.039) were significantly increased in IFNpositive pSS patients. In addition, CD25sFoxP3+ Tregs significantly correlated with the KYN/TRP-ratio (r = 0.002; p = 0.059) as well as the IFNscore (p = 0.011; r = 0.375). Peripheral monocytes showed an upregulation of IDO-expression (p < 0.0001) in IFN-positive pSS, also highly correlating with the IFNscore (<0.0001r = 0.816). Interestingly the neuroprotective downstream enzymes KAT1 (p = 0.0003), KAT3 (p = 0.016) and KAT4 (p = 0.04) were downregulated, whereas the neurotoxic enzymes KMO (p = 0.0057) and KNYU (p = 0.0001) - which convert KYN into the neurotoxic metabolite Quinolinic acid - were upregulated in these patients, suggesting a skew towards neurotoxicity.

Conclusion: Here, we find enhanced IDO activity in coherence with increased CD25FoxP3 Tregs, and evidence for a shift towards production of more neurotoxic metabolites - previously associated with "sickness behavior" - in IFNpositive pSS. This imbalance towards neurodegenerative effects might contribute to increased fatigue and depressive symptoms in these patients. However, whether this shift in Tregs reflects an immune rescue-mechanism or increases "tolerance to self" remains unknown. Understanding in these IFN and IDO-induced imbalances offers new possibilities for therapeutic interventions.

Disclosure N. L. Maria, None; C. G. van Helden-Meeuwsen, None; Z. Brkić, None; S. M. J. Paulissen, None; V. A. Dalm, None; P. L. V. Daele, None; P. M. van Hagen, None; S. M. Gilbey, None; A. Harkin, None; H. A. Drexahe, None; E. Lubberts, None; M. A. Versnel, None.
Objective: Measured Sedentary Behavior is a Distinct Risk Factor from Low Moderate-to-Vigorous Activity in Predicting Subsequent Frailty: Evidence from the Osteoarthritis Initiative

Methods: We prospectively examined the relationship between accelerometer-measured sedentary time with incident physical frailty. We studied 1570 Osteoarthritis Initiative participants aged 49 years or older at elevated measure sedentary time with incident physical frailty. If a distinct risk factor, the effectiveness of public health interventions to reduce physical frailty and its sequelae may be improved by incorporating strategies to reduce sedentary behavior.

Results: The incidence of frailty in this high-risk group was 18.5 per 1000 person-years. Greater sedentary time during waking hours was significantly related to subsequent frailty onset (unadjusted hazard ratio [HR] = 1.044 [0.85 to 1.23] for both men and women (95% CI: 0.91 to 1.20). Mode 3 and 4 were also significantly associated with sex (p=0.009); Modes 3, 5, 6, 8, and 12 were also significantly associated. See tables for effect sizes and descriptions of all modes significantly associated with sex.

Conclusion: The shape of the distal femur and proximal tibia that form the knee joint differ by sex. Additional analyses are warranted to assess whether the difference in risk of OA between the sexes arises from bone shape differences.

<table>
<thead>
<tr>
<th>Distal Femur Shape with Sex (Significant Modes)</th>
<th>Proximal Tibial Shape with Sex (Significant Modes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode</strong></td>
<td><strong>Variance Explained (%)</strong></td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>1</td>
<td>43.1</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
</tr>
<tr>
<td>5</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Disclosure: J. Song, None; L. A. Lindquist, None; R. W. Chang, None; P. A. Semanik, None; L. S. Ehrlich-Jones, None; J. Lee, None; M. W. Sohn, None; D. D. Dunlop, None.
1802

Are Outcomes after Total Knee Arthroplasty Worsening over Time? a Time-Trends Study of Activity Limitation and Pain Outcomes. Jabinder A. Singh1 and David Lewallen2. 1University of Alabama and V.A. Medical Center, Birmingham, AL, 2Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: To examine whether function and pain outcomes of patients undergoing total knee arthroplasty (TKA) are changing over time.

Methods: The Mayo Clinic Total Joint Registry provided data for time-trends in preoperative and 2-year post-operative activity limitation and pain in primary TKA patients from 1993–2005. We used chi-square test and analysis for variance, as appropriate. Multivariable-adjusted analyses were done using logistic regression.

Results: In a cohort of 7,229 patients who underwent primary TKA during 1993–2005, mean age was 68.4 years (standard deviation (SD), 9.8), mean BMI was 31.1 (SD, 6.0) and 55% were women. Crude estimates showed that preoperative moderate-severe overall limitation were seen in 7.3% fewer patients and preoperative moderate-severe pain in 2.7% more patients in 2002–05, compared to 1992–95 (p<0.001 for both). At 2-years, crude estimates indicated that compared to 1992–95, moderate-severe post-TKA overall limitation was seen in 4.7% more patients and moderate-severe post-TKA pain in 3.6% more patients in 2002–05, both statistically significant (p<0.018) and clinically meaningful. In multivariable-adjusted analyses that adjusted for age, sex, anxiety, depression, Dey-Charlson index, body mass index and preoperative pain/limitation, patients had worse outcomes 2-year post-TKA in 2002–2005 compared to 1993–95 with an odds ratio (95% confidence interval (CI); p-value) of 1.34 (95% CI: 1.02, 1.76, p=0.037) for moderate-severe activity limitation and 1.79 (95% CI: 1.17, 2.75, p=0.007) for moderate-severe pain.

Conclusion: Patient-reported function and pain outcomes after primary TKA have worsened over the study period 1993–2002 to 2005. This time-trend is independent of changes in preoperative pain/limitation and patient characteristics.

and malignant diseases) and AS-related (previous small or large joint surgery) were associated with increased risk of death in age-sex-adjusted analyses.

**Conclusion:** Mortality in this national, population-based AS cohort was increased both in men and women compared to matched controls from the general population. Both general and AS-related comorbidities predicted death suggesting that both traditional and AS-specific risk factors may affect survival.

**Table:** Predictors of Mortality in AS (age- and sex-adjusted analysis)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease or medication (CVD)</td>
<td>2.04 (1.62–2.55)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.94 (1.52–2.47)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>3.04 (2.28–4.06)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>1.75 (1.39–2.22)</td>
</tr>
<tr>
<td>Ast re-related comorbidities</td>
<td></td>
</tr>
<tr>
<td>Joint surgery (small or large joints)</td>
<td>1.44 (1.15–1.81)</td>
</tr>
<tr>
<td>Aortic valve insufficiency</td>
<td>1.24 (0.71–2.15)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1.29 (0.97–1.73)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>0.90 (0.70–1.15)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1.18 (0.85–1.64)</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>1.18 (0.96–1.45)</td>
</tr>
</tbody>
</table>

**Disclosure:** S. Exarchou, None; J. A. Askling, None; H. Forsblad-d’Elia, None; C. Turesson, None; L. E. Kristensen, None; L. T. Jacobsson, None.

**1805 Prevalence and Associating Factors with Atypical Femoral Fractures: An Asian Single Center Based Case-Control Study.** Dam Kim¹, Yoon-Kyoung Sung¹, Sae-Kyung Cho¹, Minkyung Han² and Yee-Suk Kim³
¹Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, ²Hanyang University Hospital, Seoul, South Korea.

**Background/Purpose:** Although the use of bisphosphonates has been shown to reduce vertebral and proximal femur fracture risk in patients with osteoporosis, current evidence suggests that there is an association between bisphosphonate use and atypical femoral fractures (AFFs). However, the extent of this risk remains unclear, especially in Asian population. In this study, we aimed to estimate the proportion of AFFs among total patients with femoral fractures and to compare the characteristics of patients with AFFs with that of patients with classic femoral fractures (CFFs).

**Methods:** Between 2003 and 2013, a total of 578 female patients who had been hospitalized at an Asian single university hospital were retrospectively enrolled. Radiographs and medical records were reviewed by medical doctors. Patients were classified into two groups according to the site of fracture: AFF group for patients with subtrochanteric or diaphyseal femoral fractures and CFF group for patients with intertrochanteric or neck fractures. After estimating the prevalence of AFF among patients with low-energy femoral fractures, we assessed the association of bisphosphonate use and AFFs with using multivariate logistic regression analysis.

**Results:** Twenty-seven patients (4.7%) with AFFs and 551 patients (95.3%) with CFFs were identified. Of the patients with AFFs, 11 (40.7%) had been treated with bisphosphonates compared with 40 (7.3%) in the CFF group. Patients with AFFs were younger than CFF group (71.2 ± 9.5 vs. 76.9 ± 8.7, p < 0.01). With correction for age, patients with AFFs appeared to have a higher cortical thickness index (1.1 ± 0.4 vs. 0.96 ± 0.4, p < 0.05) compared to patients with CFFs. With adjusting the age, body mass index, types of injury (slip or fall), and history of rheumatoid arthritis, bisphosphonate was the only predictor for atypical fractures (OR 9.8, CI 3.7–26.4). Among the patients with bisphosphonate when they fractured (n = 44), the proportion of AFFs was nearly 21% (n = 9). The proportions of AFFs among femoral fractures were increased according to the duration of bisphosphonate; 15.4% (6 among 39 patients) in patients with less than 5 years and 60% (3 among 5 patients) in patients over 5 years, respectively.

**Conclusion:** The proportion of AFFs was around 5% among the patients with femoral fractures and AFF were associated with bisphosphonate use in Asian ethnicity. Longer duration of treatment resulted in augmented risk, though any period in bisphosphonate use could cause atypical femur fracture.

**Disclosure:** D. Kim, None; Y. K. Sung, None; S. K. Cho, None; M. Han, None; Y. S. Kim, None.

**1806 WITHDRAWN**

**1807 Problems with Fee for Service Payments for Academic Rheumatology Practices: A Need for Payment Reform.** Allen P. Anandarajah¹ and Christopher T. Ritchlin²
¹Univ of Rochester Med Ctr, Rochester, NY, ²Univ of Rochester Med Center, Rochester, NY.

**Background/Purpose:** The current fee-for-service model rewards providers for the volume of services. The model is designed to deliver higher compensation for care of more complex cases. Rheumatologists in tertiary care institutions, who provide care for a larger proportion of complex cases, however, are under increasing pressure to care for a higher volume of patients in shorter time intervals.

**Purpose:** The purpose is to examine if care for more complex rheumatology cases provides higher financial compensation compared to less complex cases, in an outpatient, academic rheumatology practice.

**Methods:** We conducted a financial analysis of different faculty outpatient rheumatology clinics at the University of Rochester Medical Center from July 2012 to June 2013. One clinic session was defined as a 4 hour block. We compared three clinics: one dedicated to care of patients with systemic lupus erythematosus (SLE) comprised of patients with complex medical problems; one comprised of rheumatoid arthritis (RA) patients with conditions of moderate complexity and a general rheumatology (GR) clinic comprised of patients with less complex problems. The following independent variables were collected: total patient numbers, coding levels and procedures including joint injections and ultrasound. The outcome variable, average revenues for an average clinic, were analyzed.

**Results:** On average, a total of 7.5 patients (0.6 new, 6.9 established patients) were seen in the GR clinic. This compared with a total of 8.9 patients in the RA clinic (0.9 new, 8.0 established) and 6.5 patients in the GR clinic (1.2 new, 5.4 established). The SLE and RA clinics performed on average 0.7 and 1.9 joint injections respectively while the GR clinic had 4.3 joint injections and 1.2 ultrasounds per clinic. The coding patterns for the different clinics are shown in Table 1. The average revenues received for each level of visit, ultrasound and procedures was used to calculate the total revenue for each individual clinic. The average revenues and RVUs for the SLE clinic were calculated to be $1,034.58 and 13.3 respectively. The RA clinic generated 6.2% more in revenue ($1,098.66) and 19.3% more in RVUs (15.8) while the GR clinic collected 24.5% more in revenues ($1,287.81) and 65.9% more in RVUs (22.0) than the SLE clinic. The difference in payments for a year (based on 8 clinics a week for 46 weeks) was calculated to be $23,578.85 more for the RA and $93,186.36 for the GR clinics compared with the SLE clinic.

**Conclusion:** The current pay structure provides greater financial and RVU compensation for the care of less complex rheumatology cases than the care of complex multisystem diseases. Procedures may be a major contributor to the difference in revenues. Payment reforms are therefore needed to provide adequate compensation for the care of patients with complex rheumatologic problems.

**Table 1:** coding patterns in percentages for the different outpatient clinics

<table>
<thead>
<tr>
<th>FU</th>
<th>FU 3</th>
<th>FU 4</th>
<th>FU 5</th>
<th>NEW 3</th>
<th>NEW 4</th>
<th>NEW 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>0.2%</td>
<td>16%</td>
<td>39.5%</td>
<td>44.3%</td>
<td>3.5%</td>
<td>46.3%</td>
</tr>
<tr>
<td>RA</td>
<td>0.2%</td>
<td>35.2%</td>
<td>65.2%</td>
<td>0.4%</td>
<td>0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>GR</td>
<td>0.6%</td>
<td>41.25</td>
<td>55.9%</td>
<td>2.3%</td>
<td>1.4%</td>
<td>27.2%</td>
</tr>
</tbody>
</table>

**FU = established patients; NEW = new patients**

**Disclosure:** A. P. Anandarajah, None; C. T. Ritchlin, None.

**1808 Role of HLA-B*5801 Genetic Testing and a Safety Programme When Initiating Allopurinol Therapy for Chronic Gout Management: A Cost-Effectiveness Analysis.** Di Dong¹, Wei Chuen Tan-Koi², Gim Gee Teng³, Eric Finkelstein⁴ and Cynthia Sung⁴
¹Duke-NUS Graduate Medical School, Singapore, Singapore, ²Saw Swee Hock School of Public Health, National
Background/Purpose: To conduct a cost-effectiveness analysis from a health system perspective of various strategies in managing chronic gout to mitigate risk of allopurinol-induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, including three that utilize results of HLA-B*5801 genetic testing.

Methods: A decision tree model was developed to estimate costs and quality-adjusted life years (QALYs) over 20-year horizon for patients with chronic gout who fulfill the criteria for initiating ULT with either allopurinol or probenecid. Strategies modeled were: (a) Standard ULT with allopurinol as first-line drug (ULT); (b) Standard ULT with allopurinol as 1st line drug coupled to a safety programme (ULT+SP) that monitors for signs of SJS/TEN; (c) HLA-B*5801 genetic testing-guided ULT treatment (G-ULT) in which choice of 1st line ULT is based on test results (probenecid for test positive, allopurinol for test negative) and avoidance of allopurinol in HLA-B*5801 positive patients; (d) genetic testing to enrol test positive patients in a safety programme when initiating allopurinol (G-SP); test negative patients would receive allopurinol without SP; (e) HLA-B*5801 genetic guided ULT with the safety programme (G-ULT+SP) in which test positive patients are initially given probenecid, but non-responders are subsequently switched to allopurinol in the presence of the safety programme; (f) No ULT and treatment of acute flares only (no ULT). Although inputs are based on the Singapore context, the model is a general template that can be readily adapted to other populations and countries.

Results: No ULT and treating acute flares only has the lowest QALYs and highest costs. Compared with standard ULT, G-ULT increases cost by US$910 but reduces QALYs, despite the reduction in SJS/TEN risk. ULT+SP has an incremental cost-effectiveness ratio (ICER) of US$102,030/QALY compared to ULT alone. G-SP achieves the same QALYs as ULT+SP but at higher cost. G-ULT+SP results in an ICER of US$93,030/QALY compared to standard ULT. (Figure 1 and 2)

Conclusion: Standard care with allopurinol as first line treatment for chronic gout without genetic testing remains the optimal strategy from a cost-effectiveness perspective based on a threshold of US$550,000/QALY. A safety programme for all patients is not cost-effective, but may become so if implementation costs decrease. If genetic testing costs decrease, testing may become cost-effective if results are used to guide the selection of 1st line ULT, with allopurinol as 2nd line ULT for HLA-B*5801 positive patients in the presence of a safety programme.

Table: Categorical disease activity measures compared across patients seen in practices with mid-level providers versus those without, based on adjusted regression models*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary analysis (OR, 95% CI)†</th>
<th>Secondary analysis, change between visits (OR, 95% CI)†</th>
<th>Secondary analysis, area under the curve (b coefficient)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid level provider (vs not)</td>
<td>0.32 (0.17-0.60)</td>
<td>0.98 (0.94-1.03)</td>
<td>−6.35 (p = 0.0055)</td>
</tr>
<tr>
<td>Disease activity category at baseline</td>
<td></td>
<td></td>
<td>9.85 (&lt; p = 0.001)</td>
</tr>
<tr>
<td>Age, per year</td>
<td>0.99 (0.98-1.02)</td>
<td>1.00 (0.99-1.00)</td>
<td>−0.005 (p = 0.95)</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.24 (1.09-4.61)</td>
<td>0.98 (0.93-1.02)</td>
<td>0.34 (p = 0.89)</td>
</tr>
<tr>
<td>Duration of RA, per year</td>
<td>1.18 (0.87-1.61)</td>
<td>1.01 (0.99-1.03)</td>
<td>0.92 (p = 0.59)</td>
</tr>
<tr>
<td>Serositis</td>
<td>1.26 (0.69-2.30)</td>
<td>1.02 (0.98-1.06)</td>
<td>1.08 (p = 0.59)</td>
</tr>
<tr>
<td>DMARD use, any</td>
<td>0.64 (0.43-0.95)</td>
<td>0.99 (0.94-1.03)</td>
<td>−2.85 (p = 0.20)</td>
</tr>
</tbody>
</table>

* The Disease activity category at baseline was not entered into all analyses since it was part of the outcome. Abbreviations: RA, rheumatoid arthritis; DMARD, disease-modifying anti-rheumatic drug. † Odds ratio denotes the probability of a one level increase in disease activity, with odds ratios less than one denoting a reduced probability. They were calculated using a proportional odds model that accounted for the hierarchical clustering. ‡ The b coefficients describe the area under the disease activity curve for the 24 months, with scores of 0-4, interpolated for each month. They were calculated in generalized linear models.

Disclosure: D. Solomon; None; L. Fraenkel; None; B. Lu; None; E. Brown; None; P. H. Tsao; None; E. Losina; None; J. N. Katz; None; A. Bitton; None.
1810

Improper Use of Antinuclear Antibody (ANA) Test Can Result in Misdiagnosis, Increased Patient Anxiety, and Wasted Health Care Resources. Sahar Eivaz Mohammadi1, Iman H Shakh2, Parag Chevli2, Fernando Gonzalez-Ibarra3, Sohini Sarkar2, Saurav Acharya2, Preena Dogra1, Hesam Hekmatjou1, M Ashmi Savjani1, Waheed Abdul1 and V Valentin Marian3. 1Jersey City Medical Center-Baranbas Health, Jersey City, NJ, 2St. George’s University SOM, St. George’s, Grenada.

Background/Purpose: Results of serologic tests for autoantibodies, including tests for Antinuclear antibodies (ANAs) and antibodies to specific nuclear antigens such as double-stranded DNA (dsDNA), play an important role in the diagnosis of connective tissue disorders (CTDs) such as systemic lupus erythematosus (SLE). ANAs are often detected in many healthy individuals without CTDs (~13%). Although a negative ANA test makes SLE highly unlikely, the positive results without significant clinical and laboratory features will lead to inappropriate tests and misdiagnoses.

Methods: This is a retrospective chart review of patients on whom ANA test has been performed at a 330-bed community hospital in U.S. over a period of one year. All relevant details such as demographics, locations, physician service, clinical features, history of CTDs, prior ANA results, additional tests and their results were noted. The justification for ordering the ANA test was compared against clinical and laboratory parameters included in the 2012 SLICC classification criteria for SLE.

Subsequently, true and false positive incidence was calculated. For all the negative or positive ANA tests, special attention was given to the indications of testing based on chart analysis. The 2012 SLICC clinical classification criteria were applied retrospectively to all cases regardless the ANA results; more than two positive parameters by SLICC criteria were proposed as a justification to order ANA test. The results are compared using 2 × 2 chi-square test.

Results: During one year period, ANA was ordered for a total of 465 patients (Male=151, Female=314). Among them, 12.47% (n=58) had prior history of CTDs and 0.98% (n=375) had prior ANA positivity. In the remaining 403 patients, ANA was found positive (titers ≥1:80) in 6.94% (n=28) and negative in 93.05% (n=375). By applying 2 × 2 chi-square test, was shown that ANA positivity or diagnosis of CTD is very unlikely if less than 2 SLICC parameters are present with a p value <0.05 (Table 1).

Out of all 465 cases, only one new case of Anti phospholipid antibody syndrome was identified. A total of 39,297 was spent on ANA, and 88,165 on additional tests ordered in conjunction or following a positive ANA. It was noted that a large number of cases where ANA sub-parameters are ordered without knowing the ANA. It ordering pattern is against recommendation by “Choosing Wisely” campaign endorsed by AIBM and ACR.

Conclusion: Testing for ANA and related serology had cost approximately $126,000/yr for a medium size hospital and lead to no new SLE cases. ANA sub-parameters had the hospital $87,165 and according to “Choosing Wisely” campaign, were not included in more than 93% of cases, as these were negative ANA by IIF. In our hospital the lab was instructed to cancel the additional sub-parameters unless the ANA turns positive.

Table 1. ANA negative ANA positive Marginal row totals

| SLICC score 2 or above | 302 (297.77) [0.06] | 18 (22.23) [0.81] | 320 |
| SLICC score < 2 | 73 (77.23) [0.23] | 10 (5.77) [3.11] | 83 |

Marginal column totals 375 28 403 (Grand Total)

The Chi-Score statistic is 4.2058. The P value is 0.040287. The result is significant at p <0.05.

Disclosure: S. Eivaz Mohammadi, None; I. H. Shakh, None; P. Chevli, None; F. Gonzalez-Ibarra, None; S. Sarkar, None; S. Acharya, None; P. Dogra, None; H. Hekmatjou, None; M. Savjani, None; W. Abdul, None; V. Marian, None.

1811

The Burden of Depression on Healthcare Utilization in a Population-Based Cohort of Patients with Systemic Lupus Erythematosus. Alfredo Aguine1, Gaobin Bao3, S. Sam Lim1 and Cristina Drenkard2. 1Emory University, Atlanta, GA, 2Emory University School of Medicine, Division of Rheumatology, Atlanta, GA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic disease that disproportionately strikes black women. Depression is a potentially debilitating co-morbidity that affects 15–75% of SLE patients and is more severe and unrecognized among blacks compared to whites. Data from a mostly white SLE cohort suggests an association between depression and high emergency department (ED) use. However, no study has assessed the impact of depression on healthcare utilization among patients representative of the SLE population in the Southeastern United States (US). We examined the relationship between depression and healthcare utilization in a predominantly black SLE cohort, expecting depression to be associated with increased ED and inpatient usage.

Methods: Georgians Organized Against Lupus (GOAL) is a longitudinal cohort of validated SLE patients largely drawn from a population-based lupus registry established in Atlanta, Georgia. Annual patient-reported surveys furnish data on demographics, disease outcomes and healthcare utilization from GOAL participants, of whom 78% are black, 35% live under the Federal Poverty Level and 11% are uninsured. All cases fulfilled at least 4 of the American College of Rheumatology (ACR) Classification Criteria for SLE, or 3 ACR criteria with a final diagnosis of SLE by the attending rheumatologist. We used data from the 2013–14 annual survey to examine the relationship between depression, as assessed by the 9-item Patient Health Questionnaire (PHQ-9), and utilization of inpatient and ED resources in the past year.

Results: 566 participants were included in this analysis. Nearly half (46%) of the GOAL participants had visited the ED, while 27% had been admitted to the hospital. Among those with depression (PHQ-9 score ≥10), 58% had visited the ED, as compared to 41% of those with a score <10 (p=0.0001). Patients with and without depression had a mean of 1.7 ED visits and 1.1 ED visits annually, respectively (p<0.0001).

Conclusion: A greater proportion of depressed SLE patients had accessed ED resources for care. In addition, increasing depression severity was associated with higher frequency of ED visits. We did not find an association between depression and hospitalization as was hypothesized, suggesting that depressed patients who visited the ED did not meet inpatient admission criteria. Our data suggest toward deficiencies in the routine care of depressed SLE patients that may contribute to avoidable ED utilization, and suggest the potential utility of depression screening modalities in the assessment of SLE patients who resort to the ED for care. Further research is needed to determine whether demographic factors have an effect on the association between depression and ED visits and whether increased ED utilization may be due to subpar quality, coordination or type of care for those with depressive symptoms.

Depression Severity and Healthcare Utilization in the Past 12 Months

<table>
<thead>
<tr>
<th>Healthcare Utilization*</th>
<th>Minimal (0-4) n=210</th>
<th>Mild (5-9) n=282</th>
<th>Moderate (10-14) n=102</th>
<th>Moderately Severe (15-19) n=42</th>
<th>Severe (20-27) n=30</th>
<th>PHQ-9 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visits</td>
<td>1.0 ± 2.7</td>
<td>1.3 ± 2.0</td>
<td>1.7 ± 2.2</td>
<td>1.4 ± 1.9</td>
<td>2.3 ± 2.9</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.5 ± 1.4</td>
<td>0.7 ± 1.4</td>
<td>0.5 ± 1.3</td>
<td>0.5 ± 1.4</td>
<td>0.8 ± 1.2</td>
<td>0.057</td>
</tr>
<tr>
<td>Nights slept in hospital</td>
<td>2.9 ± 4.9</td>
<td>2.5 ± 6.0</td>
<td>5.8 ± 2.6</td>
<td>14.3 ± 3.2</td>
<td>26.6 ± 4.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Visited ED, n (%)</td>
<td>73 (44.0)</td>
<td>78 (48.1)</td>
<td>57 (57.0)</td>
<td>32 (42.4)</td>
<td>19 (65.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Admitted to hospital, n (%)</td>
<td>44 (21.0)</td>
<td>53 (33.3)</td>
<td>27 (27.3)</td>
<td>17 (23.3)</td>
<td>11 (36.7)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

* Unless otherwise specified, values are depicted as mean ± SD. ** Kruskal-Wallis test.

Disclosure: A. Aguine, None; G. Bao, GlaxoSmithKline, 2; S. S. Lim, NIH, 2, GlaxoSmithKline, 2, Emory University, 3; C. Drenkard, NIH, 2, Emory, 3, GlaxoSmithKline, 2.

ACR Concurrent Abstract Session

Innate Immunity and Rheumatic Disease

Monday, November 17, 2014, 2:30 PM - 4:00 PM

1812

Investigation of the Sting/Interferon Pathway Activation in a Novel Vasculopathy and Pulmonary Syndrome. Y in Liu1, A. Adriana Almeda de Jesus2, Bernardette Marerro1, Dan Y ang3, Gina A. Montallegre Sanchez2, Steve Brooks2, Zuoming Deng2, Amy Paller4, Manfred Boehm1 and Raphaela Goldbach-Mansky1, 2, 3NIAIM/SNIH, Bethesda, MD, 4National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, 5National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, 6Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: We have recently studied a group of patients with a prominent interferon (IFN) signature in the blood, distinct from IL-1 mediated autoinflammatory diseases. Six patients with de novo
gain of function mutations in TMEM173, which encodes STimulator of Interferon Genes (STING), presented with early onset systemic inflammation, vasculopathy/vasculitis, and pulmonary inflammation. STING is an adaptor molecule for cytosolic DNA sensing pathway, which leads to IFNβ production. The identification of an IFN activating mutation allows us to examine the cellular origin of the IFN and the IFN response signature in patients’ cells.

Methods: Patients alive (n=4) were evaluated clinically and immunologically. STING ligand cGAMP was used to assess its function in stimulation assays in patients’ and controls’ Peripheral Blood Mononuclear Cells (PBMCs), fibroblasts and endothelial cells. Transfection studies of STING wildtype or mutant constructs in HEK293T cells were performed and IFNβ transcription in patient peripheral blood cell subsets, fibroblasts, and healthy control endothelial cells were assessed.

Results: Whole blood transcriptional profiling by RNA_seq showed significant upregulation of IFN regulated genes compared with healthy controls. Constitutively increased transcription of IFNβ and other downstream targets of STING in patient PBMCs indicate constitutive STING/IFN pathway activation. qRTPCR analysis of RNA extracted from flow cytometry sorted cells indicates that monocytes produce by far the highest level IFNβ. Transcriptional analysis by RNA_seq suggests that the STING/IFN pathway was also constitutively activated in patient fibroblasts. When stimulated with STING ligand cGAMP, patients’ fibroblasts are more sensitive and have exaggerated transcription of IFNβ but not IL-1β, IL-6 and TNF. STING is expressed in endothelial cells (EC) and in vitro STING pathway stimulation leads to EC activation and damage.

Conclusion: STING-Associated Vasculopathy with onset in Infancy (SAVI) is a novel autoinflammatory disease caused by de novo gain of function mutations in TMEM173, which leads to constitutive STING activation and elevated IFNβ secretion. The identification of a mutation in the IFNβ pathway suggests the use of therapeutic agents blocking this pathway and allows us to study the cellular origin and the organ manifestations of the inflammation.

Disclosure: Y. Liu None; A. Almeida de Jesus None; B. Marrero None; D. Yang None; G. A. Monteleone Sanchez None; S. Brooks None; Z. Deng None; A. Paller None; M. Boehm None; R. Goldbach-Mansky None.

1813
DNA Sensors Regulate Inflammation in a Model of Autoimmune Arthritis.
Rebecca Baum1, Shruti Sharma1, Sudesh Pawaria2, Susan Carpenter2, Katherine A. Fitzgerald3, Ann M arshak-Rothstein4 and Ellen M. Gravallese5, 1University of Massachusetts Medical School, Worcester, MA, 2University of California, San Francisco, San Francisco, CA, 3UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Innate immune sensors such as cytosolic DNA sensors and toll-like receptors (TLRs) detect viral or bacterial DNA, resulting in production of proinflammatory cytokines and type I IFNs to clear infection. Pathways involved in detecting this foreign DNA include: 1) cytosolic DNA sensors that signal through interferon-stimulator of interferon genes (STING); 2) the cytosolic sensor absent in melanoma 2 (AIM2); and 3) endosomal TLRs that traffic via Unc93. DNA derived from endogenous retroelements or dying cells have also been shown to activate these pathways, contributing to autoimmune disease. We examined the role of DNA sensor pathways in a mouse model of inflammatory arthritis in which the lysosomal endonuclease DNase1 is deficient. In this model, DNA accrual results in production of proinflammatory cytokines and type I IFNs leading to lethal arthritis. Depletion of the type I IFN receptor is required (DNase1/-/IFN-IR double deficient (DKO) mouse).

Methods: To investigate the contribution of DNA sensor pathways to inflammatory polyarthritis, genes involved in DNA sensor signaling were deleted on the DKO background, yielding three triple knockout (TKO) strains: STING TKO, AIM2 TKO and Unc93 TKO mice. Inflammation was assessed by clinical scoring (scale of 1-12) and by scoring of histologic inflammation in ankle joints (scale of 1-4). Anti-nuclear antibody (ANA) staining was evaluated as another marker of disease. To determine whether STING contributes to inflammation in immune-complex mediated arthritis, serum transfer arthritis (STA) was induced in STING/–/ and littermate control mice.

Results: DKO mice develop significant distal polyarthritis. Clinical joint inflammation was completely absent in STING TKO mice, confirming a prior report (Ahn et al., PNAS 109:19386, 2013). However, STING deficiency did not diminish inflammation in the STA model, demonstrating that STING contributes to arthritis in the setting of DNA accrual. Clinical inflammation was significantly reduced in both AIM2 TKO and Unc93 TKO mice compared to DKO mice, demonstrating a role for the inflammasome and TLRs. A verage clinical scores: DKO = 5, Het control mice = 0, STING TKO = 0, Unc93 TKO = 4, AIM2 TKO = 3.5 (p<0.05 for all strains compared to DKO). Histologic inflammation scores showed a similar pattern (DKO = 3.5, Het = 0, STING TKO = 0.5, AIM2 TKO = 2, Unc93 TKO = 3) (p<0.05 for all strains compared to DKO). The bright ANA staining pattern generated from sera of DKO mice was completely abrogated in the Unc93 TKO, but was unchanged in the STING TKO and AIM2 TKO strains.

Conclusion: These data indicate that stimulation of several innate immune sensor pathways by endogenous DNA can contribute to inflammatory polyarthritids. Although deletion of STING had the greatest impact in abrogating arthritis, the AIM2 and Unc93 pathways also contributed to joint inflammation. The STING pathway is not the only, but not the STING or AIM2 pathways, mediated ANA production. These data are directly relevant to clarifying the mechanisms by which polyarthritids occurs in SLE and suggest new targets for treatment. In addition, these data demonstrate that distinct DNA sensing pathways play unique roles in disease mechanisms.

Disclosure: R. Baum None; S. Sharma None; S. Pawaria None; S. Carpenter None; K. A. Fitzgerald None; A. Marshak-Rothstein None; E. M. Gravallese None; Abbie C. Li and Company, 2.

1814
RNA-Containing Immune Complexes Shift Human Neutrophils from Phagocytosing Cells to Efficient Release of Oxidized DNA in a Process Requiring Crosstalk Between Toll-like Receptors and Fc Gamma Receptor IIa.
Christian Loos1, Xi Zhang2, Lena Tanaka2, Andrew Oberst3, Jeffrey Ledbetter1 and Kelvin B. Elkon1, 1University of Washington, Seattle, WA, 2Department of Immunology, University of Washington, Seattle, WA, 3Division of Rheumatology, University of Washington, Seattle, WA.

Background/Purpose: Neutrophil extracellular traps (NETs), the extrusion of chromatin to capture microbes, has recently emerged as a possible mechanism that may increase the autoantigenic burden as well as promote the anti-DNA antibody response in SLE. NETs are enriched in extracellular DNA that targets DNA sensors and toll-like receptors (TLRs) detect viral or bacterial DNA, resulting in the recruitment of inflammatory cells. NETs are also enriched in immune complexes (ICs) that target immune sensor pathways by endogenous DNA can contribute to immune inflammation. Although deletion of STING had the greatest impact in abrogating arthritis, the AIM2 and Unc93 pathways also contributed to joint inflammation. The STING pathway is not the only, but not the STING or AIM2 pathways, mediated ANA production. These data are directly relevant to clarifying the mechanisms by which polyarthritids occurs in SLE and suggest new targets for treatment. In addition, these data demonstrate that distinct DNA sensing pathways play unique roles in disease mechanisms.

Disclosure: R. Baum None; S. Sharma None; S. Pawaria None; S. Carpenter None; K. A. Fitzgerald None; A. Marshak-Rothstein None; E. M. Gravallese None; Abbie C. Li and Company, 2.

1814
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Christian Loos1, Xi Zhang2, Lena Tanaka2, Andrew Oberst3, Jeffrey Ledbetter1 and Kelvin B. Elkon1, 1University of Washington, Seattle, WA, 2Department of Immunology, University of Washington, Seattle, WA, 3Division of Rheumatology, University of Washington, Seattle, WA.

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Disclosure: R. Baum None; S. Sharma None; S. Pawaria None; S. Carpenter None; K. A. Fitzgerald None; A. Marshak-Rothstein None; E. M. Gravallese None; Abbie C. Li and Company, 2.
NETosis; iii) TLR-ligand activation in neutrophils downregulates FcgRIIA expression thereby inhibiting further phagocytosis of ICs but enabling NETosis; iv) ICs induce release of oxidized DNA of chromosomal and mitochondrial origin. Deciphering the underlying signaling pathways regulating the crosstalk between FcgRs and TLRs in induction of NETosis may provide novel therapeutic targets.

Disclosure: C. Lood None; X. Sun None; L. Tanaka None; A. Oberst None; J. Ledbetter None; K. B. Elkon None.

1815

STAT3-Mediated Regulation of Mitochondrial Membrane Potential Is Critical for NLRP3 Inflammasome Activation. Jehad H. Edwan1, Raphaela Goldbach-Mansky2 and Robert A. Colbert2. 1NIAMS NIH, Bethesda, MD, 2NIH Building 10 Room 6D47B, Bethesda, MD. 3NIAMS/NIH, Bethesda, MD

Background/Purpose: Self-activating mutations in NLRP3 cause a spectrum of autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS). NLRP3 is a key component of a multiprotein complex known as the inflammasome that mediates the maturation of the proinflammatory cytokine IL-1beta, and can induce rapid cell death in a process known as pyonecrosis. Although several models for inflammasome activation have been proposed the precise molecular mechanism, as well as the role of NLRP3 mutations, remains to be elucidated. Emerging evidence suggests that mitochondria are involved in inflammasome activation. STAT3 associates with mitochondrial inner membrane in a GRIM-Jo1dependent manner and has been implicated in regulating cellular respiration. Here we asked whether regulation of mitochondrial membrane potential plays a role in NLRP3 inflammasome activation.

Methods: We used whole blood cells from NOMID patients and healthy controls, THP-1 cells with STAT3, NLRP3, GRIM-19, or OSCP expression knocked down, and monocytes derived from NLRP3-deficient mice. Cells were stimulated with LPS in the presence of inhibitors of STAT3, followed by ATP. Cell supernatants were collected and incubated with IL-1beta-capturing beads. Cells were fixed and permeabilized. Then beads were added back to cells, and the mixture of cells with beads was stained with anti-IL-1beta, CD14, and CD16 antibodies and then evaluated by flow cytometry. LPS stimulated cells were also evaluated using immunofluorescence and western blot analysis.

Results: By flow analysis we provide evidence that inhibition of STAT3 function in NOMID and healthy monocytes, as well as knockdown of STAT3 in THP-1 cells, results in a significant decrease in inflammasome activation. Using confocal microscopy to visualize pyonecrosis, we provide evidence that this process is NLRP3 dependent. Knockdown of GRIM-19 in THP-1 cells also inhibited NLRP3 activation, suggesting a requirement for mitochondrial STAT3. Enhancement of the mitochondrial membrane potential in STAT3 knockdown cells bypassed the effect of STAT3 knockdown, and reconstituted inflammasome activation, whereas knockdown of OSCP significantly reduced inflammasome activation.

Conclusion: These data suggest a previously unrecognized role for STAT3 in regulating mitochondrial membrane potential, which can regulate NLRP3 inflammasome activation. These results point toward mitochondrial STAT3 as a novel therapeutic target for NOMID and other NLRP3-mediated inflammatory diseases.

Disclosure: J. H. Edwan None; R. Goldbach-Mansky None; R. A. Colbert None.

1816

Toll-like Receptor 4-Induced Interleukin-1 Defines the Intestinal Microbiome and Mucosal Immune Response in Arthritis-Prone IL-1 Receptor Antagonist Deficient Mice. Tom Edeven1, Rebecca Rogier2, Jos Boekhorst1, Harm Wopereis1, Johan Garssen1, Sacha van Hijum1, Fons A.J. van de Loo3, Maaike I. Koenders3, W. B. van den Berg3, R. Horst1, Harms Wopereis2, Johan Garssen2, Sacha van Hijum1, Fons A.J. van de Loo3, M. I. Koenders None; W. B. van den Berg None; S. Abdollahi-Roodsaz None.

Background/Purpose: Interleukin-1 (IL-1) plays a pivotal role in inflammation and autoimmunity. Mice deficient in the IL-1 receptor antagonist (IL-1Ra) spontaneously develop a T cell-driven autoimmune arthritis, which we previously showed to depend on the presence of commensal microbiota. Recent findings suggest alteration of intestinal microbiome in new-onset rheumatoid arthritis (RA). The aim of this study was to investigate the role of IL-1 receptor signaling and the involvement of Toll-like receptor (TLR) 2 and TLR4 in defining the intestinal microbiota and the associated mucosal and systemic immune response.

Methods: Multiplex 454 pyrosequencing of V5 and V6 hyper-variable regions of fecal bacterial 16S rRNA was used to define intestinal microbial communities in BALB/c wild type (WT), IL-1Ra-/- and IL-1Ra/TLR double knock-out (DKO) mice. For gene sequencing analysis, a customized workflow based on Quantitative Insights Into Microbial Ecology (QIIME version 1.2) was adopted. Intestinal T cell differentiation was studied in lamina propria lymphocytes using flow cytometry and gene expression was assessed by qPCR.

Results: Excessive IL-1R signaling strongly affected the composition of intestinal microbiota and resulted in a significant reduction in species diversity compared to WT mice. Both alpha diversity (number of unique taxonomic entities) and phylogenetic diversity (PD) whole tree (based on taxonomic distance) were significantly diminished in IL-1Ra-/- mice compared to WT. Interestingly, the loss of species diversity was absent in IL-1Ra/TLR DKO, but not IL-1a/TLR2 DKO mice, suggesting that IL-1R-driven skewing of bacterial diversity depends on TLR4.

IL-1Ra-/- mice exhibited significantly increased abundance of the genus Helicobacter and reduced Prevotella (p = 0.008 and p = 0.004, respectively). Importantly, significant alterations in the genera Xylanibacter, Prevotella, Streptococcus, and Ruminococcus were markedly normalized in TLR4, but not TLR2, deficient mice, identifying a role for TLR4 in IL-1-mediated shifts in microbial community.

In line with the relevance of intestinal microbiota in mucosal helper T cell polarization, IL-1Ra-/- mice had greatly increased Th1 and Th17 in small intestine lamina propria, while Treg proportions were unaffected. Also, small intestine lamina propria lymphocytes produced increased levels of IL-17 when stimulated with PMA and ionomycin ex vivo. Although expression of IL-1 itself remained unaltered, intestinal IL-23p19 mRNA expression was increased in IL-1a-/- mice. Interestingly, mucosal expression of both IL-1β and IL-23 was significantly diminished in IL-1Ra/TLR4 DKO mice. Moreover, splenic expression of IL-6 and RORγt was increased in IL-1Ra-/-, and suppressed in IL-1Ra/TLR4 DKO mice.

Conclusion: These data indicate a clear role for the IL-1 pathway in defining the intestinal microbial and mucosal immune response in autoimmune mice, potentially driven by TLR4. Understanding the molecular and cellular mechanisms linking the intestinal T cell response with extra-intestinal disease may help identify novel therapeutic targets in autoimmune diseases including RA.

Disclosure: T. Edeven None; R. Rogier None; J. Boekhorst None; H. Wopereis None; J. Garssen None; S. van Hijum None; F. A. J. van de Loo None; M. I. Koenders None; W. B. van den Berg None; S. Abdollahi-Roodsaz None.

1817

Connecting Two Pathways through Ca2+ Signaling: NLRP3 Inflammasome Activation Induced By a Hypermorphic PLCg2 Mutation. Jae Jin Chae1, Yong Hun Park1, Chung Park1, Il-Yong Hwang2, Patrycja Hoffmann3, John Keen4, Ivona Aksentijevich5 and Daniel L. Kastner1. 1National Human Genome Research Institute, Bethesda, MD, 2National Institute of Allergy and Infectious Diseases, Bethesda, MD.

Background/Purpose: Previously, we reported that a novel variant, Ser707Y/His2077yr, in phospholipase C gamma 2 (PLCγ2) is the cause of a dominantly inherited autoinflammatory disease, APLAID (autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation). The APLAID patients suffered from early onset recurrent blistering skin lesions, pulmonary disease, arthralgia, inflammatory eye and bowel disease, and mild immunodeficiency. The hypermorphic mutation enhances the PLCγ2 activity and causes an increase in intracellular Ca2+ release from ER stores. As increased intracellular Ca2+ signaling has been associated with NLRP3 inflammasome activation, we studied the role of the NLRP3 inflammasome in the pathogenesis of this disease.

Methods: Human peripheral blood mononuclear cells (PBMCs) were isolated from healthy controls and two affected patients. Inflammasome activation was analyzed by Western blotting of secreted interleukin-1β (IL-1β). Intracellular Ca2+ levels were measured with the FLIPR Calcium 4 assay kit.

Results: First, we confirmed that PLC-inositol trisphosphate (InsP3)-mediated Ca2+ release can trigger the activation of the NLRP3 inflammasome in human PBMCs in much the same way as was previously shown in the mouse. Since the S707Y APLAID mutation disrupts the autoinhibition of PLCγ2, which leads enhanced PLCγ2 activity, patients' leukocytes had elevated basal levels of intracellular Ca2+. Upon stimulation with extracellular...
lular CaC\textsubscript{2}O, an activator of the NLRP3 inflammasome, patients’ cells release significantly higher amounts of Ca\textsuperscript{2+} than the cells of healthy controls. Consistent with that the increase of cytoplasmic Ca\textsuperscript{2+} mediates the activation of the NLRP3 inflammasome, in the absence of inflammasome activators, PBMCs from patients with APLAID secreted IL-1\beta whereas control PBMCs secreted IL-1\beta only following the stimulation with CaC\textsubscript{2}O. The IL-1\beta secretion from LPS-primed patients’ PBMCs was attenuated by use of a PLC inhibitor and intracellular Ca\textsuperscript{2+} blockers. Finally, we found that the constitutive IL-1\beta secretion from patients PBMCs was substantially reduced by the treatment with NKH477, the water-soluble analog of forsko-
lin, which is a potent activator of adenyl cyclase. These results suggest cAMP as a potential target for therapy of APLAID and other NLRP3 mediated diseases.

Conclusion: Our findings suggest that the inflammation in patients with APLAID is partially driven by the activation of the NLRP3 inflammasome. These data link two seemingly distinct molecular pathways and provide new insights in the pathogenesis of APLAID and autoinflammation.

Disclosure J. J. Chan; None. Y. H. Park; None. C. Park; None. I. Y. Hwang; None. P. Hoffmann; None. J. Kehrl; None. I. Akcentijevich; None. D. L. Kastner; None.

**ACR Concurrent Abstract Session**

**Osteoarthritis - Clinical Aspects I: Imaging in Osteoarthritis**

**Monday, November 17, 2014, 2:30 PM-4:00 PM**

1818

**Subchondral Bone Mineral Density Improves Prediction of Knee Osteoarthritis Progression Compared with Clinical Factors Alone: Data from the Osteoarthritis Initiative.** Michael P. Lavalley1, Grace H. Lo2, Lori Lyn Price1, Jeffrey Driban3, Charles Eaton4 and Timothy E. McAlindon1. 1Boston University, Boston, MA, 2Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, 3Tufts Medical Center, Boston, MA, 4Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI.

Background/Purpose: A prediction rule for knee osteoarthritis (OA) progression would have great clinical utility in identifying at-risk patients for intervention. Rules using clinically available measurements have so far demonstrated modest predictive ability. Dual energy X-ray absorptiometry is widely available and provides rapidly evaluable quantitative data on tibial subchondral bone mineral density (BMD) that is associated with OA severity. Our goal was to create a prediction rule for medial joint space loss (a proxy for OA progression) based on clinical factors; and to quantify the benefit of adding the ratio of the periarticular medial to lateral bone mineral density (M:L paBMD) to the rule.

Methods: Subjects were from the Osteoarthritis Initiative (OAI) progression subcohort, with X-ray readings at both 24- and 48-month visits, medial joint space score < 3 at 24 months, and a valid 30- or 36-month BMD value. Weight-bearing PA flexion knee X-rays were assessed for medial tibio-femoral joint space using the OARSI atlas. Knees were imaged with GE Lunar Prodigy Advance scanners, providing M:L paBMD values. Loss of medial joint space, including within OARSI grade worsening, between 24 and 48 months was used as the outcome in logistic regression for the prediction models. Clinical factors chosen for their predictive ability from 24 months were considered for the base model. M:L paBMD was added to the base model to determine if it materially improved prediction, with cross-validation used in this evaluation. Discriminative ability was based on the area under the ROC curve (AUC) and calibration by the Hosmer & Lemeshow test (H&L). The benefit of adding M:L paBMD was considered for the base model. M:L paBMD was added to the base model to determine if it materially improved prediction, with cross-validation used in this evaluation. Discriminative ability was based on the area under the ROC curve (AUC) and calibration by the Hosmer & Lemeshow test (H&L). The benefit of adding M:L paBMD was evaluated by 1) change in AUC, 2) net reclassification improvement (NRI) based on the percent of subjects with improved prediction, and 3) integrated discrimination improvement (IDI) based on the mean improvement in predicted probabilities.

Results: 496 subjects were included; 68 (14%) experienced medial joint space loss; 48% were female; 15%, 16%, 36%, 30%, and 3% respectively had Kellgren & Lawrence scores 0 - 4; 2% had recent knee injury; 35% had hand OA (> 3 nodes) on physical exam at AUC entry. The mean (SD) for age was 64.4 (9.2) years; BMI 29.5 (4.9) kg/m\textsuperscript{2}; VAS knee-specific pain 3.4 (2.9) on a 0 – 10 scale; femoral neck BMD, 0.96 (15) g/cm\textsuperscript{2}; and M:L paBMD 1.1 (-1.4). The base model included age, BMI, gender, recent injury, knee pain, hand OA, and femoral neck BMD as predictors. The change in AUC, NRI and IDI were statistically significantly improved in the model with M:L paBMD (Table). The H&L test did not find poor calibration in either model.

Conclusion: The M:L paBMD ratio provided a meaningful improvement in predictive ability for 2-year medial joint space loss compared to using only clinical predictors. An instrument combining clinical characteristics with M:L paBMD may be useful as a predictive tool for structural progression in patients with knee OA.

**Table 1. Cross-Validated Measures of Model Prediction of Medial Joint Space Loss with addition of the Ratio of Periarticular Medial to Lateral Bone Mineral Density (M:L paBMD)**

<table>
<thead>
<tr>
<th>Base Model*</th>
<th>Base Model* + M:L paBMD</th>
<th>Comparison (95% Confidence Interval), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC Area Under the Curve (AUC)</td>
<td>0.645</td>
<td>0.745</td>
</tr>
<tr>
<td>Hosmer &amp; Lemeshow Calibration Test (H&amp;L) p-value</td>
<td>0.330</td>
<td>0.102</td>
</tr>
<tr>
<td>Net Reclassification Improvement (NRI) Subjects with medial joint space loss</td>
<td>0.681 (0.434, 0.923)</td>
<td>0.001</td>
</tr>
<tr>
<td>MeI % Improved Subjects with no medial joint space loss</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>MeI % Improved Subjects with medial joint space loss</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Integrated Discrimination Improvement (IDI) Subjects with medial joint space loss</td>
<td>0.027 (0.043, 0.101)</td>
<td>0.001</td>
</tr>
<tr>
<td>AUC-based Predicted Probability Subjects with no medial joint space loss</td>
<td>0.176</td>
<td>0.239</td>
</tr>
<tr>
<td>AUC-based Predicted Probability Subjects with medial joint space loss</td>
<td>0.140</td>
<td>0.125</td>
</tr>
</tbody>
</table>

* Base model has the predictor: age, BMI, gender, recent injury, knee pain, hand OA (> 5 hand nodes), and femoral neck BMD; outcome in both models is medial joint space loss.

 Disclosure M. P. Lavalley; None. G. H. Lo; NIH/NIAMS, 2; L. L. Price; NIAMS-NIH, 3; J. Driban; NIAMS-NIH, 2; J. Eaton; None; T. E. McAlindon; NIAMS-NIH, 2.

1819 WITHDRAWN

1820

**Discordance of Hip Pain with Radiographic Hip Osteoarthritis: The Osteoarthritis Initiative.** Chan Kim1, Michael C. Nevitt2, Pia M. Jungmann3, Irina Tolstykh4, Nancy E. Lane5, Thomas M. Link6 and David T. Felson1. 1Boston University, Boston, MA, 2UCSF (University of California, San Francisco), San Francisco, CA, 3Technische Universitaet Muenchen, Munich, Germany, 4University of California, San Francisco, San Francisco, CA, 5Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA, 6University of Manchester, Manchester, United Kingdom.

Background/Purpose: It is assumed that persons with hip pain from osteoarthritis (OA) are likely to have radiographic OA, making it possible to readily diagnose disease, but there is little data addressing the agreement of hip pain with x-ray OA. We previously reported poor agreement between hip pain and RHOA (radiographic hip osteoarthritis) in the Framingham population. However, the Framingham study used long limb x-rays that may have yielded imperfect RHOA estimates. We examined concordance of hip pain with RHOA in the Osteoarthritis Initiative (OAI) where subjects obtained multiple x-rays and were asked a more comprehensive set of questions about hip pain.

Methods: OAI is a multicenter longitudinal cohort study of OA that included 4796 individuals aged 45-79. AP pelvis x-rays were obtained, and definite RHOA was defined using UCSF criteria: 1) definite osteophytes plus definite SN (both score = 2) OR 2) definite osteophytes or definite SN plus sclerosis, cysts or femoral head flattening OR 3) definite femoral osteophytes regardless of other features OR 4) definite moderate-severe JSN (superolateral JSN >= 2 or superomedial JSN >= 3) regardless of other features. Using a card with visual honunculus, subjects were asked whether they had hip pain on most days in a month. Those who said ‘yes’ were defined as having frequent hip pain and were asked another question for location of pain: groin, front of the leg (anterior), outside the leg (lateral), lower back, buttocks, or ‘don’t know’. The pain evaluation was done for both hips. We examined sensitivity (Sn), specificity (Sp) and positive and negative predictive values (PPV, NPV) for location specific pain with RHOA. Sn was defined as % of hips with RHOA that had hip pain. PPV was % of hips with pain that have RHOA. To ensure that we included hips that may have OA and to increase our sensitivity, we defined another analysis for possible RHOA.

Results: X-rays from 8732 hips were evaluated. The prevalence of definite RHOA was 6.3%, and possible RHOA was 12.3%. For definite RHOA, the Sn of frequent hip pain was only 23.8%, and the Sp was 84.1% and the PPV for hip pain was only 9.1% (table 1). However, for analysis restricted to hip pain localized to the groin, the PPV rose to 16.5%. Of those
with RHOA, only 7.1% had pain localized to the groin. Anterior hip pain resulted similarly to groin pain, but performance for other sites was diagnostically poorer. For possible RHOA (data not shown), the diagnostic test performance did not differ greatly from definite RHOA.

**Conclusion:** We found poor agreement between hip pain on most days and RHOA in the ipsilateral hip. Hip pain questions with the highest PPV were hip pain with groin or anterior pain, but most persons with this pain had radiographic signs for OA suggesting that x-rays are insensitive to the presence of disease. Many middle aged and older persons with chronic hip joint area pain may have OA even though x-rays are negative.

### Table 1

<table>
<thead>
<tr>
<th>Pain definition* (prevalence)</th>
<th>Sensitivity: of RHOA hips that have pain (%)</th>
<th>Specificity: of OA hips that have no pain (%)</th>
<th>PPV: of painful OA hips that have RHOA (%)</th>
<th>NPV: of painless OA hips that have non-RHOA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent hip pain in past year (54.4%)</td>
<td>16.8% (125/750)</td>
<td>94.4% (688/732)</td>
<td>86.7% (71/83)</td>
<td>96.8% (651/672)</td>
</tr>
<tr>
<td>Persistent frequent (BL and 12m)</td>
<td>12.9% (71/550)</td>
<td>93.8% (767/812)</td>
<td>92.2% (702/762)</td>
<td>94.6% (159/167)</td>
</tr>
<tr>
<td>Gr1 <strong>(12.7%)</strong></td>
<td>7.1% (59/830)</td>
<td>97.6% (713/732)</td>
<td>16.2% (21/130)</td>
<td>94.0% (792/838)</td>
</tr>
<tr>
<td>Anterior or (1.8%)</td>
<td>4.4% (245/550)</td>
<td>98.4% (514/526)</td>
<td>15.3% (86/565)</td>
<td>93.9% (471/504)</td>
</tr>
<tr>
<td>Lateral <strong>(10.9%)</strong></td>
<td>77.1% (37/48)</td>
<td>99.6% (59/60)</td>
<td>9.9% (5/52)</td>
<td>96.1% (272/282)</td>
</tr>
<tr>
<td>Low back <strong>(6.9%)</strong></td>
<td>7.5% (42/550)</td>
<td>96.9% (678/702)</td>
<td>6.9% (35/500)</td>
<td>93.7% (756/812)</td>
</tr>
<tr>
<td>B-Back <strong>(8.6%)</strong></td>
<td>7.5% (38/510)</td>
<td>95.5% (732/772)</td>
<td>8.0% (26/326)</td>
<td>95.0% (750/796)</td>
</tr>
<tr>
<td>Gr0 or anterior (3.7%)</td>
<td>9.3% (96/718)</td>
<td>96.7% (751/782)</td>
<td>13.8% (13/95)</td>
<td>94.1% (662/699)</td>
</tr>
<tr>
<td>Hip, not buttock or back (52.3%)</td>
<td>20.4% (232/1140)</td>
<td>88.3% (1112/1250)</td>
<td>10.5% (124/1172)</td>
<td>94.3% (1028/1084)</td>
</tr>
<tr>
<td>Hip, buttock or low back (24.5%)</td>
<td>22.5% (124/550)</td>
<td>86.0% (512/595)</td>
<td>9.8% (39/407)</td>
<td>93.4% (522/559)</td>
</tr>
<tr>
<td>Any hip pain past year (40.8%)</td>
<td>77.1% (22/278)</td>
<td>99.6% (260/262)</td>
<td>9.4% (17/180)</td>
<td>96.4% (245/255)</td>
</tr>
</tbody>
</table>

**Note:** RHOA = Risk Indeterminate RHOA; OA = Osteoarthritis; PPV = Positive Predictive Value; NPV = Negative Predictive Value; B = Baseline; L = 12 months; M = 24 months.

### Table 2

<table>
<thead>
<tr>
<th>Baseline MRI lesions in the subgroups identified by latent class analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF joint</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>N of knees</td>
</tr>
<tr>
<td>%Cartilage morphology, 0 (no lesion)</td>
</tr>
<tr>
<td>%Meniscal tear, 1</td>
</tr>
<tr>
<td>%Meniscal extrusion, 1</td>
</tr>
<tr>
<td>%Effusion, 1</td>
</tr>
</tbody>
</table>

**Note:** TF = Tendon forearm; OA = Osteoarthritis; MRI = Magnetic Resonance Imaging; PPV = Positive Predictive Value; NPV = Negative Predictive Value.

### Background/Purpose

MRI imaging provides insights of tissue-specific lesions of osteoarthritis (OA) and has the advantage of identifying earlier pathological changes that are not evident on radiographs. While MRI lesions often co-occur, the co-occurrence patterns and their risk to the region of incident OA have not been well evaluated. We identified distinct subgroups of knees using a latent class model according to patterns of pathological changes on MRI and examined their relation to incident radiographic knee OA (incROA).

### Methods

The MOST Study recruited 3,026 subjects with or at risk for knee OA. We obtained baseline knee MRI and knee radiographs at each visit. MRIs were scored using the Whole Organ Magnetic Resonance Score (WORMS). T2*Biofilm (TF) incROA was defined by a new occurrence of KL ≥ 2 on PA view radiograph by Month 84, and patellofemoral (PF) incROA was defined by a new occurrence of PF OA on lateral view. For specific lesions on MRI in the TF joint, i.e., cartilage morphology, meniscal tear, meniscal extrusion, bone marrow lesion, synovitis, and effusion, we used the worst WORMS score among all sub-regions to represent the severity of that lesion in the knee. We performed latent class modeling (SAS: Proc LCA) to identify subgroups of knees by patterns of MRI lesions. Each knee was assigned to a specific subgroup according to its highest membership probability. We then examined the relation of subgroups of MRI lesions to the risk of TF incROA after adjusting for sex, race, clinic site, history of knee injury and surgery using logistic regression model. We took the same approach to identify subgroups of MRI lesions in the PF joint and assess their relation to PF incROA.

### Results

Among 579 knees without TF OA (mean age: 60.1 years, BMI 29.2 kg/m², 59% women), we identified 4 subgroups based on baseline MRI lesions with average posterior probability 0.82: mostly normal (Group 1, 48.0%); predominantly cartilage lesion (Group 2, 24.9%); predominantly meniscal lesions (Group 3, 13.8%); and combined cartilage and meniscal lesions (Group 4, 13.3%) (Table). In Group 3, meniscal tear was more prevalent than meniscal extrusion. Bone marrow lesion, synovitis, and effusion were common in Groups 2 and 4. The risk of TF incROA was 12.2%, 22.9%, 31.3% and 44.2%, for Group 1, 2, 3 and 4, respectively. The corresponding odds ratios (ORs) of TF incROA and 95% CI were 1.0, 2.5, 1.4, 4.4, 5.4 (2.8, 10.5), and 8.2 (4.3, 15.7), respectively. Similarly, 4 subgroups of MRI lesions were identified in PF joints among 660 knees without PF OA. The ORs of PF incROA for each subgroup were 1.0, 4.3, 8.9, and 17.0, respectively.

**Conclusion:** The latent class analysis allowed insights of the patterns of MRI lesions. Among the four subgroups of MRI lesions we identified, the co-occurrence of cartilage and meniscal lesion markedly increased the risk of incident RHOA, and the meniscal lesion subgroup posed a higher risk than the cartilage lesion subgroup.

### Discussion

Incident Synovitis and Bone Marrow Lesions Are Associated with Incident Joint Tenderness in Hand Osteoarthritis. Ida K. Haugen1, Barbara Ståtksowsky-Christensen1, Pernille Boyesen1, Sølve Sesseng1, De´es´e van der Heijde1 and Tore K. Kvien2. 1Diakonhjemmet Hospital, Oslo, Norway; 2University of California, San Francisco, San Francisco, CA, 3University of Alabama, Birmingham, Birmingham, AL, 4University of Iowa, Iowa City, IA, 5Klinikum Augsburg, Augsburg, Germany.

### Background/Purpose

As hand osteoarthritis (OA) studies with repeated MRI scans are few, longitudinal associations between synovitis and bone marrow lesions (BMLs) and pain are unknown. Our aim was to explore whether changes of synovitis and BMLs are related to changes in joint tenderness in a longitudinal hand OA study.

### Methods

We included 70 patients (43 women, mean (SD) age 67.9 (5.5) years) from the Oslo hand OA cohort with 1.0T MRI and clinical joint examination at baseline and 5-year follow-up. All patients had longitudinal Short Tau Inversion Recovery (STIR) images of the interphalangeal joints of dominant hand, n = 69 had longitudinal T1w fat-suppressed (fs) pre-Gadolinium (Gd) images, and n = 48 had longitudinal T1w fs post-Gd images. The paired MRIs were scored according to the OMERACT hand OA MRI score for synovitis and BMLs on 0–3 scales. We allowed 0.5 increments for smaller changes. The same rheumatologist examined the finger joints for evidence of joint tenderness at baseline and follow-up. Among joints without tenderness at baseline, we explored whether increase of synovitis and BMLs (no change)decreasing synovitis and BMLs as reference were associated with incident tenderness in the same joint using Generalized Estimating Equations. Among joints with tenderness at baseline, we explored whether decrease or
loss of synovitis and BMLs (no change/increasing synovitis and BMLs as reference) were associated with loss of joint tenderness. Separate models were performed for synovitis and BMLs, respectively. The analyses were adjusted for age, sex, BMI and follow-up time.

**Results:** At baseline, synovitis was present in 204/379 (53.8%) joints (n = 5 missing), of which the majority was grade 1 (n = 139) and grade 2 (n = 54). BMLs were present in 108/552 (19.6%) joints, of which the majority (n = 80) was grade 1. Joint tenderness was found in 280/664 (40.2%) joints. The mean (SD) follow-up time was 4.7 (0.4) years. Increase/incident synovitis and BMLs were seen in 96/373 (25.7%) and 88/551 (16.0%), respectively. Decrease of synovitis and BMLs occurred in 63/373 (16.9%) and 47/551 (8.5%) joints, and 39 (10.5%) and 30 (5.4%) joints had complete loss of synovitis and BMLs, respectively. Increasing/incident synovitis and BMLs were significantly associated with incident tenderness in the same joint (Table). The associations were independent of each other (data not shown). No associations were found between decreasing synovitis and BMLs and loss of joint tenderness during follow-up (Table). However, there was a non-significant trend that loss of synovitis was associated with loss of joint tenderness (OR 1.78, 95% CI 0.83, 3.77).

**Conclusion:** The Oslo hand OA cohort is the first hand OA study with longitudinal MR images of the hands. Increasing synovitis and BMLs were significantly associated with incident joint tenderness. Loss of synovitis was associated with loss of tenderness, but the association was statistically non-significant.

The association with incident joint tenderness (in joints without tenderness at baseline)

<table>
<thead>
<tr>
<th>N (%); joints with incident tenderness</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change/decrease</td>
<td>46/175 (26.3%)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Increase</td>
<td>23/45 (51.1%)</td>
<td>2.53 (1.39, 4.61)</td>
</tr>
<tr>
<td>Bone marrow lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change/decrease</td>
<td>88/265 (33.2%)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Increase</td>
<td>29/47 (61.7%)</td>
<td>2.73 (1.33, 5.59)</td>
</tr>
</tbody>
</table>

The association with loss of joint tenderness (in joints with tenderness at baseline)

<table>
<thead>
<tr>
<th>N (%); joints with loss of tenderness</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change/increase</td>
<td>41/123 (33.3%)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Decrease</td>
<td>10/30 (33.3%)</td>
<td>0.99 (0.47, 2.10)</td>
</tr>
<tr>
<td>Bone marrow lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change/increase</td>
<td>57/203 (28.1%)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Decrease</td>
<td>10/56 (17.8%)</td>
<td>0.80 (0.45, 1.42)</td>
</tr>
</tbody>
</table>

**Disclosure:** I. K. Haugen, None; B. Slatkowwsky-Chrestensen, None; P. Boysen, None; S. Sesseng, None; D. van der Heijde, None; T. K. Kven, None.

**A Randomized Double-Blind Placebo-Controlled Trial of Vitamin D Supplementation in Juvenile-Onset Systemic Lupus Erythematosus: Improvement in Disease Activity and Fatigue Scores.** Glauc Lima, Juliane Paupitz, Liliam Takayama, Eloisa Bonifa and Rosa M. Pereira. Faculdade de M edicina da Universidade de São Paulo, São Paulo, Brazil.

**Background/Purpose:** Vitamin D has an important immunomodulatory effect but there are no clinical trials that directly addressed the benefit from boosting the serum level of 25-hydroxyvitamin D in juvenile-onset Systemic Lupus Erythematosus (JoSLE). The aim of this study is, therefore, to evaluate the vitamin D supplementation in disease activity scores and fatigue in JoSLE patients.

**Methods:** This study was a randomized double-blind placebo-controlled 24-week trial. Forty female JoSLE patients were randomized (1:1) to receive either oral cholecalciferol 50,000 IU/week (JoSLE-Vit D) or placebo (JoSLE-PL). M ean glucocorticoid dose and immunosuppressive medications remained stable throughout the study. Serum levels of 25 hydroxyvitamin D (25OHD) were measured using a radioimmunossay technique (DiaSorin, Stillwater, Minnesota, USA). Disease activity was assessed by the SLE Disease Activity Index (SLEDAI) and by European Consensus Lupus Activity Measurement (ECLAM). Fatigue was assessed using Kids Fatigue Severity Scale (K-FSS), scores with an adapted range from 1 to 5 with low levels indicating higher fatigue. Longitudinal regression models were used to estimate the association between levels of 25OHD, disease activity and fatigue. T-test or Mann-Whitney test were performed to see differences between groups.

**Results:** Groups were similar regarding age (p = 0.61), body mass index (p = 0.15), frequency of organ involvements (p = 0.05), mean glucocorticoid dose (11.90 ± 9.5 vs. 15.30 ± 14.82 mg/day, p = 0.38) and frequency of immunosuppressive drugs (84 vs. 75%, p = 0.490), SLEDAI (3.57 ± 2.87 vs. 4.35 ± 4.22, p = 0.51), ECLAM (2.31 ± 1.74 vs. 2.35 ± 2.09, p = 0.95), and fatigue scores at baseline (3.21 ± 0.90 vs. 2.90 ± 0.88, p = 0.29). There was no also no difference in the serum levels of 25OHD at the baseline between JoSLE-Vitamin D and JoSLE-PL (19.1 ± 6.6 vs. 19.5 ± 4.5 ng/mL, p = 0.81). After 24 weeks of supplementation, the mean level of 25OHD was higher in JoSLE-Vit D group compared to JoSLE-PL group (31.15 ± 8.89 vs. 16.56 ± 5.88 ng/mL, p < 0.001). At the end of intervention, a decrease in SLEDAI score was observed in JoSLE-Vit. D compared to JoSLE-PL (Δfinal – baseline) SLEDAI: -0.58 ± 3.11 vs. 1.2 ± 3.67, p = 0.011) and a tendency of decrease in ECLAM score (ΔECLAM: -0.63 ± 1.11 vs. 0.3 ± 0.20, p = 0.083). Regarding fatigue evaluation, an improvement of fatigue related to social life score was found in JoSLE-Vit D compared to JoSLE-PL (Δfinal – baseline) K-FSS: -0.04 ± 0.47 vs. -0.2 ± 0.68, p = 0.04). Cholecalciferol (50,000 IU/week) intervention was well tolerated with no serious adverse events.

**Conclusion:** This study suggests that cholecalciferol supplementation 50,000 IU/week for 6 months is effective to decrease disease activity and improve fatigue in JoSLE patients. (NCT01892748).
Background/Purpose: Patients with childhood-onset SLE (cSLE) may experience neurocognitive SLE (NPSLE) manifested as neurocognitive dysfunction (NCD). Formal neuropsychological testing (FNCT) is the most accepted method for diagnosing NCD. However, access is limited and it is costly and time-consuming. The Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) is a computerized test battery that assesses multiple domains of cognitive performance. However, it is unclear how PedANAM-generated variables can be interpreted in a clinical setting as measures of NCD.

Our purpose was to explore and initially test approaches to the calculation of a summary score (PedANAM Cognitive Performance Score (PedANAM-CPS)) to screen NCD in cSLE with high sensitivity.

Methods: Two cohorts were analyzed. The development cohort included cSLE patients (pts) and controls that completed the PedANAM and FNCT at two research study visits 18 months apart. The validation cohort consisted of cSLE pts and controls recruited in a clinical setting who completed the PedANAM and Pediatric Perceived Cognitive Function-43 questionnaire (PCF-43). Candidate PedANAM-CPS were generated based upon the development cohort’s first visit using 3 statistical methods: 1) Simple summary score: Mean accuracy score of all PedANAM’s subtests; 2) Logit-based score developed by logistic regression modeling; 3) PCA-based score derived from Principal Component Analysis (PCA). The latter 2 methods assigned in a different way a statistical weight to each subtest derived from Principal Component Analysis (PCA). The latter 2 methods assigned in a different way a statistical weight to each subtest.

Receiver operating characteristic curve analysis was used to assess the accuracy of candidate scores as predictors of NCD in the study cohorts.

Results: A total of 166 pts were studied, including 108 cSLE pts (Table 1). As shown in Table 2 the candidate PedANAM-CPS significantly differentiated between NCD and non-NCD groups. The Logit-based and PCA-based scores were also able to detect NCD on the second visit of the development and validation cohorts. The usefulness of the 3 PedANAM-CPS scores and their cut-off scores to define NCD was confirmed when using visit 2 data of the development cohort and the validation cohort.

Conclusion: Candidate PedANAM-CPS showed good construct and criterion validity, with a Logit-based score performing somewhat better for discriminating cSLE pts based on the presence or absence of NCD. The PedANAM-CPS may be a useful tool to summarize cognitive performance in assessing for NCD in cSLE. Confirmation studies are required to confirm its overall accuracy and clinical usefulness in cSLE.

Table 1 Demographics of Development and Validation Dataset at Enrollment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Development Dataset (n=108)</th>
<th>Validation Dataset (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>Controls (n=54) p-value</td>
<td>Validation Dataset (n=54)</td>
</tr>
<tr>
<td>Male</td>
<td>14±3.7</td>
<td>13.8±3.2 0.03</td>
<td>14.0±2.8 0.11</td>
</tr>
<tr>
<td>Female</td>
<td>14±3.1</td>
<td>14.5±3.2 0.03</td>
<td>14.0±2.6 0.11</td>
</tr>
<tr>
<td>Gender</td>
<td>0.62</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Age (years) in median (range)</td>
<td></td>
<td>Controls (n=54) p-value</td>
<td>Validation Dataset (n=54)</td>
</tr>
<tr>
<td>Male</td>
<td>14±3.7</td>
<td>13.8±3.2 0.03</td>
<td>14.0±2.8 0.11</td>
</tr>
<tr>
<td>Female</td>
<td>14±3.1</td>
<td>14.5±3.2 0.03</td>
<td>14.0±2.6 0.11</td>
</tr>
<tr>
<td>Erythrocyte</td>
<td>3.0</td>
<td>3.1±0.9 0.01</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>7.5</td>
<td>7±2.6 0.01</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>325</td>
<td>325±100 0.001</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.6</td>
<td>10.7±0.2 0.25</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>7.0</td>
<td>7.0±2.5 0.01</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.6</td>
<td>10.7±0.2 0.25</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>7.0</td>
<td>7.0±2.5 0.01</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td>4.5</td>
<td>4.3±4.7 0.7</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td>4.5</td>
<td>4.3±4.7 0.7</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive dysfunction</td>
<td>22.5</td>
<td>7.5±3.5 0.7</td>
<td></td>
</tr>
</tbody>
</table>
regression modeling, histological activity measurement does not necessitate consideration of clinical indices but rather select LN-TM and RBM. Levels of C3, NGL, CP, MCP1 and TF were found to be candidate C-RAI’s for predicting high LN activity (GAL1>10) with outstanding accuracy [area under the ROC curve (AUC) = 0.9]. NGL and HPX were excellent predictors of high histological inflammation with active LN (TIA1 > 5; AUC = 0.88) [Figure 1].

Conclusion: C3 level, NGL, CP, MCP1, TF, and HPX are good potential components for C-RAI to measure histological LN activity in the glomerular and interstitial. Confirmation in a larger data set is required.

Table 1: Comparisons of LN biomarkers between NIH GLAI and TIA1 classes

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>NGL</th>
<th>CP</th>
<th>MCP1</th>
<th>TF</th>
<th>SLICE*</th>
<th>Protein/Cr</th>
<th>Urine Protein</th>
<th>C3</th>
<th>Urine*</th>
<th>Serum*</th>
<th>TIA1*</th>
<th>NIEHS</th>
<th>AUC</th>
<th>5; AUC</th>
<th>5; AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLGALAI*</td>
<td>7.40</td>
<td>1.88</td>
<td>1.53</td>
<td>1.06</td>
<td>0.60</td>
<td>0.005</td>
<td>0.005</td>
<td>11.36</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>BiSGAL-1*</td>
<td>10.37</td>
<td>9.23</td>
<td>11.58</td>
<td>14.62</td>
<td>0.005</td>
<td>0.005</td>
<td>11.36</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
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</tr>
<tr>
<td>BiSLICE*</td>
<td>4.80</td>
<td>1.07</td>
<td>1.53</td>
<td>1.06</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>11.36</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
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</tr>
<tr>
<td>Procor/Cr</td>
<td>1.79</td>
<td>2.21</td>
<td>2.85</td>
<td>1.47</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>11.36</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
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</tr>
<tr>
<td>Serum Pro*</td>
<td>185.74</td>
<td>101.62</td>
<td>339.49</td>
<td>423.73</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>11.36</td>
<td>0.106</td>
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<td>C3 level*</td>
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<td>101.62</td>
<td>339.49</td>
<td>120.43</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>11.36</td>
<td>0.106</td>
<td>0.106</td>
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</tr>
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</table>

Table 2: Summary of patient demographics and laboratory results

Disclosure: K. Abulaban, None; M. Bennett, None; M. Klein-Gitelman, None; S. P. Ardinon, None; K. A. Rooster-Stevens, None; L. B. Tucker, None; W. Kiley, None; S. Nelson, None; K. Onell, None; N. G. Singer, None; K. M. O’Neill, None; E. Brooks, None; B. A. Eberhard, None; D. Witte, None; J. G. Hillman, None; T. Wright, None; D. Witte, None; J. Ying, None; P. Devajaran, None; H. I. Brunner, TMA and NIJHS, 9.

1827

Anti-Ro and Anti-La Antibodies in the General Pregnant Population

Evelyn V. Rozenblyum1, Sharon Sukhdeo2, Edgar Jaggie2, Lisa Horberger1, Phillip Wyatt3, Carl A. Laskin4 and Earl D. Silverman5. 1University of Toronto, Toronto, ON; 2The Hospital for Sick Children, University of Toronto, Toronto, ON; 3Stollery Children’s Hospital, Edmonton, ON; North York General Hospital, Toronto, ON; 4University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON; 5The Hospital for Sick Children, Toronto, ON.

Background: Neonatal lupus erythematosus (NLE) is a passively transferred autoimmune disease that occurs in babies born to pregnant women with anti-Ro and anti-La antibodies. The most serious complication of NLE is congenital heart block (CHB). In pregnancies of women with a known autoimmune condition and positive anti-Ro antibodies, the incidence of CHB is approximately 1–2% of live births. We have previously shown that only pregnant women with moderate-high titre of antibodies were at risk to deliver a child with CHB. However, the rate of anti-Ro antibody positive pregnant women in an otherwise healthy population is unknown as it is their risk for delivering a child with CHB.

Objectives: 1) Determine the rate of anti-Ro/La antibodies in the general pregnant population.
2) Determine if the incidence of CHB is increased in healthy pregnant women with positive Ro/La antibodies compared to pregnant women with known autoimmune disease and positive anti-Ro/La antibodies.

Methods: Antibody testing was performed on 15198 pregnant women who were having concurrent Maternal Serum Screening in the Metropolitan Toronto area. Maternal self-reported outcomes of prenatal, pregnancy, and post-natal medical conditions were reported, along with fetal outcomes of pre and post-natal illnesses. A uterine antibody titres were stratified into negative, low, moderate, and high positive.

Results: 1152/15198 (7.6%) of the pregnant women had anti-Ro antibodies and 179/15198 (1.2%) had moderate-high titres (at risk to deliver a child with CHB). 779/15198 (5.1%) had anti-La antibodies, with the majority of these women having low titre. During the course of the study there were 13 cases of CHB that were unrelated to our maternal sample population- 10 to well women and 2 to women with an autoimmune disease. All of these women had moderate-high titre anti-Ro antibodies, while only 31% had moderate-high titre anti-La antibodies. During the course of the study 39 pregnant women with a known autoimmune disease and anti-Ro antibodies (at risk to deliver a child with CHB) were prospectively followed. 2/39 delivered a child with CHB. Both of these women had moderate-high titre anti-Ro antibodies while 15/37 pregnant women who delivered a child without CHB had moderate-high titre anti-Ro antibodies. Therefore 2/17 (11.8%) women with moderate-high titre anti-Ro antibodies were delivered a child with CHB. Conclusion: The incidence of CHB is expected to be between 1.0–1.5 per 1000 pregnancies. Therefore, on our data showing 1.2% of otherwise well pregnant women had moderate-high titre anti-Ro antibodies (at risk to deliver a child with CHB), 779/15198 (5.1%) had anti-La antibodies, while only 10/15198 (0.07%) children without CHB will be delivered to otherwise healthy women, and incidence of 0.5–0.8%. In contrast, in women with a known autoimmune disease and moderate-high anti-Ro antibody titre, we found an 11.8% incidence of CHB. Therefore the risk for a woman with a known autoimmune disease and moderate-high titre anti-Ro antibodies was approximately 10x that of otherwise healthy pregnant women. These data therefore suggest that the anti-Ro antibody repertoire differs between these 2 groups of pregnant women.

Disclosure: E. V. Rozenblyum, None; S. Sukhdeo, None; E. Jaggie, None; L. Horberger, None; P. Wyatt, None; C. A. Laskin, None; E. D. Silverman, None.

1828

Adverse Pregnancy Outcomes in Adolescents and Young Women with Systemic Lupus Erythematosus: A National Estimate


Background: Pregnant women with SLE have increased risk of adverse outcomes including lupus flare, spontaneous abortion, pre eclampsia/ eclampsia, premature birth and maternal death, but pregnancy outcomes among adolescents and young women with SLE have not been well-explored. Our goal was to compare pregnancy outcomes among adolescents and young women with and without SLE, and to identify associated risk factors.

Methods: We studied the 2000–2011 Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. The NIS contains annual discharge data from all-payer hospital stays from approximately 1,000 nationwide hospitals, to approximate a 20% stratified sample of U.S. community hospitals. Hospitalizations of individuals age 21 or less with ICD-9 discharge diagnoses associated with pregnancy were included (delivery, liveborn, abortion, ecliptic pregnancy, or intrauterine death). SLE hospitalizations were identified by a 710.0 ICD-9 code. A fter applying sampling weights, unadjusted odds ratios to estimate the risk of adverse pregnancy outcomes among individuals with and without SLE were calculated. Multi-variate logistic regression was performed to examine the independent effect of age, race, and socio-economic status on pre eclampsia/eclampsia.

Results: 9,125–24hospitalizations were included in the analysis, of which 4,142 had SLE. Hospitalized women with SLE were slightly older (mean age 19.4 with range 14–21 vs 19 with range 8–21), more likely to be black (34% vs. 23%), more likely to carry a discharge diagnosis of nephritis (11% vs. 0.02%) or aPL (2.7% vs. 0.1%), and more likely to undergo hemodialysis (0.35% vs. 0.00%), all p < 0.0001. Socio-economic status repre-
the ventricular nadir between the two groups (53.5 bpm with SLE).

In the population of SLE patients, 11,749 (0.13%) women had preterm labor, 99,426 (1.1%) had spontaneous abortion or intrauterine death, and 4.3% developed eclampsia or pre-eclampsia. The overall case fatality rate for this more extensive disease was 17.2% (10.4–28.3). The case fatality rates at 6 months of post partum life were similar between the groups (7/78, 9% for FS vs. 8/96, 8.3% for untreated, P = 1.0).

**Conclusion:** These data provide evidence for decision making regarding the use of dexamethasone in the management of isolated congenital heart block. The development of more advanced disease approaches 15% and institution of dexamethasone should not be routinely instituted solely for prevention of this complication.

**Disclosure:** U. Shah, None; A. Saxena, None; S. Sahl, None; D. Friedman, None; J. P. Buyon, None; P. M. Izmirl, None.

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**Background/Purpose:** Rheumatoid arthritis (RA) is a chronic common disease with significant morbidity, mortality, and cost. To optimize care for RA patients, we developed a novel value-based population care model - AIM FARTHER (Atribution, Integration, Measurement, and Reporting of THERapies). AIM FARTHER was designed to improve quality and reduce cost of RA care.

**Methods:** The AIM FARTHER model was designed and implemented for all RA patients cared for by the 17 rheumatologists within our health system (n ~ 2,300 patients). Components included: 1) registry development; 2) defining roles and attribution; 3) integration of primary and specialty care; 4) strategic approach to RA care; RA quality bundle development; 6) task management and performance reporting; and 7) a new financial incentive model. The RA quality bundle included 8 measures – RA on DMARD, RA with CDAI (Clinical Disease Activity Index), RA at low disease activity, TB testing if on biologic, Influenza vaccination, Pneumococcal vaccination, and LDL (low density lipoprotein) checked. These measures were collected electronically, providing the analytics for a patient scorecard (Figure 1). The scorecard was used to close care gaps, rolled up into provider and department performance reports, and shared transparently. Analysis of AIM FARTHER included quality (individual measures and "all or none" bundle score) and cost (biologic de-escalation savings).

**Results:** AIM FARTHER was implemented August 2012 (2,150 RA patients) with 22 month follow-up (2,378 RA patients). Significant improvements noted in all quality measures (except active RA on DMARD (92% vs. 93%)[Figure 2]). Final values were RA on DMARD 90%, RA with CDAI 84%, RA at low disease activity 53%, TB testing on biologic 93%, Influenza vaccine 75%, Pneumococcal vaccine 72%, and LDL checked 95%. The all or none bundle improved from 22% to 40% (40% of the 2,378 RA patients had achieved 100% of their applicable quality measures). Cost savings from biologic de-escalation were $720,000 for 2013 with projected savings estimate of $1.2 million for 2014.

**Conclusion:** AIM FARTHER is a novel care model employing provider engagement, process redesign, measurement, and information technology to provide optimal care for patients with RA. AIM FARTHER showed significant improvement in quality measures and reduction in cost of care for a population of over 2,300 RA patients. Aditionally, it supports the pivotal role that rheumatology can play in the systematic care of patients with RA.
Monday, November 17

Cedeno None; Bili None; C. Sullivan

Background/Purpose: Monitoring patients with rheumatoid arthritis (RA) in clinical practice with regular assessment of disease activity (e.g., DAS28) is recommended as part of a treat-to-target strategy, but little is known about its feasibility. In Denmark, prospective, nationwide collection of data on patients with RA in routine care has been conducted in the DANBIO database since year 2006 (1). We present the development over time in patient inclusion and disease control.

Methods: DANBIO serves as an electronic patient file in routine care. Disease activity score (DAS28) is presented in colour, encouraging a treat-to-target strategy. Patients are followed twice yearly.

Results: From Jan 1st 2006 to Dec 31st, 2013, the number of RA patients increased from 2,395 to 14,249 (age at time of inclusion: 60(50–59) years, 73% women, 87.2% IgM-RF positive, 54% erosive, disease duration 4 (0–11) years, HAQ 0.75(0.25–1.375), DAS28 3.9(2.7–5.1)).

By 2013, 9,054 patients were bDMARD naïve (MTX: 76%; other csDMARD: 21%), 4,254 pts received bDMARD (etanercept:28% and adalimumab:21%) most prevalent; 66% in combination with MTX), and 941 pts had formerly received bDMARD.

In 2006, 54% of the 2,395 patients had low disease activity (DAS28<3.2) (figure). In 2013 it was 73% of 14,249 patients. For high disease activity it was 11% and 17%, respectively. The fraction of patients in DAS28 remission it was 11% and 17%, respectively, and 73% had low disease activity.

Conclusion: By using an electronic platform, Danish rheumatologists included 40–79% of all RA patients into the DANBIO database during an 8 year period for prospective registration, thereby creating a data repository for quality improvement and research purposes with high external validity.

The demographic characteristics of the “real-life” cohort are typical for RA, and it covers all disease states regarding treatment, disability and disease activity. By 2013, 17% and 55% of patients were in ACR/EULAR remission and DAS28 remission, respectively, and 73% had low disease activity.

Thus, systematic monitoring of real-life RA patients with a treat-to-target strategy with real-time feedback to the physician is feasible, whereas the aim of treat-to-target is not achieved in a substantial proportion of patients in routine care.

Acknowledgements: We are grateful to all DANBIO members for their collaboration. This study was supported by grants from Novo Nordisk (2008–2010), LEO Pharma (2010–2012), and EUCERIN (2012–2013).

Disclosure: E. D. Newman None; W. T. Ayoub None; D. M. Pugliese None; C. Cedeno None; J. Brown None; T. M. Harrington None; T. P. Olianginski None; A. Bill None; A. E. Denier None; L. L. Schroeder None; D. Torretti None; T. Sharma None; L. Kirlilla None; S. Mathew None; J. Cote None; B. Opperman None; C. Sullivan None; S. Bishwal None; B. Del Vecchio None; H. Aylward None.

Experiences from a Treat-to-Target Strategy Using the Danbio Registry. Monitoring Patients with Rheumatoid Arthritis in Routine Care – 1831

Methods:

- **DANBIO**, Glostrup Hospital, Glostrup, Denmark, 2DANBIO, Glostrup, Denmark, 3ZiteLab ApS, Copenhagen, Denmark.

1832

National Quality Forum Measure Achievement and Costs in Rheumatoid Arthritis Patients in a Large Managed Care Population. Roxanne Meyer, Susan C. Bolger, Joseph Tkacz, Brenna Brady and Charles Ruetsch. 1Janssen Scientific Affairs, Horsham, PA, 2Janssen Scientific Affairs, LLC, Horsham, PA, 3Health Analytics, LLC, Columbia, MD, 4Health Analytics LLC, Columbia, MD.

Background/Purpose: The American College of Rheumatology and National Quality Forum (NQF) recommend monitoring quality measures among rheumatoid arthritis (RA) patients. Previously we described the proportion of RA patients within a large managed care population meeting the criteria of RA specific NQF quality measures. This study examines the relationship between NQF measure attainment and healthcare expenditure.

Methods: Using the Optum™ Clinformatics™ database of insured individuals, 8 NQF RA quality measures (0054, 0589, 0590, 0592, 0597-0599, and 0601) were assessed among a sample of RA patients during calendar year 2011. NQF definitions may be found at http://www.qualityforum.org/QPS/. Mean specific healthcare costs, in addition to total healthcare costs, were calculated for all members eligible for analyses. The standard cost field, which is an estimate of the allowed payment for all provider services, was selected as the primary outcome of interest. Results: The majority of individuals were female and in their mid-fifties (mean age of 52.6). Measure achievement ranged from 55.9% (measure 0592) to 80.8% (measure 0054). The mean cost of care for individuals meeting the measure was $18,642, range 12,488-$21,300. Those patients who did not meet the measures had an average cost of care for $14,923, range $13,013 - $19,293. The primary drivers of cost were pharmacy and office expenses, accounting for 42.3% and 28.6% of total costs, respectively.

Conclusion: By using an electronic platform, Danish rheumatologists included 40–79% of all RA patients into the DANBIO database during an 8 year period for prospective registration, thereby creating a data repository for quality improvement and research purposes with high external validity.

The demographic characteristics of the “real-life” cohort are typical for RA, and it covers all disease states regarding treatment, disability and disease activity. By 2013, 17% and 55% of patients were in ACR/EULAR remission and DAS28 remission, respectively, and 73% had low disease activity.

Thus, systematic monitoring of real-life RA patients with a treat-to-target strategy with real-time feedback to the physician is feasible, whereas the aim of treat-to-target is not achieved in a substantial proportion of patients in routine care.

Acknowledgements: We are grateful to all DANBIO members for their collaboration. This study was supported by grants from Novo Nordisk (2008–2010), LEO Pharma (2010–2012), and EUCERIN (2012–2013).

Disclosure: E. D. Newman None; W. T. Ayoub None; D. M. Pugliese None; C. Cedeno None; J. Brown None; T. M. Harrington None; T. P. Olianginski None; A. Bill None; A. E. Denier None; L. L. Schroeder None; D. Torretti None; T. Sharma None; L. Kirlilla None; S. Mathew None; J. Cote None; B. Opperman None; C. Sullivan None; S. Bishwal None; B. Del Vecchio None; H. Aylward None.
Table 1: Total HealthCare Costs (means) USD ($)

<table>
<thead>
<tr>
<th>NQF Measure</th>
<th>Measuring the Measure</th>
<th>Not Measuring the Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NQF 0564 - DMARD Therapy</td>
<td>$21,314</td>
<td>$19,356</td>
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<tr>
<td>NQF 0589 - New DMARD Baseline Serum Creatinine</td>
<td>$15,182</td>
<td>$13,388</td>
</tr>
<tr>
<td>NQF 0580 - New DMARD Liver Function Test</td>
<td>$12,922</td>
<td>$12,121</td>
</tr>
<tr>
<td>NQF 0592 - Annual ESR or CRP</td>
<td>$17,945</td>
<td>$12,329</td>
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<tr>
<td>NQF 0601 - New RA patient ESR or CRP</td>
<td>$12,910</td>
<td>$13,624</td>
</tr>
<tr>
<td>NQF 0597 - Methotrexate User Liver Function Test</td>
<td>$10,243</td>
<td>$17,767</td>
</tr>
<tr>
<td>NQF 0596 - Methotrexate User CBC Test</td>
<td>$10,173</td>
<td>$17,961</td>
</tr>
<tr>
<td>NQF 0599 - Methotrexate User Serum Creatinine</td>
<td>$10,526</td>
<td>$17,181</td>
</tr>
</tbody>
</table>

Conclusion: In general, meeting quality measures was associated with an increased cost of care. Pharmacy costs were similar between patients who did and did not meet the measures. Individuals who met the measures had higher office costs while those individuals who did not meet the measure trended towards higher inpatient costs and had significantly higher outpatient costs. These findings suggest that increased quality in healthcare may lead to lower inpatient and outpatient hospital costs, but that the overall cost of care for RA patients is likely to remain high due to intensive pharmacotherapy regimens.

Disclosure: R. Meyer, None; C. Bombardier, None; J. Young, None; N. Ivers, None; R. L. Jaakkimainen, None; S. Bernatsky, None; J. M. Paterson, None; J. C. Thorne, None; P. S. Akhavan, None; D. Butt, None; V. Aholuwalia, None; K. Tu, None.

1834

Uptake of the American College of Rheumatology’s (ACR) Rheumatology Clinical Registry (RCR): Quality Measure Summary Data. Natalie Fries, Melissa Francis, Linos Y. Azad, and Saluddin Kass. American College of Rheumatology, Atlanta, GA, 3University of California, San Francisco, San Francisco, CA, 3UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: The RCR is designed to provide ACR members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. Currently in its fifth year of operation, the RCR contains data on over 38,000 patient encounters.


Methods: Data derive from retrospective medical records abstractions performed by providers and/or designated practice staff for a sample of patients seen by rheumatologists. Data are submitted to a secure, web-based registry system. Patients included in the denominator of all quality measures are >18 years of age with a diagnosis of RA who are receiving treatment by the reporting rheumatology provider. Additional details of each measure are listed in Table 1. We report the mean performance on each quality measure, defined as percentage of eligible patients receiving recommended care. Patients classified as high risk.

Table 1 summarizes performance on RA measures reported through the RCR. The table includes data from the current reporting period (CY 2013) as well as comparative data from CY 2012 and CY 2011. For the current reporting period, 215 rheumatology providers from 123 practices submitted data on 6,963 encounters with RA patients. During CY 2012, 197 rheumatology providers in 115 practices submitted data on 9,154 encounters with RA patients. In CY 2011, 244 rheumatology providers in 129 practices submitted data on 8,096 encounters with RA patients. Reporting providers practice in sites ranging from single offices to large academic medical centers.

Table 1. Performance on RA Measures Assessed through the RCR

<table>
<thead>
<tr>
<th>Measure</th>
<th>CY2011</th>
<th>CY2012</th>
<th>CY2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity assessed at least once within 12 months, using a standardized descriptive or numeric scale or composite index, and classified as low, moderate or high risk</td>
<td>8075</td>
<td>43.3%</td>
<td>6485</td>
</tr>
<tr>
<td>Functional status assessment performed at least once within 12 months, using a standardized descriptive or numeric scale, standardized or unstandardized, or within the assessment of the impact of RA or RA as a patient, measured by the American College of Rheumatology's Functional Health Assessment Questionnaire</td>
<td>8077</td>
<td>70.5%</td>
<td>6485</td>
</tr>
<tr>
<td>Patient prescribed, dispensed, or administered at least one anti-rheumatic drug prescribed for a DPARU within 12 months</td>
<td>7800</td>
<td>91.9%</td>
<td>6485</td>
</tr>
</tbody>
</table>
Conclusion: Performance rates increased on four out of five measures from CY 2011 to CY 2012. Based on preliminary results, it appears that use of the RCR to track quality measures increases performance.

Disclosure: N. Fisk, None; M. Francisco, None; J. Yazdany, None; S. Kazi, None.

1835

Anti-Osteoporosis Medication Use after Hip or Vertebral Fracture. Robert A. Overman1 and Chad L. Deal2. 1University of North Carolina, Chapel Hill, NC, 2Cleveland Clinic, Cleveland, OH.

Background/Purpose: Current National Osteoporosis Guidelines recommend treatment with an approved osteoporosis medication after hip and vertebral fracture. Only 20% of patients receive osteoporosis therapy after hip fracture. We examined the rates of treatment within 365 days of an osteoporosis medication after hip and vertebral fracture in a large health care system.

Methods: We evaluated use of anti-osteoporosis medications after fracture by identifying all patients over age 40 who had a hip fracture that was surgically repaired and all vertebral fracture patients undergoing augmentation (kyphoplasty or vertebroplasty) based on administrative billing Common Procedure Terminology (CPT) codes between 2010 and September 2013. These patients were then linked to their electronic medical record (EMR) data. We define the index date as the date of the surgical procedure with patients followed until death, AOM use, or 365 days. AOMs in this analysis are bisphosphonates, denosumab, teriparatide, estrogen, or raloxifene. Dates of medication use are based on start and stop dates in the EMR. Basic demographic variables including age, race, gender, prior AOM use, and site of fracture, were collected from the patients EMR and are presented as mean (standard deviation [SD]) or n (%). We evaluated initiation or continuation of AOM at 90, 180, and 365 days post-index and factors associated with their initiation. Hazard ratios (HR) (95% confidence interval [CI]) were created with cox proportional hazards model and are adjusted for gender, race, age by decade, and site of fracture.

Results: There were 1,352 hip fractures and 296 vertebral fractures undergoing augmentation between January 2010 and December 2012. Mean age was 80.9 (SD 12.7) for hip and 75.0 (SD 12.5) for vertebral fractures. Women were the majority population for both hip (73.1%) and vertebral fractures (72.6%). Caucasians made up the majority of both populations (hip 89.6%; vertebral 92.2%). First event was an AOM use for 16.1% (hip: 11.1%; vertebral: 39.2%) and death for 11.3% (hip: 12.5%; vertebral 5.7%) of the population. Prior to index date 24.2% of hip and 40.5% of vertebral fracture patients were prescribed an AOM. AOMs were at fracture or within 90 days for 12.0%, 13.2%, and 14.6% for hip fracture and 34.5%, 37.8% and 45.5% for vertebral fractures at 90.180, and 365 days respectively. Vertebral fractures were associated with an increased likelihood of AOM treatment by 365 days (HR 3.1; 95% CI 2.4, 4.0), women (79.2% of population) were no more likely to be treated (HR 1.3 95% CI 0.9, 1.8) compared to men, and AOM use prior to fracture was associated with treatment by 365 days (HR 3.6; 95% CI 2.8, 4.7).

Conclusion: Treatment gaps continue to persist for hip fracture patients with 14.6% of patients receiving treatment by 365 days after fracture, and while only 45.3% of vertebral fracture patients having augmentation receiving therapy by 365 days. Patients with a vertebral fracture and those who were treated before fracture were more often placed on AOM. Treatment after fracture helps to demonstrated to reduce the likelihood of additional fractures and interventions are needed to increase treatment rates in these at risk populations.

Disclosure: R. A. Overman, None; C. L. Deal, None.

ACR Concurrent Abstract Session Rheumatoid Arthritis - Clinical Aspects III: Malignancies, Vaccinations, Pregnancy and Surgery

Monday, November 17, 2014, 2:30 pm - 4:00 pm

1836

Safety of Zoster Vaccination Administration in Rheumatic Patients on Current Biologic Therapy. Stephen Lindsey1, Brandi Oufnac2 and Holly Walker*. 1Ochsner Clinic Baton Rouge, Baton Rouge, LA, 2Ochsner Health Systems, Baton Rouge, LA.

Background/Purpose: Herpes Zoster (HZ) occurs in 1 in 3 people in the United States during their lifetime. The greatest risk factor is age. Immune suppression from illness or medications is also a strong risk factor. RA increases zoster rates 1.5 - 2 times normal as does >10mg prednisone per day. Studies are mixed on the role of MTX and anti-TNF's on HZ. Zoster vaccine has been shown to lower risk and is approved for all patients over 50 by the FDA and recommended for patients over 60 by the ACR. Guidelines from the ACR do not recommend HZ vaccine in patients on biologic therapies. However, recent large data base studies have not found an increase in zoster complications in patients inadvertently given the vaccine while on biologics. These data encouraged our group to evaluate the safety of this vaccine in current biologic users.

Methods: Since July 2012, all 160 patients with RA, PSA & AS receiving IV biologics in our infusion center have been prospectively assessed for HZ vaccine as well as 142 patients on subq biologics for the same indications. RA patients are 53% of incidence and 66% of subq patients. All biologics were represented. Remicade was the most common infusion followed by Ocrenza. Enbrel was the most common subq followed by Humira.

Inclusion/exclusion criteria for vaccination included: age > 50, no hx of anaphylaxis to neomycin or gelatin, no episodes of HZ in last 4 years, pregnancy, patient consent, and disease activity stable - moderate or less on consecutive visits. No patients had an active infection or malignancy.

If patient meets criteria, vaccine given at next interval scheduled dose of biologic, which is held. Example - hold Entbr 1 week, Humira 2 weeks, Ocrenza 4 weeks, Remicade 8 weeks. MTX was held week of vaccine and restarted 1 week post vaccine. Biologic restarted 2 weeks after vaccine. In 2011, 17 Rituxan patients vaccine was given 2-4 weeks pre Rituxan or > than 6 months post Rituxan. No other vaccines were given the week of the HZ vaccine.

Results: Of 160 infusion patients 110 (68%) have been vaccinated; over 60% had been on biologic > 5 years, 5% < 1 year. None developed disseminated HZ. One patient had significant swelling and tenderness at the injection site. Most common reasons not to vaccinate: 11 with recent HZ, 14 < age 50, and 17 with disease activity issues. Of 142 subq patients, 42 (32%) have been vaccinated; over 50% had been on biologic > 5 years, 10% < 1 year. No patients developed disseminated HZ or had a significant local reaction. Most common reasons not to vaccinate: 74 patients < 50, 12 with disease activity issues, 5 with HZ vaccine concerns and 5 with recent HZ. No patients in either group developed HZ within the six weeks post vaccination.

Two patients vaccinated since 2012 in our infusion cohort have developed HZ at 16 and 20 months and none in the subq patients. Prior to 2012, only 7 and 8% of the cohorts had received HZ vaccine.

Conclusion: HZ vaccination in chronic RA, PSA or AS patients on current IV or subq biologic therapies appears safe using this protocol. No occurrence of disseminated HZ occurred. There was no increased incidence of HZ in the early post vaccination period.

Disclosure: S. Lindsey, None; B. Oufnac, None; H. Walker, None.

1837

First Results of a European Registries Collaborative Project to Compare the Spectrum of Lymphomas Between Different Exposure Groups in Rheumatoid Arthritis. Louise Mecer1, Xavier Mariette2, William Dixon3, Eva Backlund4, Karin Helgern5, Lene Dreyer6, Merete Lund Hetland5, Lene Mellerkjær7, Kimme Hyrich8, Anja Strangefeld9, Angela Zink10, Helga Canhao11, Fernando Martins12, Victoria Hernández13, Florence Tubach14, Jacques Eric Gottenberg15, Jacques Morel16, Jakub Zavada17, Piet van Riel18, Axel Finckh19, Florenzo Jannone20, Johan Asking21 and Joachim Listing22. 1The University of Manchester, Manchester, United Kingdom, 2Université Paris-Sud, Le Kremlin Bicêtre, France, 3Uppsala University, Uppsala, Sweden, 4Karolinska Institutet, Stockholm, Sweden, 5Copenhagen University Hospital at Gentofte, Gentofte, Denmark, 6DANBIO, Glostrup Hospital, Glostrup, Denmark, 7The Danish Cancer Society, Copenhagen, Denmark, 8Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, 9German Rheumatism Research Center, Berlin, Germany, 10German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, 11Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, 12Instituto de Medicina, Universidade de Lisboa, Lisbon, Portugal, 13BIOMA Data Registry, Malmö, Sweden, 14Université Paris Diderot, Paris, France, 15Department of rheumatology CHU, Strasbourg, France, 16Universite Montpellier, Montpellier, France, 17Charles University, Prague, Czech Republic, 18Radboud University Medical Centre, Nijmegen, Netherlands, 19University of Geneva, Geneva, Switzerland, 20Reumatología Universitaria e Policlínico di Bari, Bari, Italy.

Disclosure: S. Lindsey, None; B. Oufnac, None; H. Walker, None.

ACR Concurrent Abstract Session Rheumatoid Arthritis - Clinical Aspects III: Malignancies, Vaccinations, Pregnancy and Surgery

Monday, November 17, 2014, 2:30 pm - 4:00 pm

1836

Safety of Zoster Vaccination Administration in Rheumatic Patients on Current Biologic Therapy. Stephen Lindsey1, Brandi Oufnac2 and Holly Walker*. 1Ochsner Clinic Baton Rouge, Baton Rouge, LA, 2Ochsner Health Systems, Baton Rouge, LA.
Background/Purpose: Rheumatoid arthritis (RA) is associated with a 2-3 fold increased risk of both Hodgkin and non-Hodgkin lymphoma (HL; NHL). The risk of lymphoma, in particular diffuse large B-cell lymphoma (DLBCL) is greatest in patients with persistently active RA; those patients that are also most likely to receive biologics. There has been a concern that TNF inhibitors (TNFi) could increase the risk of lymphoma via reduced immunosurveillance. Conversely, TNFi may, by improved disease control, decrease lymphoma risk, especially risk of DLBCL. This abstract describes a EULAR initiative to describe the spectrum of lymphomas occurring in biologic-naïve and –exposed cohorts of patients with rheumatoid arthritis. Importantly, the distribution of subtypes was similar across treatment groups.

Conclusion: This large collaborative analysis of European registries has successfully collated subtype information on more than 500 lymphomas. There was no evidence of modification of the distribution of lymphoma subtypes reported in patients following exposure to biologics. This collaboration facilitates more detailed analyses, accounting for age, sex, country and specific TNFi, as well as RA-related factors.

Table: Subtypes of lymphoma reported in biologic-naïve and -exposed cohorts of patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Biologic-naïve</th>
<th>Biologic-exposed</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td>19 (37)</td>
<td>26 (52)</td>
<td>1.4 (0.9, 2.2)</td>
</tr>
<tr>
<td>Nodular</td>
<td>12 (24)</td>
<td>14 (27)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
<tr>
<td>Lymphocyte-rich</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.1 (0.5, 2.5)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.1 (0.5, 2.5)</td>
</tr>
<tr>
<td>Diffuse mixed cell lymphoma</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.1 (0.5, 2.5)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>8 (16)</td>
<td>9 (18)</td>
<td>1.1 (0.7, 1.8)</td>
</tr>
<tr>
<td>Non-Hodgkin B-cell lymphoma</td>
<td>19 (37)</td>
<td>26 (52)</td>
<td>1.4 (0.9, 2.2)</td>
</tr>
<tr>
<td>Follicular</td>
<td>11 (22)</td>
<td>15 (29)</td>
<td>1.3 (0.9, 1.9)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>12 (24)</td>
<td>14 (27)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.1 (0.5, 2.5)</td>
</tr>
<tr>
<td>Diffuse mixed cell lymphoma</td>
<td>1 (2)</td>
<td>1 (2)</td>
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</tr>
<tr>
<td>Unspecified</td>
<td>8 (16)</td>
<td>9 (18)</td>
<td>1.1 (0.7, 1.8)</td>
</tr>
</tbody>
</table>

All percentages represent % of the total number of lymphomas in that cohort with % of Hodgkin lymphoma, B- and T-cell lymphomas and unspecified NHL/lymphoma totaling 100%; 272 lymphomas, but no follow up time (person-years), are included from the RATIO registry, France, sDMARD synthetic disease modifying drugs; TNFi inhibitors of TNF; RTX rituximab; TOC tocilizumab; ABA abatacept.

Disclosure: L. Mercer, None; X. Mariette, None; W. Dixon, None; E. Backlund, None; K. Helgerrn, None; L. Dreyer, None; M. L. Heltland, None; L. Mellemkjaer, None; K. Hylrich, None; A. Strangfeld, None; A. Zink, None; H. Canhao, None; F. Martin, None; V. Hernandez, None; F. Tubach, None; J. E. Gottenberg, None; M. Morel, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Bristol-Myers Squibb, 5, Union Chimio Belge, 5, Merck Pharmaceuticals, 5, Abbott Laboratories, 5; J. Zavada, None; P. van Riel, None; A. Finckh, None; F. Iannone, None; J. Askling, Astazeneca; Pfizer, 2; J. Listing, None.

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The University of Manchester, Manchester, United Kingdom, 1Karolinska Institutet, Stockholm, Sweden, 2Copenhagen University Hospital at Gentofte, Gentofte, Denmark, 3DANBiO, Glostrup Hospital, Glostrup, Denmark, 4The Danish Cancer Society, Copenhagen, Denmark, 5German Rheumatism Research Center, Berlin, Germany, 6German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, 7Reumatologoa Universita e Politecnico di Bari, Bari, Italy, 8University of Geneva, Geneva, Switzerland, 9Charles University, Prague, Czech Republic, 10Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, 11Instituto de Medicina, Universidade de Lisboa, Lisbon, Portugal, 12Université Paris-Sud, Le Kremlin Bicêtre, France, 13Université Paris-Diderot, Paris, France, 14Radboud University Medical Centre, Nijmegen, Netherlands, 15Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Swedish and Danish national biologics registers (*) have reported a possible increase in melanoma risk with TNFi inhibitors. Since melanomas are uncommon, the association is difficult to evaluate in other individual registers. We therefore planned a EULAR collaborative project.

Methods: Patients with RA from 11 European biologics registers in 9 countries were included. Patients were followed prospectively from start of a new biologic treatment until the occurrence of first invasive histology-confirmed invasive melanoma (skin, melanoma other than melanoma in situ), using an ever-exposed approach. For the TNFi cohort, prior exposure to biologic drugs was not permitted. Prior exposure to TNFi was allowed for other biologic drugs. Frequency of lymphoma subtypes was recorded for each drug class.

Results: Data for 130462 patients were available for the analysis (Sweden: n=61327, Denmark: n=21454, UK: n=17907, Germany: n=12581, Portugal: n=5031, Spain: n=4590, France: n=4512, Czech Republic: n=2860); mean age 59, 74% female. In total 520 lymphomas with subtype information were included in the table. Patient years were available for other biologic drugs. Frequency of lymphoma subtypes was recorded for each drug class.

Table: Number of melanomas, standardized incidence ratios and incidence rate ratios in different treatment groups of RA

<table>
<thead>
<tr>
<th>Biologic-naive</th>
<th>Biologic-exposed</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF ever-exposed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 2860) | mean age 59, 74% female. In total 520 lymphomas with subtype information were included in the table. Patient years were available for other biologic drugs. Frequency of lymphoma subtypes was recorded for each drug class.

All percentages represent % of the total number of lymphomas in that cohort with % of Hodgkin lymphoma, B- and T-cell lymphomas and unspecified NHL/lymphoma totaling 100%; 272 lymphomas, but no follow up time (person-years), are included from the RATIO registry, France, sDMARD synthetic disease modifying drugs; TNFi inhibitors of TNF; RTX rituximab; TOC tocilizumab; ABA abatacept.

Disclosure: L. Mercer, None; X. Mariette, None; W. Dixon, None; E. Backlund, None; K. Helgerrn, None; L. Dreyer, None; M. L. Heltland, None; L. Mellemkjaer, None; K. Hylrich, None; A. Strangfeld, None; A. Zink, None; H. Canhao, None; F. Martin, None; V. Hernandez, None; F. Tubach, None; J. E. Gottenberg, None; M. Morel, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Bristol-Myers Squibb, 5, Union Chimio Belge, 5, Merck Pharmaceuticals, 5, Abbott Laboratories, 5; J. Zavada, None; P. van Riel, None; A. Finckh, None; F. Iannone, None; J. Askling, Astazeneca; Pfizer, 2; J. Listing, None.
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Risk of Recurrent Non-Melanoma Skin Cancer with Methotrexate and Anti-TNF Use in Rheumatoid Arthritis. Frank I Scott1, Ronac Mamtani1, Colleen Brensinger1, Kevin Haynes1, Zéma Chiesa-Fuxench1, Huifeng Yun3, Jie Zhang4, Lang Chen5, Fenglong Xie5, David Margolis1, James D. Lewis2, Frank I Scott1, Ronac Mamtani1, Colleen Brensinger1, Kevin Haynes1, Zéma Chiesa-Fuxench1, Huifeng Yun3, Jie Zhang4, Lang Chen5, Fenglong Xie5, David Margolis1, James D. Lewis2.

Background/Purpose: Methotrexate (MTX) and anti-TNF drugs have been hypothesized to increase the risk of a first non-melanoma skin cancer (NMSc). Among patients with prior NMSc, it is unknown what impact use of these medications has on a second NMSc.

Methods: We performed a cohort study using Medicare data from 2006-2011. We identified Caucasian patients with rheumatoid arthritis (RA) and a first recorded NMSc on the basis of a diagnostic code for NMSc and related surgical procedure within 60 days according to a validated algorithm. We assessed for MTX, anti-TNF, abatacept, and rituximab use before and after the initial NMSc diagnosis. Hydroxychloroquine and sulfasalazine (SSA/HCQ) monotherapy, methotrexate with SSA/HCQ: Pooled analysis: 1.59 (0.79-3.20) MTX with Anti-TNF: 1.61 (0.95-2.73) MTX use stratified by cumulative duration (ref: unexposed) Short-Term (<1 year) 1.16 (0.88-1.53) Long-Term (>1 year) 1.24 (1.03-1.49) Recently discontinued 0.80 (0.57-1.11)

Disclosure: F. I. Scott, None; R. Mamtani, None; C. Brensinger, None; K. Haynes, None; Z. Chiesa-Fuxench, None; H. Y. Yun, A. Chen, Z. Chen; J. Zhang, None; L. Chen, None; P. Xie, None; D. Margolis, None; J. D. Lewis, None; J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. M. Pfizer, BMS, Crescendo, Abbvie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. M. Pfizer, BMS, Crescendo, Abbvie, 5.

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Table: Reported outcomes of pregnancies with maternal abatacept exposure

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Count, n (%)</th>
<th>Exposure to concomitant medications** n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>33 (25.0)</td>
<td>15 (11.4) 1 (0.8) 2 (1.5) 1 (0.8)</td>
</tr>
<tr>
<td>Induced</td>
<td>19 (14.4)</td>
<td>11 (8.3) 2 (1.5) 1 (0.8)</td>
</tr>
<tr>
<td>Late</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

S808
M: 1 (0.8)  |
Fetal death: 2 (1.5)  |

*Resulted in fetal death.
†One case due to intrauterine fetal death.
‡Fetal death was defined as intrauterine death of a fetus >20 weeks.
**Only concomitant medications that are Pregnancy Category D or higher in the United States are listed.
AZA, azathioprine; LFM, leflunomide; MMF, mycophenolate mofetil; MMS, mycophenolate sodium.

**Conclusion:** As shown, the available data for abatacept do not indicate any pattern of congenital anomalies. Abatacept should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. The company continues to monitor and collect information on the outcomes of abatacept-exposed pregnancies, and an ongoing registry study with the Organization of Teratology Information Specialists (OTIS) continues to collect data that will be reported separately.

**Disclosure:** M. Kumar, Bristol-Myers Squibb, 1; Bristol-Myers Squibb, 1; L. Ray, Bristol-Myers Squibb, 3; S. Vemuri, Bristol-Myers Squibb, 3; Bristol-Myers Squibb, 1; T. Simon, Bristol-Myers Squibb, 3.

1984

**Eventual Joint Failure and Surgery Rates in Rheumatoid Arthritis Remain High in Patients with Moderate Disease Activity in the First 5 Years of Disease.** Elena Nikiphorou, Lewis Carpenter, Sam Norton, Josh Dixey, Patrick Kielty, David Walsh, and Adam Y Young. 1. University of Hertfordshire, Hatfield, United Kingdom, 2. King’s College London, London, United Kingdom, 3. New Cross Hospital, Wolverhampton, United Kingdom, 4. St. Georges Healthcare NHS Trust, London, United Kingdom, 5. University of Nottingham, Nottingham, United Kingdom, 6. ERAS, St Albans City Hospital, St Albans, United Kingdom.

**Background/Purpose:** It is well-established that sustained high disease activity in RA results in worse outcomes. In reality many patients remain in low/moderate disease activity states, yet their outcomes, especially in the long term, are less well studied.

**Methods:** The study was based on the Early RA Study (ERAS, n=1465, 1986–1999) and the Early RA Network (ERAN, n=1236, 2002–2012). Standard clinical, radiological and laboratory measures were performed yearly for a maximum (median) 25(10) and 10(3) years respectively. Clinical databases were validated with national sources: the National Joint Registry (2003–2011), Hospital Episode Statistics (1997–2011) & National Death Register (1986–2011). Treatment regimens followed guidelines of the era, mainly conventional DMARDs +/- steroids, and latterly biologics. Joint interventions were categorized into major (large joint replacements), intermediate (mainly synovectomies and arthroplasties of wrist/hand, hind/forefoot) or minor (mainly soft tissue). M ean DAS28 was calculated for each patient from year 1 to 5 and categorized into either sustained low (m5DAS(low)) moderate disease (m5DAS(mod)) or high (m5DAS(high)) disease activity if DAS28 was persistently lower than 3.2, between 3.2–5.1 or greater than 5.1 respectively.

**Results:** Of 2221 (86%) with complete 5-year DAS data, 854 (37%) had m5DAS(low), 1066 (46%) m5DAS(mod) and 401 (17%) m5DAS(high). 770 (29%) patients had undergone a total of 1602 procedures over the 25 years of surveillance; cumulative incidence rate of major interventions was 21.7% (19.4–24.0%) and of intermediate 21.5% (17.8–25.5%). In multivariate Cox regression models controlling for age at disease onset, gender, recruitment center and baseline erosions, patients with m5DAS(low) were 44% and 46% less likely to have intermediate and major joint surgery respectively compared to patients with moderate disease activity over the first 5 years (P<0.05). Patients with m5DAS(high) were 49% more likely to have intermediate surgery than those with m5DAS(mod) over the first 5 years (P<0.05) (Figure 1). A similar trend was observed for major surgery, but statistical significance was not reached.

**Conclusion:** Patients with sustained moderate disease activity in the first 5 years of disease, despite conventional DMARD therapy, still remain at high risk of joint failure and surgery. This poses important management challenges in health systems where restrictions exist in the use of biologic DMARDs, which are based on DAS28 levels and exclude moderate RA. The results demonstrate that any therapy that keeps patients in low disease activity or remission states is beneficial in terms of long-term outcomes.

**Figure 1.**

**Disclosure:** E. Nikiphorou, None; L. Carpenter, None; S. Norton, None; J. Dixey, None; P. Kielty, None; D. Walsh, Pfizer Inc, 2; A. Young, None.

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**Background/Purpose:** Since the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and tight control strategies, remission has become a more feasible treatment target for an increasing number of patients. As a result, there is an increased interest in appropriate treatment strategies after achieving disease control, such as bDMARD discontinuation while in remission. However, the outcome of such discontinuation in typical clinical practice has not been widely studied. We conducted a multi-center longitudinal observational study of bDMARD discontinuation while patients were in remission to describe the proportions of RA patients who remain in remission and how treatment or disease activity changes occur after discontinuation.

**Methods:** We utilized data from the National Database of Rheumatic Diseases by iR-Net in Japan (NiNa) multi-center registry. Patients who used bDMARDs on at least two consecutive visits and had visits in remission defined by the Clinical Disease Activity Index (CDAI) ≤ 2.8 followed by discontinuation of their bDMARDs while in remission were examined. The baseline variables were defined at the first visit off bDMARDs. The outcomes were defined as the rate of all-mode failure as well as the non-mutually exclusive individual modes of failure: reuse of bDMARDs, loss of CDAI remission, intensification of non-biological DMARDs or oral glucocorticoids.

**Results:** Among 744 patients who initially achieved remission on bDMARDs, 31 patients discontinued their bDMARDs while remaining in remission and had additional follow up visits. In this 31-patient study cohort, 93.5% were female, the median disease duration was 6.0 (interquartile range 5.0, 9.0), 83.9% discontinued tumor necrosis factor inhibitors, 90.3% discontinued their first bDMARD, 72.4% had reported radiographical erosions. At the baseline, treatments were as follows: methotrexate used 54.8%, non-steroidal antiinflammatory drugs (NSAIDs) used 35.5%, oral glucocorticoids used 45.2%. The probability of being free of all-mode failure was 29.0%, at 1 year and 24.0% at 2 years. When dissected into individual modes of failure, loss of CDAI remission and reuse bDMARD were approximately 40% at 2 years, whereas non-biological treatment intensification was approximately 10–20%. Regarding changes in the non-biological treatment as non-failures,
35.5% remained in remission without bDMARDs at 1 year, and 29.6% at 2 years.

Conclusion: We found a high rate of failure by the all-mode failure, indicating difficulty of maintaining disease control after discontinuing bDMARDs even in patients who were in CDAI remission. Modification of non-biological treatment was observed in some of the patients who remained in remission. Considering the cost of bDMARDs, such coping strategy to maintain disease control after bDMARD discontinuation may need further investigation.

Disclosure: K. Yoshida, None; M. Kishimoto, Santen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Abbott Japan, 8; H. Radner, None; K. Matsui, None; M. Okada, Santen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Abbott Japan, 8; Y. Saeki, Tanabe-Mitsubishi Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Janssen Pharmaceutical Co., Ltd, Nippon Kayaku Co., Ltd, and Nichi-Iko Co., Ltd, 2; D. H. Solomon, Eli Lilly, and CORRONA, 2, UpToDate, 7, Pfizer, Novartis, and Eli Lilly, & S. Tohma, Pfizer Japan Inc., Eisai Co., Ltd, and Chugai Pharmaceutical Co., Ltd, 2.

1843
Randomised Controlled Non-Inferiority Study of Dose Reduction and Withdrawal of Adalimumab and Etanercept in Rheumatoid Arthritis.
Noortje van Herwaarden1, Aatke van der Maas1, Michiel Minten1, Frank H.J. van den Hoogen2, Ronald F. van Vollenhoven3, Johannes W.J. Bijlsma4, Bart van den Bemt1 and Alfons A. den Broeder1. 1Sint Maartenskliniek, Nijmegen, Netherlands, 2Rheumatology Centre Sint Maartenskliniek and Radboud University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: TNF inhibitors (TNFi) have proven to be effective in the treatment of rheumatoid arthritis (RA). They are however associated with side effects and high costs, making dose reduction or discontinuation an attractive option. The primary aim of this study (DRESS) was to assess non-inferiority with regard to persistent disease worsening (flare) between a TNFi dose reduction strategy and usual care in daily clinical practice.

Methods: Patients with RA and low disease activity using adalimumab or etanercept were randomised (2:1) to a dose reduction strategy or usual care, both in tight control setting. The TNFi dose reduction strategy consisted of stepwise increasing the interval between injections every 3 months until flare or discontinuation. In case of flare, the TNFi was restarted or escalated. A flare was defined as DAS28-CRP increase >1.2 or DAS28-CRP increase >0.6 and current DAS28-CRP >3.2, compared to baseline DAS28-CRP. A persistent flare was defined as a flare duration >12 weeks. During 18 months follow up, data were collected on DAS28-CRP, HAQDI, EQ-5D, RA medication use, and costs. The primary outcome was the difference in proportions of patients with persistent flare between the two groups compared against a non-inferiority (NI) margin of 20%.

Results: 180 patients were included (table 1). Cumulative incidence of persistent DAS28-CRP flare was not significantly higher in the dose reduction group compared to the usual care group, 10% versus 12% of patients respectively (difference 2%, 95% CI −10 to 12), the upper limit of the 95% CI being clearly below the NI margin. Mean DAS28-CRP remained low, with only at 9 months follow up a significant, but small, difference between groups (figure 1A). HAQ scores remained stable in both groups (figure 1B) as did quality of life (figure 1C). In the dose reduction group, the TNFi could successfully be stopped at 18 months in 20% (95% CI 13 to 28) of patients, the interval successfully increased in 43% (95% CI 34 to 53) and in 37% (95% CI 28 to 46) of patients no dose reduction was possible. Incidence and nature of serious adverse events were similar between groups. Costs were significantly lower in the dose reduction group (mean difference per patient €9k).

Conclusion: A simple tight control TNFi dose reduction strategy has been shown to be non-inferior to usual care in maintaining disease control, function and quality of life, while reducing exposition to TNFi and costs.

References:

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dose reduction (n = 122)</th>
<th>Usual care (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>59 (10.5)</td>
<td>58 (9.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>75 (62)</td>
<td>41 (69)</td>
</tr>
<tr>
<td>Disease duration, years median [p25–p75]</td>
<td>10 (6–17)</td>
<td>10 (6–16)</td>
</tr>
<tr>
<td>Rheumatoid factor positive, n (%)</td>
<td>95 (78)</td>
<td>49 (83)</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>86 (71)</td>
<td>45 (76)</td>
</tr>
<tr>
<td>DAS28 CRP at inclusion (SD)</td>
<td>2.2 (0.6)</td>
<td>2.1 (0.7)</td>
</tr>
<tr>
<td>DAS28 BSE at inclusion (SD)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>2011 ACR/EULAR Boolean-based remission, n (%)</td>
<td>31 (26)</td>
<td>21 (36)</td>
</tr>
<tr>
<td>DAS28 CRP ≥ 3.2, n (%)</td>
<td>8 (7)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Etanercept/adalimumab (%)</td>
<td>79/42 (65/35)</td>
<td>68/20 (66/34)</td>
</tr>
<tr>
<td>Duration of current anti-TNF therapy, years (SD)</td>
<td>3.5 (2.5)</td>
<td>3.6 (2.3)</td>
</tr>
<tr>
<td>Previous DMARDS, median [p25–p75]</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Previous anti-TNF, median [p25–p75]</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Concomitant DMARD use, n (%)</td>
<td>73 (60)</td>
<td>47 (80)</td>
</tr>
<tr>
<td>Concomitant MTX use, n (%)</td>
<td>58 (48)</td>
<td>41 (69)</td>
</tr>
<tr>
<td>Concomitant corticosteroid use, n (%)</td>
<td>6 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Concomitant NSAID use, n (%)</td>
<td>65 (54)</td>
<td>35 (59)</td>
</tr>
<tr>
<td>Employment, n (%)</td>
<td>44 (36)</td>
<td>21 (36)</td>
</tr>
</tbody>
</table>

Figure 1. Mean disease activity, functioning and quality of life during the study

Disclosure: N. van Herwaarden, None; A. van der Maas, Roche, MSD, 9; M. Minten, None; F. H. J. van den Hoogen, None; R. F. van Vollenhoven, A bbbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 2; Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 5; J. W. J. Bijlsma, A bbVie, Roche, Pfizer, MSD, UCB, BMS, 2, A bbVie, Roche, Pfizer,
Identification of a Patient Phenotype Which Impacts Response to Therapy in Rheumatoid Arthritis Clinical Trials: Certolizumab Pegol Phase 4 Trial Data, Jeffrey R. Curtis, Melvin Churchill, Alan Kivitz, Laura Gauer, Christopher Herrem, David Carter, Jeffrey Melin and Yusuf Yazici.

Background/Purpose: The PREDICT trial (NCT01255761) examined predictability of certolizumab pegol (CZP) treatment success at Wk 52 based on response at Wk 12 assessed by RAPID3 and CDAI in RA patients (pts). The objective of this post-hoc analysis was to evaluate whether a defined somatic comorbidity phenotype (SCP) influenced treatment response.

Methods: Pts were randomized to RAPID3 or CDAI for treatment response assessment and received CZP standard dosing regimen for 52 wks. Response at Wk 52 was assessed (RAPID3 Responder, ≤60 vs ≥60 improvement from Baseline [BL]; CDAI Responder, ≤10 or ≥20 improvement from BL), and pts with no improvement (<1 point CDAI improvement/no RAPID3 improvement) were to be withdrawn. The SCP, hypothesized to have suboptimal treatment response, was defined as a diagnosis of depression, chronic pain, fibromyalgia or myalgias, and use of medications indicated for the treatment of depression, anxiety or neuropathic pain; insomnia diagnosis and narcotics were not included. The full analysis set (FAS; N = 733), of which 313 pts had SCP at BL and ongoing during trial, is presented.

Results: At BL, 43% (313/733) of pts met the SCP classification: 23% due to medical diagnoses only (predominantly depression), 29% due to concomitant medications only (predominantly SSRIs, angesics/antipryretics and other centrally acting agents), and the remaining 48% were due to both (predominantly depression and SSRIs use). The proportion of pts with SCP was similar in the RAPID3 and CDAI arms: a similar proportion, with and without SCP, were withdrawn due to lack of efficacy by Wk 12.

Among all pts randomized to CDAI (n = 365), 79% without vs 73% with SCP were classified as Responders at Wk 12 (Table); Wk 12 Responders without SCP were approximately twice as likely to achieve LDA at Wk 52 compared to those with the phenotype (41% vs 21%, respectively; Table). In addition, overall, pts without SCP were twice as likely to achieve LDA at Wk 52, compared to those with the phenotype (32% vs 16%, respectively; Table).

In contrast, this phenotype was less differentiating among pts randomized to RAPID3 in the 3 outcomes examined (Table). Comparing CDAI to RAPID3, the likelihood of being classified as a Wk 12 Responder was incrementally greater for those without (79% vs 63%) than those with the SCP (56% vs 60%) (Table).

Conclusion: In this large RA clinical trial population we have identified a potentially important phenotype that includes depression and chronic pain syndromes. Pts with this phenotype appear less likely to achieve LDA or be classified as a Responder when using CDAI as the outcome measure; however response rates were similar regardless of SCP when RAPID3 was used. Depending on the outcome measure used, enrolling large numbers of pts with this phenotype into an RA trial may affect the proportion of pts able to achieve LDA/remission making it advisable to consider identifying such pts at screening.

Reference

Table 1. Patients with and without somatic comorbidity phenotype: A) LDA at Wk 52, B) Response classification at Wk 12, and C) LDA at Wk 52 for Wk 12 Responders (FAS; NRI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Somatic Comorbidity Phenotype</th>
<th>Management Tool Used</th>
<th>CDAI</th>
<th>RAPID3</th>
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<tr>
<td>Achieve LDA at Wk 52, overall</td>
<td>No</td>
<td>32% (65/203)</td>
<td>21% (45/217)</td>
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<td></td>
<td>Yes</td>
<td>16% (26/162)</td>
<td>23% (34/151)</td>
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<tr>
<td>Classified as a Responder at Wk 12</td>
<td>No</td>
<td>79% (160/203)</td>
<td>63% (136/217)</td>
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<td></td>
<td>Yes</td>
<td>73% (119/162)</td>
<td>68% (102/151)</td>
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Table 1. Efficacy and Safety End Points

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<th>Treatment</th>
<th>TCBZ + MTX</th>
<th>TCBZ Mono</th>
<th>TCZ4 + MTX</th>
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<td>104</td>
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<td>104</td>
<td>104</td>
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<td>Week 104</td>
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<td>104 Orig Tx (escape Tx)</td>
<td>104 Orig Tx (escape Tx)</td>
<td>104 Orig Tx (escape Tx)</td>
<td>104 Orig Tx (escape Tx)</td>
</tr>
<tr>
<td>DAS 28</td>
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<td>40.4</td>
<td>43.5</td>
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<tr>
<td>ACR 20, %</td>
<td>67.9</td>
<td>65.2</td>
<td>64.5</td>
<td>66.5</td>
<td>63.6</td>
</tr>
<tr>
<td>ACR 50, %</td>
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<td>57.6</td>
<td>56.7</td>
<td>53.1</td>
<td>54.9</td>
</tr>
<tr>
<td>ACR 70, %</td>
<td>43.4</td>
<td>46.6</td>
<td>37.0</td>
<td>39.4</td>
<td>37.8</td>
</tr>
<tr>
<td>Mean DAS28</td>
<td>0.33</td>
<td>0.19</td>
<td>0.30</td>
<td>0.62</td>
<td>0.75</td>
</tr>
<tr>
<td>MTX</td>
<td>2418</td>
<td>1701</td>
<td>1545</td>
<td>1249</td>
<td>1249</td>
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</tbody>
</table>

Safety at wk 104

Tx received (safety population)*

AEs, n (rate/100 PY) 2418 (336.6) 1701 (338.7) 1545 (391.5) 1249 (367.9)

Serious AEs, n (rate/100 PY) 25 (3.5) 20 (4.0) 16 (4.1) 6 (1.8)

Deaths, n (rate/100 PY) 4 (0.56) 3 (0.60) 5 (1.27) 2 (0.59)

1846

The Association Between Hydroxychloroquine Treatment and Cardiovascular Morbidity Among Rheumatoid Arthritis Patients. Michael Shapiro1 and Y. Levy2. 1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, 2Meir Medical Center, Kfar Saba, Israel.

Background/Purpose: A number of observational studies have demonstrated that HCQ has additional beneficial effects on cardiovascular risk factors by lowering LDL levels, reducing the risk for diabetes and demonstrating that HCQ has additional beneficial effects on cardiovascular morbidity among RA patients, particularly when using the higher dose of 400 mg per day. This newly demonstrated effect of HCQ should be considered in the overall management of RA.

Disclosure: M. Shapiro, None; Y. Levy, None.

1847

Effect of Disease Duration on Clinical Outcomes in Moderate Rheumatoid Arthritis Patients Treated with Etanercept Plus Methotrexate in the Preserve Study. Josef S. Smolen1, David Collier2, Anne Z. Szumski3, Heather Jones1 and Lisa Marshall1. 1PsAID taskforce, EUULAR, Zurich, Switzerland, 2Amgen, Inc.; Thousand Oaks, CA, 3Pfizer Inc, Collegeville, PA.

Background/Purpose: Previous studies evaluating various treatment strategies indicate that disease duration is a key determinant of outcomes in rheumatoid arthritis (RA). While data suggest that RA patients with longer established disease do not respond as well to treatment compared with patients with early disease, this evidence is limited. The objective of this sub-analysis was to determine the effect of disease duration on treatment response in patients with moderate active RA receiving induction therapy with etanercept (ETN) plus methotrexate (MTX) for 36 weeks in the PREserve study.

Methods: In the induction phase of the PRESERVE study, patients with moderately active RA (DAS28 >3.2 and <5.1) despite stable doses of oral MTX received open-label ETN 50 mg OW plus MTX (titrated to ≤25 mg/week as needed through week 28) for 36 weeks. Patients were stratified by disease duration at baseline: 0–<6 mo, >6mo–<2 yr, >2yr–<5 yr, >5yr–<10 yr, and >10 yr. Baseline demographic and disease characteristics and treatment response (DAS28, CDAI, HAQ) were compared across disease duration categories. Analyses using observed cases (OC) were conducted in all patients who received ≥1 ETN/MTX dose (ITT population).

Results: A total of 833 patients receiving E/R50/MTX (baseline disease duration: 0–<6 mo, n=41; >6mo–<2 yr, n=198; >2yr–<5 yr, n=204; >5yr–<10 yr, n=172; >10 yr, n=218) were included. At baseline, more established disease was significantly associated with higher age and a higher swollen joint count (Table). In addition, a significantly greater proportion of patients with longer disease duration were rheumatoid factor and CCP antibody positive. HAQ score at baseline significantly correlated with greater duration of disease while baseline DAS28 and CDAI were similar across disease duration subgroups. Significant changes from baseline in DAS28, CDAI and HAQ were observed at Week 4 and at all time-points up to Week 36 in all disease duration categories (all P<0.0001). These observed improvements in clinical measures of disease activity and quality of life were similar among disease duration subgroups (Table).
**1848**

**Risk of Cancer in Patients with Severe Psoriatic Arthritis Requiring Tumour-Necrosis Factor Alpha Inhibition.** Karen M. Fagerli1, Louise K. Mercer2, K ath D. Watson2, Jonathon Packham2, Deborah PM Symmons1, Kimmie L. Hyrich1 and. On behalf of the BSRBR 6. 1Diakonhjemmet Hospital, Oslo, Norway, 2, Atritis Research UK. Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, 3Institute of Science and Technology in Medicine, Keele, United Kingdom, 4Arthritis Research UK. Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, 5Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, 6British Society for Rheumatology, London, United Kingdom.

**Background/Purpose:** Few studies have explored risk of cancer in psoriatic arthritis (PsA). There are concerns that the risk may be raised, not only by the primary disease, but also by the treatments given including conventional disease modifying treatments (especially ciclosporin), tumour necrosis factor inhibitors (TNFi) and phototherapy. Skin psoriasis itself is associated with an increased risk of non-melanoma skin cancer (NMSC). Our objective was to compare the incidence of cancer among a cohort of patients with severe PsA patients receiving tumour TNFi to that in the general population.

**Methods:** All patients with PsA starting a TNFi in the British Society for Rheumatology Biologics Register (BSRBR), recruited 2002–2006 were included. Cancers were identified by flagging patients with the national cancer register which reported using the International Classification of Diseases version 10 (ICD 10). All patients were followed from registration (start of TNFi) until death or 2011/12/31, whichever came first. Standardised incidence ratios (SIR) with 95% confidence intervals (CI) were calculated using age and gender specific cancer rates for the general English population for (1) overall cancer risk (ICD 10: C1-C9) and (2) NMSC (C44) for the whole cohort and separately for men and women.

**Results:** 709 patients contributed 5286 patient years of follow-up; mean (SD) age was 54.7 (12.2), median disease duration (IQR) was 11 (6–17) years. Mean (SD) DA528 was 6.0 (1.2). 11 (1.6%) patients had a cancer registered prior to baseline, none of which had a further cancer. Nearly all (98%) had previous or current exposure to methotrexate at baseline and 46.5% had previous or current exposure to ciclosporin. Information on baseline PUVA exposure was only available for 163 (23%) patients and 11 (6.7%) had been exposed. 27 cancers in 26 patients were observed, including 14 cutaneous cancers (1.2% NMSC and 2.1% melanoma). Overall, there was no increased risk of melanoma observed in this cohort (SIR 0.87, 95% CI 0.58–1.27) compared to the general population. There was a significantly increased incidence for NMSC although the precision of the estimate was low (SIR 1.97, 95% CI 1.02–3.45) likely reflecting low number of events.

**Table:** Overall and non-melanoma skin cancer standardised incidence ratios

<table>
<thead>
<tr>
<th>Overall n=709</th>
<th>Male n=331</th>
<th>Female n=378</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total follow-up (person-years)</td>
<td>5286</td>
<td>2437</td>
</tr>
<tr>
<td>O/E</td>
<td>5286</td>
<td>2437</td>
</tr>
<tr>
<td>SIR (95% CI)</td>
<td>0.87 (0.58–1.27)</td>
<td>1.02 (0.84–1.24)</td>
</tr>
<tr>
<td>O/E</td>
<td>5286</td>
<td>2437</td>
</tr>
<tr>
<td>SIR (95% CI)</td>
<td>0.87 (0.58–1.27)</td>
<td>1.02 (0.84–1.24)</td>
</tr>
<tr>
<td>All malignancies</td>
<td>27/309</td>
<td>13/128</td>
</tr>
<tr>
<td>NMSC</td>
<td>12/161</td>
<td>5/42</td>
</tr>
</tbody>
</table>

O = Observed, E = Expected

**Conclusion:** In this population of severely active PsA patients recruited early in the TNFi-era, the overall incidence of malignancy was reassuringly similar to that of the general population. Incidence of NMSC was increased, which may be related to PsA itself, skin psoriasis, phototherapy and/or immune-modulatory treatment.

Disclosures: K. M. Fagerli, None; L. K. Mercer, None; K. D. Watson, None; J. Packham, None; D. P. Symmons, None; K. L. Hyrich, Pfizer Inc; 9, Abbott Immunological Pharmaceuticals, 9; On behalf of the BSRBR, Pfizer Inc, Abbvie, UCB, Merck, Roche, 2.

**1849**

**Risk of Malignancy Among Medicare Psoriasis/Psoriatic Arthritis Patients.** Huifeng Y1, Kevin L. Winthrop2, Lang Chen3, William Smith3, Benjamin Chan4, Fenglong Xie5, Allison Taylor6 and Jeffrey R. Curtis6. 1University of Alabama at Birmingham School of Public Health, Birmingham, AL, 2Oregon Health & Science University, Portland, OR, 3University of Alabama at Birmingham, Birmingham, AL, 4Oregon Health and Science University, Portland, OR.

**Background/Purpose:** The introduction of biologics has greatly changed the treatment of psoriatic arthritis (PsA) and psoriasis (PsO). However, there are concerns regarding the risk of malignancy associated biologic medications. This analysis evaluated the association between malignancy and biologics among US patients with PsA or PsO enrolled in the Medicare program.

**Methods:** Using data from 2006–2011 for 100% of patients with patients with PsA and PsO, we defined separate PsA and PsO cohorts based upon >= 1 rheumatologist visit for PsA or >= 1 dermatologist visit for PsO, followed by a prescription or administration of etanercept (ETA), adalimumab (ADA), ustekinumab (UST), methotrexate (MTX), cyclosporine (CIC) or ultraviolet light therapy (UV). Patients could be in both cohorts if they meet criteria for each cohort. We identified new treatment episodes, defined specific to each drug as no use of that therapy in the prior 6 month ‘baseline’ period. Patients contributing treatment episodes with history of organ transplantation, infection with human immunodeficiency virus, advanced kidney (hemodialysis-dependent), severe liver disease, or cancer diagnoses were excluded. Eligible subjects were continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow-up. We excluded treatment episodes of UV if patients were on biologics or DMARDS at baseline, and episodes of non-biologic therapy if patients were on biologics during the baseline. Follow up started from the drug initiation date and ended at the earliest date of: malignancy (exclude non-melanoma skin cancer), a 90 day gap in current exposure, death, loss of coverage or Dec 31, 2011. We identified malignancy using validated claims-based algorithm using physician diagnoses (ICD 140–208, except 173.x), cancer-related procedures and chemotherapy. We calculated the incidence rate (IR) of malignancy for each exposure. Using pairwise propensity scores (PS) to balance multiple confounders, we compared malignancy risk using Cox regression, adjusting for PS quintile.

**Results:** We identified 10,261 PsA and 31,052 PsO new treatments episodes. For the PsA cohort, 50% of treatment-episode exposure time was in common with the PsO, and 20% of PsO exposure time was in common with PsA exposures. During follow up, patients in the PsA cohort experienced 13 (ADA), 26 (ETA), 50 (MTX), 10 (UV) malignancies, the PsO cohort experienced 29 (ADA), 26 (CIC), 28 (ETA), 123 (MTX), 64 (UV) malignancies. The overall IR in PsA was 8.1/1000, ranging from 0.5(ETA) to 12.9 (CIC). After multivariable adjustment, there was a significantly lower risk for ETA compared to non-biologic therapies: ETA versus CIC (HR: 0.50 95% CI: 0.27–0.93), ETA versus MTX (HR: 0.56 95% CI: 0.35–0.87), ETA versus UV (HR: 0.49 95% CI: 0.29–0.83).

**Conclusion:** Among older patients with psoriasis and psoriatic arthritis, there was no evidence of an increased risk of malignancy for patients treated with biologics compared to non-biologic therapies, and some possibility of a reduced risk.

Disclosures: H. Yum, A. Mengen, 2; K. L. Winthrop, Pfizer Inc, 2; Pfizer UCB, Abbvie, Genentech, 5; L. Chen, None; W. Smith, None; B. Chan, None; F. Xie, None; A. Taylor, None; J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. Mengen, Pfizer, BMS, Crescendo, Abbvie, 2; Roche, Genentech, UCB Pharma, Janssen, CORRONA, A. Mengen, Pfizer, BMS, Crescendo, Abbvie, 5.

S813

Background/Purpose: There are limited data regarding the incidence of PsA in patients with psoriasis. We aimed to estimate the incidence of PsA in a prospective cohort of psoriasis patients and to identify risk factors for the development of PsA in these patients.

Methods: A prospective longitudinal cohort study of psoriasis patients without arthritis at baseline. Patient with a diagnosis of psoriasis confirmed by a dermatologist were enrolled. All patients were evaluated by a rheumatologist at baseline. Exclusion criteria included the presence of inflammatory arthritis or spondylitis in the past or at the time of assessment. All study participants were then reassessed annually by a rheumatologist for signs and symptoms of arthritis. Information was collected about their lifestyle habits, co-morbidities, skin activity and medications. Patients who developed inflammatory arthritis or spondylitis were classified as PsA if they fulfilled the CASPAR criteria. Patients who failed to come to the yearly assessment were requested to fill out the Toronto Psoriatic Arthritis Screen (TOPAS II) questionnaire, a screening questionnaire designed to detect PsA among patients with psoriasis. Subjects scoring ≥8 points on the TOPAS II were classified as suspected PsA.

Results: The results of the 579 patients who were recruited from January 2006 and followed until December 2013 are summarized. The mean duration of follow-up was 3.5 ± 1.9 years per person. A total of 46 patients developed PsA since enrollment and 9 additional patients were considered suspected cases of PsA according to their scoring in TOPAS II. The annual incidence rate of confirmed cases was 3.1 (95% confidence interval (CI) 2.2, 4.0) PsA cases per 100 psoriasis patients. When suspected cases were included in the analysis, the annual incidence rate increased to 3.7 (95% CI 2.7, 4.7) PsA cases per 100 psoriasis patients. The distribution of the time to development of PsA was fit with an exponential model, suggesting a constant hazard rate. The following variables predicted the development of PsA: flexural psoriasis (RR 4.9 p = 0.03), nail pitting (RR 2.3 p = 0.006), higher modified Nail Psoriasis Severity Index score (RR 2.8 p = 0.008) and lower level of education (high school incomplete vs. University RR 3.3, p = 0.04). Obesity vs. normal weight predicted the development of PsA when suspected cases of PsA were included in the analysis (RR 2.3 p = 0.03).

Conclusion: The incidence of PsA in patients with psoriasis is higher than previously reported. Flexural psoriasis, psoriatic nail involvement, lower level of education and obesity predict the development of PsA in patients with psoriasis.

Disclosure: L. Eder, None; A. Haddad, None; H. Shen, None; C. Rosen, None; V. Chandran, None; R. J. Cook, None; D. D. Glidan, None.

1851

Serious Infections in the Psoriasis Longitudinal Assessment and Registry Study: Cumulative Experience. Robert Kalb 1, David Fiorentino 2, Mark Lebwohl 3, Craig Leonard 1, John Toole 1, Kavitha Goyal 4, Steve Calabro 5, Wayne Langhoff 5 and Steve Fakharzad 6.

Background/Purpose: Rates have not been adjusted for demographic and clinical differences among treatment groups.

Methods: Analysis of serious infections further and adjust for differences among treatment groups.

Results: PSOLAR is fully enrolled with 12 095 patients reflecting 31 818 cumulative patient-years of follow up. 36% of the 12 095 patients had a self-reported diagnosis of psoriatic arthritis. The median duration of follow-up is 2.5 years. Unadjusted rates of serious infection, based on exposure within 91 days preceding the event, were 1.50 per 100 patient years of observation (PY) [95% CI: 0.71, 2.14; 52/5497 PY, infliximab 2.77 per 1000 PY [95% CI: 2.15, 3.51; 68/2457 PY], etanercept 1.67 per 1000 PY [95% CI: 1.32, 2.09; 78/6466 PY], adalimumab 1.88 per 95% PY [95% CI: 1.54, 2.27; 106/5645 PY], non-biologics 1.26 per 100 PY [95% CI: 1.08, 1.46; 169/13421 PY], and overall 1.50 (95% CI: 1.37, 1.64; 478/31817). Limitations: Rates have not been adjusted for demographic and clinical differences among treatment groups and are subject to attribution rules.

Conclusion: With nearly 32 000 patient years of follow-up, the overall rate of unadjusted cumulative rate of serious infections in the PSOLAR registry population is 1.50 per 100 PY. The rates of serious infection for use of infliximab and the non biologic treatment groups are lower than rates for etanercept, adalimumab and etanercept. Future analyses may characterize infections further and adjust for differences among treatment groups.

Disclosure: R. Kalb, Janssen Scientific Affairs, LLC, 2; D. Fiorentino, None; M. Lebwohl, Janssen Scientific Affairs, LLC, 2; C. Leonard, Janssen Scientific Affairs, LLC, 3; J. Toole, Janssen Scientific Affairs, LLC, 2; K. Goyal, Janssen Scientific Affairs, LLC, 3; C. Rosen, Janssen Scientific Affairs, LLC, 3; S. Calabro, Janssen Scientific Affairs, LLC, 3; W. Langhoff, Janssen Scientific Affairs, LLC, 3; S. Fakharzad, Janssen Scientific Affairs, LLC, 3.

1852


Background/Purpose: Patients diagnosed with rheumatoid arthritis and psoriatic arthritis (PsA) have an increased risk of multiple comorbidities that predispose them to cardiovascular disease (CVD). Although it has been documented that the Framingham Risk Score (FRS) underestimates the 10-year risk of CVD in patients with rheumatoid arthritis, the predictive accuracy of the FRS has not been evaluated in PsA.

Methods: The study population comprised a population-based inception cohort of patients with PsA who fulfilled theCLASSification of Psoriatic Arthritis (CASPAR) criteria between 1989 and 2008. Data on CVD risk factors and all CVD events (myocardial infarction, CV death, angina, revascularization procedures, heart failure, stroke and intermittent claudication) were collected via medical record review. For each patient, the 10-year FRS (Circulation 2008;117:743–753) was calculated at time of PsA diagnosis. Poisson regression models were used to obtain the standardized incidence ratio (SIR), which is the ratio of observed CVD in PsA to predicted CVD obtained from the FRS.

Results: Among 150 incident PsA patients, without a history of CVD, 32 patients experienced a CVD event during a mean follow-up of 11.6 years corresponding to an absolute risk of 17.4 per 1000 person years. Of 126 patients who were ≥30 years of age and without a history of CVD at time of PsA diagnosis, the mean FRS was 9.7%. Accounting for length of follow-up, this translated to 10 predicted events. However, 18 patients experienced a CVD event in the first 10 years, corresponding to a 10 year cumulative incidence of 17% (95% confidence interval [CI]: 10.5–24%). This was almost twice as high as predicted by the FRS (SIR: 1.80; 95% CI: 1.14–2.86; p = 0.012). This two-fold increased CVD risk was consistent across age groups.

Conclusion: We observed a higher than expected incidence of CVD events within our inception cohort of patients with PsA, with an actual risk of about twice that predicted by the FRS. This increased risk underscores the need for close cardiovascular follow-up in this population.

Disclosure: K. Wilton, None; F. C. Ernst, None; C. S. Crowson, None; E. L. Matteson, None; H. Maradit Kremers, Amgen, 9; M. Sánchez-Meneñez, None.
Persistence and Predictors of Biologic TNF\(\alpha\) Therapy Among Biologic-naive Psoriatic Arthritis Patients in a US Registry.

**Background/Purpose:** Registry data regarding biologic DMARD therapy as a mono or combo (combined with a traditional oral DMARD) in subjects with Psoriatic Arthritis (PsA) is limited. Our aim was to characterize biologic-naive PsA patients who initiated TNFi as mono or combo therapy, estimate length of time on initial TNFi, and identify characteristics associated with longevity of initial TNFi use.

**Methods:** Data from the US Corrona registry was used. Patients (pts) with a diagnosis of PsA \(\geq 18\) yrs of age, bio-naive and initiated TNFi on Jan 1st 2005 or later with at least 3m of follow-up were included. Survival analyses were performed using Kaplan-Meier curves estimating time on initial therapy since TNFi initiation, either as mono/combo therapy. Proportional hazard models were used to identify factors associated with risk of therapy change since initiation. A propensity score (PS) for mono vs combo was estimated and comparisons made using inverse probability weightings based on propensity probabilities. Median time to therapy change was calculated.

**Results:** 519 biologic-naive PsA pts met the inclusion criteria, with 61% vs. 39% initiating a TNFi as mono or combo therapy, respectively. 51% of pts initiating a TNFi were female, mean age was 51.6 yrs and mean disease duration \(\leq 10\) yrs. The combined therapy group had significantly higher proportion of women (57.1% vs. 42.8%), higher clinical disease activity index (CDAI) (mean (SD): 12.5 (11.1) vs. 9.6 (9.9)), higher body mass index (mean (SD): 31.9 (7.4)) vs. 30.7 (6.5), higher proportion of history of diabetes (11.3% vs. 6.5%) and higher history of methotrexate use (89.9% vs. 68.2%) compared to monotherapy initiators.

Median time to mono or combo therapy since TNFi initiation in the PS matched pts was 32.8 months and 30.8 months respectively (Figure 1). Significant factors associated with change in initial therapy were disability index measured by mHAQ (HR (95% CI): 2.6 (1.7-3.9)) and CDAI (HR (95% CI): 1.03 (1.01-1.04)). The models were adjusted for age, gender, body mass index, alcohol use, smoking history, mHAQ, and whether the patient was on mono/combo therapy. Persistency for mono vs combo therapy differed by individual TNFi. For example, pts on ETN mono therapy had higher persistency than combo therapy (47.3m vs 19.1m in combo) with a HR of 1.93 (95% CI, 1.15-3.25). A mong the pts on IFX, combo therapy was more persistent with a HR of 0.46 (95% CI, 0.24-0.88).

**Conclusion:** Over a third of PsA pts in the Corrona registry initiated TNFi as monotherapy. Even when adjusting for channeling bias with PS, overall survival on TNFi therapy was similar between mono and combo-treated pts. Greater degree of disability and disease activity use were associated with shorter duration of mono therapy. Some differences in survival on drug were noted between TNFi medicines, potentially related to background disease severity, immunogenicity, and/or other factors.

**Disclosure:** P. Mease, Celgene, Merck, Novartis, AbbVie, Amgen, Biogen Idec, BMS, Genentech, Janssen, Lilly, Pfizer, UCB; 2, Celgene, Merck, Novartis, AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, Vertex; 5, AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, B. D. Collier, Amgen, 3, Amgen, 1; C. Karki, Corrona, LLC, 3; G. Ll, Axio Research, LLC, 3; B. Bitman, Amgen, 1, Amgen, 3; J. D. Greenberg, Corrona, LLC, 1, Corrona, LLC, 3, AstraZeneca, Celgene, Novartis and Pfizer, 5.

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**Table 1:** Multivariate Logistic regression

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<thead>
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<th>A) Any Adverse Event</th>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>P-value</th>
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<tbody>
<tr>
<td>SLE vs. OA</td>
<td>3.77</td>
<td>1.74-8.16</td>
<td>0.0008</td>
</tr>
<tr>
<td>Charson-Deyo Comorbidity Index(**) (&gt; -1) vs 0</td>
<td>1.69</td>
<td>0.76-3.76</td>
<td>0.20</td>
</tr>
<tr>
<td>Epidural Block vs no</td>
<td>1.29</td>
<td>0.35-4.73</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) Any Major Adverse Event: (Major AE = DVT, PE, fall, fracture, additional surgery, acute renal disease, cardiac event- MI, cardiac event-dysrhythmia, deep surgical site infection, bleeding event requiring transfusion, pneumonia, neurophytis, death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>SLE vs. OA</td>
</tr>
<tr>
<td>Charson-Deyo Comorbidity Index(**) (&gt; -1) vs 0</td>
</tr>
<tr>
<td>Epidural Block vs no</td>
</tr>
</tbody>
</table>
C) Any Minor Adverse Event: (Minor Adverse Event= superficial infection, ecchymosis, erythema, incision site drainage, spinal headache, poor wound healing)

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Limits</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE vs. OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.54</td>
<td>1.41-8.91</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Charlson-Deyo Comorbidity Index**

- **≥ 1 vs. 0:**
  - 1.99 (0.46-3.12) 0.72

- **Epidural Block vs. no**
  - 1.91 (0.37-9.86) 0.44

* All models control for disease (SLE vs. OA), comorbidities and type of anesthesia

**Charlson-Deyo comorbidity index was calculated by excluding SLE

This study was supported by the Clinical Translational Science Center (CTSC) (UL1-TR000457-06) and the HSS Medical Student Research Fellowship.

Disclosure: J. Roberts, None; L. A. Mandl, None; E. Su, None; D. J. Mayman, None; M. P. Figge, None; A. Fein, None; Y. Y. Lee, None; U. Shah, None; S. M. Goodman, None.

1855

Not Keeping up with the Times: High Mortality and Early Death Due to Disease in North American Natives with Systemic Lupus Erythematosus (SLE)

Ripneet Puar, None; Carol A. Hitchon, None; David B. Robinson, None; Hani El-Gabalawy, None; Navjot Dhindsa, None; Christine A. Peschken, None. University of Manitoba, Winnipeg, MB; University of Manitoba, Winnipeg, MB.

**Background/Purpose:** Reports in recent decades show drastic improvements in survival of SLE patients, with 10–15 year survival rates of ~90%. However, little is known about North American Natives (NAN) with SLE. We compared mortality in NAN SLE patients to Caucasian (CA) SLE patients.

**Methods:** Patients from a single academic center were followed from 1990–2013 using a custom database. Variables included date of birth, diagnosis, age at disease onset, ethnicity, clinic visits dates, and vital status if known. Records of all patients with a diagnosis of SLE (≥4 American College of Rheumatology criteria) were abstracted. For patients who had not been seen in the last 2 years, updated vital status was obtained from the hospital medical records department. Ethnicity was by self-report, and categorized into NAN, CA and other. Age at diagnosis, disease duration and age at last follow up or age at death was calculated and compared between ethnic groups. Survival time was compared between NAN and CA using Kaplan Meier and Cox proportional hazard models, and person years of life lost (PYLL) was calculated for the 2 groups.

**Results:** A total of 861 patients with SLE were identified: 217 (25%) NAN, 534 (62%) CA, and the remaining 110 (13%) were of other ethnic groups. Age at diagnosis, disease duration and year of last follow up were younger (51 vs. 62 years) and predominantly female (89% vs. 54%), but had a similar comorbidity index (1.2 for both groups). In adjusted logistic regression models with an effect modification term for SLE and year were used to investigate differences in rates of infections over time among individuals.

**Conclusion:** While survival in our CA patients was comparable to recent standards, we have found a twofold higher risk of mortality and threefold increase in PYLL in NAN SLE compared to CA SLE patients. Reasons for this remain unclear and highlight an urgent need for improved care delivery for NAN with SLE to decrease the significant morbidity and mortality burden from this disease.
Determinants of Annual Healthcare Utilization and Overall Cost of Care in Individuals with Systemic Lupus Erythematosus in a Large Insurance Claims Database: Glucocorticoid Use.

Shih-Yin Chen1, Chan-Bum Choi2, Qian Li3, Wei-Shi Yeh1, Yuan-Chi Lee4, Amy H Kao1 and Matthew H. Liang5. 1Biogen Idec, Cambridge, MA, 2VA Healthcare System, Boston, MA, 3Evidera, Lexington, MA, 4Formerly of Evidera, Lexington, MA, 5Harvard Medical School, Boston, MA.

Background/Purpose: Newer therapeutic agents in systemic lupus erythematosus (SLE) may increase cost of care but their effect on limiting the duration and the dosage of glucocorticoids (GC) use (“steroid sparing”) may reduce costs and improve other outcomes. This study investigated the determinants of healthcare utilization and costs with the use of GC among adult SLE patients (18–64 years old) in the US using a large administrative database.

Methods: This cross-sectional study analyzed insurance claims in 2007–2011 from established SLE patients identified by their ICD-9-CM diagnosis codes. Five patient groups defined by their oral GC use during the one-year study period were studied: non-GC users, <60 day of GC use, 60–66 days of GC in low-dose (<7.5mg), medium-dose (>7.5 to 15mg), or higher-dose (>15mg). Annual healthcare utilization and costs were compared across these groups and dose-response was examined among users with >60 days of GC. Incremental costs of GC groups, calculated as the difference in total healthcare costs compared with non-GC group, were estimated from multivariable regressions adjusting for demographic and clinical characteristics and stratified by immunosuppressant use. Immunosuppressant use as a surrogate for SLE disease severity was stratified to evaluate the potential cost-saving associated with GC-sparing therapies.

Results: A total of 50,230 patients with SLE were identified, including 52% non-GC users, 20% with <60 days of GC use, and 28% medium-dose, and 8% higher-dose with ≥60 days of GC use. GC users had higher healthcare utilization and costs (Figure 1). Incremental costs were significant (all p < 0.01) for medium-dose ($5,319–$6,913) and higher-dose ($12,517–$15,019) GC groups, regardless of other immunosuppressant use (Figure 2). The incremental costs for low-dose GC group with concomitant immunosuppressants ($1,285; p = 0.04) were smaller than the incremental costs for low-dose GC group without concomitant immunosuppressants ($2,514; p < 0.01).

Conclusion: In this large national sample, any GC use especially at higher dose was associated with higher healthcare utilization and costs in patients with SLE. Therapies with GC-sparing effect that can allow patients to maintain on low GC dose may potentially reduce the healthcare economic burden in the treatment of SLE.
**1858**

**Standardized Mortality Ratios for Cause-Specific Deaths in Lupus Patients Followed Prospectively at a Single Centre Lupus Clinic.** Barry J. Sheane, Dominique Ibanez, Dafrna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

**Background/Purpose:** Despite the significant improvement in survival rates of patients with systemic lupus erythematosus (SLE) over the last four decades, mortality rates and a related mortality risk remain increased at least three times that of the general population. We have recently reported from our longitudinal cohort study that infection is responsible for almost half of all deaths in lupus within the first 5 years of disease, and for over a third of deaths overall.

The aim of this study was to examine the standardized mortality ratios (SMR) for all-cause and cause-specific deaths in SLE patients followed prospectively at a large lupus clinic between 1970 and 2012.

**Methods:** Primary causes of death were recorded and acquired from autopsy reports, discharge summaries, hospital notes, and death certificates and divided into 5 categories: active lupus, atherosclerosis-related, infection, malignancy and ‘other’, all as determined by the certifying clinician. For determination of the SMRs, cause-of-death data for the general population (by age, sex and year) were extracted from official records of the relevant provincial registry. SMRs were calculated as the ratio of observed deaths in the SLE cohort to the age, sex and year-match in the general population for all-cause, infection, atherosclerosis and malignancy.

SMRs were modelled using Poisson regression with the log of the expected number of events as an offset, and adjusted for age, sex, disease duration and decade of death.

**Results:** Of 259 patients known to have died, causes of death were established in 198 cases. Mean disease duration to time of death was 15.0 ± 11.3 years. Sixty-eight deaths were attributable to infection, 44 to atherosclerosis, 23 to malignancy and 39 due to active lupus.

For deaths due to all causes, the SMR falls significantly for the succeeding decade, from 12.02 (CI 7.67 - 18.82) for a female with < 5 years SLE in the 1970s to 5.08 (CI 2.18 - 11.87) in the 2000s (p < 0.0001), with a similar decrease in those with SLE ≥ 5 years.

For infection, there is a significant decade-on-decade reduction in the SMR, from 188 (CI 86 - 409) in the 1970s, to 117 (CI 42 - 324) in the 1980s, 73 (CI 21 - 256) in the 1990s and 46 (CI 10 - 203) in the 2000s (p < 0.0001), regardless of duration of disease.

The SMRs for atherosclerosis and malignancy have also decreased over the 4 decades, from 14.09 (CI 9.99 – 16.86) and 1.79 (CI 1.12 – 2.87) in the 1970s, to 11.3 years. Sixty-eight deaths were attributable to infection, 44 to atherosclerosis and malignancy. The aim of this study was to examine the standardized mortality ratios (SMR) for all-cause and cause-specific deaths in SLE patients followed prospectively at a large lupus clinic between 1970 and 2012.

**Conclusion:** Infectious causes have improved in the last three decades, whereas atherosclerotic events have decreased over the last four decades. Antimalarials have a protective effect on death in younger patients, as does age. A clinical tool for determining individual risk. Immunosuppressives have a negligible effect in all age groups.

**Disclosure:** Predicators for mortality change with age intervals. Disease activity, damage and steroids are predictors of mortality in all age intervals. In older patients, male gender is a predictor and in younger patients infection and CAD ever are predictors for mortality. The use of antimalarials is protective for individuals younger than 60.

**1860**

**Age-Specific Predictors of Mortality in SLE.** Dominique Ibanez, Dafrna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

**Background/Purpose:** Mortality is 3 to 5 times greater in SLE patients then it is in the general population – especially among younger patients where it can be over 10 times greater.

**Aim:** The aim of this study is to determine the age-specific predictors of mortality in Lupus patients.

**Methods:** All patients followed in a longitudinal cohort of lupus patients since 1970 were studied. Potential predictors for mortality were sex, coronary artery disease (CAD) ever (M1 or Angina), AAdjusted Mean SLEDAI-2K (AMS), SLICC/ACR Damage Index (SDI), current use of steroids, antimalarials, immunosuppressives, and infection. Each of the variables was evaluated at every clinic visit and used to predict mortality. Prediction models were evaluated using all of the deaths and for all visits with age < 40, for ages between 40 & 60 and for ages ≥ 60 separately. In the models with separate ages, AMS was evaluated only for the visits included in the period of analysis.

**Statistical Analysis:** Risk factors for death were evaluated using time-dependent covariate survival analysis.

**Results:** 1439 patients are included in the analysis. Depending on duration of followup, patients could be included in one or more age group. 967 were seen at ages < 40, 730 were seen at ages between 40 & 60 and 262 were seen at ages ≥ 60. In total, there are 1264 (87.8%) female, 958 (67%) Caucasian, 178 (12%) black, 140 (10%) Asian and 163 (11%) other. Age at SLE diagnosis was 30.3 ± 13.6.

A total of 211 patients died. 51 (24.2%) deaths occurred in patients aged < 40, 80 (37.9%) deaths in patients between the ages of 40 & 60 and 80 (37.9%) deaths occurred in patients over 60 years old.

Table 1 shows the hazard ratio for each of the potential predictors for mortality for age-specific intervals. The proportion of patients who died at each age interval increases from 5.3% for ages < 40, 11.0% for ages between 40 & 60, 30.5% for ages ≥ 60.

**Disease duration is a predictor when all age groups are combined but not in age-specific analysis. Sex differences are only seen in older age with male at an increased hazard. AMS in the age specific intervals, SDI and steroids increases the hazard for death in all age intervals (with borderline significance in younger patients for steroids). Presence of infection increases the risk of death in patients aged < 60 while previous CAD ever increases the chance of mortality only in patients between the ages of 40 & 60. Antimalarials have a protective effect for patients under the age of 60. Immunosuppressives have a negligible effect in all age groups.

**Conclusion:** Predictors for mortality change with age intervals. Disease activity, damage and steroids are predictors of mortality in all age intervals. In older patients male gender is a predictor and in younger patients infection and CAD ever are predictors for mortality. The use of antimalarials is protective for individuals younger than 60.
The Role of Macrophage Migration Inhibitory Factor (MIF) and MIF Gene Polymorphisms in the Pathogenesis of Granulomatosis with Polyangiitis.

Antoine G. Sreih1, Rana Ezzeddine2, Juan Fan3, Lin Leng3, Simon Gene Polymorphisms in the Pathogenesis of Granulomatosis with Polyangiitis.

Disclosure: J. B. Draibe, None; R. J. Pepper, None; P. A. Merkel, Genentech and Biogen IDEC, Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline line, 2, Actelion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5; A. D. Salama, None; F. T. RAVE-ITN Investigators, None.

1861

The Role of Macrophage Migration Inhibitory Factor (MIF) and MIF Gene Polymorphisms in the Pathogenesis of Granulomatosis with Polyangiitis.

Antoine G. Sreih1, Rana Ezzeddine2, Juan Fan3, Lin Leng3, Simon Gene Polymorphisms in the Pathogenesis of Granulomatosis with Polyangiitis.

Background/Purpose: Macrophage Migration Inhibitory Factor (MIF) is an immunoregulatory cytokine that may play a central role in the pathogenesis of granulomatous diseases. Two functional polymorphisms have been identified in the MIF gene promoter that correlate with MIF production in vivo: -794 CATT repeat (rs5844572) and a -173 G/C SNP (rs755622). This project aimed to study the association of MIF polymorphisms and MIF cytokine in granulomatosis with polyangiitis (Wegener’s, GPA) and to examine the role of MIF in a murine model of granulomatous vasculitis induced by Candida albicans water-soluble fraction (CAWS).

Methods: The human study involved 488 Caucasian patients with GPA and 551 healthy age- and sex-matched controls. Genotyping for the CATT site was performed by PCR plus capillary electrophoresis; SNP analysis was performed by real-time PCR. The frequencies of high expression MIF genotypes (>5 CATT repeats and -173 C SNP) were compared between patients and controls. MIF plasma levels were measured by ELISA in 78 patients and 45 controls. Wild type C57BL/6 mice and MIF lung-transgenic mice, some treated with anti-MIF, were injected with CAWS and analyzed for survival and for pulmonary pathology.

Results: The percentage of individuals carrying more than 5 CATT repeats (high MIF expression) was 60.9% in patients with GPA and 53.7% in controls (p = 0.02). There was no difference in the -173 G/C SNP polymorphisms between these groups. Patients with GPA had higher mean plasma MIF levels than controls (15.9 ± 10.4 ng/dl vs. 6.7 ± 5 ng/dl, p = 0.0001). A significantly higher percentage of MIF transgenic mice died when injected with CAWS as compared to wild type (Figure 1A). Injection of anti-MIF mAb protected transgenic mice from dying (Figure 1B). MIF lung-transgenic mice also exhibited more pulmonary granulomas than wild type mice (Mean number = 11.5 ± 0.8 mm² in transgenic vs. 7.9 ± 1.4 mm² in controls, p = 0.01) (Figure 2A and 2B).

Conclusion: Compared to controls, patients with GPA have an increased frequency of high-expression MIF CATT, and higher plasma MIF levels. In a murine model of granulomatous vasculitis, higher MIF expression increased mortality and pulmonary granulomas while injection of anti-MIF mAb protected mice from dying. MIF seems to play a critical role in the pathogenesis of GPA. Pharmacologic MIF inhibition may offer a promising therapy for GPA.

1862

The Association of Low-Density Granulocytes with Disease Activity and Response to Treatment in ANCA-Associated Vasculitides.

Peter C. Grayson1, Carmelo Carmona-Rivera1, Lijing Xu2, Noha Lim3, Adam A'are2, Deborah J. Phippard4, Mariana J. Kaplan1, Peter A. Merkel3 and Paul A. Monach4.

Background/Purpose: To discover new pathways involved in the pathophysiology of ANCA-associated vasculitis (AAV) and identify potential clinical biomarkers through use of whole-genome gene expression profiling. Given the recent discovery of a pathogenic link between AAV and neutrophil extracellular trap (NET) formation, the study also sought to determine if patients with AAV have low-density granulocytes (LDGs) in peripheral blood. LDGs are a distinct subset of neutrophils described in systemic lupus erythematosus (SLE) that separate with PBMC in density gradient preparations and are prone to form NETs.

Methods: The human study involved 488 Caucasian patients with GPA and 551 healthy age- and sex-matched controls. Genotyping for the CATT site was performed by PCR plus capillary electrophoresis; SNP analysis was performed by real-time PCR. The frequencies of high expression MIF genotypes (>5 CATT repeats and -173 C SNP) were compared between patients and controls. MIF plasma levels were measured by ELISA in 78 patients and 45 controls. Wild type C57BL/6 mice and MIF lung-transgenic mice, some treated with anti-MIF, were injected with CAWS and analyzed for survival and for pulmonary pathology.

Results: The percentage of individuals carrying more than 5 CATT repeats (high MIF expression) was 60.9% in patients with GPA and 53.7% in controls (p = 0.02). There was no difference in the -173 G/C SNP polymorphisms between these groups. Patients with GPA had higher mean plasma MIF levels than controls (15.9 ± 10.4 ng/dl vs. 6.7 ± 5 ng/dl, p = 0.0001). A significantly higher percentage of MIF transgenic mice died when injected with CAWS as compared to wild type (Figure 1A). Injection of anti-MIF mAb protected transgenic mice from dying (Figure 1B). MIF lung-transgenic mice also exhibited more pulmonary granulomas than wild type mice (Mean number = 11.5 ± 0.8 mm² in transgenic vs. 7.9 ± 1.4 mm² in controls, p = 0.01) (Figure 2A and 2B).

Conclusion: Compared to controls, patients with GPA have an increased frequency of high-expression MIF CATT, and higher plasma MIF levels. In a murine model of granulomatous vasculitis, higher MIF expression increased mortality and pulmonary granulomas while injection of anti-MIF mAb protected mice from dying. MIF seems to play a critical role in the pathogenesis of GPA. Pharmacologic MIF inhibition may offer a promising therapy for GPA.

Disclosure: J. B. Draibe, None; R. J. Pepper, None; P. A. Merkel, Genentech and Biogen IDEC, Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline line, 2, Actelion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5; A. D. Salama, None; F. T. RAVE-ITN Investigators, None.
Methods: The source of clinical data and link biospecimens was a randomized controlled treatment trial in AAV. RNA-sequencing of whole blood from 112 subjects with AAV was performed during active disease at the baseline study visit (BL) and during remission 6 months later (6M). Gene expression in subjects who met the primary trial outcome of clinical remission at 6M was compared to patients who did not enter remission at 6M (responders vs. nonresponders) using the generalized linear model likelihood ratio test. A multi-gene composite score was created by calculating z-scores on a per gene per sample basis. Enrichment of relevant gene set signatures was tested using Gene Set Enrichment Analysis (GSEA). Measurement of neutrophil-related gene expression in PBMC collected concomitantly to whole blood samples was performed by qPCR and compared by ANOVA. LDGs were directly isolated from PBMC fraction by negative selection in 5 additional patients with AAV not enrolled within the clinical trial. Results: There were no baseline differences in disease activity, clinical features, treatment status, and neutrophil counts between responders (n = 77) and nonresponders (n = 35). A filter separating transcripts expressed in <50% of subjects, there were 44,532 total aligned reads. Differential expression between responders and nonresponders was seen in 2,346 transcripts at BL visit (p < 0.05). Unsupervised hierarchical clustering demonstrated a distinct cluster of granulocyte-related genes that included genes coding for myeloperoxidase (MPO) and proteinase 3 (PR3), the major autoantigens in AAV. A granulocyte gene signature composite score was 10-fold higher in nonresponders versus responders (p < 0.001) and 4-fold higher in subjects during active disease (BL) than remission (6M) (p < 0.001). The signature in AAV strongly overlapped an LDG signature seen in lupus (FRDGSEA < 0.01). Increased transcription of PR3, but not MPO, measured in PBMC collected in a subset of subjects was associated with active disease (p < 0.01) and failure to meet the primary trial outcome of remission at 6M (p < 0.001), validating the findings from whole-blood profiling and localizing the source of granulocyte gene expression to LDGs. In isolation studies, LDGs were found in every patient with AAV and, similar to SLE, were noted to readily form NETs in the absence of stimulation.

Conclusion: In patients with AAV increased expression of a granulocyte gene signature is associated with disease activity and response to treatment. The source of this signature is likely LDGs, which may be a key pathogenic cell in AAV.

Disclosure: P. C. Grayson, None; C. Carmona-Rivera, None; L. Xu, None; N. Lim, None; A. Asare, None; D. J. Phippard, None; M. J. Kaplan, None; P. A. Merkel, Genentech and Biogen IDEC, Inc.; 2, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, Aetion Pharmaceuticals US, 2, Aetion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5; P. A. Monach, None.

1863 CCX168, an Orally Administered C5aR Inhibitor for Treatment of Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Pirow Bekker1, David Jayne2, Annette Bruchfeld3, Mathias Schäfer4, Kazimierz Ciechanowski5, Lorraine Harper6, Michel Jadoul7, Martin Segelmark8, Henrik Selga9, Istvan Szombati10, Michael Venken11, Christian Hugo12, Paul L. van Daalen13, Ondrej Vilikicky14, Antonia Patarca15, and Thomas Harper16, 1Chemocentryx, Inc., Mountain View, CA; 2Addenbrooks Hospital University of Cambridge, Cambridge, United Kingdom; 3Karolinska Institute, Stockholm, Sweden; 4University of Heidelberg, Heidelberg, Germany; 5Pomeranian Medical University, Szczecin, Poland; 6University of Birmingham, Birmingham, United Kingdom; 7Cliniques, Saint-Luc, Brussels, Belgium; 8Linkoping University, Linkoping, Sweden; 9Lund University, Lund, Sweden; 10Budács University, Budapest, Hungary; 11Manchester University, Manchester, United Kingdom; 12Dresden University, Dresden, Germany; 13Erasmus Medical Center, Immunology, Rotterdam, Netherlands; 14Institut of Clin and Exp Med, Prague, Czech Republic; 15Chemocentryx, Inc., Mountain View, CA.

Background/Purpose: CCX168 is a potent, specific C5aR inhibitor in clinical development for ANCA-associated vasculitis. The initial focus of this randomized, double-blind, placebo-controlled clinical trial was on renal disease activity, since CCX168 showed profound efficacy in a mouse model of MPO ANCA-induced glomerulonephritis. CCX168 indeed showed renal disease efficacy of oral 30 mg CCX168 given twice daily for 12 weeks based on eGFR (up to 6.5 mL/min/1.73 m² increase over 12 weeks), urinary ACR (mean decrease up to 63% over 12 weeks), and MCP-1 creatinine (up to 72% decrease over 12 weeks).

Methods: The purpose of this investigation was whether CCX168 treatment also has any effect on non-renal disease activity. The Birmingham Vasculitis Activity Index (BVAS) is a global disease activity index. Efficacy based on BVAS was evaluated to assess the potential non-renal disease activity of CCX168. 25 patients completed this clinical trial: 9 received placebo+cyclophosphamide (CYC) + full dose prednisone (60 mg/day), 8 received CCX168 + CYC + low dose prednisone (20 mg/day), and 8 received CCX168 + CYC + no prednisone.

Results: Baseline characteristics and Week 12 results on renal and non-renal disease activity are shown in the table.

Disclosure: P. Bekker, Chemocentryx, 1, Chemocentryx, 3; D. Jayne, Chemocentryx, 5; A. Bruchfeld, Chemocentryx, 5; M. Schäfer, None; K. Ciechanowski, None; L. Harper, Chemocentryx, 5; M. Jadoul, None; M. Segelmark, Chemocentryx, 5; D. Selga, None; I. Szombati, None; M. Venken, Chemocentryx, 5; C. Hugo, None; P. L. van Daalen, None; O. Vilikicky, None; A. Patarca, Chemocentryx, 1, Chemocentryx, 5; T. J. Schall, Chemocentryx, 1, Chemocentryx, 6, Chemocentryx, 3.

1864 Granulomatosis with Polyangitis or Microscopic Polyangitis: Long-Term Outcomes of the Prospective Wegtren Trial Comparing Azathioprine Vs Methrotrexate for Remission-Maintenance in 126 Patients. Xavier Puechal1, Christian Pagnoux2, Elodie Perorden2, Mohamed Hamidou3, Jean-Jacques Boffa4, Xavier Knysh5, François Lifermann1, Thomas Papa6, Dominique Merrien7, Amael Smail8, Philippe Delaval9, Catherine Hanrot-Saliou10, Bernard Imbert11, Chahéra Khouatra12, Marc Lambert13, Charles Leské14, Kim Heang Ly15, Edouard Periout6, Pascal Roblot16, Marc Ruviard17, Jean-François Subra18, Jean-François Viallard19, Benjamin Terrier20, Pascal Cohen21, Luc Mouton22, Philippe Ravard23 and Loïc Guillemé for the French Vasculitis Study Group. 1National Reference Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France; 2University of Toronto, Toronto, ON, 3Epidemiology, Université Paris-Descartes, Paris, France, 4CHU Hôtel Dieu, Nantes, Nantes, France, 5Hôpital Tenon, Paris, Paris, France, 6CH, Vaulx-en-Velin, Vaulx-en-Velin, France, 7CH Côtes-d’Azur, Nice, 8CH, Angers, Angers, France, 9CH, Poitiers, Poitiers, France, 10CHU Estai, Clermont-Ferrand, Clermont-Ferrand, France, 11CHU Dupuytren, Limoges, Limoges, France, 12René Dubos Hospital, Pontoise, France, 13CH, Poitiers, Poitiers, France, 14CHU Estai, Clermont-Ferrand, Clermont-Ferrand, France, 15CHU Angers, Angers, France, 16Hôpital Haut-Lévêque, Bordeaux, CHU Bordeaux, France.

* Response: BVAS decrease ≥50% plus no worsening in any body system; ** Remission: BVAS of 0 plus prednisone dose ≤10 mg/day.

Conclusion: In addition to an effect on renal disease activity, CCX168 treatment of patients with ANCA-associated vasculitis also resulted in a salutary effect on non-renal disease activity based on the non-renal component of the BVAS.
Background/Purpose: Results of the previously reported randomized-controlled WEGENT trial demonstrated that, at 28 months, methotrexate (MTX) is as effective as azathioprine (AZA) for maintaining remission of granulomatosis with polyangiitis (GPA, Wegener's) or severe microscopic polyangiitis (MPA) (NEJM 2008;359:2790–803). The long-term outcomes of patients included in the WEGENT trial were analyzed in this study.

Methods: Long-term outcomes were ascertained for 126 patients enrolled in the WEGENT Trial between 1999 and 2004. Data on survival, relapse, immunosuppressant use, cancer, infection and cardiovascular morbidity were collected. All patients were analyzed according to their randomization group. Demographic, clinical, and laboratory parameters at trial entry were evaluated as potential prognostic factors for death or relapse in multivariate models.

Results: Median follow-up was 11.8 years. The 10-year overall survival rate was 74.8% (95% CI 64.5–86.9) for the AZA arm and 79.9% (95% CI 70.3–90.7) for the MTX arm, with no between-arm survival difference (HR MTX vs AZA 0.90 [95% CI 0.37–2.07]; P = 0.55). No significant between-arm differences were observed for adverse events, severe adverse events, infections, cancer, relapses and severe relapses. The 10-year survival rate without relapse was 26.3% (95% CI 17.3–40.1) in the AZA arm and 35.1% (95% CI 24.9–49.4) in the MTX arm, with no significant between-arm difference (HR MTX vs AZA 0.78 [95% CI 0.51–1.20]; P = 0.26). The 10-year survival rate without severe side effects was also comparable for the two groups (HR MTX vs AZA 1.02 [95% CI 0.64–1.63]; P = 0.93), as was survival without relapse and severe side effects (HR MTX vs AZA 1.04 [95% CI 0.66–1.63]; P = 0.87). Taking into account only the 97 GPA patients, no between-arm differences were observed for these survival parameters.

Conclusion: This long-term analysis confirmed that AZA and MTX are comparable options for maintaining GPA or MPA remission. It showed that the odds of adverse events, relapse, and severe adverse events remain matters of concern. Further studies are needed to reduce the long-term relapse rate of AANCA-associated vasculitides.

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1865

Increased Risk of Myocardial Infarction and Cerebrovascular Accidents after Diagnosis of Granulomatosis with Polyangiitis: A General Population-Based Cohort Study. Neda Amiri1, Natasha Dehghan2, Eric C. Sayre2, Kamran Shojania1 and J. Antonio Avina-Zubieta2. 1University of British Columbia, Vancouver, BC, 2Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Limited literature is available on the incidence of myocardial infarction (MI) and cerebrovascular accidents (CVA) in patients with Granulomatosis with Polyangiitis (GPA). We assessed the risk of MI and CVA in cases of GPA compared to controls from the general population using hospitalization databases and physician billings that encompasses the entire province of British Columbia, Canada. We further determined the time trend risks of MI and CVA since diagnosis of GPA.

Methods: Our data included all visits to health professionals and all hospital admissions from 1990 to 2010 as well as all dispensed medication from 1996 to 2010 for all individuals.

We conducted a retrospective matched cohort study among new cases with GPA meeting a pre-defined criteria as follows: a) diagnosis of GPA (ICD-9-CM 446.4) in adults; b) age at least 20 years old; c) diagnosis within a two-year period between 1996 and 2010 by a non-rheumatologist physician; d) diagnosis of GPA on at least one visit by a rheumatologist or from hospitalization; e) absence of a prior GPA diagnosis between 1996 and 2010 (to ensure incident GPA cases); f) cases matched by birth year, sex and calendar year of follow-up were selected from the general population.

Incident MI and CVA events based on hospitalization or death certificate were recorded as an outcome. We estimated relative risks (RRs) comparing GPA with age-, sex- and entry-time-matched comparison cohorts, adjusting for potential cardiovascular risk factors. Sensitivity analyses were conducted to assess for unmeasured confounders (e.g. smoking).

Results: Among 640 incident cases of GPA (54.2% female, mean age 58.6 ± 12 years, 42% GPA), 28 developed a first time MI and 25 CVA events with an incident rate (IR) of 13.9 and 12.3 per 1000 person-years, respectively. Compared with the age, sex, and entry-matched controls, the incidence rate ratio (IRR) were 3.3 (95% CI 2.1–5.0) and 3.2 (95% CI 2.0–5.1) for MI and CVA respectively. The risk of developing MI and CVA was highest within the first year following diagnosis of GPA, decreasing over time and persisting after 5 years (see table). After adjusting for covariates, the results remained significant for both MI and CVA. The results also remained statistically significant after adjusting for the potential impact of unmeasured confounders (adjusted RRs ranging between 2.57 and 3.84 in all sensitivity analyses).

Conclusion: This large general population-based study found an increased risk of MI and CVA in patients with GPA. Furthermore, the risk is highest in the first year of disease and decreases subsequently persisting at 5 years of follow up. Our results support increased monitoring for cardiovascular disease in patients with GPA, including management of traditional risk factors to reduce this risk.

Table: Risk of Incident MI and CVA according to GPA Status

<table>
<thead>
<tr>
<th>GPA N = 608</th>
<th>Non-GPA N = 6,169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of MI, n</td>
<td>28</td>
</tr>
<tr>
<td>Incidence Rate/1000 PY</td>
<td>13.9</td>
</tr>
<tr>
<td>Age-, sex-, and entry-time-matched RRs (95% CI)</td>
<td>3.3 (2.1–5.0)</td>
</tr>
<tr>
<td>1 year of disease duration</td>
<td>6.0 (2.7–12.7)</td>
</tr>
<tr>
<td>2 years</td>
<td>3.9 (1.9–7.4)</td>
</tr>
<tr>
<td>3 years</td>
<td>3.1 (1.6–5.6)</td>
</tr>
<tr>
<td>4 years</td>
<td>3.5 (2.0–5.9)</td>
</tr>
<tr>
<td>5 years</td>
<td>3.4 (2.0–5.6)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)</td>
<td>3.9 (2.2–6.7)</td>
</tr>
</tbody>
</table>

Cases of CVA, n | 25 | 99 |
| Incidence Rate/1000 PY | 12.3 | 3.8 |
| Age-, sex-, and entry-time-matched RRs (95% CI) | 3.2 (2.0–5.1) | 1.0 |
| 1 year of disease duration | 7.1 (3.3–14.5) | 1.0 |
| 2 years | 5.1 (2.7–9.2) | 1.0 |
| 3 years | 4.5 (2.5–7.8) | 1.0 |
| 4 years | 4.0 (2.3–6.8) | 1.0 |
| 5 years | 4.1 (2.4–6.7) | 1.0 |
| Multivariable RR (95% CI) | 3.1 (1.7–5.7) | 1.0 |

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ACR/ARHP Combined Session
Pediatric Rheumatology
Monday, November 17, 2014, 2:30 PM – 4:00 PM

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Birth Outcomes in Women with a History of Juvenile Idiopathic Arthritis. Debbie Ehrmann Feldman1, Evelyne Vinet2, Sasha Bernatsky3, Clarian Duffy4, Elizabeth Hazle5, Marie-Pierre Sylvestre6, Garbis M Esheidjian4 and Anick Bérard2. 1Université de Montréal, Montréal, QC, 2McGill University Health Center, Montréal, QC, 3McGill University, Montréal, QC, 4Children’s Hospital of Eastern Ontario, Ottawa, ON, 5McGill University Health Center, Montréal, QC, 6Public Health Department of Montréal, Montréal, QC.

Background/Purpose: Although there is a higher frequency of adverse birth outcomes in women with rheumatoid arthritis, little is known on the subject regarding women who had juvenile idiopathic arthritis (JIA) as children or adolescents. The objective of our study was to determine whether children born to women who had JIA in childhood and adolescence had more adverse birth outcomes than children born to mothers who never had JIA.

Methods: We designed a retrospective cohort study using administrative data that covered the entire population of the province of Québec, Canada. We identified 1765 females with a diagnosis of JIA who had given birth (first birth: stillbirth or live birth) between 01/01/1983 and 12/31/2010 from the
Quebec physician reimbursement and hospitalization databases. We also assembled a cohort of women from the population database who did not have a diagnosis of JIA, matched 4:1 for date of first birth (≥ 3 months), age (≥ 5 years) and region of residence (using the postal code) to serve as a control group (n = 7024). We compared birth outcomes (stillbirth, prematurity, small for gestational age, and the presence of major congenital anomalies diagnosed within the first year post birth) in those who had JIA and those who did not. We used logistic regression, adjusting for maternal age, sex of the infant, maternal education, hypertension during pregnancy and gestational diabetes.

Results: For the entire cohort, the mean age at delivery was 24.9 years (standard deviation 4.4; range 16 to 46 years). There were more adverse birth outcomes in the JIA group, except for stillbirths. Women who had had JIA were at higher risk for having a premature baby (adjusted relative risk (95% confidence interval) 1.18 (1.00–1.4)), a small for gestational age baby (adjusted relative risk (95% confidence interval) 1.19 (1.04–1.36)), and a child with a major congenital anomaly (adjusted relative risk (95% confidence interval) 6.49 (4.88–8.10)). The prevalence of neural tube defects was especially high in the JIA group (1.7% vs 0.04% in the non JIA group) as were congenital heart and circulatory defects (1.2% in the JIA group vs 0.6% in the non JIA group).

Conclusion: Women who had JIA are at higher risk for adverse birth outcomes. The implications are that women with a history of JIA who are pregnant must be monitored closely. Further research is needed to understand possible pathophysiologic mechanisms in JIA and pregnancy as well as pharmacoepidemiologic studies to explore the effects of medications during childhood and youth (including during the peri-pubescent period) on future birth outcomes.

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1867
Mandibular Movement in Healthy Individuals from 4-17 Years of Age.
Peter Stoustrup1, Kasper Dahl Kristensen2, Annelise Kuseler3, Thomas Klit Madsen4 and Troels Herlin4. 1University of Aarhus, Aarhus C, Denmark, 2Specialist Oral Health Center for Western Norway, Rogaland Stavanger, Norway, 3Aarhus University, Aarhus, Denmark, 4Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: A measurement of mandibular movement capacity is an important part of the clinical orofacial examination of patients with juvenile idiopathic arthritis (JIA). The aim of the present study was twofold: 1) To establish age-related normative values for maximal mouth opening capacity and mandibular laterotrusion in healthy individuals. 2) To establish a universal cut-off value for "normal" range of motion in children and adolescent patients to be used in future clinical orofacial examinations of patients with JIA.

Methods: A total of 1114 healthy Danish individuals between the ages of 4-17 years were included in this cross-sectional population-based study. During a routine dental examination the maximal mouth opening capacity and laterotrusion capacity (the sideway excursion of the mandible) were assessed in each individual according to a standardized measurement protocol with calibrated metallic rulers. The measurements were adjusted for overbite and midline deviations. Exclusion criteria: diagnosis with temporomandibular dysfunction, previous orofacial complaints, jaw fractures or hypermobility.

Results: The mean maximal mouth opening gradually increased from 38 mm (SD 6.1 mm) at age four to 54.5 mm (SD 6.8 mm) at age 17. A linear increase in the opening capacity was observed between the age of four to 11; beyond the age of 11 only minor changes of 4 millimeters were observed. No inter-gender difference in maximal mouth opening capacity was observed (p>0.15).

The mean total laterotrusion capacity (right excursion + left excursion) gradually increased from 15.4 mm (SD 3.1 mm) at age four to 20.1 mm (SD 3.7 mm) at age 17. A statistical significant inter-gender difference of 0.8 mm (SD 0.4 mm) was observed in relation to the total laterotrusion capacity; however, the clinical relevance of this significant difference is questionable.

Conclusion: Normal values of maximal mouth opening capacity and laterotrusion capacity in individuals between four and 17 years of age were established. Our findings oppose the use of a single universal cut-off value for "normal" range of motion in children and adolescent patients. Instead we recommend including the age-related normative values of mandibular range of motion in the orofacial examination of patients with JIA.

Disclosure: P. Stoustrup, None; K. D. Kristensen, None; A. Kuseler, None; T. K. Pedersen, None; T. Herlin, None.

1868
Can DAS 28 at 3 Months after the 1st Biologic Therapy Predict Subsequent Sustainable Clinical Remission in Particular Juvenile Idiopathic Arthritis Patients?
Tomohiro Kubota1, Syuji Takei2, Tsuyoshi Yamabu2, Tomokazu Nagakura3, Hiroyuki Imanaka2, Yuikiko Nonaka2, Tomoko Takezaki2, Harumi Akaike3 and Mio Matsuura5. 1Kagoshima University Hospital, Kagoshima City, Japan, 2Kagoshima University, Kagoshima, Japan, 3Kagoshima University Hospital, Kagoshima, Japan, 4House of Mrameworks, USuki, Japan, 5Kagoshima University, Kagoshima-Shi, Japan.

Background/Purpose: To avoid the progression of joint damage, early decision making is important in JIA patients who failed to achieve sustainable clinical remission by the 1st biologic agents. Therefore, we examined whether the scores of DAS 28 at 3 months after initiating the 1st biologic therapy can predict subsequent sustainable remission with the 1st biologic agents in the polyarticular JIA (pJIA) patients.

Methods: pJIA patients who had started the 1st biologic agents at the Kagoshima University Hospital were involved in this study. The patients were divided into two groups according to the subsequent efficacy of the 1st biologic agents; patients who successfully maintained clinical remission with the 1st biologic agents (remission group) and the patients who were eventually obliged to switch to the 2nd biologic agents due to the lack of efficacy (switching group).

Results: Scores of DAS 28 of 14 pJIA patients involved in this study gradually improved after starting the 1st biologic agents. However, 6 of 14 patients (43%) failed to maintain their clinical remission and eventually switched to the 2nd biologic agents at 9 months (median, range 6-18 months) after initiating the 1st biologic agents (switching group). The rest of 8 patients (57%) achieved sustainable clinical remission with the 1st biologic agents (remission group).

There were no significant differences between the two patients' groups as to sex ratio, age at onset, disease duration at initiating biologics. However, DAS28 score at 3 months after the 1st biologic therapy was significantly higher in switching group (1.75 ± 1.0) than that of remission group (3.8 ± 0.87) (p = 0.001) (Figure 1). The receiver operating characteristic (ROC) analysis revealed that the cut-off point of DAS28 to discriminate the two patients' group was 2.37 (sensitivity 100%, specificity 88.9%).

Conclusion: Evaluating DAS28 at 3 month after initiating biologic therapy was useful in predicting subsequent sustainable clinical remission. Patients with DAS28 >2.37 at 3 month after initiating the 1st biologic agents should be considered to switch to the 2nd biologic agents in the treatment of pJIA.

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Background/Purpose: We examined the functional, psychological, and pain-related outcomes among children with chronic pain completing an intensive interdisciplinary pediatric pain rehabilitation program. We hypothesized that baseline psychological measures (i.e., anxiety, depression) will predict longer treatment course while baseline pain severity would not correlate with program duration in an interdisciplinary pain rehabilitation program.

Methods: This outpatient program provides 5-6 hours of daily intensive physical and occupational therapy in addition to yoga, self-regulation training, and behavioral health intervention. All pain medications are discontinued, and no invasive therapeutic procedures are utilized. 31 patients (27 female) age 11–18 with chronic musculoskeletal pain completed Functional Disability Inventory, 100 mm Visual Analog Scale, PROMIS Anxiety, Depression, and Mobility, PRQ-catastrophizing, and the Pain Acceptance Questionnaire for Adolescents at baseline, the end of each week, and 28 have completed a one-month follow-up and 14 have completed a six-month follow-up. Paired samples t-tests and correlations were conducted with SPSS (V.20) and supplemented with hierarchical linear modeling (HLM 7) for time-series analyses of pain, functioning, and psychological factors.

Results: The mean program duration was 3.7 (± 0.9) weeks, determined by achievement of functional goals. Using paired samples t-tests, current pain (VAS 0-100) significantly decreased from 59.1 to 36.7 (P = .001) and 26.9 (P = .004) at 1- and 6-month follow-up, respectively. FDI improved from 27.3 to 13.8 between baseline and program end (P < .001), and continues to improve at 1- and 6-month follow-up to 7.7 (P < .001) and 4.4 (P = .006) respectively, reflecting increased physical ability. Patient-reported anxiety and depression decline significantly (P < .001), while pain acceptance increases significantly during treatment (P < .001). Treatment program duration correlated with greater baseline disability (FDI r = .462; P = .009), and presence of conversion symptoms (r = .548; P = .004). Patients with greater pain acceptance (CPAQ-A; r = -.433; P = .015) at baseline required shorter treatment intervention.

Conclusion: Children with chronic musculoskeletal pain successfully restore function and improve pain without pharmacotherapy. Baseline functional disability and psychological factors correlate with treatment program duration. Prospective studies are warranted to determine long-term efficacy and effectiveness of this interdisciplinary program.

Disclosure. J. Tekano, None; L. B. Tucker, None; A. Chen, None.

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Puberty and Disease Activity in JIA. Philomine A. van Pelt1, Aikea. Kruize2, Anita C.S. Hokken-Koelega1, Radboud JEM Dolhain5, Johannes WJ Bijlsma1 and Nico M. Wulffraat2. 1Erasmus MC, Rotterdam, Netherlands, 2University Medical Center Utrecht, Utrecht, Netherlands. 3Erasmus Medical Center- Sophia Children’s Hospital, Rotterdam, Netherlands. 4Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands. 5University Medical Centre Utrecht, Utrecht, Netherlands.

Background/Purpose: Delayed puberty and decreased final height has been reported in chronic diseases like Crohn’s disease and JIA with a disease onset at prepubertal age. This may be due to systemic effects of inflammation, undernutrition or medication, for example glucocorticoids or MTX. Treatment with anti TNF has shown to restore delayed growth in JIA.

Nowadays patients are treated intensively with disease modifying drugs including biologicals to reach remission. Our objectives are to describe growth, onset and progression of puberty in established JIA patients who are treated intensively.

Methods: All consecutive JIA patients aged 10-24 years were asked to participate in this observational follow-up study. Demographic and disease related items were obtained yearly as well as Tanner puberty stages: Pubic Hair Girls (PHG), Breast stage (Bre), Menarche (Men), Pubic Hair Boys (PHB), Genital Stage (Gen). Reference Values were obtained from the Dutch National Growth Study. Median age at reaching each pubertal stage was estimated by Kaplan-Meier survival estimates based on data from patients of Caucasian origin and younger than 21 years. The progression of puberty is defined as the difference in median age between the Tanner stage 2 & 4 and 4 & 5. Parametric tests are used to determine differences between patients and healthy controls, non parametric tests are used to determine differences between patient groups.

Disclosure. C. Hoffart, None; R. Anderson, None; A. Chapman, None; B. Dorton, None; D. Petrop, None; M. Wilson, None; D. Wallace, None.
Results: 138 patients were included: 91 girls (66%) and 47 boys (34%). Ten percent have systemic onset type of JIA, 24% oligo-persistent, 55% oligo-extended and polyarticular course, 11% other subtypes of JIA. Median disease duration is 7.8 years (IQR 6.7), median active joint count is 0.0 (2.0), median DAS28 is 2.16 (1.30). MTX is used in 79% of the patients, and TNF in 14% and systemic corticosteroids in 23%. Median SDS length is −0.29 (IQR 1.38), SDS weight −0.27 (1.46), SDS BMI −0.08 (1.71). PHG, Bre, PHB and Gen are delayed in all stages 2-5, more pronounced in stage 5. Median delay compared to healthy controls in PHG stage 5 is 3.4 years, in Bre stage 5 3.4 years, in Menarche 3.5 years, in PHB stage 5 1.6 years and in Gen stage 5 1.7 years. The progression of puberty was delayed between all stages in both girls and boys, most markedly delay was seen between stage 4S of PHG 4 and Bre. No significant differences are seen between users and non-users of systemic corticosteroids, MTX or biologicals. Subtype of JIA, disease activity and age at onset did not significantly influence results.

Conclusion: Due to intensive treatment, disease activity in JIA patients is low and growth is comparable to healthy age related persons. However, puberty is still remarkably delayed. Further investigation into clinical relevance and cause of delayed puberty is needed.

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Gout in Older Adult. M. A. C. Dams-DeMarco1, A. N. Kottgen2, Bridget Burke1, Andrew Law1, Josef Corsh3 and Alan N. Baer4. 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 2University of Freiburg, Freiburg, Germany, 3Johns Hopkins University, Baltimore, MD, 4Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: To evaluate whether general and genetic risk factors in middle-aged members of a longitudinal population-based cohort predict the onset of gout in older age.

Methods: We studied the incidence and prevalence of gout in white older adults using the Atherosclerosis Risk in Communities Study, a prospective US population-based cohort study of middle-aged adults enrolled between 1987-1989 with ongoing follow-up. A genetic urate score (GUS) was formed from common urate-associated single nucleotide polymorphisms for eight genes. The adjusted hazard ratio (HR) and 95% confidence intervals (CI) of incident gout by traditional and genetic risk factors in middle age were estimated using a Cox Proportional Hazards model.

Results: Of the 9,526 participants, 46.2% were male and the mean (SD) age at cohort enrollment was 54.0 (5.7). The overall prevalence of gout was 8.9%; 31.9% of those with a history of gout reported a physician diagnosis of this inflammatory arthritis at age 65 or older. By age 65 the prevalence of gout was 9.0% for men and 3.3% for women, conditioned on survival to age 65. The cumulative incidence from middle age to age 65 was 8.6% in men and 2.5% in women as well as 8.0% for those in the 4th quartile of GUS. 5.0% for those in the 3rd quartile, 3.8% for those in the 2nd quartile and 3.3% for those in the 1st quartile, conditioned on survival to age 65 (Figure). In middle age, increased adiposity, beer intake, protein intake, smoking status, hypertension, diuretic use, and kidney function (but not sex) were associated with an increased risk of gout in older age. In addition, high genetic risk (100 μmol/L increase in GUS) was associated with a 3.29-fold (95% CI: 1.63, 6.63) increased risk of gout in older age.

Conclusion: In this US population-based cohort, traditional risk factors that were present in middle-age were associated with the development of gout in older age.

Figure: Cumulative incidence of gout by quartile of genetic urate score. The incidence of gout for participants of ARIC was estimated using a Kaplan-Meier approach. All cumulative incidences (%) should be interpreted as the percentage of participants with gout, conditioned on survival to that age. The genetic urate score is measured in μmol/L. Quartile 1 of the genetic urate score ranges from −59.1 to −13.1; quartile 2 from −13.2 to 0.3; quartile 3 from −4.0 to 12.0 and quartile 4 from 12.1 to 60.8.

Disclose M. Mcdams-DeMarco, None; A. Kottgen, None; B. Burke, None; A. Law, None; J. Coresh, None; A. N. Baer, None.

1873
Food Sources of Protein and Risk of Incident Gout in the Singapore Chinese Health Study. Gim Gee Teng1, An Pan2, Jian-Min Y. Tan3 and Woon-Puay Koh4. 1Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, 2Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore, 3Division of Cancer Control and Population Sciences, University of Pittsburgh Cancer Institute, and Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, 4Duke-NUS Graduate Medical School Singapore, Singapore, Singapore.

Background/Purpose: The Health Professional Follow up Study in Caucasian men showed that intakes of meat and seafood increased risk of gout, while dairy products, especially low-fat dairy products, reduced the risk. (1) Purine rich vegetable intake had no association with incident gout. Studies evaluating diet on gout risk in Asian populations are lacking. Most of these studies focused on alcohol intake and evaluated on hyperuricaemia rather than gout as the dependent variable. We examined the relation of dietary protein and protein sources with incident gout among Chinese men and women.

Methods: We used data from the Singapore Chinese Health Study, a prospective cohort study with 63,257 Chinese adults aged 45-74 years at recruitment from 1993 to 1998. Dietary information was collected via a validated food frequency question, and physician-diagnosed gout was self-reported during the two follow-up visits of 1999-2004 and 2006-2010. We conducted analysis among 51,114 participants without gout at baseline and who responded to the follow-up questionnaires. Cox proportional hazards models were used to calculate the relative risk (RR) and 95% confidence interval (CI) with adjustment for potential confounding factors, including age, sex, alcohol intake, body mass index and hyperuricaemia. Multivariate models were further adjusted for protein sources.

Results: Among 51,114 subjects interviewed at either or both interviews, after a mean follow-up of 11.1 (SD 3.7) years, there were 2,167 incident gout cases with mean age of onset at 61.3 (SD 8.1) years. Participants with gout were more likely to be men, more highly educated, ever smokers, weekly or daily alcohol drinkers and to have higher BMI than those without gout. 36.8% of gout subjects had hypertension compared with 21.4% among those without gout. Compared to the lowest quartile intake, the multivariate-adjusted RRs (95% CI) of incident gout in the highest quartile were 1.27 (1.12-1.44) for total protein (P trend = 0.001; 1.28 (1.12-1.47) for poultry (P trend = 0.001); and 1.16 (1.02-1.32) for fish and shellfish (P trend = 0.014). Conversely, intakes of soy and other legumes were associated with reduced risk, the RR (95% CI) in the highest quartile intake being 0.87 (0.77–1.00) for soy foods (P trend = 0.01) and 0.85 (0.74-0.97) for legumes (P trend = 0.02). There was no association between intake of red meat (including pork), eggs, dairy products, grain products, nuts and seeds, and risk of gout. There was no significant interaction between sex, BMI, history of hypertension, smoking and alcohol consumption status, and intake of foods on risk of gout.

Conclusion: Total protein intake, mainly contributed by poultry, fish and shellfish, was associated with increased risk of gout in this population. Conversely, soy and legume foods may be related to reduced risk of gout. The general advice of replacing red meat with “white meat” such as poultry may
not be advisable. Myths of deleterious effect of soy and legume intake on gout may be debunked. Other health benefits of soy plus a possible protective effect on gout makes it a plausible vegetable-based meat substitute.

Reference

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1874

Obesity Paradox in Recurrent Gout - A Metrological Clarification and Remedy, Uyen Sa D.T. Nguyen1, Qiong Louie-Gao2, Yuying Zhang3, David T. Felson4, Michael P. Lavalle5 and Hyon Choi6. 7Boston University School of Medicine, Boston, MA, 8Boston University, Boston, MA, 9Harvard Medical School, Boston, MA.

Background/Purpose: Obesity is a strong risk factor of incident gout, but previous research showed no such association with recurrent gout among gout patients. These paradoxical findings occur because the causal net effect (i.e., total effect) of obesity on recurrent gout in gout patients cannot be validly estimated using conventional methods. We demonstrate that the paradox can be clarified using an appropriate mediation analysis, and illustrate a design to estimate the total effect of BMI on recurrent gout in incident gout patients.

Methods: We used data from the Multiple Risk Factor Intervention Trial (MRFIT), prospectively collected at baseline and annually over 7 years. BMI at baseline was categorized as: >30 kg/m² (obese), 25-29.9 (overweight), and <25 (normal) and self-report of physician-diagnosis of gout was our outcome. We followed subjects without gout at baseline to determine the first occurrence of gout and their recurrent gouts by the 84-month visit. We assessed the effect of BMI on recurrent gout with the conventional method of restricting on incident gout patients and using logistic regression. We then clarified the paradox using marginal structural modeling (MSM) for mediation analysis. We estimated the total effect of BMI on recurrent gout by decomposing the total effect into its components (Table): the indirect effect of BMI via its effect on incident gout, and the direct effect of BMI on recurrent gout not through its effect on incident gout. Finally, we determined the association of change in BMI categories before and after incident gout on risk of recurrent gout in incident gout patients. All analyses were adjusted for known confounders.

Results: Of 11,635 subjects without gout at baseline (mean age 46 years; 21% normal, 56% overweight, 23% obesity), 408 people developed incident gout, and 131 had recurrent gout. Conventional method showed that the adjusted odds ratio (OR) for recurrent gout was 1.10 (95% CI: 0.52, 2.30) for obese compared with normal BMI (Table). Using MSM, the indirect effect of obesity compared with normal weight was on the risk of recurrent gout (via its effect on incident gout) was 2.62 (95% CI: 2.01, 3.40); the direct effect not through incident gout was 1.13 (95% CI: 0.82, 1.56); and the total effect was 2.94 (95% CI: 1.39, 5.41) (Table). Among incident gout patients, the adjusted total effect of increasing BMI after gout occurs was 2.62 (95% CI: 2.01, 3.40); the adjusted total effect of increasing BMI after recurrent gout was 1.10 (95% CI: 0.52, 2.30) for obese patients. These paradoxical findings occur because the causal net effect (i.e., total effect) of obesity on recurrent gout in gout patients cannot be validly estimated using conventional methods.

Conclusion: We showed that the effect of obesity at baseline on risk of recurrent gout is almost entirely through its effect on incident gout. Conditioning on incident gout and estimating the effect of baseline obesity on the risk of recurrent gout would provide only an estimate of its direct effect, as the indirect effect is blocked. In order to examine the total effect of obesity on recurrent gout in those with incident gout, BMI change must be assessed before and after incident gout.

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Can Allopurinol Survival Impact Reverse Depending on Patients’ Characteristics? A Propensity-Score Based Subgroup Analysis, Na Lu1, Hyon Choi2, M aureen Dubreuil3, Qiong Louie-Gao2 and Yuying Zhang1. 1Boston University School of Medicine, Boston, MA, 2Harvard Medical School, Boston, MA, 3Boston University Medical Center, Boston, MA.

Background/Purpose: Several studies have reported that allopurinol use is associated with a decreased risk of death or cardiovascular outcomes. While these studies reported the overall average effect of allopurinol, the impact may vary depending on the patients’ characteristics. This line of research could help identify patients who will get the greatest benefit from allopurinol use, as well as those who may face a hazardous impact (thus conferring a patient-oriented, personalized medicine approach). To address these issues, we assessed whether the survival impact of allopurinol varies across the distribution of propensity scores (PS) in a general population-based cohort study.

Methods: We conducted an incident user cohort study with PS matching using a UK general population database. Eligible subjects were aged ≥40 years and had a record of hyperuricemia (serum urate >357 μmol/L for women and >416 μmol/L for men) between January 2000 and May 2010. For each 6-month period during the study follow-up, each allopurinol initiator was matched to a non-initiator by PS using the greedy-matching method. Subjects were followed until death, loss to follow-up, or the study period ended, whichever came first. We calculated the all-cause mortality rate and examined the association of allopurinol initiation with the risk of mortality using a Cox proportional hazard model. We then examined whether the effect of allopurinol varied across PS level categories (Table). Results: Our study included 6,947 allopurinol initiators and 6,947 non-initiators. All measured potential confounders were evenly distributed between the two groups. The mortality rate was 39/1000 person-years in allopurinol initiators and 46/1000 person-years in non-initiators, resulting in an overall HR of 0.86 (95% CI: 0.78-0.96). Our subgroup analysis by PS showed a reversal of HR from hazardous in the lowest PS group (HR of the lowest PS group, 1.67) to increasingly protective with higher PS groups (HR of the highest PS group, 0.65) (Table). The most obvious difference in patient characteristics between the top and bottom 20th percentile PS groups was the presence of gout (>98% vs. 38%), suggesting that treatment of gout patients is life-saving (compared to the hazardous impact of treating asymptomatic hyperuricemia).

Conclusion: Our findings suggest that the association of allopurinol with the risk of all-cause mortality may vary widely from conferring a protective versus hazardous impact, according to patients’ characteristics (reflected in PS). However, a potential alternative explanation may be extreme levels of residual confounding. Nevertheless, if confirmed, these potentially opposite subgroup effects would help to identify individuals who will receive the maximum benefit from allopurinol, thus helping to achieve a germane patient-oriented, personalized medicine approach in this common practice context.

Table 1. Risk of Mortality Associated with Initiation of Allopurinol According to Propensity Score Categories

<table>
<thead>
<tr>
<th>Propensity Score Percentile</th>
<th>Mean Propensity Score</th>
<th>No.</th>
<th>Death</th>
<th>Person-Year</th>
<th>Death</th>
<th>Person-Year</th>
<th>IRR</th>
<th>IRR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2%</td>
<td>0.006</td>
<td>278</td>
<td>17</td>
<td>435</td>
<td>0.039</td>
<td>11</td>
<td>468</td>
<td>0.024</td>
</tr>
<tr>
<td>2%-10%</td>
<td>0.016</td>
<td>1127</td>
<td>57</td>
<td>1524</td>
<td>0.037</td>
<td>64</td>
<td>1589</td>
<td>0.028</td>
</tr>
<tr>
<td>10%-20%</td>
<td>0.052</td>
<td>1388</td>
<td>79</td>
<td>1937</td>
<td>0.041</td>
<td>68</td>
<td>1967</td>
<td>0.034</td>
</tr>
<tr>
<td>20%-40%</td>
<td>0.093</td>
<td>2708</td>
<td>94</td>
<td>3780</td>
<td>0.025</td>
<td>109</td>
<td>3733</td>
<td>0.029</td>
</tr>
<tr>
<td>40%-60%</td>
<td>0.137</td>
<td>2780</td>
<td>92</td>
<td>4019</td>
<td>0.023</td>
<td>113</td>
<td>3863</td>
<td>0.029</td>
</tr>
<tr>
<td>60%-80%</td>
<td>0.198</td>
<td>2780</td>
<td>741</td>
<td>4723</td>
<td>0.033</td>
<td>155</td>
<td>4028</td>
<td>0.039</td>
</tr>
<tr>
<td>80%-90%</td>
<td>0.288</td>
<td>1388</td>
<td>115</td>
<td>2184</td>
<td>0.053</td>
<td>152</td>
<td>2039</td>
<td>0.071</td>
</tr>
<tr>
<td>90%-98%</td>
<td>0.423</td>
<td>1128</td>
<td>148</td>
<td>1602</td>
<td>0.092</td>
<td>175</td>
<td>1499</td>
<td>0.117</td>
</tr>
<tr>
<td>&gt;98%</td>
<td>0.605</td>
<td>276</td>
<td>44</td>
<td>383</td>
<td>0.113</td>
<td>68</td>
<td>341</td>
<td>0.199</td>
</tr>
</tbody>
</table>

* Mean propensity score within the percentile, IRR = incidence rate, IRR* = incidence rate ratio; HR = hazard ratio.

Disclosure: N. Lu None; H. Choi, Takeda, S, AstraZeneca, S. M. Dubreuil None; Q. Louie-Gao None; Y. Zhang, None.

1876

Influence of Alcohol Consumption on the Risk of SLE Among Women in the Nurses’ Health Studies, Medha Barbhaiya, Bing Lu, Shun-Chiao Chang, Jeffrey A. Sparks, Elizabeth W. Karirson and Karen H. Costenbader. Brigham and Women’s Hospital, Harvard Medical School, Boston, M.A.

Monday, November 17
Background/Purpose: Prior case-control studies have reported an inverse association between moderate alcohol consumption and the development of SLE. However, case-control studies may be prone to recall bias and reverse causation. A prior prospective study did not demonstrate an association between alcohol intake and SLE development, although this study was limited by small sample size (34 confirmed cases, Formica MK et al, J Rheum, 2003). We assessed the association between alcohol consumption and risk of SLE among women followed in the Nurses’ Health Study (NHS) and NHSII. We hypothesized that alcohol consumption, possibly through anti-inflammatory effects, would be associated with lower risk for SLE compared to no alcohol consumption.

Methods: The NHS enrolled 121,701 U.S. female registered nurses in 1976. NHS II began in 1989, enrolling 116,430 female nurses. Lifestyle and environmental exposures were collected through biennial questionnaires. Alcohol consumption was assessed with a semi-quantitative food frequency questionnaire completed every 4 years. Participants in NHS and NHSII who provided alcohol data at baseline (1980 in NHS and 1989 in NHSII) were included. Cumulative average alcohol consumption until 2–4 years prior to SLE diagnosis date (for cases) across repeated measures was used instead of one-time measure to best represent long-term alcohol consumption. The incident SLE cases were identified using the connective tissue disease screening questionnaire (CSQ), followed by medical record review. Cox proportional hazards models were used to assess associations, after controlling for time-varying covariates. HRs from the two cohorts were meta-analyzed using DerSimonian and Laird random effects models.

Results: 118 incident SLE cases developed in NHS from 1980–2008, and 92 incident SLE cases developed in NHSII, 1991–2009. Mean age at diagnosis was 53.6 (+/- 8.2) years in NHS and 57.1 (+/- 8.9) years in NHSII. Most SLE cases (97% in NHS, 100% in NHSII) were ANA positive, while 33% of NHS SLE cases and 53% of those in NHSII had a positive anti-dsDNA antibody test at diagnosis. In both NHS and NHSII, there was a suggestion of a protective effect of alcohol intake on risk of SLE, although it was not statistically significant (Table). Meta-analysis of the multivariable-adjusted results from both cohorts demonstrated a suggested protective effect of alcohol consumption in women who consume 0 to 10 gms/day (HR 0.75, 95% CI 0.54, 1.04) and >10 gms/day (HR 0.61, 95% CI 0.37, 1.01).

Conclusion: In these large prospective cohorts of women followed for many years before the diagnosis of SLE, we found a potential protective association between long-term alcohol consumption and reduced risk of developing SLE. Further studies are needed to confirm these findings.

Table. Cumulative Updated Alcohol Intake and Risk of SLE among women in the Nurses’ Health Study (1980–2008) and the Nurses’ Health Study II (1991–2009)

<table>
<thead>
<tr>
<th>Alcohol Intake</th>
<th>NHS Cases</th>
<th>NHSII Cases</th>
<th>Multivariable HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>36</td>
<td>41</td>
<td>0.93 (0.63, 1.38)</td>
</tr>
<tr>
<td>1–2 glasses</td>
<td>42</td>
<td>55</td>
<td>1.01 (0.67, 1.53)</td>
</tr>
<tr>
<td>3–4 glasses</td>
<td>20</td>
<td>30</td>
<td>0.69 (0.37, 1.31)</td>
</tr>
<tr>
<td>&gt;=5 glasses</td>
<td>12</td>
<td>11</td>
<td>0.95 (0.42, 2.13)</td>
</tr>
</tbody>
</table>

Discussion: E. V. Arkena, None; K. Palmsten, None; C. Sjöwall, None; E. Svenungsson, None; J. E. Salmon, None; J. F. Simard, None.
Methods: A total of 143 patients selected using the ACR 2010 FM criteria were enrolled at 12 sites in a 16-week, double-blind, placebo-controlled trial. Patients were randomized (1:1) to receive a proprietary combination of celecoxib + famciclovir or placebo. Outcome measures included a 24-hour recall pain numeric rating scale (NRS), Fibromyalgia Impact Questionnaire (FIQ-R), Patient Global Impression of Change (PGIC), and the PROMIS fatigue short form at baseline, and after 6, 12 and 16 weeks of study participation.

Results: The primary efficacy endpoint was change in pain from baseline. Pain reduction was evaluated using the pain NRS and the 7-day recall pain item from the FIQ-R. Change from baseline was determined using an MMRM approach with LOCF/BOCF imputation for missed data. A significant decrease in pain was observed for patients on treatment vs. placebo at 16 weeks by both measures. The absolute change on the NRS was −1.9 units vs −1.1, comparing active to placebo (p=0.031). On the FIQ-R item, the change was -2.2 vs -0.92 (p=0.001). Key secondary endpoints included analysis of the PGIC, where a value of “1” or “2” was considered a clinical responder. Significantly improved PGIC response rates were noted at endpoint: 33.3% for active vs 19.2% in placebo patients (p=0.031). Total FIQ-R score change at the endpoint visit was −17.54 vs −7.87 (p=0.002), while changes in the 3 domains were 14.29 vs −5.44 (p=0.004) for Function; −4.29 vs −1.89 (p=0.003) for Overall Impact, and −16.77 vs −7.90 (p=0.004) for Symptoms. In addition, improvements in fatigue were seen at endpoint on the PROMIS fatigue (−7.62 units vs −4.15; p=0.020).

The safety profile was especially encouraging. Despite the celecoxib component, gastrointestinal and nervous system treatment emergent adverse events were reported significantly more often in the placebo treatment group (GI: 20.0% vs 42.3%; nervous system: 17.4% vs 23.3%; active vs placebo), and study completion rates favored active treatment over placebo (82.6% vs 60.8%) (largely driven by higher placebo discontinuation rates due to adverse events and lack of efficacy).

Conclusion: A proprietary combination of famciclovir, which we postulate is inhibiting herpesvirus replication, and celecoxib, known to inhibit both herpesvirus replication and reactivation, was efficacious in treating multiple symptoms of FM. Given the simultaneous improvement in many domains and the surprising tolerability of this combination of drugs, we believe this combination warrants further study as a potential new therapy for fibromyalgia patients.


1879

The Efficacy of Pregabalin for Treating Fibromyalgia Patients with Moderate or Severe Baseline Widespread Pain. Andrew Clair and Birol Emir. Pfizer Inc, New York, NY.

Background/Purpose: Pregabalin has demonstrated efficacy for the treatment of fibromyalgia (FM), but insufficient evidence exists on how the efficacy of pregabalin may differ by baseline pain severity. The objective of these analyses was to assess the efficacy of 12 weeks of pregabalin treatment to provide symptomatic pain relief in FM patients with moderate or severe baseline pain scores.

Methods: These analyses used data from 5 Phase III clinical trials ranging between 8–15 weeks of pregabalin versus placebo (study numbers 1008105, A0081056, A0081077, A0081100, A0081208) to evaluate the efficacy of pregabalin at doses of 300 mg/day, 450 mg/day, or flexible dosing (300–450 mg/day BID) for the treatment of FM. FM was defined by ACR 1990 criteria at screening of widespread pain ≥3 months and pain in ≥11 of 18 specific tender point sites. Patients were adult (aged ≥18 years), with mean baseline pain scores that were classified as moderate (≥4 <7) or severe (≥7–10) and a score ≥40 mm on the Visual Analog Scale of Short-Form McGill Pain Questionnaire. A mixed effects model repeated measures analysis was used to estimate change in pain at 12 weeks after treatment initiation by baseline severity (moderate or severe) and treatment.

Results: Overall, 679 (300 mg pregabalin), 670 (450 mg pregabalin), 250 (flexible dosing pregabalin), and 927 (placebo) patients were evaluated. The results of change in pain score at 12 weeks are displayed in the figure.

Among patients who had moderate baseline pain, significantly larger mean ± SE reductions in pain score were observed with pregabalin versus placebo at doses of 450 mg (−0.572 ± 0.161, P<0.001) and flexible dosing (−0.647 ± 0.203, P=0.002) with a non-significant reduction at the 300 mg/d dose (−0.28 ± 0.165). Patients with severe baseline pain showed significant improvements over placebo with pregabalin doses of 300 mg/d (−0.516 ± 0.164, P=0.002) and 450 mg/d (−0.822 ± 0.165, P<0.001), but not with flexible dosing (−0.200 ± 0.242). When patients were grouped by pregabalin dose assignment, patients with severe baseline pain exhibited greater improvements in pain score than patients with moderate baseline pain with 300 mg/d (−0.461 ± 0.191, P=0.016) and 450 mg/day doses (−0.476 ± 0.189, P=0.012), but not with flexible dosing (+0.220 ± 0.272).

Conclusion: Pregabalin is efficacious at 12 weeks of treatment in reducing pain in FM patients with baseline moderate pain and severe pain severity, with reductions that appear larger in patients with severe pain. The trend of larger changes following flexible dosing in patients with moderate versus severe baseline pain scores comes from a study of Japanese patients and additional research would be required to determine if this may be accounted for by differences in the average daily dose.

Disclosure: A. Clair, Pfizer Inc, 3; Pfizer Inc, 1; B. Emir, Pfizer Inc, 1; Pfizer Inc, 3.

1880

Moderate Alcohol Consumption Is Associated with Lower Risk (and severity) of Chronic Widespread Pain: Results from a Population-Based Study. Gary J. Macfarlane and Marcus Basley. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: Amongst patients with fibromyalgia, alcohol consumption has been reported in a single clinical study to be associated with lower severity of symptoms. This study aimed to a) determine whether alcohol consumption is associated with the reporting of chronic widespread pain (CWP) in an unselected population sample, and whether a dose-risk relationship is evident; b) amongst persons with CWP confirm whether the level of reported alcohol consumption is associated with symptom severity.

Methods: The MUSICAN study sampled patients, aged over 25 years, registered at general practices in two areas of Great Britain. Information, collected by postal questionnaire, included current pain and usual alcohol consumption. Respondents were classified according to whether they satisfied the definition of chronic widespread pain (CWP) in the ACR 1990 criteria for fibromyalgia. Pain intensity and disability was measured by the Chronic Pain Grade and disabling pain defined as grade III or IV. Respondents reported whether they had ever drunk alcohol regularly and if so how much they currently drank per week (in units). Potential confounders of the relationship collected were: age, body mass index, employment status and amount smoked. A nalysis was by logistic regression with those who had never regularly consumed alcohol as the referent group compared with 0–5, 6–10, 11–12, 21–35, 35+ units/week.

Results: 13587 persons participated (mean age 55 yrs, 57% female) of which 2060 reported CWP and answered the questions on Chronic Pain Grade. There was a significant relationship between level of alcohol consumption and risk of reporting CWP. Risk decreased with increasing consumption with the lowest risk amongst those consuming 21–35 units/week (OR 0.61; 95% CI 0.50–0.75) while those consuming higher amounts did not have a reduced risk. This protective effect persisted after adjustment with only minor attenuation of effect (21–35 units/week 0.63; 0.51; 0.78). The effect was evident in both males and females. Amongst persons with CWP there was a strong and significant relationship between increasing alcohol consumption and lower likelihood of disability (table) which was not explained by measured confounders.
Conclusion: Moderate alcohol consumption was associated with a lower prevalence of CWP and associated with markedly lower levels of disability in those with CWP. One possible mechanism is through alcohol's agonist effects on the neurotransmitter γ-aminobutyric acid (GABA) and disruptions to GABA pain inhibitory pathways have been suggested in persons with fibromyalgia. Another is through the psychological benefits of alcohol including stress relief and mood enhancement. However alcohol consumption as a marker for other lifestyle factors, or that people avoided alcohol because of their pain and disability, cannot be excluded.


1881

Patients Who Fail Biologics Are More Likely to Have Concomitant Fibromyalgia. Robert S. Katz1 and Jessica L. Polyak2. 1Rush Medical College, Chicago, IL; 2Rheumatology Associates, Chicago, IL.

Background/Purpose: One area not assessed by studies to evaluate the efficacy of new medications in patients with inflammatory arthritis is whether the patient may have concomitant fibromyalgia. This may well impact response to treatment. We evaluated whether patients who have inflammatory arthritis and failed various biologic therapies were more likely to also have fibromyalgia.

Methods: Patients taking biologics were evaluated in a rheumatology office practice. We determined patients whether they responded or failed various biologic therapies. Diagnoses included rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and lupus.

Results: 219 patients in a rheumatology office practice taking biologic response modifiers were divided into those with inflammatory arthritis (RA/psA/AS/SLE) who were thought to have concomitant fibromyalgia (36pts, 16.4%) and those with only inflammatory arthritis but without fibromyalgia (183pts, 83.5%).

Of the patients with inflammatory arthritis or lupus with concomitant fibromyalgia, those who failed 2 or more biologics was 15, (41.7%). Patients with inflammatory arthritis or lupus but without concomitant fibromyalgia who failed 2 or more biologics was 41 pts (22.4%).

Conclusion: Patients who failed biological therapies often had concomitant fibromyalgia. This may be a significant factor in the lack of efficacy of these drugs. Whereas they may control the symptoms of inflammatory disease and patients get partial satisfaction, the fact that they want to try other biologic therapy may be due, in part, to the presence of concomitant fibromyalgia. This should be assessed in future studies to evaluate new medications for patients with inflammatory joint disease.


1882


Background/Purpose: Fibromyalgia (FM) affects 2–5% of adults in the United States. Pregabalin (antiepileptic drug [AED]), and duloxetine and milnacipran (serotonin and norepinephrine reuptake inhibitors), are approved to treat FM. FM treatment guidelines also include gabapentin (AED), amitriptyline (tricyclic antidepressant), selective serotonin reuptake inhibitors (SSRIs), and tramadol; in general, opioids, particularly strong opioids, are not recommended. This study evaluated treatment patterns of recommended and non-recommended medications among patients newly diagnosed with FM.

Methods: This retrospective study used medical and pharmacy claims data and enrollment information for adult commercial health plan members of a large US health plan. Patients had ≥2 medical claims with a diagnosis (dx) of FM from January 2008–February 2009; the date of the first FM dx was the index date. Patients also had: 6 months of pre-index and 12 months of post-index continuous enrollment; no pre-index FM dx; and ≥1 pharmacy claim for an FM guideline medication (pregabalin, gabapentin, duloxetine, milnacipran, amitriptyline, or SSR1) or for an opioid on or within 6 months after the index date. The date of the first medication (Rx) was the treatment date. The principal outcomes were indicators identifying patients with ≥1 fill of an FM guideline Rx or opioid during each 3-month interval (quarter) of the 12-month post-index period. Descriptive analysis was conducted.

Results: The study sample was 96,175 patients with mean age 47.3 years and 72.5% female. Fifty-six percent of patients were prescribed opioids on their treatment dates and 44% received an FM guideline Rx: 17% of opioid recipients were prescribed tramadol. The figure shows that 55% of patients were prescribed opioids only or opioids as well as FM guideline Rx in the first quarter after FM dx. The percentage of patients with FM guideline Rx (with or without opioids) was consistent through the post-index period. The percentage of patients who received opioids only decreased over time. However, ≥20% of patients were treated only with opioids in each quarter and an additional 18% received opioids in addition to FM guideline Rx.

Conclusion: In the 12-month post-index, a substantial proportion of patients were prescribed opioids and more than half did not receive FM guideline Rx. These real-world utilization results indicate that an opportunity may exist for improved FM management using recommended therapies in clinical practice.

Disclosure: S. N. Shah, Pfizer Inc, 1, Pfizer Inc, 3; R. Halperrn, Pfizer Inc, 9; J. C. Cappelleri, Pfizer Inc, 1, Pfizer Inc, 3; E. T. Masters, Pfizer Inc, 1, Pfizer Inc, 3; A. G. Clair, Pfizer Inc, 1, Pfizer Inc, 3; C. Blauerpeter, Pfizer Inc; 9; D. Van Voorhis, Pfizer Inc, 9.

1883 WITHDRAWN

ACR Concurrent Abstract Session

Genetics, Genomics and Proteomics I: Epigenetic Mechanisms in Autoimmunity

Monday, November 17, 2014, 4:30 PM–6:00 PM

1884

Differential DNA Methylation Associated with Rheumatoid Arthritis in Disease Discordant Monozygotic Twins. Amy Webster4, Flore Zufferey7, Darren Plant7, Anne Barton7, Francies Williams1 and Jane Worthington7. 1Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom; 2Dept Twin Research and Genetic Epidemiology, Kings College London, London, United Kingdom; 3NIHR Manchester Muscuskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom; 4Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom; 5The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Previous epigenetic studies of rheumatoid arthritis (RA) using prevalent cases and unrelated controls have indicated that DNA methylation is altered in patients with RA. However case control studies of unrelated individuals do not allow matching for important confounders such as the underlying genetic variability and environmental exposures, which may influence disease development and the epigenome. By investigating DNA methylation differences in disease discordant monozygotic (MZ) twins, such confounding effects may be mitigated, increasing the power to detect alterations to the methylene which might be associated with RA.


**Objectives:** To identify a DNA methylation signature in RA using disease discordant monozygotic twins.

**Methods:** Twin subjects were recruited from the Rheumatoid Arthritis Twin Study (Manchester) and TwinsUK (London). Each twin pair included one twin classified as having RA according to established classification criteria (n=63) while the other was classified as not having RA (n=63) at the time samples were collected. Whole blood DNA was bisulfite converted and an epigenome-wide association study was performed using the HumanMethylation450 BeadChip (Illumina). A detection threshold was applied and probes with a detection-p value >0.01 were removed. Differentially methylated positions (DMPs) were identified using linear regression following quantile normalisation.

**Results:** 30 CpG sites were differentially methylated at a false discovery rate of 10%. One of the most significant DMPs, cg07693617 (p=1.05×10^{-6}) lies in the PRKCZ gene which contains 22 differentially methylated CpG sites in the gene body and 5' UTR. Interestingly this gene was found to be hypermethylated in RA fibroblast-like synoviocytes in a previous epigenome-wide association study.

**Conclusion:** This is the largest study to date of DNA methylation in RA discordant MZ twin pairs. We have identified 30 CpG sites with a potential role in RA development and added to the evidence for an association at PRKCZ. While further validation and replication studies are required, these preliminary data support the hypothesis that DNA methylation is altered in patients with RA and provides a plausible biological mechanism to account for the observed twin discordance in RA.

**Acknowledgements:** This work was supported by the innovative medicines initiative joint undertaking (IMI JU) funded project BeTheCure, (contract number 115142-2). The work was supported by the NIHR Manchester Musculoskeletal Biomedical Research Unit. We also acknowledge support from Arthritis Research UK, TwinsUK. The study was funded by the Welcome Trust; European Community's Seventh Framework Programme (FP7/2007–2013) and also received support from the National Institute for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. The Chronic Disease Research Foundation also supported this work.

**Disclosure:** A. Webster, None; F. Zufferey, None; D. Plant, None; A. Barton, None; F. Williams, None; J. Worthington, None.

**1885**

**Integrative Omics Profiling Reveals Dysregulated Novel Pathways Mediated by microRNAs and DNA Methylation in Osteoarthritis.** Kathleen M. Fisch1, Ryuichiro Akagi2, Oscar Alvarez-Garcia2, Takeshi Teramura3, Yuta Muramatsu1, Masahiko Saito1, Stuart Duffy1, Shawn Grogan1, Takahisa Sasho4, Darryl D'Lima1, Andrew I. Su1 and Martin K. Lotz1. 1The Scripps Research Institute, La Jolla, CA, 2The Scripps Research Institute, San Diego, CA, 3Toho University Sakura Medical Center, Sakura, Japan, 4Chiba University School of Medicine, Chiba, Japan.

**Background/Purpose:** Osteoarthritis (OA) is a prevalent joint disease, with several identified clinical risk factors. However, the search for genetic risk factors by candidate gene and genome-wide association studies of human OA populations has identified only a small number of candidate genes and pathways potentially involved in the disease. Thus, we aim to build a genome-wide molecular profile of OA to elucidate regulatory mechanisms of OA pathogenesis and to identify possible therapeutic targets.

**Methods:** We extracted total RNA from full-thickness articular cartilage from 18 human donors (8 normal and 10 OA) and performed mRNA and microRNA sequencing on an Illumina HiSeq 2000 (single-end, 100bp reads). DNA was extracted from full-thickness articular cartilage from 23 different human donors (11 normal and 12 OA) and we performed a DNA methylation assay on the Illumina Infinium HumanMethylation450 BeadChip. The RNA sequencing data were analyzed using the Tuxedo package to align raw reads to the human genome, quantify gene expression and perform differential expression analysis. We used the Bioconductor package ChAMP to perform differential methylation analysis. We employed downstream functional enrichment analyses for transcription factors and microRNAs using Fisher's Exact Test, pathway analyses using the Bioconductor package SPIA, and networks using Cytoscape. Finally, we created an interaction network using the Human Integrated Protein-Protein Interaction Reference using enriched and additional OA related transcriptional factors. This network was annotated with differentially expressed microRNAs, microRNAs with validated targets in this network and their methylation status.

**Results:** Several genes, microRNAs and transcription factors are differentially expressed and reveal unique molecular signatures of OA (Figure 1). Many of these genes and microRNAs possess differentially methylated promoters. In addition, they are key regulators of a novel OA regulatory network (e.g., miR-21, miR-155, CEBPB, FOXO3) (Figure 2). We validated the microRNA targets in this network and the hypomethylation of the miR-21 promoter. We discovered that miR-21 targets the transcription factors HIF1A and CEBPB, providing a regulatory mechanism for the downregulation of these transcription factors and their targets.

**Conclusion:** Our findings reveal a complex regulatory interaction network of OA pathogenesis controlled by microRNAs, transcription factors and DNA methylation and suggest therapeutic targets to treat or delay disease progression.

Background/Purpose: A major finding of the GWAS era of common disease gene-mapping has been that observed associations more often involve regulatory positions than protein-coding regions. Whilst there has been substantial interest in the potential role of ncRNA in heritable diseases, as yet to our knowledge in no common disease has a polymorphism in a ncRNA been demonstrated to cause disease, and very few examples exist in monogenic diseases. Of the 43 independent genetic associations that have been reported for ankylosing spondylitis, most occur in intergenic, intronic or other untranslated regions of the genome. Two in particular, at chromosomes 21p13 and 21q22, occur in intergenic regions with no annotated transcription.

Methods: We have used a new technique known as CaptureSeq, which utilises RNAseq on samples enriched for transcripts from a genomic region of interest allowing the detection of transcripts expressed at too low levels for detection by conventional RNAseq. Using this technique, we undertook ultra-deep transcriptional profiling in peripheral blood mononuclear cells from 5 cases carrying the protective allele and 5 carrying the susceptibility allele at the 21q22 locus.

Results: We identified two completely novel divergently transcribed long non-coding RNAs (lncRNA) expressed from this region, which were upregulated in AS cases compared with healthy controls, as well as those subjects carrying the susceptibility allele. This overexpression in PBMC was confirmed in two independent data sets, using both RNAseq and qPCR.

To further elucidate the potential function of this novel transcript we mined the FANTOM5 Atlas of human gene expression which showed expression of the 21q22 transcripts almost exclusively in CD14+ monocytes. We confirmed this in purified CD14+ cells from our PBMC samples with no expression seen in any other cell type. Expression was also significantly enhanced by stimulation of the monocytes with microbial components.

Conclusion: This is the first example of a role for a lncRNA in AS, and one of the first in any human disease where a polymorphism influences disease by effects on a ncRNA. Our findings strongly support a role for monocytes in AS aetiology possibly through responses to microbes. Monocyte antigen presentation has previously been implicated in AS and is strengthened by the identification of the HLA-B27-ERAP1 genetic interaction. A aberrant microbial-induced CD14+ monocyte expression of the 21q22 transcript presents a novel potential mechanism by which AS might be influenced by microbes.

Disclosure: K. Haynes, None; T. Kenna, None; E. Glazov, None; M. A. Brown, None; G. Thomas, None.

1888

PU.1, Mitf, and Their Novel Co-Partner, Eomes, Set up a T Transcription Factor Network That is Critical for Osteoclast Differentiation. Carey Heathc, Sankha Ghosh, Eason Hilldred III, Jennifer Cabrera, Dia Kurmashe, Wael N. Jarjour, Ramiro Toribio, Sudarshana Sharma and Michael Ostrowski. 1The Ohio State University, Columbus, OH, 2The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: Osteoclasts are bone resorbing cells which differentiat from myeloid precursors. The crosstalk between osteoblasts and osteoclasts tightly regulates the dynamic and continuous process of bone remodeling. Deregulation of this delicate balance is implicated in osteoporosis pathology. A variety of transcription factors including PU.1, MITF, NFATc1, and T-box4 are essential for osteoclast differentiation. However, the interplay between these factors is not fully defined. We have previously shown that the transcription factors MITF and PU.1 act as a complex to regulate multiple genes required for osteoclast function. This study was designed to understand the global transcriptional regulatory processes involved in osteoclast differentiation.

Methods: We examined transcriptional regulation of target genes by MITF and PU.1 in myeloid precursors and osteoclasts using Chip-Seq to map the genome-wide binding of these factors. In parallel, microarray analysis was performed to monitor target gene expression changes over the course of differentiation. We also queried the sequences jointly bound by PU.1 and MITF to search for conserved binding sequences potentially indicating novel co-partners in osteoclasts. We used micro-computed tomography and histological analysis to examine the effects of myeloid lineage-specific and osteoclast-specific deletion of PU.1 and its copartners in vivo and in vitro.

Results: Chip-Seq and microarray profiling revealed that MITF and PU.1 jointly regulate the transcription of over 1000 genes in developing osteoclasts. Most of the MITF/PU.1 co-bound regions were found in distal enhancer-like elements at the same sites in both myeloid precursors and osteoclasts. Overlap of our Chip-Seq and microarray data sets utilizing Gene Set Enrichment Analysis (GSEA) revealed that transcription factor genes were the only subset significantly enriched in genes with PU.1/ MITF co-bound regions. These transcription factors include NFAc1, c-FOS, and NFkB, which are already known to be essential for osteoclast differentiation. Additionally, 33% of genomic regions jointly bound by PU.1 and MITF in developing osteoclasts contained the binding motif of the T-box transcription factor EOMES. Conventional Chip assays validated binding of EOMES to MITF/PU.1 bound regions. Micro-computed topography analysis of murine bone has demonstrated that the loss of PU.1 or EOMES in osteoclasts and skin fibroblasts cultured from dermal punch biopsies of 12 twin pairs discordant for SSc. An efficiency analysis was performed with caGEDA to determine best normalization and feature selection methods and identify differentially methylated probes between unaffected and affected twins. Ingenuity Pathway Analysis (IPA) was used for pathway analysis.

Results: We identified 68 CpGs in blood and 103 CpGs in dermal fibroblasts with significant changes in DNA methylation levels between the SSc-affected and healthy twins. These CpGs locate to 55 genes in the blood and 27 in the fibroblasts. While 45 (66%) CpGs were hypomethylated in the blood of the affected twin, 63 (58%) were hypomethylated in the dermal fibroblasts. Pathway analysis of the genes differentially methylated in the blood revealed an enrichment of genes in the antigen-presentation pathway (P = 2.47E-06) and genes involved in dermatological, immunological and hematological diseases (P = 1.98E-05). These enrichments were mostly driven by multiple probes in genes in the HLA region that consistently showed either hyper- or hypomethylation in the affected twins. In skin fibroblasts, pathway analysis revealed an enrichment of genes involved in gene expression (P = 8.5E-06) and organismal development (P = 1.90E-05). Prominent members of the differentially methylated genes included HOX and T-box transcription factor genes that showed multiple probes with consistent hyper- or hypomethylation in the affected twins.

Conclusion: These data support a role for DNA methylation differences in modifying susceptibility to SSc and identify gene sets with differential methylation that may be involved in the pathogenesis of the disease. The distinct methylation profiles observed between blood and dermal fibroblasts suggest that tissue-specific epigenetic signatures may be responsible for the clinical heterogeneity of the disease.

Disclosure: P. S. Ramos, None; R. Jordan, None; J. Lyons-Weiler, None; T. A. Medsger Jr., None; C. A. Feghali-Bostwick, None.

1887

Genome-Wide DNA Methylation Analysis of Twin Pairs Discordant for Systemic Sclerosis Reveals Distinct Signatures in Blood and Dermal Fibroblasts. Paula S. Ramos1, Rick Jordan2, James Lyons-Weiler2, Thomas A. Medsger Jr. 2 and Carol A. Feghali-Bostwick. 1Medical University of South Carolina, Charleston, SC, 2University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Systemic sclerosis (SSc) is a chronic, multisystem, autoimmune inflammatory disease with genetic and non-genetic contributions to risk. The etiology of SSc, including the reasons underlying the wide variation in disease heterogeneity and severity remain unknown. The low concordance rate (4.2%) between monozygotic twins suggests an important role for acquired genetic changes such as epigenetic factors in SSc susceptibility. In order to characterize the genome-wide DNA methylation profile of blood and dermal fibroblasts in SSc, we performed an epigenome-wide analysis of DNA methylation in twin pairs discordant for SSc.

Methods: DNA methylation profiling was performed using the Illumina Infinium HumanMethylation450 BeadChip, which allows the annotation of approximately 480,000 CpG sites. Genome-wide methylation was assessed in genomic DNA isolated from: (1) blood from 34 discordant twin pairs, and (2) skin fibroblasts cultured from dermal punch biopsies of 12 twin pairs discordant for SSc. An efficiency analysis was performed with caGEDA to determine best normalization and feature selection methods and identify differentially methylated probes between unaffected and affected twins. Ingenuity Pathway Analysis (IPA) was used for pathway analysis.

Results: We identified 68 CpGs in blood and 103 CpGs in dermal fibroblasts with significant changes in DNA methylation levels between the SSc-affected and healthy twins. These CpGs locate to 55 genes in the blood and 27 in the fibroblasts. While 45 (66%) CpGs were hypomethylated in the blood of the affected twin, 63 (58%) were hypomethylated in the dermal fibroblasts. Pathway analysis of the genes differentially methylated in the blood revealed an enrichment of genes in the antigen-presentation pathway (P = 2.47E-06) and genes involved in dermatological, immunological and hematological diseases (P = 1.98E-05). These enrichments were mostly driven by multiple probes in genes in the HLA region that consistently showed either hyper- or hypomethylation in the affected twins. In skin fibroblasts, pathway analysis revealed an enrichment of genes involved in gene expression (P = 8.5E-06) and organismal development (P = 1.90E-05). Prominent members of the differentially methylated genes included HOX and T-box transcription factor genes that showed multiple probes with consistent hyper- or hypomethylation in the affected twins.

Conclusion: These data support a role for DNA methylation differences in modifying susceptibility to SSc and identify gene sets with differential methylation that may be involved in the pathogenesis of the disease. The distinct methylation profiles observed between blood and dermal fibroblasts suggest that tissue-specific epigenetic signatures may be responsible for the clinical heterogeneity of the disease.

Disclosure: K. Haynes, None; T. Kenna, None; E. Glazov, None; M. A. Brown, None; G. Thomas, None.
their myeloid precursors leads to a severe osteopetrotic phenotype in neonatal mice due to highly deficient osteoclast differentiation and function.

**Conclusion:** Our results demonstrate that MTF and PU.1 set up a transcription factor regulatory network in myeloid precursors which triggers osteoclast differentiation in response to cues from the bone microenvironment. A blation of PU.1 or its novel copartner EOMES results in disruption of this transcription factor network and therefore halts the differentiation program.

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**1889**

Rheumatoid Arthritis (RA)-Associated Risk Allele LBH Alters the Function of a Differentially Methylated LBH Enhancer. Deepa Hammaker1,2, Gary S. Firestein3, Wei Wang4, John W. Whitaker5 and Ann-Karin Ekwall6. 1University of California San Diego, La Jolla, CA, 2University of California at San Diego School of Medicine, La Jolla, CA, 3UCSD, La Jolla, CA, 4UCSD, San Diego, CA, 5UC San Diego, La Jolla, CA.

**Background/Purpose:** Recent data suggest that epigenetics, including DNA methylation, contributes to imprinting RA fibroblast-like synoviocytes (FLS) and alters their behavior. To understand how RA-associated risk alleles and differential methylation affect circulatory regulatory regions, we compared differentially methylated loci (DML) in RA FLS with fibroblast DNA I hypersensitive sites. The differentially methylated enhancers (DMEs) were then integrated with RA-associated SNPs to identify key regulatory sites. In this study, we found and characterized an RA-associated SNP (rs906868, G/T) that co-localized with a DME in a key cancer-related gene that regulates cell growth and differentiation, namely limb-bud and heart development (LBH).

**Methods:** 15,220 RA-associated DMLs identified using Illumina 450k chips from 11 RA and 11 OA FLS were integrated with DNase I hypersensitive sites in the Encode database for 125 cell-types/conditions, including lung fibroblasts. These DMLs were then compared with GWAS data. Genomic DNA was isolated and the 1.4kb region with the WT allele (G) or RA SNP (T) of LBH was cloned into minimal promoter pGL4.23-luciferase construct. For methylation studies, plasmids were methylated with the CpG-methyltransferase M.SssI and S-adenosyl methionine. Methylation of all CpGs was verified by bisulfite modification and pyrosequencing. The WT, RA SNP or control plasmids (1ug) were transfected into cultured RA FLS by nucleofection with Renilla construct. Firefly luciferase activity was normalized to renilla.

**Results:** A DNA I hypersensitive site that is hypomethylated in RA FLS was identified in a 1400 bp region upstream of the LBH gene transcription start site. An RA and SLE-associated SNP (rs906868, G/T) was identified in the 1.4kb region with the WT allele (G) or RA SNP (T) of LBH. Genomic DNA was isolated and the 1.4kb region with the WT allele (G) or RA SNP (T) of LBH was cloned into minimal promoter pGL4.23-luciferase construct. For methylation studies, plasmids were methylated with the CpG-methyltransferase M.SssI and S-adenosyl methionine. Methylation of all CpGs was verified by bisulfite modification and pyrosequencing. The WT, RA SNP or control plasmids (1ug) were transfected into cultured RA FLS by nucleofection with Renilla construct. Firefly luciferase activity was normalized to renilla.

**Conclusion:** Our results suggest that epigenetics, including DNA methylation, contributes to imprinting RA fibroblast-like synoviocytes (FLS) and alters their behavior. To understand how RA-associated risk alleles and differential methylation affect circulatory regulatory regions, we compared differentially methylated loci (DML) in RA FLS with fibroblast DNA I hypersensitive sites. The differentially methylated enhancers (DMEs) were then integrated with RA-associated SNPs to identify key regulatory sites. In this study, we found and characterized an RA-associated SNP (rs906868, G/T) that co-localized with a DME in a key cancer-related gene that regulates cell growth and differentiation, namely limb-bud and heart development (LBH).
denosumab could inhibit the progression of bone destruction in RA patients with risk factors for radiographic damage.


**1891**

**Early MRI Endpoints Provide a Valid Measure of Structural Damage While Reducing Study Duration and Participant Numbers in Rheumatoid Arthritis Clinical Trials.** Joshua Baker, Philip G. Conaghan, Paul Emery, Daniel Baker and Mikkel Østergaard.

**Background/Purpose:** We used data from a large randomized controlled clinical trial of an effective biologic (golimumab, GO-BEFORE study) to compare the associations of disease activity and disease severity with two imaging techniques to measure joint erosion: 1) early progression in rheumatoid arthritis magnetic resonance imaging scores (RAMRIS) and 2) radiographic progression. We subsequently assessed the potential impact of incorporating the MRI as an outcome in clinical trials of new agents for RA.

**Methods:** MRI of the dominant hand was performed and RAMRIS scores were determined at baseline, week 12 and week 24. Van der Heijde-Sharp (vdHS) scores were determined for x-rays at baseline and week 52. Progression in vdHS and RAMRIS erosion scores were defined as a change of >0.5. Associations between X-ray and MRI outcomes with clinical features associated with severe disease and structural damage were evaluated to assess convergent validity. Iterative Wilcoxon ranksum tests assessed the sample size requirements to detect a significant difference in the change in structural damage score between combination therapy (methotrexate + golimumab) and methotrexate monotherapy. Sample size calculations were also performed based on dichotomous progression outcomes.

**Results:** MRI progression at 12 and 24 weeks was associated with greater DA2528 (CRP), CRP, and vdHS at baseline, and greater HAQ scores at 2-years (Table 1). These associations were similar in magnitude to those seen with X-ray progression at 1-year. Ranksum testing for differences in the change in structural damage between treatment and controls arms achieved significance (p<0.05) with fewer total study subjects when MRI erosion score was the outcome assessed (175 for MRI at 12/24 weeks vs. 300 subjects for vdHS at 52 weeks, respectively). Despite the study's limited power with x-rays, it achieved a significant difference in X-ray erosion score at 52 weeks of follow-up. MRI erosion scores >5 had 80% power to detect a difference in the proportion of subjects progressing on MRI at 12 weeks. A sample size calculation based on an unenhanced population and using 1-year x-ray progression as the outcome estimated a study size of 470 subjects.

**Conclusion:** Early MRI erosion score outcomes have convergent validity comparable to that of 52-week x-ray progression. Use of MRI in clinical trials would decrease sample sizes and reduce length of follow-up for studies assessing differences in structural damage progression between groups.

**Table 1:** Clinical characteristics of MRI x-ray progressing and non-progressors within the MRI sub-study (convergent validity).

**Figure 1:** Iterative study of the sample size needed to demonstrate significant p<0.05 differences between the golimumab + MTX combination and methotrexate arms using the anatomical ACR50, ACR20, and ACR5 at 52 weeks (solid black), 2 change in MRI erosion score at 12-weeks (grey dashed) or 24-weeks (solid grey), and 3 (grey) the change in MRI erosion score at 9 weeks among those with synovitis scores >5 at baseline (black dashed).

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conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BFS). Patients participated after signing informed consent.

Results: 187 patients (N = 56, M:F = 36/20, mean age 47.0 ± 13.8 y) were compared to HS (N = 24, M:F = 10/14, mean age 43.8 ± 11.9 y). The subjects were comparable per age and sex. PSO patients exhibited moderately severe disease (PASI 7.9 ± 8.9) and disease duration of 12.7 ± 14.3 y, the most frequent phenotype being psoriasis vulgaris (78.6%), 60.7% presented scalp lesions, 48.2% had nail lesions. Imaging analysis was blindly performed by two readers. Inter- and intra-reader reliability was high (r = 0.96; r = 0.98). In PSO patients 607 CMC were found vs. 97 in HS in the MCH2. Expressed as mean number of CMC this accounts for 10.8 ± 9.1 vs. 4.1 ± 3.7 (p < 0.001). No correlation was found for the CMC number in the PSO patients and the severity of the cutaneous disease and its duration nor for the age of the subjects.

Conclusion: Visualization of cutaneous pathologies as small as 81 microns can be obtained by this technique. These images resemble rather histopathologic slices in vitro (Fig. 1). In our study cutaneous psoriatic patients with no clinical history of arthritis showed a significant higher number of these cutaneous channels compared to healthy subjects, suggesting an increased communication between bone marrow and joint in this phase of disease previous to the onset of joint involvement.

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1893


Background/Purpose: Treatment of axial SpA is increasingly aimed at the early stage of disease. MRI is not included in the ASAS classification criteria of axial SpA. We investigated the prevalence of axial MRI structural lesions in psoriatic arthritis patients fulfilling the ASAS classification criteria of axial SpA.

Methods: All pts with MRI-spine and MRI-SIJ (n = 650) were included in the DESIR-cohort (n = 708). All available baseline MRI scans were independently scored by 2 well-calibrated central readers who were blind to any other data. MRI-SI and MRI-spine were scored according to the ASAS definition.

Results: There were 231 pts (35.5%) with a positive MRI-SI. MRI-SI were scored according to the ASAS criteria.

Conclusion: MRI-SI was scored according to the ASAS criteria.

Disclosure W. Maksymowych, Pfizer Inc; S. Wichuk, Pfizer Inc; H. Jones, Pfizer Inc; A. Szumski, Pfizer Inc; L. Marshall, Pfizer Inc; J. Bukowski, Pfizer Inc; R. Lambert. None.

1894


Background/Purpose: Spinal MRI lesions suggestive of axial Spondyloarthritis (axSpA) are not included in the ASAS definition of a positive MRI, but do occur in the absence of affected sacroiliac joints (SIJ). It is unknown how often this happens and if it is useful to perform a MRI of the spine in patients with negative MRI-SI. The objective of this study was to investigate the prevalence of positive MRI-spine in pts with short symptom duration and a negative MRI-SI.

Methods: Pts aged 18-50 with inflammatory back pain (IBP) (≥ 3 months, ≤ 3 years) from 25 participating centers in France were included in the DESIR-cohort (n = 708). All available baseline MRI scans of the spine were independently scored by 2 well-calibrated central readers who were blind to any other data. MRI-SI and MRI-spine were scored according to the ASAS definition.

Results: There were 231 pts (35.5%) with a positive MRI-SI. MRI-SI were scored according to the ASAS criteria.

Conclusion: MRI-spine was scored according to the ASAS criteria.

Disclosure W. Maksymowych, Pfizer Inc; S. Wichuk, Pfizer Inc; H. Jones, Pfizer Inc; A. Szumski, Pfizer Inc; L. Marshall, Pfizer Inc; J. Bukowski, Pfizer Inc; R. Lambert. None.

References

1895


Background/Purpose: The prevalence of sacroiliitis in children with juvenile spondyloarthritis (JSpA) at diagnosis is unknown. We aimed to evaluate: 1) the prevalence of sacroiliitis at diagnosis using radiographs and MRI; and 2) the association of physical examination and a history of back pain with acute sacroiliitis, using MRI as the reference standard.

Methods: We performed a single center prospective cross-sectional study of 39 children with newly diagnosed JSpA. Children were eligible for inclusion if they were diagnosed with enthesitis-related arthritis (ERA) or psoriatic arthritis (PsA) according to the International League of Associations for Rheumatology criteria in the prior 6 months. On the same day subjects had a musculoskeletal examination and imaging, which included a single AP pelvic radiograph and a non-contrast pelvic MRI with STIR. Radiographs were scored using the modified New York criteria. A cute sacroiliitis on MRI was defined as bone marrow edema within the sacrum or adjacent ilium with or without accompanying capsulitis, enthesitis, or effusion. Univariate logistic regression was used to test the association of clinical factors with acute sacroiliitis.

Results: Mean age of the JSpA subjects was 14.0 ± 2.7 years. 49% were male and 44% were HLA-B27. 35 and 4 children met criteria for ERA and psoriatic arthritis, respectively. Nine (23%) children had acute sacroiliitis; in 5 subjects it was bilateral. Of the 9 children with acute sacroiliitis on MRI, 7 (78%) had erosions or sclerosis on MRI and 5 (56%) had changes on conventional radiography. 2 subjects met radiologic criteria for ankylosing spondylitis. Of the subjects with acute sacroiliitis only 4 (44%) reported a history of back pain or tenderness on palpation of the sacroiliac joints. 33% and 14 (47%) of children with JSpA with and without sacroiliitis met the ASAS inflammatory back pain criteria. Male sex, hip arthritis, alternating buttock pain, higher C-reactive protein, and loss of lumbar lordosis were associated with a higher criteria. Male sex, hip arthritis, alternating buttock pain, higher c-reactive protein, with JSpA with and without sacroiliitis met the ASAS inflammatory back pain criteria in the prior 6 months. On the same day subjects had a musculoskeletal examination and imaging, which included a single AP pelvic radiograph and a non-contrast pelvic MRI with STIR. Radiographs were scored using the modified New York criteria. A cute sacroiliitis on MRI was defined as bone marrow edema within the sacrum or adjacent ilium with or without accompanying capsulitis, enthesitis, or effusion. Univariate logistic regression was used to test the association of clinical factors with acute sacroiliitis.

Conclusion: This is the first study reporting the prevalence of acute sacroiliitis at diagnosis in children with JSpA. Sacroiliitis is common at diagnosis and may be asymptomatic. Nearly half the cases of sacroiliitis would have been missed if radiographs were only the imaging modality.

Table. Clinical features in MRI+ and MRI- subjects (N=39)
Background/Purpose: Localized scleroderma (LS) is an autoimmune disease of the skin and underlying tissues which results in disfigurement and orthopedic complications, especially when the onset is in childhood. LS has both inflammatory and fibrotic components, making it similar to systemic sclerosis (SSc), its ‘companion’ disease. Identifying potential biomarkers involved with disease propagation may lead to future therapeutic targets. T-helper (Th) cell subsets and their associated cytokines are thought to contribute to the pathogenesis of systemic sclerosis (SSc). Traditionally, a Th2 predominant response has been supported but more recent data also implicate Th1, Th17 and various chemokine involvement. This concept in LS has only been partially investigated, with studies evaluating only a handful of cytokines associated with Th cell lineages, and not examined in reference to disease activity. This study was designed to extensively evaluate the Th-cell associated plasma cytokine and chemokine profiles of patients with pediatric LS.

Methods: Plasma samples were obtained from 69 pediatric LS patients and 76 pediatric controls. Twenty-nine cytokines and chemokines were analyzed using a Th1, Th2, and Th17 Millipore lumox panel comparing LS to healthy controls, with additional analyses predetermined to be dedicated to disease activity parameter. The modified Localized Scleroderma Severity Index (mLoSSI) and the Physician Global Assessment of Disease Activity (PGA-A) were the main parameters compared to the cytokinechemokine levels. Mann-Whitney U test was employed to compare cytokine levels between LS and healthy groups and Spearman rank correlation was used to determine relationships between individual analytes and clinical parameters (p < 0.05). Type I error due to multiple testing was controlled for using the Benjamini-Hochberg method.

Results: The levels of the following cytokines were significantly elevated in LS patients compared with healthy controls: IP-10, MCP-1, IL-17A, IL-12p70, IFN-γ, TNF-α, GM-CSF and IL-6. When LS patients were further divided into active (n=30) and inactive states (n=39), IP-10 was significantly elevated in the active group compared to inactive (median: 208.7 vs. 880.5 pg/ml, respectively). IP-10 levels were also significantly correlated with the Physician Global Assessment of Disease Activity (PGA-A) score (r = 0.450, p = 0.005) and with the modified Localized Scleroderma Severity Index (mLoSSI) score (r = -0.343, p = 0.004).

Conclusions: LS and SSc share a similar histopathology with infiltration of lymphocytes and their associated effector cytokines in skin specimens. In the current study we demonstrated a serological presence of IP-10, MCP-1, lymphocytes and their associated effector cytokines in skin specimens. These findings suggest a potential immunological link between these two clinically different diseases.
HFL has not been investigated in this study. In this study, we sought to determine whether blockade of IL-33 signaling in the LCMV/PKO model of FHL would sufficiently limit the CD8+ T cell response to prevent the development of disease.

Methods: PKO mice were infected i.p. with 2×10^6 PFU LCMV-Armstrong and received 150 μg i.p. of either IL-33-RB-blocking antibody or isotype control every 2 days, beginning on day 3 post-infection. Mice were monitored for weight loss, survival, complete blood count, serum cytokines, spleen cellularity, LCMV viral load, frequency of antigen-specific CD8+ T cells, and T cell cytokine production.

Results: LCMV-infected PKO mice receiving IL-33-RB blocking antibody (IL-33RB) showed reduced weight loss (P = 0.0170) and highly reduced mortality (HR = 11.79, P = 0.0021). IL-33-RB blocked reduced levels of IFN γ and IFNγ/IFNγ-γ-fused producing CD8+ T cells (P = 0.0003). Additionally, IL-33RB mice had reduced hepatic parenchymal damage although leukopenia and thrombocytopenia were not improved. Despite the reduced inflammation in IL-33RB mice, they maintained similar frequencies of LCMV-specific CD8+ T cells compared to isotype-treated controls and showed equivalent titers of LCMV in the spleen.

Conclusion: IL-33-RB blockade improves morbidity and mortality in a mouse model of FHL without exacerbating viral infection. Our results identify signaling via the tissue damage-associated cytokine IL-33 as an additional path to disease and suggest blockade of this pathway as a viable treatment strategy for FHL.

Disclosure: J. Rood, None; P. Kreiger, None; E. Stelekati, None; E. J. Wherry, None; E. M. Behrens, Amgen, 2.

1900


Background/Problem: Systemic juvenile idiopathic arthritis (sJIA) is a severe inflammatory disease of unknown etiology. We utilized a genomic approach to interrogate the molecular pathogenesis of this disorder.

Methods: Single nucleotide polymorphism (SNP) genotypes from Illumina arrays were obtained in 988 children with sJIA and 431 healthy subjects and combined with in silico SNP data from 7579 healthy subjects. The collection was divided into 9 strata by country of origin, and after stringent quality control, we performed genome-wide SNP imputation and association testing in each stratum, followed by meta-analysis. A second round of imputation using a more densely genotyped reference panel was performed in regions with p < 1E-7. To investigate the role of specific major histocompatibility complex (MHC) proteins, we imputed classical HLA alleles and their subordinate amino acid positions. To assess whether sJIA-associated noncoding MHC variation conferred risk through regulatory mechanisms, we used RegulomeDB to analyze MHC SNPs with p < 1E-5. RegulomeDB integrates and queries regulatory information from over 100 tissues and cell lines, including DNA se hypersensitivity, transcription factor (TF) ChiP-seq and histone ChiP-seq data from ENCODE, plus expression quantitative trait loci (eQTL) data.

Results: Meta-analyses of >13M SNPs identified significant associations (p < 1.5E-8) between sJIA and 6 SNPs between BTLN2 and HLA-DQA1, as well as a susceptibility locus in a noncoding region of chromosome 1 nearest to the long intergenic noncoding RNA, LOC284661. Conditional analysis of the phase 2 imputation data identified HLA-DRB1 (p_int = 1.6E-10) and HLA-DQA2 (p_regression = 4.6E-7) as independent susceptibility loci. It also revealed a 10kb sJIA-associated region on chromosome 1 that contained 8 sJIA-associated SNPs (p < 1.5E-8). Conditional analyses of imputed HLA alleles identified HLA-DRB1*1101 (p = 3.1E-9) and HLA-DPB1*03 (p_regression = 3.2E-4) as independent risk factors, while position 58 of HLA-DRB1, which defines the-DRB1*11 alleles, was also significantly associated with sJIA (p = 1.4E-7). Using RegulomeDB to examine 886 MHC SNPs with p < 1E-5, we found 13 sJIA-associated SNPs with strong evidence that they influenced transcription factor binding and were also linked to expression of a gene target (RegulomeDB scores 1a - 3f). These SNPs were located nearest to HLA-DQA1, HLA-DRB1, HLA-DRB1, TNXB, NOTCH4 and C4. 12 of 13 SNPs were cis eQTLs for 1 or more MHC class II (MHCII) genes in lymphoblastoid cell lines (LCLs) and/or monocytes, 8 of which were cis eQTLs for HLA-DRB5. 3 of 13 SNPs resided within TF ChiP-seq peaks in GM12878 LCLs. 7 of 13 SNPs resided in H3K27ac ChiP-seq peaks (marks of active enhancers) in GM12878 LCLs and/or monocytes, 6 of which were cell-type specific. In all, 9 of 13 SNPs were located within histone modification signatures that were specific to GM12878 LCLs.

Conclusion: This study implicates the MHCII locus and a region of chromosome 1 upstream of LOC284661 as areas of sJIA susceptibility. The data suggest that the MHCII locus influences sJIA susceptibility through both protein coding variation and noncoding variation that alter gene expression.
GlycA was strongly correlated with DAS28 and its components including tender and swollen joint count, global health visual analog scale score and acute phase reactants CRP and ESR (P < 0.001, Table). Similarly, GlycA was strongly associated with proinflammatory cytokines, IL-6 and TNF-α, and RA functional capacity (P ≤ 0.002, Table).

| Table: Association between GlycA and RA disease activity and inflammation |
|------------------|--------|--------|
|                  |      |        |        |
| **DAS28**        | 0.813 | <0.001 |
| **Tender joints** | 0.783 | <0.001 |
| **Swollen joints** | 0.756 | <0.001 |
| **Global health** | 0.518 | <0.001 |
| **IL-6**         | 0.452 | <0.001 |
| **TNF-α**        | 0.388 | <0.001 |
| **mHAQ**         | 0.634 | <0.001 |

Conclusion: GlycA is a novel inflammatory marker that is useful for assessment of disease activity and systemic inflammation in patients with RA.

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**2003**

Change in 14-3-3-σ Expression in Early RA Patients Treated with DMARDs Correlates with Change in DAS28 and Good EULAR Responses. Dirkjan van Schaardenburg,1 Mairaed Murphy,2 Yuan Gu,1 Samina Turk1, Walter F. Maksymowycz1 and Anthony Marotta1,2. 1Reade, Amsterdam, Netherlands; 2LipoScience, Inc., Raleigh, NC.

Background/Purpose: 14-3-3-σ is a mechanistic marker that up-regulates inflammatory and joint damage factors that are implicated in the RA pathobiological process. It is a potent inducer of TNF-α and IL-6 and we have previously described that low 14-3-3-σ levels prior to the initiation of anti-TNF and tocilizumab therapy marks good EULAR response and DAS remission. There is an unmet need for mechanistic biomarkers that enhance prediction of response to therapy. We also recently described that lower baseline plasma 14-3-3-σ levels mark good EULAR response in an RA cohort treated with DMARDs. In this study we tested plasma levels in the same cohort at year 1 to determine whether a change in 14-3-3-σ expression from baseline informs the change in DAS28 and response to therapy.

Methods: Three hundred and eighty (380) patients from the Reade early RA cohort were assessed for 14-3-3-σ titre at baseline and at year 1 follow up. All patients were DMARD naïve at baseline, mean age was 54 years, 73% were female and median duration of symptoms was 4 months (IQR 2–7). Fisher’s Exact test was performed to assess the relationship between baseline to year 1 change in 14-3-3-σ and a Good EULAR response and DAS remission (≥2.6) at year 2 follow up. Spearman rank correlations were used to identify associations between change in 14-3-3-σ and change in DAS28. A nominal logistic regression, controlling for baseline DAS, was used to investigate if change in 14-3-3-σ is a predictor of Good EULAR response.

Results: Mean (SD) year 1 plasma 14-3-3-σ levels (3.3 ng/ml (6.0)) were significantly lower than baseline levels (4.4 ng/ml (6.9), p = 0.0004 reflecting the modifiability of 14-3-3-σ plasma concentrations over this period. The change in 14-3-3-σ levels significantly correlated with the change in DAS from baseline to year 2 (r = 0.12, p = 0.02) across the whole cohort. The Fisher Exact test was performed to determine the 14-3-3-σ change from baseline to year 1 was significantly associated with a Good EULAR response (LR = 4.4, OR(95%CI)=1.6 (1.1–2.4), p = 0.023) and remission (LR = 4.5, OR(95%CI)=1.3 (1.0–1.7), p = 0.022) at year 2. In a bivariate model controlling for baseline DAS28, a decrease in 14-3-3-σ was an independent predictor of a Good EULAR response yielding an LR of 4.2, p = 0.04. Both baseline DAS28 (LR = 15.6, p=0.0001) and the change in 14-3-3-σ (LR = 5.1, p=0.0074) were independent predictors of Remission at year 2.

Conclusion: 14-3-3-σ plasma levels decrease with DMARD therapy and their change correlates with the change in DAS28 and predict both a Good EULAR response and DAS remission. These clinical findings align with the mechanistic understanding of 14-3-3-σ as a potent upregulator of inflammatory and joint damage factors and how a decrease in its expression corresponds with a reduced burden of disease.
1904


Background/Purpose: Rheumatoid arthritis (RA)-related autoantibody (Ab) testing for Abs to cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) are used in the clinical diagnosis of RA. In addition, RA-related Ab elevations in asymptomatic individuals indicate an increased risk of future RA and define a preclinical period of RA development. These risk-prone individuals could be considered for prevention strategies in RA, but a challenge in effective identification of individual at-risk for RA is the varied methods of Ab testing. For example, RF can be tested by nephelometry (RFneph) as is commonly used in clinical labs or by ELISA for RF isotypes (IgM/A/G). Studies demonstrate RFIgM and/or RFIgA is highly sensitive in classifiable RA, but the utility of RF isotype testing in addition to RFneph is not well known in preclinical RA.

Methods: We evaluated subjects with classifiable RA (1987 ACR criteria) from the Studies of the Etiology of RA (SERA) project (N=566) and the Department of Defense Serum Repository (DoDSR; N=83). All with pre-diagnosis and/or post-diagnosis samples). Controls were 200 random blood donors for SERA RA cases and 83 DoDSR matched controls for DoDSR RA cases. All subjects were tested for RFneph and RF isotypes (IgM/A/G by ELISA). Cut-off levels for all RF assays were determined as <5% positive in a separate set of 491 blood donors. CCP3.1 (IgG/IgA/IgM) testing was performed in all subjects using manufacturers cut-off levels.

Results: The diagnostic accuracy of Ab testing is listed in Table 1. All RFs and CCP3.1 had high specificity for classifiable RA including SERA RA and DoDSR post-diagnosis. In DoDSR pre-diagnosis testing, sensitivity for future RA was 41% for RFneph and 63% for CCP3.1. Sensitivity increased to 69% when positivity for the following Abs was considered: RFneph, CCP3.1, RFIgA or RFIgM. In DoDSR RA cases who were negative for RFneph and CCP3.1 in pre-diagnosis testing (N=29), adding RFIgA or RFIgM (but not IgG) testing identified an additional 10% of subjects who developed classifiable RA (Table 2).

Conclusion: Herein RFneph and CCP3.1 had high diagnostic accuracy for future RA; however, RFIgA and IgM (but not IgG) testing allowed for identification of 10% more individuals who would develop future RA, while maintaining high specificity (93% for RFIgA or IgM pre-diagnosis). These findings suggest that RFneph misses some RF positivity that is detectable by isotype testing. As such, in addition to CCP3.1 and RFneph, RFIgM and RFIgA testing may be clinically meaningful in identifying subjects at-risk for future RA, especially if interventions become available to prevent progression from preclinical to classifiable RA.

Table 2. RF Isotype Positivity in DoDSR RA Cases Negative for RF by Nephelometry and CCP3.1 in Pre-diagnosis Testing

<table>
<thead>
<tr>
<th>RFneph(−)</th>
<th>CCP3.1(−)</th>
<th>RFIgA or RFIgM†</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFIgM</td>
<td>14.3</td>
<td>12.8</td>
<td>6.9</td>
<td>94.0</td>
</tr>
<tr>
<td>RFIgA</td>
<td>14.3</td>
<td>6.5</td>
<td>3.4</td>
<td>93.6</td>
</tr>
<tr>
<td>RFIgG</td>
<td>2.0‡</td>
<td>3.2‡</td>
<td>0‡</td>
<td>98.8</td>
</tr>
<tr>
<td>≥1 RF isotypes</td>
<td>24.5</td>
<td>16.1</td>
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*From the 83 DoDSR RA cases, these results include cases of testing who were negative for RFneph and/or CCP3.1 in their pre-diagnosis sample that was closest to the time of their diagnosis; median 1.4 years prior to RA diagnosis. †RFIgG testing did not identify any subjects pre-diagnosis of RA that were not identified as seropositive by CCP3.1 or RFneph testing. ‡RFIgA or RFIgM positivity was present in only 6 of 83 (7.2%) of DoDSR matched controls, and this high specificity (90.8%) adds further value to the identification of 4 of 29 (10.3%) preclinical RA subjects who will go on to develop classifiable RA.


2. Discourse: D. van Schaardenburg, Augurex Life Sciences Corp.; M. Murphy, Augurex Life Sciences Corp.; Y. G. Mei, Augurex Life Sciences Corp.; S. Turk, None; W. P. Maksymowych, None; A. Marotta, Augurex Life Sciences Corp., 3.

Reference


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Figure 1. Galectin-3 increments in healthy controls, and in patients with early (ERA) and longstanding rheumatoid arthritis (LRA) before and after termination of exercise.

Conclusion: Circulating Galectin-3 was increased in early and longstanding RA. Galectin-3 did not exhibit circadian variation. Galectin-3 increased comparably in RA patients and healthy controls following submaximal exercise, which should be avoided before bloodsampling for Galectin-3 determination.

Acknowledgements: We would like to thank The Danish Rheumatism Association for financial support.

References:

Disclosure: S. F. Issa None; A. F. Christensen None; T. Lottenburger None; K. Junker None; H. M. Lindegaard None; K. Hoerslev-Petersen None; K. K. Hoerslev-Petersen None; P. Junker None.

1906

IL-6 Blockade Reduces Circulating N-Terminal Pro-Brain Natriuretic Peptide Levels in Patients with Active Rheumatoid Arthritis. Atsuna Nishiwaki1, Hitomi Kobayashi2, Yasuyuki Kobayashi2, Isamu Yoko2, Noboru Kitamura3, Hitokate Shiraiva4, Takamasa Nozaki5, Hiroto Inomata6, Natsumi Ikumi7, Kaia Sugiyama8, Yousuke Nagasawa8 and Masami Take9.1. Nihon University School of Medicine, Tokyo, Japan. 2. St. Marianna University School of Medicine, Kawasaki, Japan. 3. St. Marianna University School of Medicine, Kawasaki, Japan. 4. St. Marianna University School of Medicine, Kawasaki, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have a 1.5–2.0 fold higher risk of developing congestive heart failure (CHF) than the general population. Small increases in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels predict left ventricular (LV) dysfunction and cardiac stress. NT-proBNP is also associated with pro-inflammatory cytokines such as interleukin 6 (IL-6). Data relating to the effects of IL-6 blocking agents (tocilizumab, TCZ) on circulating NT-proBNP levels in patients with active RA are lacking but may be informative. We therefore investigated the effects of TCZ therapy on the NT-proBNP levels in RA patients without cardiac symptoms before and after 24 weeks of treatment.

Methods: RA patients with active disease with an inadequate clinical response to non biologic DMARDs and non-RA healthy control were enrolled. Exclusion criteria were diabetes, previous cardiovascular events, cardiopathy, hypertension and renal disease. The RA patients received TCZ once a month for 24 weeks. Serum NT-proBNP levels were measured at baseline and week 24. Clinical and biological monitoring was performed at baseline and 24 weeks after the start of TCZ treatment. We explored the associations between NT-pro BNP and the RA disease activity score for Simple Disease Activity Index (SDAI) scores. The anti-citrullinated protein antibody (ACPA) titre was divided into high and low levels using a cut-off of 30 units/mL. Fisher test and multivariable linear regression analyses were performed to identify the correlations.

Results: 90 patients (mean age, 56.4 ± 10.4 years; 85% female) and a matched 30-patient control group (mean age 56.6 ± 3.4 years; 86% female) were enrolled. The SDAI at baseline was 22.5 ± 12.7. The 24-week SDAI scores were significantly lower than those at baseline (p = 0.03). The NT-proBNP levels at baseline were significantly higher than control group (p = 0.04). The median (interquartile range) levels of the NT-proBNP significantly decreased from baseline (121.78 [52.81–230.24] pg/mL) to 24 weeks (75.13 [29.50–128.67] pg/mL, p = 0.004) following TCZ treatment. NT-proBNP levels in the high ACPA group tended to be higher than the low ACPA group (p = 0.07). The change in NT-proBNP levels was significantly correlated with the change in SDAI score (r = 0.455, p = 0.003). After adjustment for age, gender, erythrocyte sedimentation rate (ESR), and RA duration, the association between the change in NT-proBNP levels and the change in SDAI remained significant (p = 0.023).

Conclusion: This is the first study to report the effect of IL-6 blocking agent on circulating NT-proBNP levels in patients with active RA. Our results suggest that blocking IL-6 in patients with RA without cardiac symptoms does not increase but rather decreases circulating NT-proBNP levels by around 52%, which was also related to a reduction in disease activity. Our data also suggest that RA-specific autoimmunity against citrullinated proteins might relate to subclinical cardiac stress. TCZ treatment may influence the presence of subclinical left ventricular dysfunction or cardiac stress which may progress to overt CHF.

Disclosure: A. Nishiwaki None; H. Kobayashi None; Y. Kobayashi None; I. Yokoe None; N. K. Itamura None; H. Shiraiwa None; T. Nozaki None; H. Inomata None; N. Ikumi None; K. Sugiyama None; Y. Nagasawa None; M. Takei None.

1907

Clinical Evaluation of Anti-Aminoacyl tRNA Synthetase Antibodies in Rheumatoid Arthritis Patients. Masakazu Matsushita, Ken Y amaji, Naoto Tamura and Yoshihiti Takasaki. Juntendo University School of Medicine, Tokyo, Japan.

Background/ Purpose: Anti-[j]-o-1 is an autoantibody that is specifically detected in the blood sera of patients with polymyositis/dermatomyositis (PM/DM). The corresponding antigen is known to be histidyl-tRNA synthase, an aminoacyl-tRNA synthase (ARS) localized to the cytoplasm. Recently, autoantibodies to other ARSs have been identified and patients with these antibodies have distinguishing clinical symptoms such as lesions of the lung or skin, a condition known as anti-ARS antibody syndrome. We measured anti-ARS antibodies in rheumatoid arthritis (RA) patients and evaluated its clinical characteristics.

Methods: At our hospital, 228 ambulatory RA patients were selected for the study. We evaluated the positive rate of anti-ARS antibodies in the blood sera of these patients. Anti-ARS antibodies were measured using the EUROLINE Miosytis Profile 3 test system (EUROIMMUN Inc., Lubeck, Germany). Five anti-ARS antibodies can be measured using this kit: anti-OJ, anti-E, anti-PL-12, anti-PL-7, and anti-[j]-o-1 antibodies. For blood serum testing positive for any one of these antibodies, we performed an indirect immunofluorescence assay using HEP-2 cells to determine whether a reaction occurred in the cytoplasm. We grouped the participants into anti-ARS antibody-positive and -negative groups, and evaluated age, gender, male-to-female ratio, anti-CCP antibodies, rheumatoid factor levels, presence of interstitial pneumonia (IP), and frequency of usage of methotrexate or biologics.

Results: Anti-ARS antibodies were detected in 6.1% (14 patients) of all 228 RA patients. Specifically, anti-PL-7 antibodies were detected in 6 patients (2.6%), anti-[j]-o-1 antibodies in 4 patients (1.8%), anti-PL-12 antibodies in 2 patients (0.9%), anti-OJ antibodies in 1 patient (0.4%), and anti-[j]-o-1 antibodies in 1 patient (0.4%). When the blood sera of these patients were allowed to react with HEP-2 cells by using the indirect immunofluorescence method, we detected staining in the cytoplasm of all patients. When we compared the anti-ARS antibody-positive and -negative groups, differences in age and gender were not observed. However, the frequency of interstitial pneumonia in the anti-ARS antibody-positive group was significantly higher (P < 0.05). A detailed investigation of the antibodies revealed that anti-PL-7 and anti-PL-12 antibodies were detected at a significantly higher level in patients with IP. Biologics were administered in 3 patients in the anti-ARS antibody-positive group; however, concomitant myositis or exacerbation of IP was not observed. No significant difference was observed between the positive and negative groups in terms of anti-CCP antibody values or rheumatoid factor levels.

Conclusion: Anti-ARS is an autoantibody that is detected specifically in PM/DM patients; however, we demonstrated that it is also detected in RA patients with anti-ARS antibody syndrome.
patients. In particular, anti-PL-7 and anti-PL-12 antibodies were detected efficiently in RA patients with IP, suggesting that these autoantibodies are associated with IP. Our investigation showed that biologics could be administered safely to RA patients with anti-ARS antibodies.

Disclosure: M. Matsushita, None; K. Yamaji, None; N. Tamura, None; Y. Takasaki, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy IV: Safety of Biologics and Small Molecules in Rheumatoid Arthritis - Cardiovascular and Other Systems
M Monday, November 17, 2014, 4:30 PM - 6:00 PM

1908
Pregnancy Outcomes in the Tofacitinib RA Safety Database through April 2014. A. Maren1, Y. Chen1, D. Frazier2 and J. Geier3. 1Pfizer Inc, Collegeville, PA, 2Pfizer Inc, Groton, CT, 3Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Its effect in pregnant women is of interest, as tofacitinib has been shown to be fetotoxic and teratogenic in rats and rabbits at exposures 146 times and 13 times (respectively) the maximum recommended human dose. There are no adequate, well-controlled tofacitinib studies in pregnant women; per the RA clinical development program protocols, all studies exclude pregnant subjects and require use of highly effective contraception by females with child-bearing potential, and study treatment discontinuation if a subject becomes pregnant. To understand potential effects of tofacitinib, pregnancies in the RA clinical development program were reviewed.

Methods: Cases were identified from Pfizer's internal safety database through April 30, 2014, from interventional (one clinical study is ongoing; database not locked) and non-interventional studies, plus cases from post-marketing reporting. Cases were limited to females administered tofacitinib/placebo/blinded therapy at time of conception and/or fetal subjects exposed to tofacitinib/placebo/blinded therapy through maternal exposure. Potential duplicate cases were eliminated; remaining cases were reviewed for any pregnancy-related outcome and abnormalities, which were categorized as healthy newborns, spontaneous abortion, medical termination, still-birth, pending, or lost to follow-up.

Results: A total of 35 cases were identified. In the tofacitinib RA clinical studies of ~6,000 subjects with nearly 17,000 patient-years of follow-up, there were 32 cases of maternal tofacitinib exposure. Subject age ranged from 22 to 40 years. Of the 32 cases, 31 received tofacitinib; 13 had 5 mg BID, 1 had 5 mg QD, 12 had 10 mg BID, 2 had 20 mg QD, 1 had 15 mg BID, and 2 whose therapy at conception is still blinded. One subject received placebo/methotrexate (MTX). Ten of the 32 cases were also taking MTX.

The pregnancy outcomes with tofacitinib were: 14 healthy newborns (including 1 low birth weight and 1 pre-term birth), 6 spontaneous abortions, 4 medical terminations, 1 stillbirth, pending, or lost to follow-up.

Conclusion: Most cases with reported outcomes had healthy newborns. A diverse outcomes including spontaneous abortions and congenital malformation were observed in RA subjects who became pregnant during tofacitinib therapy. Pregnancy outcomes in subjects receiving tofacitinib will continue to be monitored through routine pharmacovigilance and via a post-approval safety study within the Organization of Teratology Information Specialists (OTIS) registry.

Disclosure: A. Maren, Pfizer Inc; Y. Chen, Pfizer Inc; D. Frazier, Pfizer Inc; J. Geier, Pfizer Inc.

1909
Incidence of Congestive Heart Failure in Subjects with Rheumatoid Arthritis Receiving Anti-Tumour Necrosis Factor Drugs: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Alper van Sijl1, M. Mamas2, M. Lunt3, BSRBR Control Centre Consortium4, K. Watson5, D. Frazier2 and J. Geier3. 1Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom; 2University of Manchester, Manchester, United Kingdom; 3Arthritis Research UK. 4Centre for Epidemiology, University of Manchester, Manchester, UK; 5Institute of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom; 6Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Subjects with rheumatoid arthritis (RA) are at a higher risk of developing cardiovascular (CV) disease compared to the general population, with an increased incidence of congestive heart failure (CHF) possibly mediated by chronic inflammation. Anti-tumour necrosis factor (TNFi) drugs might reduce the incidence of new CHF by supressing inflammation. However, TNFi are associated with a worsening of existing CHF. The aim of this analysis was to compare the incidence of CHF in subjects with RA treated with TNFi to that in those receiving non-biologic drugs (nbDMARDs).

Methods: Patients with a physician diagnosis of RA enrolled in the British Society for Rheumatology Biologics Register, a national prospective cohort study established in 2001 to monitor the long-term safety of TNFi. Potential CHF events were verified according to Framingham criteria by a cardiologist from death certificates and from clinical follow-up forms of consultants. New CHF which occurred within 6 months after another cardiac event (eg. myocardial infarction) was excluded. Risk of CHF was compared between the two cohorts using a Cox regression model, propensity scores adjusted. Subjects were censored at first episode of CHF, death, first missed dose of TNFi + 180 days, last returned clinician follow-up or 31/01/2014, whichever came first.

Results: A total of 87 validated first CHFs were analysed: 48 in 3,662 nbDMARD subjects and 39 in 12,397 TNFi-exposed subjects. After adjustment for differences in baseline characteristics, the hazard ratio (95%-confidence interval) of CHF in patients on TNFi compared to nbDMARD was: 0.31 (0.18–0.52). Similar results were found and the analysis was limited to first CHF only and in patients with prior history of ischaemic heart disease.

Conclusion: No increased risk of CHF was observed in those patients selected for TNFi therapy compared to those receiving nbDMARD therapy. A reduced risk of CHF was noted in patients treated with TNFi.

Table. Association between exposure to TNFi and development of first CHF

<table>
<thead>
<tr>
<th>nbDMARD (n=3662)</th>
<th>TNFi (n=12397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of follow-up per subject, median (IQR)</td>
<td>5.0 (2.5–7.7)</td>
</tr>
<tr>
<td>Person-years of exposure, yrs</td>
<td>18 698</td>
</tr>
<tr>
<td>Number of verified CHFs, n (%)</td>
<td>48 (1.31)</td>
</tr>
<tr>
<td>Crude incidence rate of verified CHFs per 10 000 person-years (95%-confidence interval)</td>
<td>25.67 (19.53–34.40)</td>
</tr>
<tr>
<td>Risk of CHF between nbDMARD and TNFi</td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95%-CI)</td>
<td>Referent</td>
</tr>
<tr>
<td>Age- and gender adjusted HR (95%-CI)</td>
<td>Referent</td>
</tr>
<tr>
<td>PD-adjusted HR (95%-CI)</td>
<td>Referent</td>
</tr>
</tbody>
</table>

Fully adjusted model by propensity score (PD) consisting of age, gender, DAS28, disease duration, HAQ, steroid use, NSAIDs, COXIBs, hypertension, diabetes mellitus, angina pectoris, myocardial infarction, smoking history and use of statins, antiplatelets, ACE-inhibitors, warfarin and digoxin.

Disclosure: A. van Sijl, None; M. Mamas, None; M. Lunt, None; BSRBR Control Centre Consortium, None; K. Watson, None; D. Frazier, None; J. Geier, None; K. Yamaji, None; M. Lunt, None; BSRBR Control Centre Consortium, None; K. Watson, None; D. Frazier, None; J. Geier, None; K. Yamaji, None; A. van Sijl, None; M. Mamas, None; M. Lunt, None; BSRBR Control Centre Consortium, None; K. Watson, None; D. Frazier, None; J. Geier, None; K. Yamaji, None; A. van Sijl, None; M. Mamas, None; M. Lunt, None; BSRBR Control Centre Consortium, None; K. Watson, None; D. Frazier, None; J. Geier, None; K. Yamaji, None.
1910

Risk of Hypersensitivity Among Medicare Patients with Rheumatoid Arthritis Who Were Taking Biologics. Huiying Yun,1,2 Fengdong Xie,1,2 Lang Chen,1,2 James Lewis3,2 and Jeffrey R. Curtis3,2 1University of Alabama at Birmingham School of Public Health, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL, 3University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Healthcare providers have been alerted to the potential drug hypersensitivity reactions (HSRs), an adverse drug reaction that are uncommon but may be severe and can result in mortality in patients (pts) with RA, especially those receiving intravenously (IV) administered biologics. One case of a fatal HSR has been reported and associated with tocilizumab (TCZ). The risks of HSRs in population-based RA cohorts are unclear, as is understanding whether risks differ by specific agent. We compared drug-specific risks for HSR among RA pts enrolled in the US Medicare.

Methods: Using Medicare data from 2006–2011 of 100% of pts with RA, we identified new users of infliximab (INF), abatacept (ABA), rituximab (RIT), TCZ and injected biologics (e.g. anti-TNF therapy). For each biologic administration (Adm), follow up started on the date of drug infusion/injection and ended at the earliest date of: HSR, subsequent biologic Adm, death, coverage loss, 30-day follow-up period, or Dec 31, 2011. We identified HSR using validated claims-based algorithms in three settings: A) Inpatient (IP) or emergency departments (ER) for anaphylactic shock, B) Outpatient (OTP) for anaphylactic shock plus a diagnosis of bronchospasm, stridor, hypotension, epinephrine, injection of diphenhydramine and CPR (Disease and symptom list); C) IP or ER for unspecified allergy plus a diagnosis from the above disease and symptom list. We calculated the incidence rate (IR) of HSR for each biologic within 0–1, 2–14 and 15–30 days of Adm. Robust Poisson regression was used to compare the HSR risks across biologics adjusting for age, gender, Charlson comorbidity score, concomitant steroid (GCs) and CVD risk factor in the general population. The objective of this study was to compare the risk of incident hyperlipidemia in early RA patients after initiation of disease modifying anti-rheumatic drugs (DMARDs).

Results: Of the 17,145 RA patients included in the study, 364 developed hyperlipidemia. The incidence rates (95% confidence interval (CI)) for hyperlipidemia per 1,000 person-years were 30.7 (21.9–41.8) for TNF-α inhibitors, 28.9 (24.9–33.4) for methotrexate, 20.1 (16.3–24.6) for hydroxychloroquine, and 36.4 (26.5–48.7) for other nbDMARDs. The adjusted hazard ratios (HR) (95% CI) for hyperlipidemia were 1.41 (0.99–2.00) for TNF-α inhibitors, 1.84 (1.33–2.53) for other nbDMARDs compared with methotrexate in the full cohort, while 1.18 (0.80–1.73), 0.75 (0.58–0.98) and 1.41 (1.01–1.98), respectively in the PS trimmed cohort. In the subgroup analysis, hydroxychloroquine use showed significant reduction in low density lipoprotein (LDL-C) (0.8 mg/dl, 95% CI 0.5–1.1) and triglyceride (−19.5 mg/dl, 95% CI −38.7, −0.3) from baseline compared with methotrexate.

Conclusion: Based on both a reduced adjusted HR for incident hyperlipidemia and a reduction in lipid levels, use of hydroxychloroquine may be associated with a lower risk of hyperlipidemia among early RA patients. A possible increase in the risk of hyperlipidemia in TNF-α inhibitor initiators was noted in our primary analysis, but not in the PS stratified analysis. These findings suggest a complex relationship between DMARDs, inflammation and lipid levels.

Table. Events, absolute incidence rate and adjusted risk ratio of hyperlipidemia reaction, by biologic exposures and timing of exposure

<table>
<thead>
<tr>
<th>Biologic and Timing of Exposure</th>
<th>Incidence rate per 1,000,000 person years</th>
<th>Adjusted Risk Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Batacept</td>
<td>&lt;11</td>
<td>3.10 (2.05–13.17)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>36</td>
<td>3.57 (17.2–74.3)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>13</td>
<td>4.41 (18.9–103.5)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>&lt;11</td>
<td>4.72 (16.8–132.6)</td>
</tr>
<tr>
<td>2–14 days</td>
<td></td>
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<tr>
<td>A Batacept</td>
<td>&lt;11</td>
<td>0.52 (0.17–1.55)</td>
</tr>
<tr>
<td>Infliximab</td>
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<tr>
<td>Rituximab</td>
<td>12</td>
<td>1.66 (0.45–6.14)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>&lt;11</td>
<td>1.23 (0.16–9.73)</td>
</tr>
<tr>
<td>15–30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Batacept</td>
<td>&lt;11</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>12</td>
<td>1.76 (0.74–4.17)</td>
</tr>
<tr>
<td>Rituximab</td>
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<td>0.74 (0.09–5.84)</td>
</tr>
<tr>
<td>Tocilizumab</td>
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<td>1.18 (0.15–9.36)</td>
</tr>
<tr>
<td>0–30 days, any injectable anti-TNF</td>
<td></td>
<td>0.84 (0.40–1.80)</td>
</tr>
</tbody>
</table>

* Adjusting for age, gender, Charlson comorbidity score, concomitant steroid and methotrexate use

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Disease Modifying Anti-Rheumatic Drug Use and the Risk of Incident Hyperlipidemia in Patients with Early Rheumatoid Arthritis: A Retrospective Cohort Study. Rishi Desai, Wendy Eddings, KP Liao, DH Solomon and Seoyoung C. Kim. Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: Rheumatoid arthritis (RA) increases patients’ risk of developing cardiovascular diseases (CVD). Hyperlipidemia is an important CVD risk factor in the general population. The objective of this study was to compare the risk of incident hyperlipidemia in early RA patients after initiation of disease modifying anti-rheumatic drugs (DMARDs).

Methods: We conducted a cohort study in patients receiving their first RA diagnosis after at least 12 months without evidence of RA or DMARD prescription, using insurance claims data (2001–2012). Four mutually exclusive groups were defined based on DMARD initiation, TNF-α inhibitors ± non-biologic (nb) DMARDs, methotrexate ± non-hydroxychloroquine nbDMARDs, hydroxychloroquine ± non-methotrexate nbDMARDs, and other nbDMARDs only. The primary outcome was incident hyperlipidemia as defined by a diagnosis and a prescription for a lipid-lowering agent. For the subgroup of patients with laboratory results available, we analyzed change in lipid levels as the secondary outcome. Multivariable Cox proportional hazard regression models estimated the relationship between DMARD use and incident hyperlipidemia. Propensity scores (PS) were calculated to improve confounding control. PS strata-stratified analyses were performed for each pairwise comparison after asymmetrically trimming at 2.5th and 97.5th percentile of the PS distribution to address confounding by indication.

Results: Of the 17,145 RA patients included in the study, 364 developed hyperlipidemia. The incidence rates (95% confidence interval (CI)) for hyperlipidemia per 1,000 person-years were 30.7 (21.9–41.8) for TNF-α inhibitors, 28.9 (24.9–33.4) for methotrexate, 20.1 (16.3–24.6) for hydroxychloroquine, and 36.4 (26.5–48.7) for other nbDMARDs. The adjusted hazard ratios (HR) (95% CI) for hyperlipidemia were 1.41 (0.99–2.00) for TNF-α inhibitors, 1.84 (1.33–2.53) for other nbDMARDs compared with methotrexate in the full cohort, while 1.18 (0.80–1.73), 0.75 (0.58–0.98) and 1.41 (1.01–1.98), respectively in the PS trimmed cohort. In the subgroup analysis, hydroxychloroquine use showed significant reduction in low density lipoprotein (LDL-C) (0.8 mg/dl, 95% CI 0.5–1.1) and triglyceride (−19.5 mg/dl, 95% CI −38.7, −0.3) from baseline compared with methotrexate.

Conclusion: Based on both a reduced adjusted HR for incident hyperlipidemia and a reduction in lipid levels, use of hydroxychloroquine may be associated with a lower risk of hyperlipidemia among early RA patients. A possible increase in the risk of hyperlipidemia in TNF-α inhibitor initiators was noted in our primary analysis, but not in the PS stratified analysis. These findings suggest a complex relationship between DMARDs, inflammation and lipid levels.

Table. Relative risk of hyperlipidemia in patients with early rheumatoid arthritis based on DMARD use

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Unadjusted HR (95% CI)</th>
<th>Multivariate adjusted* HR (95% CI)</th>
<th>Propensity score adjusted** HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>TNF-α inhibitors</td>
<td>1.08 (0.76–1.52)</td>
<td>1.41 (0.99–2.00)</td>
<td>1.18 (0.80–1.73)</td>
</tr>
<tr>
<td>Other nbDMARDs</td>
<td>1.25 (0.90–1.74)</td>
<td>1.33 (0.95–1.84)</td>
<td>1.41 (1.01–1.98)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cardiovascular risk factors and comorbidities, cardiovascular drug use, pain medications and healthcare use in the prior year in a cox proportional hazard regression model.

**Propensity score decile stratification was used to derive hazard ratios after asymmetrically trimming at 2.5th and 97.5th percentile of the PS distribution.
Tocilizumab Therapy for Rheumatoid Arthritis Patients with Chronic Renal Insufficiency. Shunsuke Mori, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan.

Background/Purpose: Renal involvement is relatively common in rheumatoid arthritis (RA) patients. Recent randomized controlled trials of anti-tumor necrosis factor-α (anti-TNFα) showed that the concomitant administration of methotrexate (MTX) is superior to monotherapy. However, the dose of MTX must be reduced in RA patients with chronic renal insufficiency (CRI) because MTX elimination is delayed in these patients. In contrast, the ACT-RAY trials indicated that the efficacy of tocilizumab (TCZ) monotherapy is comparable with combination therapy with MTX. The present study was intended to evaluate the efficacy and safety of TCZ therapy in RA patients with CRI.

Methods: The subjects were all patients with RA who had started TCZ therapy at our hospital from April 2008 to December 2013. Pretreatment characteristics were compared between patients with and without CRI. Clinical disease activity index (CDAI) levels and hemoglobin values as well as adverse events were recorded during the follow-up period of the first 24 weeks. CRI was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min for 3 months.

Results: A total of 105 patients were included in this study and among these, 35 patients (33.3%) were diagnosed with CRI. Mean eGFR levels in the CRI group and in non-CRI group were 43.7 ml/min and 80.9 ml/min, respectively. Sixty percent of CRI patients and 70% of non-CRI patients were refractory to anti-TNFα agents. CRI patients were significantly older (75.3 years versus 62.0 years, p < 0.0005) and had longer RA duration (9.8 years versus 5.4 years, p = 0.005). There was no significant difference in the other RA-related markers between both groups. Approximately 85% of patients in each group showed high or median disease activity. Biopsy-proven amyloidosis was observed in one patient in the CRI group. Hypertension was observed at a significantly higher rate in the CRI group (81% versus 36.8%, p < 0.0005). Of note, serum levels of hemoglobin were significantly lower in CRI patients compared with non-CRI patients (11.2 g/dl versus 12.5 g/dl, p < 0.0005). Eighty-one percent of CRI patients received TCZ monotherapy, while 49% of non-CRI patients used MTX concomitantly with TCZ. Mean changes of CDAI at week 24 from baseline were 17.1 (26.7 to 9.6) in the CRI group and 17.5 (25.8 to 8.3) in the group without CRI. Rates of patients with low disease activity or remission at week 24 were 62.2% of CRI patients and 55.9% of non-CRI patients. Mean hemoglobin levels were significantly increased over time during TCZ therapy. At week 24, mean increases of 1.2 g/dl (11.2 to 12.4, p < 0.0005) and 0.8 g/dl (12.5 to 13.3, p = 0.005) were observed in the CRI group and in the non-CRI group, respectively. Adverse events occurred in two patients without CRI (diverticulitis and acute cholecystitis). Neither serious adverse event nor aggravation of renal function was reported in the CRI group.

Conclusion: TCZ therapy was effective in reduction of disease activity and improvement of hemoglobin levels in RA patients with CRI. In addition, TCZ showed stable safety and tolerability profiles even in CRI patients.

Disclosure: S. Mori, Chugai Pharmaceutical Co., 8;
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IL-17A Deficiency Promotes Periostal Bone Formation in a Model of Inflammatory Arthritis. A. T. Shaw1, Y. Maeda2, C. Manning3, E. Gravallese4. 1University of Massachusetts Medical School, Worcester, MA, 2UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Enthesial and periosteal bone formation in spondyloarthopathies (SpA) is important sequelae of disease that contribute to patient morbidity. Anti-TNF therapies do not significantly alter progression of this debilitating process; therefore, new agents that inhibit both inflammation and bone formation are being sought. IL-17A contributes to inflammation in many diseases, including SpA, and is a potential therapeutic target. IL-17A promotes osteoclastogenesis through induction of RANKL in synovial fibroblasts and by induction of expression of the proinflammatory cytokines TNF, IL-1 and IL-6. However, the effects of IL-17A on bone-forming osteoblasts (OB) have not been fully elucidated and data are conflicting as to whether it promotes or protects from bone loss. We investigated the impact of IL-17A on OB differentiation in vitro and determined its role on bone formation in an in vivo murine model of arthritis.

Methods: The effect of IL-17A on the Wingless (Wnt) signaling pathway, a critical pathway for OB differentiation, was determined using calvarial OBs from TOPGAL mice containing a reporter construct for Wnt signaling. Cells were cultured in the presence of IL-17A throughout differentiation and Wnt activity was determined. Calvarial OBs were also treated with IL-17A at early, mid and late stages of differentiation and qPCR analysis of Wnt signaling antagonist expression was performed. Periosteal bone formation is a prominent feature in the K/BxN serum transfer arthritis (STA) model. To determine the effects of IL-17A on OB function in vivo, STA was induced in IL-17A null and wild type mice. Periosteal bone formation was quantitated and ankle joints were also analyzed for erosion severity.

Results: Long-term culture of TOPGAL calvarial OBs with IL-17A suppressed Wnt signaling, as reflected by a reduction in Wnt reporter activity. In addition, preliminary staining with von Kossa demonstrated inhibition of matrix mineralization in these cells cultured with IL-17A. Expression of the Wnt antagonists dickkopf (DKK1), DKK2, DKK3, secreted frizzled related protein (sFRP)2 and sFRP4 mRNA expression in calvarial OBs was reduced to one-fifth of baseline levels by treatment with IL-17A at an early stage of differentiation (day 7). However, inhibition was reversed by day 21 of differentiation. IL-17A null and wild type mice displayed similar clinical and histologic inflammation scores, as well as similar articular bone erosion scores. Importantly however, IL-17A null mice formed significantly more periosteal bone than wild type mice (p < 0.05).

Conclusion: IL-17A may promote OB differentiation in early stages by suppressing expression of antagonists of Wnt signaling. However, the net effect of long-term treatment of OBs with IL-17A is inhibition of differentiation. These in vitro findings are borne out in vivo, as mice lacking IL-17A develop a significantly greater amount of periosteal bone than wild type mice. However, deficiency of IL-17A did not affect inflammation or the degree of bone erosion in this model. These findings have potential clinical significance, as blocking IL-17A in patients with SpA may further exacerbate the extent of periosteal bone formation.

Disclosure: A. T. Shaw, None; Y. Maeda, None; C. Manning, None; E. M. Gravallese, Abbvie, 2, Eli Lilly and Company, 2.

1915


Background/Purpose: IL-17 is elevated in both the lesional skin and arthritis-affected joints of psoriatic arthritis (PsA) patients. Although the IL-23/IL-17 axis has been linked with PsA pathology, the direct effect of IL-17 on myeloid cells in PsA is elusive.

Methods: We performed gene transfer of IL-17 and GFP control by hydrodynamic delivery of minicircle (MC) DNA in control (C57BL/6) mice and mice treated with topical imiquimod. The psoriatic features were analyzed and scored for disease progression histologically. Further phenotypic analysis of cell populations was performed by flow cytometry, RT-qPCR, and in vivo imaging using nanoprobes. Characterization of molecular pathways was also performed in IL12β-/- Rag1-/- and Tcrd-/- transgenic mice.

Results: We have identified a unique IL-17Rα+CD11b+ Gr-1+ cell subset induced by IL-17 that is associated with epidermal hyperplasia. Specifically 4 days post-IL-17 gene transfer we observed evidence of exacerbated epidermal hyperplasia, acanthosis, parakeratosis and Munro microabscess formation that were absent in GFP control mice. Gene expression of keratinocyte proliferation and inflammation biomarkers such as Keratin 16 (K16), S100a7, S100a8, Cxcl1, Cxcr2 and Ltb4r1 were consistently elevated post-IL-17 gene transfer and this correlated with an increase of Cxcl1 (a neutrophil chemotactant) in the serum. Utilizing IL12β-/- Rag1-/- and Tcrd-/- mice, we demonstrated that genetic ablation of IL-23r, or the complete absence of T, B and γδ T cells did not affect epidermal and histological features induced by IL-17. On the contrary, depletion of CD11b+ Gr-1+ cells resulted in a complete rescue of skin pathology as evidenced by histology and gene expression.

Conclusion: Herein we demonstrate that IL-17 induces the expansion of an IL-17Rα+CD11b+ Gr-1+ pathogenic cell subset, which is directly responsible for inducing a constellation of features that resemble human psoriatic disease. Collectively our data underscore the importance of innate immune cells in the pathogenesis of PsA and pave the way for the design of novel therapeutics to combat this disabling condition.

Disclosure: E. Suzuki, None; R. Sarin, None; E. M averakis, None; I. E. Adamopoulos, None.

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Stromal Overexpression of Transmembrane TNF Induces SpA-like Arthritis and Spondylitis in Mice. Leonie M. van Duivenvoorde1, Melissa N. van Tol1 and Dominique L. Baeten2. 1Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, 2Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: The immunopathology of spondyloarthopathies (SpA) is determined by inflammation and structural damage, in particular osteoproliferation, of axial and peripheral joints. The failure of TNF blockers to prevent ongoing osteoproliferation raised the concept that inflammation and osteoproliferation are uncoupled processes in SpA. However, inflammation and osteoproliferation are linked in HLA-B27 rats, high CRP is associated with radiographic progression in axial SpA, and NSAID treatment can retard osteoproliferation. Here, we propose that inflammatory mediators distinct from soluble TNF can drive pathologic osteoproliferation in SpA. Based on our observations on soluble versus transmembrane TNF (tmTNF) expression in SpA synovitis, we explored if and how tmTNF drives experimental spondyloarthritis.

Methods: tmTNF mice (TgA86), provided by Dr Kollias (Athens), were studied clinically over time for arthritis and spondylitis development. At 3, 6 and 8 months joints were collected and analyzed for inflammation and osteoproliferation. To assess the contribution of stromal versus hematopoietic tmTNF expression, tmTNF tg mice and WT mice were lethally irradiated and reconstituted with bone marrow (BM) of both WT or tmTNF tg mice. Mice were evaluated for 16 weeks until sacrifice for histologic analysis.

Results: tmTNF mice (100%; n=50) spontaneously developed arthritis, visualized by deformed joints and loss of grip strength, and spondylitis as evidenced by crinkled tails and hunchback formation, starting at 4 weeks of age and progressing over time. Analysis of 3 months old mice revealed that arthritis was characterized by inflammation of synovium and enthesis. Hypertrophic chondrocytes were observed at the edge of the vertebral body, in conjunction with the ongoing inflammation. X-ray images from 8 months old mice also revealed bridging of the tail vertebra. These typical SpA-like features were not observed in any of the non-transgenic littermates.

In the functional experiments, irradiated tmTNF tg mice receiving tmTNF tg BM developed arthritis and spondylitis with 100% incidence 3 weeks after BMT, albeit the arthritis was less severe than in non-irradiated tmTNF tg mice. Interestingly, tmTNF tg mice receiving WT BM also developed both arthritis and spondylitis with the same incidence, onset and severity as the control group. In sharp contrast, WT mice that received tmTNF tg BM did not develop any arthritis, and spondylitis occurred less frequently (66%) and later (10 weeks after BMT) than in the control group.

Conclusion: tmTNF overexpression induces experimental arthritis and spondylitis with radiographic and histologic proven new bone formation,
indicating that inflammatory mediators can indeed drive osteoproliferation. The data indicate the relevance of the transmembrane form of TNF and the role of the stromal compartment in the pathophysiology of SpA.

Reference

Disclosure: L. M. van Duivenvoorde, None; M. N. van Tok, None; D. L. Baeten, None.

1917
IL-23 Expression and Activation of Autophagy in Synovium and PBMCs of HLA-B27 Positive Patients with Ankylosing Spondylitis. Barbara Neerinckx, Shea Carter and Rik Lories. KU Leuven, Leuven, Belgium.

Background/Purpose: IL-23 may play a key role in the pathogenesis of ankylosing spondylitis (AS). Some studies describe indeed increased serum levels of IL-23 in AS patients compared to healthy controls [1–3]. Recent evidence also shows enhanced IL-23 production in the gut of AS patients. This upregulation of IL-23 expression in the gut seems to be the result of activation of autophagy rather than of an activated unfolded protein response [4]. We investigated IL-23 expression and the role of autophagy ex vivo in the synovium and peripheral blood mononuclear cells (PBMCs) of HLA-B27 positive AS patients.

Methods: Synovial tissues were obtained by needle arthroscopy from actively inflamed knees from patients with AS (HLA-B27 positive; n=11), other forms of spondyloarthritides (SpA) (HLA-B27 positive; n=9 or HLA-B27 negative; n=10), rheumatoid arthritis (RA) (HLA-B27 positive or negative; n=10) or other inflammatory joint diseases (non SpA/RA inflammatory joint disease) (HLA-B27 positive or negative; n=10) and from multiple organ donars as non-inflammatory controls (HLA-B27 negative; n=10). PBMCs were isolated from whole blood samples taken from patients with AS (HLA-B27 positive; n=17), RA (HLA-B27 negative; n=19) and healthy controls (HLA-B27 negative; n=12). None of the patients was treated with TNF inhibitors. Expression of IL-23 and autophagy genes in all samples was analyzed using quantitative RT-PCR (SYBR green) with primers for IL23p19 and autophagy genes (ATG16L1, IRGM, MAP1LC3A, ATG5, HSPA8 and HSP90AA1).

Results: In the synovial tissues, IL-23p19 expression was consistently increased in the inflammatory samples compared to the non-inflammatory samples. There was no difference in IL-23p19 expression in AS patients as compared to non-AS SpA and other inflammatory diseases. In PBMCs, surprisingly, the expression of IL-23p19 was significantly lower in AS patients than in healthy controls with expression levels in RA patients extending over the whole range between AS patients and controls. No difference in expression of autophagy associated genes was found in the synovial tissues between the groups. In the PBMCs, there was a lower expression of ATG16L1, IRGM and HSP90AA1 in AS patients compared to healthy controls. The expression of MAP1LC3A, ATG5 and HSPA8 was not statistically different between the three groups.

Conclusion: Notwithstanding the recent evidence in gut samples of AS patients, our data do not support evidence for IL-23 expression and activation of autophagy in synovium or PBMCs of HLA-B27 positive AS patients. The production of IL-23, possibly driven by autophagy, in AS patients seems to be a tissue specific phenomenon with an important role reserved for the gut.

References

Disclosure: B. Neerinckx, None; S. Carter, None; R. Lories, Pfizer, 2.

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IL23 Overexpression Demonstrates Gut-Joint Inflammation Link and Increased Expression of Spondyloarthopathy Associated Genes in Vivo. Donald Souza II, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT.

Background/Purpose: It has been well established that a close relationship exists between gut inflammation and spondyloarthopathies. Polymorphisms in the receptor for IL23 are associated not only with ankylosing spondylitis (AS) but also with inflammatory bowel disease (IBD). AS and IBD are both associated with elevated concentrations of serum IL23. Moreover, IL23 is active at mucosal surfaces and is produced by the gut, suggesting that the intestinal mucosa could be a key site of IL23 production in spondyloarthopathy. M incircles are small circular DNA vectors which can be used in vivo to provide for long-term transient expression of transgenes without the risk of immunogenic responses that can be caused by the bacterial backbone in standard plasmids. Recently, Sherlock et al. demonstrated that overexpression of IL23 using minicircle DNA technology in the hepatocytes of mice was sufficient to lead to severe eneathal inflammation with infiltration by macrophages and neutrophils, and expansion of perioseal osteoblasts. Disease features included saccroilitis, axial enthesitis, psoriasis, and aortic root inflammation. However, no gut phenotype was reported.

Methods: IL23 minicircle DNA vector or empty vector was administered via hydrodynamic injection to adult B10R1II male mice obtained from Jackson Labs (Bar Harbor, ME). A volume equivalent of 10% body mass (~2ml) was injected IV to the lateral tail vein in 6–8 seconds to facilitate cellular uptake of material. Mice were monitored daily for signs of arthritis and skin lesions. Arthritis severity was graded using a 0–4 score per paw for a maximum score of 16. Upon sacrifice (14 and 28 days), serum was collected for cytokine analysis, paw and gut tissue for histologic assessment (8-Oleophosphat, Boulder, CO), skin, entheses and gut tissues for mRNA analysis via RT-PCR.

Results: IL-23 overexpression using minicircle DNA transfection resulted in a similar rapid and pronounced rheumatic and skin phenotype as previously reported (e.g. development of synovitis, enthesitis, and psoriatic-like skin lesions). In addition, sustained and elevated serum concentration of IL-23 is associated with intestinal inflammation. Significant and region specific gut expression of IL23 pathway associated genes IL17A, IL17F & IL22 induced by IL23 overexpression was demonstrated, with maximal expression seen in proximal ileum and lesser expression seen in colon. Furthermore, ileum expression of disease associated genes S100A8 and REG3g were increased with IL23 overexpression versus empty vector control. Histologic analysis of affected regions revealed the presence of fasciitis and mild periarticular inflammation, minimal to mild ileum inflammation and ileum displaying minimal to moderate inflammation with crypt abscesses, mild hyperplasia and inflammatory infiltrates in the lamina propria, characteristic of features seen in IBD.

Conclusion: These studies demonstrate that minicircle DNA transfection offers a powerful tool for interrogating molecular and tissue specific mechanisms in vivo and provides opportunities to dissect the influence of the IL-23 pathway on the inflammatory gut-joint link seen in spondyloarthopathies.

Disclosure: D. Souza II, Boehringer Ingelheim, 3.

1919
HLA-B27 Expression Shapes the Intestinal Microbiota. Mark Aquisith1, Phoebe Lin1, Tepal Gill2, Justine Debelius3, Patrick Stauffer4, Sean Davin5, Gal Ackerman6, Robert A. Colbert7, Rob Knight8 and James Rosenbaum9.

1Oregon Health and Science University, Portland, OR, 2NIAMS/NIH, Bethesda, MD, 3University of Colorado Boulder, Boulder, CO, 4Legacy Hospital, Portland, OR.

Background/ Purpose: The intestinal microbiota plays a central role in both health and disease. Beyond shaping local immune responses in the gut, it is increasingly clear that the microbiota also influences immune responses in the periphery. With respect to spondyloarthopathies (SpA’s), the development of protective arthritis for specific gut pathogens without the need for minimal inflammation and ileum displaying minimal to moderate inflammation with crypt abscesses, mild hyperplasia and inflammatory infiltrates in the lamina propria, characteristic of features seen in IBD.

References

Disclosure: B. Neerinckx, None; S. Carter, None; R. Lories, Pfizer, 2.

References

Disclosure: L. M. van Duivenvoorde, None; M. N. van Tok, None; D. L. Baeten, None.
contribution of defined bacteria to B27-mediated SpA and to identify their contribution of defined bacteria to B27-mediated SpA and to identify their biological mechanisms by which HCQ might delay disease onset or flares is not well understood.

Conclusion: These pilot findings suggest that cell bound complement activation products (C4d deposition on erythrocytes [EC4d] and platelets [PC4d]) in the monitoring of disease improvement in systemic lupus erythematosus (SLE) and urinary TWEAK were significantly associated with future disease activity. After adjusting for the time to follow-up visit, urinary TWEAK was linear with a 1 standard deviation (SD) increase in TWEAK being associated with a 0.56 increase in mean SLEDAI (p = 0.0006).

In a similar analysis focusing on renal disease activity, a 1 SD increase in the IFN signature was associated with a mean renal SLEDAI increase of 0.11 (p = 0.04). The Neutrophil signature remained consistent at a similar level as for overall disease activity, and the relationship between renal SLEDAI score and urinary TWEAK was linear with a 1 SD increase in TWEAK being associated with a 0.25 increase in mean renal SLEDAI (p = 0.0001).

Conclusion: BAAF gene transcript, LDG-associated Neutrophil gene signature, and high levels of urinary TWEAK appear to be independently and additively associated with disease activity. Our results suggest that the association between IFN and overall disease activity is due to the association between IFN and BAAF. Our results also suggest that an observed association between PC and disease activity is due to confounding by race. Thus, given that biomarkers are correlated with each other and other risk factors for disease, it is important to adjust for confounding when assessing biomarker/disease relationships.

Disclosure: L. S. Magder, None; E. Zollars, Biogen Idec; J. Bienkowska, Biogen Idec; M. Staubuff, None; S. Davis, None; G. Ackermann, None; R. A. Colbert, None; R. Knight, None; J. Rosenbaum, None.

Background/Purpose: Multiscale gene transcripts and proteins in blood or urine have been observed to correlate with disease activity in SLE. However, some observed associations might be spurious, due to confounding by correlation with other biomarkers or patient characteristics. In this study, we explored the relationship between six proposed biomarkers and SLE activity over a 1 year period while controlling for potential confounding variables.

Methods: At an initial visit, two proteins and four gene transcripts (anti- 

Conclusions: Predicting SLE Disease Activity in the Next Year Based on Measures of Four Gene Transcripts and Two Proteins.

Laurence S Magder1, Eric Zollars2, Jadwiga Bienkowska3, Chris Stebbins4, Carrie Wagner5, Linda Burkly6, Nicolas Wisiacki7, Ann Ranger4 and Michelle Petri8. University of Maryland School of Medicine, Baltimore, MD, 2Johns Hopkins University School of Medicine, Baltimore, MD, 3Biogen Idec Inc., Cambridge, MA, 4Biogen Idec, Cambridge, MA, 5Formerly with Biogen Idec, Cambridge, MA.

Background/Purpose: Multiple gene transcripts and proteins in blood or urine have been observed to correlate with disease activity in SLE. However, some observed associations might be spurious, due to confounding by correlation with other biomarkers or patient characteristics. In this study, we explored the relationship between six proposed biomarkers and SLE activity over a 1 year period while controlling for potential confounding variables.

Methods: At an initial visit, two proteins and four gene transcripts/nucleotide signatures were measured in 280 SLE patients. Levels of the BAAF gene transcript, plasma cell (PC) gene signature, IFN gene signature, and an LDG-associated Neutrophil gene signature were measured in PAX-gene preserved peripheral blood by global microarray and qPCR. For proteins, BAAF was measured in serum and TWEAK in urine (both by ELISA). Disease activity during the next year was quantified by SELENA-SLEDAI and BILAG. Non-linear relationships between biomarker levels and disease activity were also explored.

Results: In univariate analyses, all markers analyzed except BAFF protein were significantly associated with future disease activity. After controlling for race, the PC signature was no longer significantly associated. After controlling for BAAF mRNA levels, the IFN signature was no longer significantly associated. Controlling for sex, race, and other biomarkers we found that: 1) a 1 standard deviation (SD) increase in BAAF was associated with a mean SLEDAI increase of 0.26 in the follow-up (p = 0.0034), 2) those patients within the top 15% of the Neutrophil gene signature expression had a 0.66 higher mean SLEDAI during follow-up (p = 0.0056), and 3) the relationship between the SLEDAI score and urinary TWEAK protein was constant until the 85th percentile of TWEAK after which a 1 SD increase in TWEAK was associated with a 0.58 increase in mean SLEDAI (p = 0.0006).

In a similar analysis focusing on renal disease activity, a 1 SD increase in the IFN signature was associated with a mean renal SLEDAI increase of 0.11 (p = 0.04). The Neutrophil signature remained consistent at a similar level as for overall disease activity, and the relationship between renal SLEDAI score and urinary TWEAK was linear with a 1 SD increase in TWEAK being associated with a 0.25 increase in mean renal SLEDAI (p = 0.0001).

Conclusion: BAAF gene transcript, LDG-associated Neutrophil gene signature, and high levels of urinary TWEAK appear to be independently and additively associated with disease activity. Our results suggest that the association between IFN and overall disease activity is due to the association between IFN and BAAF. Our results also suggest that an observed association between PC and disease activity is due to confounding by race. Thus, given that biomarkers are correlated with each other and other risk factors for disease, it is important to adjust for confounding when assessing biomarker/disease relationships.

Disclosure: L. S. Magder, None; E. Zollars, Biogen Idec; J. Biewkowska, Biogen Idec; M. Staubuff, None; S. Davis, None; G. Ackermann, None; R. A. Colbert, None; R. Knight, None; J. Rosenbaum, None.

The Deposition of Complement C4d Split Product on Platelets and Erythrocytes Correlate with Disease Activity and Improvement in Systemic Lupus Erythematosus.

Joan T. Merrill1, Alkaterini Thanou2, Stan Kamp3, John Conklin4, Deren Barker5 and Thierry Dervieux6. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: We sought to evaluate the usefulness of cell bound complement activation products (C4d deposition on erythrocytes [EC4d] and platelets [PC4d]) in the monitoring of disease improvement in systemic lupus erythematosus (SLE).

Methods: 58 patients with SLE from the Oklahoma Lupus Cohort were evaluated at two visits (baseline and follow-up) with the stipulation that there must be at least mild/moderate disease activity, in the clinician’s opinion, at the first visit. Standard of care treatments were given. Clinical assessments included the Systemic Lupus Erythematosus Disease Activity Index without the complement and anti-dsDNA descriptors (non serologic SLEDAI or ns-SLEDAI) and the British Isles Lupus Assessment Group (BILAG) 2004 index. Serum C3 and C4 levels were measured with nephelometry. EC4d and PC4d were determined using flow cytometry (expressed as mean fluorescence intensity [MFI], and natural log transformed). Statistical analysis included linear regression, and multivariate linear mixed effect models using a random intercept and fixed slope.

Results: At baseline, mean ns-SLEDAI score was 6.4 ± 0.4 while the cumulative BILAG multorgan score was 10.3 ± 0.9. At baseline, C3 and C4 levels were negatively associated with disease activity using the ns-SLEDAI score (<0.04) but less consistently with the BILAG index score (p = 0.06). Baseline natural log transformed EC4d and PC4d levels were both positively and significantly associated with the SLEDAI and BILAG scores (p = 0.05). At the time of the follow-up visit (median 1.5 month, range 1–9 months from the baseline visit), there was a significant decrease in the SLEDAI (average decrease = 2.4 ± 0.4) and BILAG (average decrease = 3.1 ± 0.9) compared to baseline with linear mixed effects models indicating greater clinical improvement associated with the time to follow-up visit (Table). After adjusting for the time to follow-up, linear mixed effects model analysis revealed that the change in C3 or C4 levels correlated with the change in BILAG index scores (p = 0.03) but less well with the ns-SLEDAI score (p = 0.10). In contrast, the change in EC4d and BC4d correlated with the clinical change on both instruments (p < 0.03). Finally, multivariate analysis of the change in the BILAG index score with PC4d, serum C3 and C4 as predictors (after adjusting for the time to follow-up) revealed that PC4d was associated with change in disease activity (slope estimate = 1.80 ± 0.76; p = 0.02) while C3 and C4 were not (p > 0.7).

Conclusion: These pilot findings suggest that cell bound complement activation products could provide a sensitive marker for SLE disease improvement which might be useful for early optimization of treatment dosing.

Table. Linear Mixed Effects Model Estimates

<table>
<thead>
<tr>
<th>Non-serologic SLEDAI score</th>
<th>BILAG Index score</th>
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<tbody>
<tr>
<td>Mths since baseline</td>
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<tr>
<td></td>
<td>0.66 ± 0.18 p &lt; 0.01</td>
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<tr>
<td>Complement C3 (mg/dL)</td>
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<td></td>
<td>-0.02 ± 0.01 p &lt; 0.12</td>
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<tr>
<td>Complement C4 (mg/dL)</td>
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<td></td>
<td>-0.06 ± 0.03 p &lt; 0.11</td>
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<tr>
<td>EC4d (Log. net MFI)</td>
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<td></td>
<td>0.08 ± 0.01 p &lt; 0.04</td>
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<tr>
<td>PC4d (Log. net MFI)</td>
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<td></td>
<td>0.02 ± 0.01 p &lt; 0.04</td>
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Hydroxychloroquine Use Is Associated with Decreased Soluble TNF Receptor Levels in SLE Patient Samples.

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disorder with a waxing and waning clinical course. Hydroxychloroquine (HCQ) is a well-tolerated and effective antimalarial medication which decreases disease flares and delays damage accrual in SLE. Additionally, a pre-disease study has shown that HCQ can potentially be useful preventative therapy for delaying the onset of SLE. The exact mechanism by which HCQ might delay disease onset or flares is not well understood. One major obstacle of HCQ mechanistic studies is the confounding effects from other major immune modulating therapies used by SLE patients.
patients. Our goal is to elucidate the effects of HCO on cellular changes and circulating soluble mediator concentration without the confounding effects of other major immunosuppressants (IS) in human lupus patients in vivo.

**Methods:** As part of the Biomarkers of Lupus Disease (BOLD) study, 103 patients donated baseline blood samples of whom 41 had transient IM steroid therapy, then all IS and some hydroxychloroquine treatments stopped. Patients were followed until flare. Eligibility criteria included (≥ 4 ACR SLE classification criteria and SLEDAI > 6 or BILAG = 2 B or 1 A scores. Cellular and immunophenotyping, and soluble mediators, including 52 cytokines, chemokines, and soluble receptors, were measured over time using xMAP multiplex technology and sandwich ELISA. Significant differences were determined using non-parametric tests. A longitudinal analysis was performed using mixed generalized linear models.

**Results:** At baseline, SLE patients taking HCO (n = 27) had significantly lower levels of soluble TNFRI (median, 112.67 pg/mL; interquartile range [IQR], 33.86 pg/mL–1,046 pg/mL) compared to SLE patients not taking HCO (n = 10) (TNFRI median, 186.63; IQR, 120.09–301.44; TNFRII median, 519.6; IQR, 332.16–641.00; p-value < 0.05). In addition to the soluble TNFRs, SLE patients taking HCO had significantly lower frequency of CD194hi naive B cells population (median, 1.54%; IQR, 0.15%–5.48%) compared to SLE patients not taking HCO (median, 5.57%; IQR, 2.03%–13.19%; p-value < 0.05). SLE patients that stayed on HCO during the six month study (n = 17) retained their low levels of TNFRII. Patients who had never taken HCO or were taken off of HCO (n = 20) showed a significant reduction in their TNFRII levels at the time of the next flare (p-value < 0.05). TNFRII levels did remain higher than those observed in individuals that remained on HCO.

**Conclusion:** HCO may contribute to disease suppression via an effective reduction in soluble TNF and other chemokines receptor levels. These findings suggest a likely focus for further pathophysiological studies of SLE.

**Disclosure:** R. Lu, None; A. Przebinda, None; M. E. Munroe, None; J. M. Guthridge, None; J. T. Merrill, Pfizer Inc; J. A. James, None.

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**1923**

**Vitamin D Restores Lupus Myeloid Angiogenic Cell Function Via Down-Regulation of IP-10/CXCL10**

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**Background/Purpose:** Endothelial repair is important for the maintenance of vascular integrity and is impaired in patients with SLE. Myeloid angiogenic cells (MACs) contribute to endothelial repair via paracrine secretion of pro-angiogenic factors. These cells express vitamin D receptors (VDR) and so may be modulated by vitamin D status. Given the prevalence of vitamin D deficiency in SLE we aimed to determine whether vitamin D could restore MAC function in lupus.

**Methods:** SLE patients were screened for vitamin D deficiency (25(OH)D <20ng/ml) using LC-MS and deficient patients were treated with high-dose cholecalciferol for 3 months. Myeloid angiogenic cells (MACs) were cultured from PBMCs of vitamin D deficient lupus patients (or healthy controls, HC) for 7 days. 1,25(OH)2D3 (calcitriol) 10nM or vehicle was added to day 1 and replaced when the media was changed. Myeloid marker expression was measured using RT-qPCR. MAC migration towards SDF-1 was assessed using Transwell assays. Conditioned media from MACs was used to establish the cutoffs yielding 95% specificity for C3, C4, CBCAPS, reduced complement levels and SLE disease activity.

**Results:** Vitamin D deficient SLE patients had an increased number of MACs compared to controls (p = 0.04). Despite this, these cells had impaired migratory capacity (p = 0.006) and a trend toward reduced angiogenic capacity (p = 0.13). Culture with vitamin D had no effect on lupus MAC migration.

Vitamin D significantly increased the number of MACs in vitro, and in vivo after the patients were treated (p = 0.04 and p = 0.03 respectively). MACs expressed surface markers consistent with M2 macrophages. The expression CD206 and CD68 was significantly increased in SLE and reversed by vitamin D. HAOEC network formation was not affected by vitamin D directly but media from vitamin D-treated MACs significantly increased angiogenesis toward that seen in HCs (p = 0.01). There was no correlation between MAC number and angiogenesis. IP-10 has previously been reported to be anti-angiogenic and vitamin D significantly reduced IP-10 expression by MACs (p = 0.001). Blockade of IP-10 in the angiogenesis model restored the angiogenic capacity of MACs (figure).

**Conclusion:** MACs are important for endothelial repair and are dysfunctional in SLE. The addition of vitamin D in vitro restores the phenotype of the cells towards that of healthy subjects. Lupus MACs show reduced angiogenic capacity and vitamin D restores this via the down-regulation of the anti-angiogenic cytokine IP-10. Restoration of endothelial repair mechanisms is an important target to reduce vascular damage in SLE and vitamin D is a novel agent to improve MAC function.

**Disclosure:** J. A. Reynolds, None; D. W. Ray, None; Y. Alexander, None; I. N. Bruce, None.

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**Cell Bound Complement Activation Products Have Higher Sensitivity Than Serum C3 and C4 Levels in Systemic Lupus Erythematosus**

**Authors:** Rosalind Ramsey-Goldman1, Richard Furie2, Chaim Putnamman3, Anka Askana4, Jill P. Buyon5, Kenneth Kallanjan6, W. Winn Chatham7, E Massarotti8, Kyriakos A. Kirou9, A. Weinstein10, Puja Chitkara11, Susan Manzi12, Joe Ahearn13, Leilani Wolovery14, John Conklin14, Tyler O’M alley14, Claudia Ibarr14, Derren Barren14 and Thierry Dervieux14

**Institutes:** 1Northwestern University, Chicago, IL, 2North Shore-LIJ Health System, Great Neck, NY, 3Albert Einstein College of Medicine, Bronx, NY, 4Colombia University, New York, NY, 5New York University School of Medicine, New York, NY, 6UCSD School of Medicine, La Jolla, CA, 7University of Alabama at Birmingham, Birmingham, AL, 8Brigham and Women’s Hospital, Boston, MA, 9Hospital for Special Surgery, New York, NY, 10Washington Hospital Center, Washington, DC, 11Sharp Memorial Hospital, San Diego, CA, 12Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 13Wes Penn Allegheny Health System, Pittsburgh, PA, 14Exagen Diagnostics, Inc., Vista, CA.

**Background/Purpose:** Elevated levels of cell bound complement activation products (CBCAPS) have been established as valuable biomarkers in the diagnosis of Systemic Lupus Erythematosus (SLE). In this study, we compared the sensitivity of CBCAPS to reduced complement C3 and C4 proteins levels in SLE. We also evaluated the relationship between elevated CBCAPS, reduced complement levels and SLE disease activity.

**Methods:** A total 288 SLE patients (mean age 41±1 years, 92% females) all meeting the 1982 American College of Rheumatology SLE classification criteria were enrolled. Serum complement C3 and C4 protein levels were determined using immunoturbidimetry while complement C4d fragment deposited on erythrocytes (ECD4) and B-lymphocytes (BCD4) were determined using flow cytometry (and expressed as net mean fluorescence intensity [MFI]). A group of 476 subjects comprising 274 patients with other rheumatic diseases and 202 healthy subjects was used to establish the cutoffs yielding 95% specificity for C3, C4, EC4d and BC4d. Among SLE subjects, disease activity was determined using the...
Systemic Lupus Erythematosus Disease Activity Index SELENA Modification (SELENA-SLEDAI) score (without low complement and anti-dsDNA reactivity components). Difference in sensitivity (while controlling for specific specificity) was evaluated using χ2 test.

Results: Reduced C3 or C4 were both 32% sensitive for SLE (95% specific). In contrast, EC4d at a cutoff above 14 net MFI yielded 45% sensitivity (95% specific) while BC4d above 60 net MFI yielded 54% sensitivity (95% specific) (p = 0.002). Elevated EC4d or BC4d (above their respective cutoffs as above) yielded a 22% higher sensitivity (66%) than reduced C3 or C4 (44%). Among 273 SLE patients with evaluable SELENA-SLEDAI scores, the median score was 1 (range 0-23). Higher level of disease activity resulted in a higher proportion of patients testing positive for elevated CBCAPS (p = 0.027) and reduced complement (p = 0.002) (Figure).

A more severe Lupus disease (SELENA-SLEDAI score >0) showed a difference in sensitivity was 26% greater for elevated CBCAPS (62%) than for reduced complement C3 or C4 (36%) (p < 0.001). The difference in sensitivity remained higher (17%) for CBCAPS compared to low complement among SLE having a SELENA-SLEDAI score greater than 6 points but without reaching statistical significance (p = 0.21).

Conclusion: Among SLE patients, elevated CBCAPS have higher sensitivity than reduced C3 or C4. The higher sensitivity of CBCAPS is particularly significant among SLE with less active disease, and this supports the diagnostic utility of these markers for SLE.

Disclosure R. Ramsey-Goldman, None; R. Furie, Exagen, 2; C. Putterman, Exagen, 2; Exagen, 5; A. Askasani, Exagen, 2; J. P. Buyon, Exagen, 2; K. Kalunian, Exagen, 2; Exagen, 5; W. W. Chatham, None; E. Massarotti, None; K. A. Krou, None; A. Weinstein, Exagen, 1; Exagen, 6; Exagen, 5; P. Chitkara, Exagen, 8; S. Manzi, Exagen, 5; J. A. Ahearn, Exagen, 5; J. A. Ahearn, Exagen, 5; J. L. Wolover, Exagen, 3; J. Conklin, Exagen, 3; T. O’Malley, Exagen, 3; C. Ibarra, Exagen, 3; D. Barken, Exagen, 3; T. Dervieux, Exagen, 3.


Hydroxychloroquine (HCQ) is now recognized as an important treatment of systemic lupus erythematosus (SLE). Blood HCQ levels ([HCQ]) can be quantified by high performance liquid chromatography (HPLC). [HCQ] varies widely between individual: a pharmacokinetic/pharmacodynamic (PK/PD) relation has been found in different situations, and very low [HCQ] is a simple marker of non-adherence to treatment (2). Accordingly, the interest in the [HCQ] measurement has recently grown, but little is known regarding the determinants of variation of [HCQ].

Methods: Retrospective analyses of our databases 000 using the PLUS study (1) to determine the relationship between [HCQ] and different factors, including the daily dosage regimen, the weight and height, the renal function, the drug interactions, the smoking status and the ethnicity. Non-adherent patients ([HCQ] <200 ng/ml) were excluded.

Results: To have homogenous pharmacological data, we restricted the analyses to the 509 patients treated with 400 mg/day. There was no correlation between [HCQ] and ethnicity or between [HCQ] and smoking. The median [HCQ] was 913 ng/ml (range: 213-2067), 951 (541–1701), and 916 (208–3316) in the patients who received enzyme inhibitors, enzyme inducers or none of these two groups of drugs respectively (p = 0.07). Similarly, we did not find any significant differences in [HCQ] whereas the patient received or not antacids.

In multivariate analysis, higher BMI (p = 0.008), absence of treatment with corticosteroids (p = 0.04), higher delay between the last tablet intake and the measurement of [HCQ] (p = 0.031), lower platelet (p = 0.001) and neutrophil counts (p < 0.001) and higher estimated creatinine clearance (p < 0.001) were significantly associated with lower [HCQ].

Since patients with serum creatinine clearance lower than 60 ml/min were excluded from the PLUS study, we also studied 22 SLE patients with chronic renal insufficiency who were also treated with 400 mg/d of HCQ. Their median concentration of creatinine was 52 mg/d and their median [HCQ] was significantly higher than those of the 509 patients from the PLUS study: 1338 ng/ml (504-2229) versus 917 (208-3316) (p < 0.001). Finally, we studied 2 patients on long-term dialysis. Their [HCQ] did not change significantly after the dialysis and [HCQ] in the dialysis bath was undetectable for both patients (<30 ng/ml).

Conclusion: We report for the first time a comprehensive analyze of determinants of [HCQ]. Since this blood measurement is increasingly used, such data might be useful for clinicians.


Disclosure: M. J. Aliou1, None; L. Galicher3, None; O. Aumaitre3, None; C. Frances4, None; V. Le-Guen4, None; F. Liote2, None; A. Smail5, None; L. Hulot7, None; J. Stirnemann7, None; O. Ackermann8, None; T. Papo, None; K. Sacre9, None; O. Fain9, None; J. E. Kahn, None; J. Pourrat, None; L. Sailler, None; F. Ackermann, None; T. Papo, None; K. Sacre, None; O. Fain, None; J. Stirnemann, None; P. Caboc, None; G. L. Le-Mesurier, None; J. Cohen-Bittan, None; J. Hulot, None; Z. Amoura, None; J. C. Piette, None; N. Costedoat-Chalumeau10.

ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Clinical Aspects and Therapeutics II: Approaches to Cardiac and Vascular Manifestations in Systemic Sclerosis
Monday, November 17, 2014, 4:30 PM–6:00 PM


Calcinosis and acro-osteolysis are frequent in systemic sclerosis (SSc). They can be assessed by nailfold videocapillaroscopy (NVC). Our aim was to determine whether calcinosi and acro-osteolysis are associated with specific NVC features.

Methods: Consecutive SSc patients were consecutively included during a 24-month period. NVC was performed and analysed by one investigator (J.A.) blinded for the results of X-rays and classified as early, active and late pattern (2). Two independent investigators carried out radiological assessment on standard anteroposterior views of the hands and wrists (LM, MS), followed
Results: 155 patients were included, with a mean age of 57±13 years and a mean disease duration of 9±5 years; 65 (42%) had the diffuse cutaneous subset. 15 (10%) patients had a normal, 46 (30%) an early, 47 (30%) an active, and 47 (30%) an active NVC pattern. Using logistic regression analysis, the kappa coefficient of inter-rater agreement was 0.75. 43 (28%) patients had calcinosis, of whom 26 (17%) had moderate or severe lesions; 25 (16%) patients had acro-osteolysis; of whom 13 (8%) had severe lesions. Patients with calcinosis were more likely to have acro-osteolysis (p = 0.02), but Cramer’s V coefficient of association was 0.19, supporting low association between these variables. Patients with calcinosis and acro-osteolysis were more likely to have the late NVC pattern (p = 0.04 and p = 0.001 respectively). In line with this result, significant capillary loss was observed in patients with calcinosis (2.8±3.1 vs. 5.6±2.27 capillaries/finger, p = 0.001) and acro-osteolysis (2.8±3.1 vs. 5.6±2.27 capillaries/finger, p = 0.001). Of note, association with the late NVC pattern was stronger (p = 0.01) and capillary loss was more pronounced in patients with moderate or severe calcinosis (p = 0.001). No association was observed between calcinosis and irregular enlargement of capillaries (neoangiogenesis). Conversely, neoangiogenesis was more frequently observed in patients with severe acro-osteolysis (p = 0.03). M ultivariate logistic regression analysis confirmed the independent association between calcinosis (p = 0.03) and acro-osteolysis (p = 0.01) with the late NVC pattern, together with a modified Rodnan skin score >14 (p = 0.008) and positive antiproteinase-1 antibodies (p = 0.01).

Conclusion: We show for the first time an independent association between calcinosis/acro-osteolysis and the late NVC pattern, and in particular, with reduced number of capillaries. This result suggests that these lesions may be related to the severe capillary loss observed at this stage. A cro-osteolysis, but not calcinosis, was associated with neoangiogenesis, which may suggest an attempt to compensate bone resorption. Further studies are now needed to determine whether capillaroscopy may predict the further occurrence or worsening of these lesions.

Disclosure: J. Avouac, None; L. Morardet, None; M. Sammour, None; A. Kahan, None; A. Feydy, None; Y. Allanore, None.

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A Retrospective Look at the Recurrence of Digital Ulcers in Patients with Scleroderma after Discontinuation of Oral Treprostinil. Aimi A. Shah1, Elena Schiopu2, Soumya Chatterjee3, Mary Ellen Csuka4, Tracy Fresch5, Avariya Goldberg6, Robert F. Spiera7, Stanford L. Peng8 and Virginia D. Steen9, Joohs Hopkins University School of Medicine, Baltimore, MD, 1University of Michigan, Ann Arbor, MI, 2Cleveland Clinic, Cleveland, OH, 3Medical College of Wisconsin, Milwaukee, WI, 4University of Utah, Salt Lake City, UT, 5North Shore-LIJ Health System, Great Neck, NY, 6Hospital for Special Surgery, New York, NY, 7Baylor Research Institute/Virginia Mason, Seattle, WA, 8Georgetown University Medical Center, Washington, DC.

Background/Purpose: Ischemic digital ulcers (DU) occur in over 40% of systemic sclerosis (SSc) patients. Treprostinil diolamine, a newer prostacyclin analog that has been developed for oral delivery, improves cutaneous perfusion and temperature in SSc. A large randomized, double-blind, placebo-controlled clinical trial of treprostinil was conducted in SSc patients with DU. While this trial did not meet the desired endpoint (change in net ulcer burden at 20 wks), there was a significant improvement in several secondary endpoints that measured Raynaud’s severity. Subjects enrolled into an open label extension study (DISTOL-EXT) after the clinical trial; after termination of DISTOL-EXT, all participants were withdrawn from oral treprostinil. We investigated whether active, indeterminate, and total DU burden increased in DISTOL-EXT participants after they discontinued treprostinil.

Methods: In a multi-center, retrospective study, medical records for the year after discontinuation of treprostinil were reviewed. Data from three routine clinical visits were abstracted into a template designed a priori to capture information on the number of active and indeterminate DU at the end of the extension study and at subsequent visits. Participants who did not have a subsequent visit with documentation of DU status were excluded. We examined the number of new DU that developed from the end of the extension study (baseline) through the first year after discontinuation of treprostinil. The number of active, indeterminate and total DU 3–6 months (time A) and >6–12 months (time B) after discontinuation of treprostinil were compared to baseline by the paired t-test.

Results: Fifty-one subjects from 9 SSc Centers were included for analysis. At the conclusion of the treprostinil extension study, the mean number of active, indeterminate and total DU was 0.25 (SD 0.63), 0.22 (SD 0.54) and 0.47 (SD 0.78), respectively. The number of active DU increased from baseline to time A (mean 1.62, p = 0.004, N = 23) and time B (mean 1.03, p = 0.076, N = 30). The number of indeterminate DU increased from baseline to time B (mean 0.42, p = 0.03, N = 30) but not time A. The total DU burden increased significantly from baseline to time A (mean 2.1, p = 0.002, N = 23) and time B (mean 1.45, p = 0.01, N = 30) as shown in the Figure. The majority of patients required intensive vasodilator therapy and pain medication; calcium channel blockers (60.8%), PDE 5 inhibitors (21.6%), any pain medication (58.8%), opioids (33.3%). Three patients were hospitalized for complications from digital ulcers, and 4 patients required surgical intervention. Five patients were subsequently diagnosed with pulmonary hypertension.

Conclusion: Total DU burden increased significantly after discontinuation of oral treprostinil diolamine. These data provide supportive evidence of a beneficial effect of oral treprostinil diolamine for the vascular complications of SSC.

Disclosure: A. A. Shah, United Therapeutics, 2; E. Schiopu, United Therapeutics, Aetion, MedImmune, Celgene, 2; United Therapeutics, 8; S. Chatterjee, United Therapeutics, 2; M. E. Csuka, United Therapeutics, 2; T. Fresch, United Therapeutics, 2; A. Goldberg, United Therapeutics, 2; R. F. Spiera, United Therapeutics, 2; S. L. Peng, United Therapeutics, 2; V. D. Steen, Aetion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berghing, 2, InterGene, 2, Bayer, 5.

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A Multicenter, Prospective Cohort Study Using Nailfold Videocapillaroscopy and Other Clinical Characteristics to Determine the Risk of Developing New Digital Ulcers in Patients with Systemic Sclerosis. Vanessa Smith1, Maurizio Cutolo2, Anane Hercik3, Oliver Distler4, Mike Becker5, Emma Beltran6, Patrick Carpentier7, Clodoveo Ferri8, Murat Inanc9, Panayiotis Vlachoyiannopoulos10, Harbajan Chadha-Boreham11, Emmanuelle Cottell12, Thomas Pfister13, Daniel Rosenberg14 and Juan Torres on behalf of the CAP study investigators12, 1Ghent University Hospital, Ghent, Belgium, 2Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, 3Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, 4Zurich University Hospital, Zurich, Switzerland, 5Charité - Universitätsmedizin Berlin, Germany, 6Hospital La Fe, Valencia, Spain, 7La Tronche Hospital, Grenoble, France, 8University of Modena & Reggio E, Modena, Italy, 9Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, 10School of Medicine, National University of Athens, Athens, Greece, 11Aetion Pharmaceuticals Ltd, Allschwil, Switzerland, 12Syntax for Science SL, Basel, Switzerland.

Background/Purpose: Digital ulcers (DU) are painful and disabling and affect almost 30% of systemic sclerosis (SSc) patients. Nailfold videocapillaroscopy (NVC) non-invasively assesses SSc-related micro-angiopathy and may be useful in predicting clinical progression of digital vasculopathy, especially DU. 1-4 The objective of this study was to identify NVC variables and clinical characteristics which predict the occurrence of new DU in SSc patients.

Methods: International, prospective, multicenter cohort study in SSc. Eligibility was not restricted by medication use. SSc patients (American College of Rheumatology/L.E.roy and M.edger) were enrolled in two strata:
‘DU History’ and ‘No DU History’. The No DU History patients had early disease (<2 years).

Variables were classified into bundles for statistical analysis: demographics, SSc clinical characteristics, DU characteristics, NVC characteristics and other clinical characteristics. NVC variables for fingers II–V were evaluated locally in a standardized way. Patients were followed up to 6 months for new DUs (confirmed by the investigator). Univariable Logistic Regression (ULR) was performed on all variables and Multivariable Logistic Regression (MLR) was performed within and across bundles to assess statistical significance (Wald chi-square p<0.15 for linear and p<0.05 for quadratic) and discriminatory ability (receiver operator characteristic area under the curve [ROC AUC]). Clinical relevance to predict new DU in 6 months was portrayed by model performance characteristics in a binary risk chart and two-by-two tables at different risk probability thresholds.

Results: Of the 623 patients enrolled in 59 centers, 591 had data on DU outcome (new DU or no new DU) during the study. 486 (79%) patients had a DU history, of whom 103 (22%) developed new DU. 123 (21%) patients had no DU history, of whom 5 (4%) developed new DU. Due to low event numbers in the no DU history group, the present analysis focuses on the DU history stratum. The mean age was 54.0 years, 79.5% were females, and 59.8% patients had limited cutaneous SSc. The final model consisted of the following 3 co-variables to predict the occurrence of DU within 6 months: number of DU at baseline visit categorized into 0, 1, 2 and ≥ 3, mean number of capillaries in the middle finger of the dominant hand (evaluated on two adjacent fields in the middle of the nailfold) and presence/absence of critical digital ischemia at enrolment. AUC of this model was 0.735 (C.I. 0.681–0.785). Internal validation through bootstrap generated AUC 0.635 (C.I. 0.510–0.756). At a probability threshold of 37.3%, the binary risk table shows a specificity of 90.6%, a sensitivity of 39.4%, a negative predictive value (NPV) of 83.8% and a positive predictive value (PPV) of 54.9%.

Conclusion: The CAP study is the first and largest prospective study producing a simple prognostic model with acceptable performance which can be useful in the management of patients with history of DU.

References


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Echocardiographic Phenomics for Novel Classification of Cardiac Involvement in Systemic Sclerosis. Monique Hinrichs, Vlasta Daruwalla, Lauren Beusink-Nelson, Sofia Podusky, Mary A. Carns, John Varga and Sanjiv J. Shah. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Traditional studies of systemic sclerosis (SSc) cardiac involvement have examined one or a few echocardiographic (echo) variables; however, cardiac involvement in SSc can be multi-faceted and heterogeneous. We hypothesized that evaluation of dense quantitative echo phenotypic data using repurposed genetic analytic software would allow for novel classification of SSc cardiac involvement.

Methods: We studied 377 patients with SSc enrolled in the Northwestern Scleroderma Program. All patients underwent comprehensive echo with Doppler and tissue Doppler imaging using a standardized protocol for image acquisition and interpretation. A total of 57 unique, quantitative echo phenotypes were standardized to mean = 0 and SD = ±1. The quantitative phenotypic data was entered into gene expression analysis software (Cluster), and a phenotype heatmap (“pheno-map”) was generated (TreeView). Cluster groups (“pheno-groups”) were defined based on the resultant hierarchical dendogram. We used linear, logistic, and Cox regression analyses to determine differences in clinical, laboratory, pulmonary function testing, and survival characteristics among pheno-groups.

Results: The mean ± SD age was 51 ± 13 years, 82% were female, 51% had limited cutaneous SSc, 32% had diffuse cutaneous SSc, and 17% had other forms of SSc (e.g., overlap syndromes). Prevalence of SSc complications were as follows: PAH in 9%, ILD in 17.5%, and LV systolic dysfunction (EF < 50%) in 4%. After the phenomapping analysis, 4 distinct, mutually exclusive pheno-groups were identified. The 4 groups differed significantly on clinical characteristics and outcomes. The pheno-groups did not differ by SSc subtype (limited vs. diffuse cutaneous SSc), but autoantibodies did differ by pheno-group (e.g., anti-centromere antibody was most prevalent in pheno-group #4 [38%]). PAH prevalence differed across groups (highest [18.5%] in pheno-group #1, P = 0.002). Clinical ILD did not differ among groups (P = 0.24), but FVC and DLCO were lowest in pheno-group #1 (P < 0.001). LV, RV, and left atrial mechanics were also worse in pheno-group #1 (P < 0.02 for all comparisons). Pheno-group #1 had the highest risk for death (HR 6.0, 95% CI 1.3–26.5; P = 0.024 after adjustment for age, sex, SSc subtype, disease duration, ILD, and PAH).

Conclusion: Hierarchical cluster analysis of high-density, quantitative echo phenotypes results in novel, clinically relevant classification of cardiac structure/function in SSc. Further research into the identified echo pheno-groups of SSc may enhance pathophysiologic insight into SSc cardiac involvement.

Figure. Echocardiographic Phenotype Heatmap “Pheno-Map” (top panel) and Cumulative Hazard for Death by Pheno-Group (bottom panel)

Disclosure: M. Hinrichs, Gilead Science, 9; V. Daruwalla, None; L. Beusink-Nelson, None; S. Podusky, None; M. A. Carns, None; J. Varga, None; S. J. Shah, None.

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The Value of Repeated Nailfold Capillaroscopy in Raynaud’s Phenomenon in Daily Practice: A Follow-up Study in the Netherlands. B. de Boer1, J. Meij2, J. van Aken2, T.W.J. Huizinga2, A.A. Schouver2 and J.K. de Vries-Bouwstra1. 1Leiden University Medical Center, Leiden, Netherlands, 2Slaarne Ziekenhuis, Hoofddorp, Netherlands, 3Haga Hospital, The Hague, Netherlands.

Background/Purpose: Nailfold capillaroscopy is an important tool to differentiate primary Raynaud’s phenomenon (PRP) from secondary Raynaud’s phenomenon (SRP). Based on possible transition from PRP to SRP (semi)annual capillaroscopy has been advocated to detect transition to SRP as early as possible.
Objective of this study is to evaluate the additive diagnostic value of repeated nailfold capillaroscopy after one year in patients with Raynaud’s phenomenon (RP).

Methods: Patients with RP who underwent capillaroscopy at the outpatient clinic at least six months ago were invited for follow-up capillaroscopy. PRP was defined according to the definition of LeRoy (1); SRP as suspected Raynaud phenomenon, based on biopsy proven myositis, and three patients changed from sSRP to PRP due to normalization of capillaroscopy (Table 2). Thus, capillaroscopy contributed to change in diagnosis in three out of 43 patients (7%) with PRP or sSRP, all improving from sSRP to PRP.

Results: In total 107 patients with RP underwent capillaroscopy. Of these 71 underwent follow-up capillaroscopy after a mean period of 12 months (range 6–25 months). At baseline, eight (11%) patients had PRP, 28 (40%) SRP and 35 (49%) sSRP. The rate of progression from PRP to SRP was 12.5% (one of eight patients). The rate of progression from sSRP to RP was 3% (one of 35 patients). Capillaroscopy pattern changed in 21 (30%) patients: six (8%) worsened (Table 1) and 15 (21%) improved. In total five patients (7%) had a different diagnosis at follow-up, two of which based on clinical symptoms, three based on capillaroscopy pattern only: one changed from PRP to SRP, based on development of sclerodactyly, one changed from sSRP to RP based on biopsy proven myositis, and three patients changed from sSRP to PRP due to normalization of capillaroscopy (Table 2).

Conclusion: Although progression from PRP to SRP was observed in 12.5% and progression from sSRP to RP in 3%, changes in capillaroscopy did not contribute to change in clinical diagnosis in these patients. Based on the findings of this study, a follow-up capillaroscopy after one year in patients with PRP or sSRP without a change in clinical symptoms cannot be advocated. Extended follow-up in a larger population is needed to confirm this observation.


Table 1. Capillaroscopy pattern at baseline and follow-up of patients with a worsened capillaroscopy over time

<table>
<thead>
<tr>
<th>PRP Diagnosis</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>PRP</th>
<th>SSc</th>
<th>Normal/aspecific Borderline</th>
<th>Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Normal/aspecific</td>
<td>Borderline</td>
<td>PRP</td>
<td>SSc</td>
<td>Diagnosis</td>
<td>Before follow-up</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>2 Normal/aspecific</td>
<td>Borderline</td>
<td>Suspected SRP</td>
<td>Suspected SRP</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Normal/aspecific</td>
<td>Borderline</td>
<td>UCTD</td>
<td>UCTD</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Borderline</td>
<td>SSc</td>
<td>SSc</td>
<td>SSc</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Borderline</td>
<td>SSc</td>
<td>SSc</td>
<td>SSc</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Borderline</td>
<td>SSc</td>
<td>UCTD</td>
<td>UCTD</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments: Baseline: Before follow-up visit; Follow-up: Follow-up visit;

Table 2. Capillaroscopy pattern and clinical diagnosis of patients with a changed diagnosis

<table>
<thead>
<tr>
<th>PRP Diagnosis</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>PRP</th>
<th>SSc</th>
<th>Normal/aspecific Borderline</th>
<th>Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PRP</td>
<td>SSc</td>
<td>Normal/aspecific</td>
<td>Borderline</td>
<td>PRP</td>
<td>SSc</td>
<td>Diagnosis</td>
<td>Before follow-up</td>
</tr>
<tr>
<td>2 Suspected SRP</td>
<td>DM</td>
<td>Borderline</td>
<td>Borderline</td>
<td>Diagnosis</td>
<td>Before follow-up</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>3 Suspected SRP</td>
<td>PRP</td>
<td>Borderline</td>
<td>Normal</td>
<td>No symptoms</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Suspected SRP</td>
<td>PRP</td>
<td>Borderline</td>
<td>Normal</td>
<td>No symptoms</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Suspected SRP</td>
<td>PRP</td>
<td>Borderline</td>
<td>Normal</td>
<td>No symptoms</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPR primary Raynaud phenomenon, SSc systemic sclerosis, SRP secondary Raynaud phenomenon, UCTD undifferentiated connective tissue disease.

Disclosure B. de Boer, None; J. Miejs, Actelion Pharmaceuticals Ltd., 2; J. van Aken, None; T. W. J. Huizinga, None; J. van Aken, None; A. A. Schuffoer, None; J. K. de Vries-Bouwstra, None.

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Mycophenolate Mofetil (MMF) Use in Scleroderma Patients with Pulmonary Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort. Lesley A. McSkechnie, Matthew R. Lammi, Aly Rehy Fischer, Jerry A. Ollot, and Virginia D. Stem.

Background/Purpose: Systemic sclerosis (SSc) related pulmonary hypertension (PH) carries a high mortality and patients with SSc-PH related to restrictive lung disease having an even worse prognosis. Speculation regarding the potential of MMF to exert anti-fibrotic and anti remodeling effects on parenchymal lung and vascular intimal fibrosis, led us to query the possible differences in outcomes and survival between 4 groups based on forced vital capacity (FVC) and use of MMF in SSc PH.

Methods: PHAROS is a prospective registry designed to provide substantive data to recognize aspects of PH unique to SSc. For this analysis patients were stratified by an FVC of >70%, or ≤70% and evaluated on spirometry at the time of PH diagnosis by right heart catheterization (RHC) and then by MMF use greater than 6 months after the diagnosis of PH. Cyclophosphamide use was exclusionary to all groups. Calculations are derived from one-way ANOVA with Tukey’s post test or Kruskal Wallis with Dunn’s post-test. Categorical variables were compared with Chi square. These analyses were followed by Cox and stepwise backward regression analysis to assess baseline characteristics associated with risk of death and Kaplan-Meyer analysis.

Results: 256 cases from the PHAROS database matched criteria and had baseline spirometry results coincident with diagnostic RCH, of those 173 had a baseline FVC of >70% with 23 on MMF and 150 without; and 83 had a baseline FVC ≤70% with 26 on MMF and 57 without. Across groups, no differences were found in age, disease duration, racial distribution or smoking history in skin score, 6 minute walk test for distance or NYHA Class. No detectable differences were found between groups in 6-18 month interval change of baseline FVC% in MMF- groups or from post-RHC initiation of MMF in the MMF+ groups. Of interest, baseline mPAP and PVR were lower in both MMF+ groups regardless of FVC. Though survival is numerically worst with FVC<70% without MMF at 4 years, it did not quite reach statistical significance in Kaplan-Meier analysis at 4 (p = 0.03) and 6 years (p = 0.08). Survival for both MMF groups was between 70% and 82% but only 56% for the patients with a low FVC not treated with MMF. Male sex was a significant independent predictor of death in all groups especially when FVC was <70%.

Table 1. Comparison between the baseline characteristics of the four groups at time of RHC, change of FVC between baseline and 18 months at RHC and survival analyses. Values reported in mean, unless otherwise stated. * = significant. NS = not significant.

<table>
<thead>
<tr>
<th>PH Group I % (n)</th>
<th>PH Group II % (n)</th>
<th>PH Group III % (n)</th>
<th>PH Group IV % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>150</td>
<td>26</td>
</tr>
<tr>
<td>Age – yes, mean</td>
<td>56.70</td>
<td>60.33</td>
<td>53.31</td>
</tr>
<tr>
<td>Time from diagnosis in years, mean</td>
<td>6.529</td>
<td>8.864</td>
<td>6.159</td>
</tr>
<tr>
<td>Female sex %</td>
<td>69.6</td>
<td>91.3%</td>
<td>73</td>
</tr>
<tr>
<td>White race %</td>
<td>73.9</td>
<td>73</td>
<td>58</td>
</tr>
<tr>
<td>Diffuse cutaneous %</td>
<td>52.2</td>
<td>27.2%</td>
<td>58.3</td>
</tr>
<tr>
<td>Skin score</td>
<td>11.38</td>
<td>8.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Moderate to Severe Fibrosis on HRCT (%)</td>
<td>52.4 (11)</td>
<td>21 (21)*</td>
<td>65 (13)</td>
</tr>
<tr>
<td>NYHA Class III/IV % (n)</td>
<td>22.8 (5)</td>
<td>42.1 (61)</td>
<td>44 (11)</td>
</tr>
<tr>
<td>PH Group I % (n)</td>
<td>77.2 (17)</td>
<td>86.1 (25)*</td>
<td>34.8 (8)</td>
</tr>
<tr>
<td>PH Group II % (n)</td>
<td>9 (2)</td>
<td>2.1 (3)</td>
<td>47.2 (11)</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>87.43</td>
<td>82.79</td>
<td>52.08*</td>
</tr>
<tr>
<td>Change in FVC %</td>
<td>11.8</td>
<td>3.350</td>
<td>10.0</td>
</tr>
<tr>
<td>DCO % predicted</td>
<td>44.34</td>
<td>48.42</td>
<td>36.06*</td>
</tr>
<tr>
<td>FVC/DLCO Ratio</td>
<td>2.333</td>
<td>2.181</td>
<td>1.696*</td>
</tr>
<tr>
<td>MWT Distance</td>
<td>418.1</td>
<td>329.3</td>
<td>358.9</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>31.91*</td>
<td>36.82</td>
<td>31.77*</td>
</tr>
<tr>
<td>Survival at 1 year</td>
<td>95%</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Survival at 3 years</td>
<td>85%</td>
<td>56</td>
<td>70</td>
</tr>
</tbody>
</table>

Univariate Predictors of Death in All Groups, 7 survival multivariate stepwise regression

<table>
<thead>
<tr>
<th>DLCO (p = 0.0001)*</th>
<th>FVC/DLCO (p = 0.0001)*</th>
<th>FVC (p = 0.0001)*</th>
<th>mPAP (p = 0.0001)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (p = 0.01)*</td>
<td>Male sex (p = 0.0001)*</td>
<td>SKIN score (p = 0.04)</td>
<td>MMT Use (p = 0.06)</td>
</tr>
</tbody>
</table>

Univariate Predictors of Death in FVC <70% group, 7 survival multivariate stepwise regression

<table>
<thead>
<tr>
<th>DLCO (p = 0.0005)*</th>
<th>FVC/DLCO (p = 0.0001)*</th>
<th>FVC (p = 0.0001)*</th>
<th>MMT Use (p = 0.0007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (p = 0.007)</td>
<td>Male sex (p = 0.0001)*</td>
<td>SKIN score (p = 0.04)</td>
<td>MMT Use (p = 0.07)</td>
</tr>
</tbody>
</table>
Conclusion: The trend for improved survival in patients with PH with FVC <70% who were treated with MMF even in the absence of improvement of FVC is intriguing. Whether it has an effect on pulmonary artery remodeling should be considered. These findings warrant prospective controlled investigations of MMF in SSc PH particularly in those with restrictive lung disease.

Disclosure: L. A. Saketkoo, None; M. R. Lammi, None; A. Fischer, Actelion Pharmaceuticals US, 5, Gilead Sciences, 5, InterMune, 5, Gilead Sciences, 8; J. A. Molitor, UCB, 2, Actelion Pharmaceuticals US, 2, United Therapeutics, 5, Gilead Science, 6, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berhing, 2, Intermune, 2, Bayer, 5.

ARHP Concurrent Abstract Session 1932

Increasing Access to Inflammatory Arthritis Education in Rural and Remote Communities Using Telemedicine. Carol Kennedy1, Kelly Warminston, Carol Flewelling, Rachel Shupak, Angelo Papachristos, Caroline Jones, Dorcas Beaton, Sydney Brooks and Denise Linton.1 St. Michael’s Hospital, Toronto, ON, 2The Hospital for Sick Children, Toronto, ON, 3St Michael’s Hospital, Toronto, ON, 4St. Michael’s Hospital, Toronto, ON, 5Mobilization Program Clinical Research Unit, Li Ka Shing Knowledge Institute, 6Institute of Population Hlth, Ottawa, ON.

Background/Purpose: Telemedicine-based approaches to healthcare service delivery improve access to care. It was recognised that people with inflammatory arthritis living in rural areas had limited access to patient education and could benefit from the “Prescription for Education (RxEd)” program, an evidence-based inflammatory arthritis education program. (format: one-day; audience: adults with inflammatory conditions, facilitators: specialized arthritis care providers). The one-day program includes a variety of short presentations and panel discussions by the team, and small group, facilitator-led discussions.

The program was adapted to be delivered via interactive videoconferencing through two workshops for local and rural facilitators: Telemedicine Best Practices/Adult Education Principles; Improved Public Speaking.

The objective of this study was to evaluate the effectiveness of telemedicine delivery of “Prescription for Education” in improving arthritis self-efficacy and other secondary outcomes (arthritis knowledge, coping efficacy, illness intrusiveness, and effective consumer).

Methods: Two group, pre-post design comparing two methods of delivery, local (I, in-person) versus videoconferencing (R, remote using telemedicine), of the RxEd program.

Data were collected at baseline (T1), immediately following RxEd (T2), and at 6 months (T3). Self-report questionnaires served as the data collection tool. Measures included demographics, disorder-related, Arthritis Self-Efficacy Scale (SE), arthritis knowledge [ACREU RA knowledge questionnaire (AK)], coping efficacy (CE), Illness Intrusiveness (II), and Effective Consumer Scale (ECS). Analyses included: Univariate statistics for primary and secondary outcomes; Repeated measures analyses of variance (MANOVA) to assess change in primary outcome (SE) across T1–3 (I vs R); and Repeated measures ANOVA to assess change from pre- to immediate-post (AK) and pre- to 6-month post (CE, II, ECS) (I vs R).

Results: 123 persons completed baseline questionnaires (I n = 36; R n = 87), with follow-up of 81% (n = 100) immediate post (T2) and 61% (n = 75) at 6 months (T3). No significant baseline differences were found: demographics, disorder-related, SE, AK, CE, II, and ECS measures.

Both groups (I and R) showed immediate effect (improved SE) after the intervention that diminished slightly over 6 months. MANOVA significant across T1–3, p < 0.001 for SE. No significant differences (SE p = 0.31) between groups (I vs R).

Both groups showed significant increase in knowledge (AK) from pre- to immediate-post RxEd (p < 0.0001), and no significant difference I vs R (ANOVA p = 0.41). Both groups showed significant improvement in CE (ANOVA II (p < 0.0001) from pre- to 6-month follow-up. No significant differences (ANOVA, p-values 0.20 – 0.78) between groups (I vs R) for all secondary outcomes.

Conclusion: Improvements in arthritis self-efficacy and other secondary outcomes were equally effective in local (in-person) and remote participant groups. Access to inflammatory arthritis education in rural and remote communities is greatly increased with using Telemedicine.

Disclosure: C. Kennedy, CIORA, 2, Abbvie, Roche, UCB, 9; K. Warmington, None; C. Flewelling, None, R. Shupak, None, A. Papachristos, None, C. Jones, None; D. Beaton, None, S. Brooks, None, D. Linton, None.

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Getting a Grip on Arthritis Online: Web-Based Continuing Education Supports the Dissemination of Arthritis Clinical Practice Guidelines Among Rural/Remote Primary Care Providers. Sydney Lineker1, Mary Bell2, Lisa Fleet2, Elizabeth M. Badley2, Vernon Currans, Marilyn Del Pino3, Frank Kirby3, Anne Lydiatt4, Lynn M. Koren5,5, Karla Simmons5, Raquel Sweezie5, Peter Tugwell6 and Ed Z Ramos1. 1The Arthritis Society, Toronto, ON, 2Sunnybrook Health Sciences Ctr, Toronto, ON, 3Memorial University, St. John’s, NF, 4Division of Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, 5Health Canada, Regina, SK, 6Patient Partners in Arthritis, Toronto, ON, 7Institute of Population Hlth, Ottawa, ON.

Background/Purpose: Primary care providers (physiotherapists, occupational therapists, nurses, family physicians) are often challenged with accessing relevant up-to-date arthritis information to enable delivery of optimal care. An online arthritis continuing health education program to disseminate arthritis clinical practice guidelines was developed, piloted, and evaluated to address this issue.

Methods: Online learning modules were developed for Osteoarthritis (OA) and Rheumatoid Arthritis (RA) based on published guidelines adapted for primary care (best practices), input from subject matter experts, and a needs assessment. The program was piloted in two tele/remote areas with high arthritis prevalence and health human resource shortages. Evaluation included 1) paired samples analyses of pre/post measurements of best practice recommendations and confidence and satisfaction with ability to manage arthritis, 2) evaluation of module content and design. Knowledge of best practice guidelines was measured by assigning one point for each best practice applied to a hypothetical case scenario and then summing the points into a total best practice score. Confidence and satisfaction were measured on 10 point numerical rating scales (0 = not satisfied/not at all confident; 10 = extremely satisfied/confident).

Results: Primary care providers that completed the modules (OA n = 34; RA n = 32) demonstrated significant improvements in best practice scores (OA p = .06, post – 3.8/10, p = 0.01; RA p = .06, post – 4.6/12, p = 0.01). More providers recommended occupational therapy/joint protection for the OA case scenario (pre = 32.4%, post = 58.8%, p = 0.01) after taking the module and more providers recommended patient education for the RA case scenario (pre = 46.9%, post = 68.8%, p = 0.04). Satisfaction with ability to manage arthritis also improved (OA p = .07, post = 8.0, p = 0.01; RA p = .06, post = 7.0, p = 0.01). Significant increases in confidence with different aspects of arthritis care (except mobility) were found (OA p = .06, RA p = .04). After taking the OA module, participants’ confidence improved (for prescribing/recommending joint injections of the knee, DMARDs, and...
corticosteroids, and managing common musculoskeletal conditions. Most respondents agreed that the modules were consistent with stated objectives (OA = 97.5%; RA = 97.1%), addressed learning needs (OA = 97.2%; RA = 94.3%) and were relevant to practice (OA = 80.0%; RA = 91.4%). The planned use of relevant resources in practice and with patients highlighted the participants’ commitment to change.

Conclusion: With knowledge gained from the online modules, participants were able to apply a greater number of best practices and they reported an increase in both satisfaction and confidence with managing arthritis. The modules were also relevant to practice and the content addressed their learning needs. As a result of the success of the pilot evaluation, both modules were accredited and launched nationally at the end of February 2014.


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Racial Disparities in Attitude Towards Treatment in Young Women

Raluca Cozmuta, Sonal Bhalla1 and Liana Fraenkel2. 1Yale University School of Medicine, New Haven, CT, 2Yale University, New Haven, CT, 3Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT.

Background/Purpose: Previous research has found that young minority women tend to be more risk averse compared to their Caucasian counterparts. The reasons underlying these differences, however, are not well understood. The objective of this study was to examine whether factors influencing perceived treatment importance vary by minority status.

Methods: Women between the ages of 20 and 45 receiving treatment at an academic hospital either as an inpatient or in an infusion center completed a survey. The survey ascertained sociodemographic data, affect, trust in healthcare systems, and medication beliefs using validated instruments. The survey included a hypothetical scenario in which subjects were asked to rate the importance of taking a medication for a patient with joint pain, migraines and fatigue that benefits 70% of people and is well tolerated except for the side effects. A series of questions about patient characteristics, affect, medication beliefs, and trust with perceived importance of taking the medication were evaluated using two sample t-test, Mann Whitney U test, and Spearman correlation as appropriate. Variables found to be statistically significant (p < 0.05) were subsequently evaluated using multiple linear regression. Minority women were defined as women who did not self-identify as White non-Hispanic.

Results: 174 women completed the survey. Patient characteristics by minority status are summarized in the table below. Perceived importance of taking the medication varied by minority status. A mong minority women, perceived medication importance was correlated with trust in healthcare systems (r = 0.2, p = 0.03), hopefulness regarding the medication (r = 0.3, p = 0.002), and difficulty paying for medications (r = 0.3, p = 0.03). The relationship between trust and perceived importance was completely mediated by hopefulness. Among non-Hispanic White women, medication beliefs (r = 0.3, p = 0.001), hopefulness (r = 0.2, p = 0.01) and worry related to the medication (r = 0.4, p = 0.002) were correlated with perceived medication importance. Hopefulness and difficulty paying for medications remained significantly associated with perceived medication importance in the multivariate regression model among minority women, as did affect and medication beliefs in non-Hispanic White women.

Conclusion: In contrast to previous findings, minority women rated the importance of taking medication higher than non-Hispanic White women. Our findings confirm the important influence of affect on decision making, and suggest that financial constraints can influence the perceived value of treatment among minority women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Hispanic White</th>
<th>Minority</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>32.8 (7.2)</td>
<td>33.1 (7.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Medication beliefs (mean, SD)</td>
<td>26.9 (4.8)</td>
<td>21.8 (4.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Trust (mean, SD)</td>
<td>28.5 (5.3)</td>
<td>26.7 (6.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hopefulness (mean, SD)</td>
<td>4.1 (1.6)</td>
<td>3.6 (1.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Worry (median, range)</td>
<td>5 (1–7)</td>
<td>5 (1–7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Important (median, range)</td>
<td>5 (2–7)</td>
<td>6 (1–7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Some college education (%)</td>
<td>79.1%</td>
<td>51.4%</td>
<td>(-0.001)</td>
</tr>
<tr>
<td>Difficulty paying for meds (%)</td>
<td>21.2%</td>
<td>25.7%</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Disclosure: R. Cozmuta, None; S. Bhalla, None; L. Fraenkel. None.

Table. Patient characteristics by minority status

Emerging Themes

Impact of constrained resources

They don’t want to be sitting, lying around somewhere recovering. They want to be able to go to work and play their skills, take care of their families.

We are not that risky because in the end we really cannot afford what a lot of white people can afford.

Impact of perceived discrepancies in access to high quality healthcare

A lot of times doctors don’t have the time like they used to because of the current health care systems of factory working, kind of pushing people out, getting them in and out.

Impact of erroneous illness perceptions

There is a lot to lose. I rather hear that there is no, stay in pain, use my knee and avoid those side effects like not being able to use it or move it.

"more minorities have health problems... worse health problems than the white people generally", I am going to be that odd number because we are that odd number for everything else.

Disclosure. S. Bhalla, None; K. Mattocks, None; L. Fraenkel, None.

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Examining Why Minority Women Are At Risk Averse: A Qualitative Study

Sonal Bhalla1, Kristin Mattocks2 and Liana Fraenkel3. 1Yale-New Haven Hospital, New Haven, CT, 2VA Central Western Massachusetts Healthcare System, University of Massachusetts Medical School, Leed, MA, 3Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT.

Background/Purpose: Prior research has shown that when making choices about the risks and benefits of medications, women from minority ethnic groups tend to be more risk averse compared to their Caucasian counterparts. We conducted a qualitative study to better understand how young women of three racial groups: non-Hispanic Blacks, non-Hispanic Whites and Hispanics approach trade-offs between the risks and benefits of medications.

Methods: Participants were drawn from inpatient wards and infusions centers at a large academic hospital. Women age 20–45 years, able to speak English or Spanish, who self-identified as Hispanic Black, non-Hispanic White or Hispanic, were eligible to participate. We performed individual in-depth interviews following a semi-structured interview guide. In the initial prompt, all participants were asked why they think minority ethnic groups tend to be more risk averse. Interviews were audiorecorded and subsequently transcribed verbatim. Transcripts were analyzed using the constant comparative method of grounded theory. Coding ended with thematic saturation (36 interviews).

Results: We coded 36 transcripts (30.6% non-Hispanic Blacks, 33.3% non-Hispanic Whites and 36.1% Hispanics). The participants’ mean age (SD) was 34.8 (6.8); 66.7% had a college education or higher, 58.3% had annual income $40k or more; 41.7% were employed full-time, and 55.6% were married. The four main themes that emerged from the transcripts were the impact of 1) constrained resources (limited means, responsibilities of work and family, lack of knowledge or information); 2) deep-rooted health beliefs (familial narratives, religious beliefs, mistrust); 3) perceived discrepancies in access to high quality healthcare (access to type of care, relationship with doctors, lack of communication and disclosure) and 4) erroneous illness perceptions (perceived susceptibility to side effects, inaccurate medication beliefs) on attitudes towards treatment. References were made towards the importance of taking a medication for a patient with joint pain, migraines and fatigue that benefits 70% of people and is well tolerated except for the side effects. A series of questions about patient characteristics, affect, medication beliefs, and trust with perceived importance of taking the medication were evaluated using two sample t-test, Mann Whitney U test, and Spearman correlation as appropriate. Variables found to be statistically significant (p < 0.05) were subsequently evaluated using multiple linear regression. Minority women were defined as women who did not self-identify as White non-Hispanic.

Conclusion: Decision making is influenced by factors far beyond the importance of the medication itself. Our findings confirm the important influence of affect on decision making, and suggest that financial constraints can influence the perceived value of treatment among minority women.

Table. Patient characteristics by minority status

Variable                                      | Non-Hispanic White | Minority | P value |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>32.8 (7.2)</td>
<td>33.1 (7.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Medication beliefs (mean, SD)</td>
<td>26.9 (4.8)</td>
<td>21.8 (4.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Trust (mean, SD)</td>
<td>28.5 (5.3)</td>
<td>26.7 (6.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hopefulness (mean, SD)</td>
<td>4.1 (1.6)</td>
<td>3.6 (1.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Worry (median, range)</td>
<td>5 (1–7)</td>
<td>5 (1–7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Important (median, range)</td>
<td>5 (2–7)</td>
<td>6 (1–7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Some college education (%)</td>
<td>79.1%</td>
<td>51.4%</td>
<td>(-0.001)</td>
</tr>
<tr>
<td>Difficulty paying for meds (%)</td>
<td>21.2%</td>
<td>25.7%</td>
<td>0.50</td>
</tr>
</tbody>
</table>
Ageism, Fear, and Competing Co-Morbidities - Why Older Patients May Not Seek Care for Restricting Back Pain: A Qualitative Study. Una Makris1, Robin Higashi2, Emily Marks2, Liana Fraenkel3, Joanna Sale4 and CM Reid5. 1Dallas VA Medical Ctr, Dallas, TX, 2UT Southwestern Medical Center, Dallas, TX, 3Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, 4University of Toronto, St. Michael’s Hospital, Toronto, ON, 5Weill Cornell Medical College, New York City, NY.

Background/Purpose: Back pain is highly prevalent among older adults and often undertreated. The reasons for this gap in care are poorly understood, especially in older adults from diverse racial and ethnic backgrounds. Our objective was to understand why older adults, in a racially diverse population, with restricting back pain (RBP - back pain severe enough to restrict activity), may not seek care.

Methods: We conducted one-on-one interviews and focus groups with older adults (ages ≥65 years) who reported RBP within the past 3 months. We recruited participants from 3 different sources (interviews and focus groups in Connecticut and focus groups in New York) to ensure a racially diverse sample; recruitment efforts were targeted at community settings, regional medical and surgical interventions.

Results: We conducted 23 one-on-one interviews and 16 focus groups (total = 39 participants, for a total of 93 participants. Participants were mostly female (68%), older (median age ≥83 years), over one-half lived alone, and 46% self-identified as belonging to a minority group. We identified 3 themes for why older adults may not seek care for RBP (Table 1): (1) participant and perceived provider beliefs about age-related inevitability of RBP, (2) participants' fear of medication and/or surgery, and (3) older adults' perceived relative importance of RBP versus other comorbidities. There did not appear to be any trends in our findings based on race/ethnicity.

Conclusion: Findings demonstrated that a range of illness perceptions influence older adults willingness to seek care for RBP. Many of the barriers discussed may be addressed by improved patient-physician communication. Understanding the older adult's perspective regarding reasons they may not choose to seek care is an important step toward identifying opportunities to improve the quality of care for older adults with RBP. Providers, in turn, might benefit from clinical guidance regarding the treatment of low back pain specifically in older adults (e.g. poly-pharmacy, frailty, multiple co-morbidities), that recognizes the impact of ageist myths and assumptions, and providers' focus on medical and surgical interventions.

Theme Sample Quotes
1. Participant and provider beliefs about inevitability of back pain in older adults
   I honestly think that at this point, my body is broken, it's worn out. I mean, [chuckle] that's why I say, someone in their 70's you could help a lot more, but I honestly don't know what could be done now outside of keeping comfortable. I'll tell you what the doctor thinks: "you're 93 years old!" I see that all the time when I go to the office. Like everything is taken very lightly. They [providers] always want to give me medicine. I don't want medicine [emphasis original]! Because I don't think it helps anywhere! Don't want another medication.
   That's the thing. They don't tell you much. They'd rather give you medication.
   He told me (the surgery was a success) he said "it worked out" from the X-ray, that it looks like it's going to be successful, but the pain(that's what to me), what I would say is successful, if I didn't have any more pain. It was not successful!
   I am having back pain right now for years. Not only for months, for years. My doctor I have other problems. So she even told me that, they are only patching me up because I have other problems; prostate, liver, heart, and all different problems. That's what is being told me about this pain.
   My concentration at this point is my diabetes. I've had that and I've had that for almost 30 years. And I that has presented problems along the way.Even they know more about that than what I'm going through with my back.

2. Participant fear of medication and/or surgery

3. Relative importance of back pain compared to comorbidities

Disclosure: U. Makris None; R. Higashi, None; E. Marks, None; L. Fraenkel, None; J. Sale, None; C. Reid, None.
Effects of Mesenchymal Stem Cells on Human B Cell Proliferation. Erin Collins, Maosong Qi and Gary S. Gilkeson. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Human mesenchymal stem cells (MSC) are progenitor cells that have immunomodulatory properties. MSCs have been used to treat a variety of autoimmune diseases, including lupus. However, literatures have reported conflicting results of MSC function in regards to B cell biological behaviors. We tested the ability of MSCs from umbilical cords, and MSCs from healthy and lupus bone marrow in modulating the B cell functions of healthy and lupus patients.

Methods: Human MSCs were isolated from umbilical cords (UC), healthy bone marrow (HBM), and lupus patient bone marrow (LBM). Passages between 4 and 7 were used for these assays. B cells were isolated from peripheral blood of healthy and lupus donors using CD19 micro-beads, then labeled with CFSE for detection of proliferation. B cells were plated at 5x10^4 per well in 96-well plates, with or without pre-plated MSCs, at the same number with or without T cells. The cells were incubated at 37°C and 5% CO2 for 96 hours ± stimulation (Cpg, CD40L, IL2, and anti-human IgG/IgA/IgG). B cells were then collected and analyzed for proliferation by flow cytometry. Supernatants were collected for detection of antibodies and cytokines via ELISA.

Results: When co-cultured, UC-MSC and HBM-MSC inhibited healthy B cell proliferation better than LBM-MSC. However, only UC-MSC appeared to reduce the proliferation of lupus patient B cells. Regardless of proliferation, healthy B cells cultured in the presence of MSCs experienced increased IgM and IgG production. Supernatants of healthy B cells cocultured with MSCs also presented increased levels of IL-6 while having decreased amounts TNF-α when compared to the supernatants of wells with B cells alone.

Conclusion: In our experiments, MSCs obtained from umbilical cords exhibited cell activity in suppressing both healthy and lupus B cell proliferation while MSCs from healthy bone marrow suppressed healthy, but not lupus B cell proliferation. Lupus patient derived MSCs were unable to significantly suppress B cell proliferation from healthy or lupus patients. Furthermore, MSCs from all sources did not inhibit healthy B cell IgG or IgM secretion. These studies aim to improve our understanding of the in vitro effects of MSCs on B cell function in order to predict in vivo efficacy of MSCs to be used in the treatment of SLE.

Disclosure: E. Collins None; M. Qi None; G. S. Gilkeson None.

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Development of Cell-Based Enzyme-Linked Immunosorbent Assay for the Quantification of Anti-M-type Phospholipase A2 Receptor Antibodies and Its Clinical Usefulness in Patients with Membranous Nephropathy. Yashiro Katsumata1, Yoko Okamoto2, Takahiro Mionyama1, Manabu Kawamoto3, Hiroka Kaneko4, Yasuhiro Kawaguchi5, Yukiho Kono6, Masanori Hanaoka7, Tomoaki Higuchi8, Hidenaga Kawasumi9, Kenko Uchida3, Koosaku Nitta10 and Hidetsugu Yamanaka11. 1Washington Univ School of Med, St. Louis, MO, 2Washington University School of Medicine, Saint Louis, MO, 3King’s College, London, United Kingdom, 4University of Michigan, Ann Arbor, MI.

Background/Purpose: uropathy in nephritis (LN) remains the leading cause of mortality for SLE patients, and is associated with proteinuria and foot process effacement. Podocyte foot process effacement is a feature of proteinuria, thought to be a stereotyped response of the podocyte to injury. The stimulus for podocyte injury and foot process effacement is unknown. B cell depletion therapies have demonstrated efficacy in some patients with proteinuria including those with minimal change disease. Since pathogenic antibodies are not causative, we hypothesized that a B cell derived cytokine might be capable of directly inducing podocyte injury and foot process effacement.

Methods: B cell model antigen model hen egg lysozyme (HEL) was biotinylated, complexed to avidin and injected into mice. Naive HEL-specific B cells were adoptively transferred and proteinuria assessed. Kidneys were processed for immunofluorescence and scanning electron microscopy (SEM). Cultured podocyte membrane ruffling was assessed with DIC videomicroscopy. IL-4 expression in mice was achieved by hydrodynamically injecting a copy of murine IL-4 in the piggyBac vector system. Human kidney biopsies were assessed for phospho-STAT6 by immunohistochemistry.

Results: We identified IL-4 as a B cell derived cytokine capable of altering actin cytoskeletal dynamics by stimulating podocyte membrane ruffling (lamellipodia). In addition, IL-4 generated foot process retractions on in vivo fragments of renal cortex. Using a novel model of B cell induced proteinuria, B cells polarized to secrete IL-4 upon activation by induced proteinuria and local foot process effacement without antibody or complement deposition. Intravital two-photon microscopy demonstrated that HEL-specific B cells arrested traffic within glomeruli only in the presence of membranous/ocularized HEL. Inhibition of IL-4 signaling with a JAK1/3 inhibitor markedly reduced proteinuria in IL-4 overexpressing mice. A subset to validate the absence of anti-PLA2R antibodies in patients with systemic lupus erythematosus (SLE).

Methods: The synthesized human PLA2R gene was transfected into the HEK293T cells using the pcDNA 3.1/Hygro (+) vector. Stable cell line expressing PLA2R was generated through limited dilution and evaluated by flow cytometry and Western blot. Using this cell line, we developed a quantitative cell-based ELISA for anti-PLA2R antibodies as follows. HEK293T cells stably expressing PLA2R were seeded and cultured in wells of 96-well plates coated with HEL. Cells were cultivated 96-well plates coated with HEL. Cells were then fixed, serum samples were added. Subsequently, the peroxidase-conjugated anti-human IgG and TMB were added in order, and color development was measured. The usefulness of this test was studied in 26 patients with biopsy-proven primary MN, and 16 SLE patients with pure MN. Western blots using the lysates of HEK293T cells stably expressing PLA2R were also performed with these samples. Clinical data of these patients were retrospectively evaluated. Treatment was determined by physician preference in each individual based on clinically available information without prior knowledge of anti-PLA2R antibody positivity.

Results: Stable expression of PLA2R was detected in the HEK293T cells by flow cytometry and Western blot. A nbt-PLA2R antibodies were positive in 7/26 (27%) by cell-based ELISA and 7/26 (27%) by Western blot. Cohen’s k coefficient of the 2 tests was 0.61 which means there is substantial agreement. Retrospective analyses revealed that all of the 7 patients who were anti-PLA2R positive by cell-based ELISA were treated with immunosuppressive therapy. In contrast, only 5 out of 26 patients with negative results received immunosuppressive therapy. Thus, the results of cell-based ELISA were associated with physicians’ decision on immunosuppressive therapy (p < 0.001). Renal function did not decline in any of the anti-PLA2R negative patients. All 16 of the SLE patients with pure MN were negative for both cell-based ELISA and Western blot.

Conclusion: This study showed that our cell-based ELISA is reliable and clinically useful examination for MN. Anti-PLA2R antibodies may serve as predictive biomarker in MN. The absence of anti-PLA2R antibodies in patients with SLE was reconfirmed.
of patients with steroid-sensitive nephrotic syndrome demonstrated glomerular STAB 6 activation.

Conclusion: These findings suggest a potential explanation for the utility of immunosuppression and more targeted anti-B cell therapy with rituximab in the treatment of minimal change disease. These results supporting the role of IL-4 in human nephrotic syndromes and a novel therapeutic target.

Disclosure: A. Kim, Pfizer Inc., 5; A. Amon, 5; Jansen Pharmaceuticals Product, L.P., 5; KyoPha Inc., 2; S. Akilesh, None; A. Koziel, None; S. Jain, None; J. Hodgin, None; M. Miller, None; J. Miner, None; A. Shaw, None.

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Neuropsychiatric Lupus Is Substantially Unaffected By B-Cell Deficiency. Ting Wen1, Ariel Stock1, Haowei Wang2, Mark Shlomchik2, Maria Gulino3 and Chaim Putterman4. 1Albert Einstein College of Medicine, Bronx, NY, 2University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background/Purpose: Neuropsychiatric lupus (NPSLE) is one of the earliest clinical manifestations in human lupus. However, its mechanisms are not fully understood. In lupus, a compromised blood brain barrier may allow for the passage of circulating autoantibodies into the brain, where they can induce neuropsychiatric abnormalities. Autoantibody titers can correlate with the severity of depressive-like behavior, and injection of anti-ribosomal P or anti-NMDA receptor antibodies into the brain induces neuronal damage and memory deficits. Since antibodies play an important role in lupus pathogenesis, B-cell depletion has been proposed as a targeted treatment approach. To determine if indeed B-cells and/or autoantibodies are instrumental in the pathogenesis of murine NPSLE, we evaluated neuropsychiatric disease in constitutively B cell deficient (JhD/MRL/lpr) and conditionally B-cell deficient mice (Cre-human CD20 MRL/lpr x Rosa26-Flox-STOP-DTA MRL/lpr, referred to as hCD20-DTA MRL/lpr, inducible by tamoxifen), as compared to MRL/lpr lupus mice.

Methods: hCD20-DTA MRL/lpr mice were B cell depleted at 13–14 weeks of age with tamoxifen treatment for 5 days. Blood and cerebrospinal fluid (CSF) were collected from JhD/MRL/lpr, hCD20-DTA MRL/lpr, MRL/lpr (positive controls) and MRL/MpJ (negative controls) at 18 weeks of age. Total IgG and IgG anti-dsDNA antibody concentrations in the serum and CSF were measured by ELISA. Comprehensive neurobehavioral testing including forced swim, anhedonia, open field, object recognition, object placement, and social preference were employed to evaluate the neuropsychiatric manifestations in the B cell sufficient and deficient MRL/lpr strains.

Results: Autoantibody levels were negligible (JhD/MRL/lpr) or significantly reduced (hCD20-DTA MRL/lpr) in the serum and CSF of B cell deficient mice. Nevertheless, we found that in the forced swim test, both JhD/MRL/lpr and hCD20-DTA MRL/lpr mice showed profound depressive-like behavior, which was different from MRL/lpr mice. However, JhD/MRL/lpr mice displayed an increase in both total track length and number of rears (standing on the hind feet) in open field. Additionally, hCD20-DTA MRL/lpr mice exhibited an increased trend in preference score for the passage of circulating autoantibodies into the brain, where they can induce neuropsychiatric disease in constitutively B cell deficient (JhD/MRL/lpr) and conditionally B-cell deficient mice (Cre-human CD20 MRL/lpr x Rosa26-Flox-STOP-DTA MRL/lpr, referred to as hCD20-DTA MRL/lpr, inducible by tamoxifen), as compared to MRL/lpr lupus mice.

Conclusion: We found that B-cell depleted MRL/lpr mice surprisingly had no significant attenuation of key features of neuropsychiatric disease, including depressive-like behavior and cognitive dysfunction. However, increased motor activity was observed in JhD/MRL/lpr mice. Additionally, a trend toward improved visual memory was found in hCD20-DTA MRL/lpr mice. Finally, the decreased cellular infiltrates in the brain of hCD20-DTA MRL/lpr mice indicate that B cells play an important role in facilitating the immune cell entry into the choroid plexus.

Disclosure: J. Wen, None; A. Stock, None; H. Wang, None; M. Shlomchik, None; M. Gulino, None; C. Putterman, None.

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Regulation of the Responses of Human B Cell Subsets to Innate Immune Signals By Epratuzumab, a Humanized Monoclonal Antibody Targeting CD22. Natalia V. Giltiay1, Geraldine L. Shu2, Anthony Shock2 and Edward A. Clark1. 1University of Washington, Seattle, WA; 2UCB Pharma, Slough, United Kingdom.

Disclosures: N. V. Giltiay, None; G. L. Shu, None; A. Shock, UCB Pharma, 3; E. A. Clark, UCB Pharma, 2.

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In Vivo Effects of Epratuzumab, a Monoclonal Antibody Targeting Human CD22, on B Cell Function in Human CD22 Knock-in (Huki) Mice. Carolin Brandl1, Laima Ozgur2, Miriam Wohner3, Anthony Shock1 and Lars Nitschke1. 1University of Erlangen, Erlangen, Germany, 2Research Institute of Molecular Pathology, Vienna, Austria, 3UCB Pharma, Slough, United Kingdom.

Background/Purpose: Epratuzumab is a humanized monoclonal antibody that targets the B cell-specific protein CD22 currently in Phase 3 clinical trials in patients (pts) with systemic lupus erythematosus (SLE). Epratuzumab does not deplete B cells but does cause long-term changes in B cell numbers (~50–60% reduction after 9–12 months) in SLE pts. The mechanism of action of epratuzumab appears to involve immunomodulation of B cells e.g. by inhibiting activation through the B cell receptor (BCR). It has also been shown to modulate B cell adhesion molecule expression and responsiveness to chemokines. This study aimed to understand the effect of epratuzumab on B cells in vivo using human CD22 knock-in (Huki) mice in which B cells express the human, instead of murine, CD22 gene.

Methods: Huki mice (n=4–8) received a single intravenous injection of epratuzumab (0.5mg) or phosphate-buffered saline (PBS) and at time points 4–8) received a single intravenous injection of epratuzumab (0.5mg) or phosphate-buffered saline (PBS) and at time points up to 12 weeks (wks) B cell sub-populations (immature, transitional, mature, germinal center, marginal zone) in peripheral blood, bone marrow, spleen and lymph nodes were measured along with B cell activation markers (CD69, MHCII) and the CD62L homing marker. Ex vivo functional assays were also performed: Ca2+ flux after anti-BCR stimulation, apoptosis (based on numbers of sub-G1 phase cells) and CD22 internalization on B cells were measured (flow cytometry) and the proliferation of B cell subsets assessed after 7 days in vivo administration of BrdU.

Results: In Huki mice, a single dose of epratuzumab did not appear to affect absolute numbers or proportions of B cell subsets in...
Peripheral blood or lymphoid organs at Wks 3, 5, or 12 (comparable to PBS-treated Huki mice). Similarly, there were no consistent changes in activation markers or CD62L. However Huki mice receiving epratuzumab showed human CD22 internalization in B cells from blood and all other organs. Internalization was detected at 24 hours and maintained for 8 wks; long after antibody clearance. Splenic B cells purified 10 days after receiving epratuzumab demonstrated an increased rate of apoptosis when cultured ex vivo relative to PBS-treated mice and decreased BCR-activated Ca²⁺ flux was demonstrated in Huki mouse splenic B cells after epratuzumab treatment in vitro. BrDU incorporation in several B cell subsets was unchanged 7 days after administration of epratuzumab, suggesting there was no increase in proliferation.

**Conclusion:** Epratuzumab administration to Huki mice induced functional effects on B cells assessed ex vivo in keeping with in vitro data using human B cells. Specifically, epratuzumab decreased CD22 expression for a long time period, increased B cell apoptosis and decreased Ca²⁺ flux upon BCR activation. Single dose epratuzumab did not seem to strongly influence B cell development or B cell populations in blood and various organs. These data have implications for understanding the effects of epratuzumab treatment on B cell function in SLE pts particularly in relation to how BCR inhibition leads to long-term changes in the survival and physiology of B cells.

**REFERENCES**

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**Disclosure C. Brandl, None; L. Özgör, None; M. Wöhner, None; A. Shock, UCB Pharma, 3; L. Nitschke, None.**

**1944**

**Targeting CD22 with Epratuzumab Impacts Cytokine Production By B Cells.**

Vanessa Fleischer, Julia Sieber, Sarah J Fleischer, Anthony Shock, Guido Heine, Capucine Daridon and Thomas Dörner. German Rheumatism Research Centre Berlin, Berlin, Germany. Charité University Medicine, Dept. Med/Dermatolog and Clinical Immunology/German Rheumatism Research Center (DRFZ), Berlin, Germany, UCB Pharma, Slough, United Kingdom, Charité University Medicine Berlin, Berlin, Germany.

**Background/Purpose:** CD22 is a negative co-receptor of the B-cell receptor (BCR) and, when targeted by epratuzumab, partially inhibits BCR signaling, for example by reducing Syk phosphorylation and Ca²⁺ flux. Cytokines produced by B cells have been described as playing important roles during certain stages of autoimmune diseases such as systemic lupus erythematosus (SLE) and their secretion is known to be driven by antigens and/or Toll-like receptor (TLR)-ligand stimulation. However, the impact of epratuzumab, a monoclonal antibody that targets CD22, on cytokine production has not yet been addressed. The current study aimed to analyze the role of epratuzumab on the production of key cytokines by B cells, and compare the response of B cells from SLE patients to those from healthy donors (HD).

**Methods:** Peripheral blood mononuclear cells were isolated and B cells purified by Magnet Activated Cell Sorting™. After 2 days of culture in the presence of TLR9 and/or BCR stimulation (CpG and anti-IgM/IgG, respectively), cytokine production (IL-6, TNF-α and IL-10) by B cells from SLE patients and HD was analyzed in the supernatants by bioplex. A special focus was made on IL-10-producing B cells using intracellular staining by flow cytometry. The balance between IL-10 and pro-inflammatory cytokines were assessed using the ratios of the concentrations of IL-10 to either IL-6 or TNF-α.

**Results:** The secretion of the pro-inflammatory cytokines TNF-α and IL-6 by anti-BCR activated HD and SLE B cells was significantly inhibited by epratuzumab co-treatment. The production of both cytokines was also inhibited by epratuzumab when B cells were stimulated concomitantly through the BCR and TLR9, although this failed to reach statistical significance for IL-6 production from HD. In contrast, the production of IL-10 in B cell supernatants was not affected by epratuzumab under any stimulation conditions; similarly, the development of IL-10 + cells in culture, which was enhanced upon TLR and BCR activation, was unaffected by epratuzumab. The cytokine balance between IL-10 and pro-inflammatory cytokines was influenced toward the regulatory cytokine IL-10.

**Conclusion:** Epratuzumab, through the targeting of CD22, inhibited the production of the pro-inflammatory cytokines IL-6 and TNF-α by B cells after stimulation through BCR and TLRs pathways, but had no effect on IL-10. This suggests that this antibody has the capacity to regulate the balance between the regulatory cytokine IL-10 and pro-inflammatory cytokines, and suggests a potential mechanism of action of epratuzumab on the effector function of B cells.

**Disclosure V. Fleischer, None; J. Sieber, None; S. J. Fleischer, None; A. Shock, UCB Pharma, 3; G. Heine, None; C. Daridon, None; T. Dörner, UCB Pharma, 2.**

**1945**

**Pharmacodynamic Effects of the CD22-Targeted Monoclonal Antibody Epratuzumab on B Cells in Patients with Systemic Lupus Erythematosus.**

Anthony Shock ‡ Brian Kilgallen *, Willem Koetse, Christian Stach, Sabine Bongardt and Catrinel Galateanu. UCB Pharma, Slough, United Kingdom, UCB Pharma, Raleigh, NC, UCB Pharma, Mönheim, Germany, UCB Pharma, Brussels, Belgium.

**Background/Purpose:** Epratuzumab is a humanized monoclonal antibody (mAb) that targets the B cell-specific protein CD22 and is currently in Phase 3 clinical trials in patients (pts) with systemic lupus erythematosus (SLE). The mechanism of action of epratuzumab appears to involve immunomodulation of B cells, for example by inducing loss of B Cell Receptor (BCR)-related proteins from the cell surface, and inhibiting signaling through the BCR. The present analysis aimed to understand the effect of epratuzumab on B cells in SLE pts enrolled in the Phase 2b EMBLEM study (NCT00624351), and its open label extension (OLE), SL0008 (NCT00660881), in which epratuzumab produced clinically relevant, sustained improvements in disease activity in pts with moderate-to-severe SLE.

**Methods:** In EMBLEM ‡, pts were treated with placebo or 1 of 5 cumulative doses (cd) of epratuzumab (200mg–3600mg cd over the 12-week [wk] study). In the OLE, all pts received 2400mg cd epratuzumab (1200mg at Wks 0 and 2 of repeating 12-wk cycles). Blood samples withdrawn at various time points were analyzed by flow cytometry using a panel of antibodies against cell surface markers (CD45, CD22, CD27, IgD, CD95) in order to identify B cell subsets. CD22 expression was monitored using S-HCL-1, a non-competing anti-CD22 mAb.

**Results:** There was a (10–15%) median decrease in the numbers of CD22⁺ naïve B cells and a quantitatively similar increase in CD22⁺ memory B cells in pts treated with epratuzumab but not placebo, which did not appear to be dose-dependent. During OLE, total B cell numbers continued to decline, reaching a median decrease of 50–60% after 9–12 months epratuzumab treatment before stabilizing with no further decrease. There was a rapid decrease (~80%) of CD22 expression on naïve memory and transitional B cell subsets demonstrated at the first time point assessed (1 week) in the epratuzumab treatment groups (no changes were observed in the placebo group), which was maintained throughout the OLE. In vitro data demonstrated that this loss occurred primarily through epratuzumab-induced internalization of cell surface CD22. Moreover, the in vitro data demonstrated a bell-shaped concentration response, suggestive of bivalency. Finally, there was a gradual decline in the numbers of CD27⁻/Igd⁻ B cells expressing CD95 throughout the OLE, from 41% at EMBLEM ‡ baseline to 27% at OLE Year 2.

**Conclusion:** Epratuzumab treatment of pts with SLE induced a protracted but defined reduction in the number of peripheral blood B cells over time, reaching a median reduction of 50–60% after 9–12 months treatment. CD22 expression was rapidly lost on all B cell subsets, and the loss maintained throughout the OLE. There was a gradual decline with epratuzumab treatment in the number of CD27⁻/Igd⁻ B cells expressing CD95, a subset of activated memory B cells previously shown to be elevated in SLE and increased during lupus flare.*

**References**


**Disclosure A. Shock, UCB Pharma, 3; B. Kilgallen, UCB Pharma, 3; W. Koetse, UCB Pharma, 1, UCB Pharma, 3; C. Stach, UCB Pharma, 1, UCB Pharma, 3; S. Bongardt, UCB Pharma, 3; C. Galateanu, UCB Pharma, 3.**

**1946**

**CD22 Is Required for Formation of Memory B Cell Precursors within Germinal Centers.**

Craig Chappell, Kevin Draves and Edward Clark. University of Washington, Seattle, WA.
Results: Using real-time PCR and flow cytometry, we observed that the PRL-receptor is expressed in bone marrow early B cells (pro-B, pre-B, immature); in lupus prone mice the highest level of expression was found in pro-Bs and immature cells. Immature cells from lupus-prone strains showed a decrease in the absolute numbers of cells with high PRL-receptor expression in response to PRL. Since immature B cells are permanently being subjected to anti-self-elimination mechanisms, we assessed the survival in immature B cell line and immature B cells from mice. Immature B cells incubated with an anti-IgM antibody have increased survival rates in hyperprolactinemic conditions, in the same way in immature B cells lines the mRNA expression of Bcl-xL was increased.

Conclusion: Taken together, these data indicate an important effect of PRL on B cell development, both favouring positive selection and counter-acting mechanisms against self-specificity. In this scenario, increased PRL levels would result in the maturation of B cell clones with self-reactivity and an increased risk for developing auto-immune diseases.

Disclosure: K. Chávez-Rueda, None; R. Flores-Fernández, None; F. Blanco-Favela, None; M. Legorreta-Haque, None; L. Chávez-Sánchez, None; R. Hernández-González, None; E. Tesoro-Cruz, None.

1948

A Dual Role for IFN-γ in Development of Peripheral B Cells in Lupus-Prone MRL/lpr Mice. Takeshi Machida, Natsumi Sakamoto, Gary S. Gilkeson and Hideharu Sekine. 1Fukushima Medical University School of Medicine, Fukushima, Japan, 2Medical University of South Carolina, Charleston, SC.

Background/Purpose: It had been reported previously that IFN-gamma and IFN-gamma-receptor-1 (IFNGR1) were required for auto-Ab production and development of renal disease in lupus-prone MRL/lpr mice. At ACR 2011, we reported that MRL/lpr mice deficient for the transcription factor IFN regulatory factor-4 (IRF-4), that is required for Th2/Th17 differentiation, developed granulomas in multiple organs with significantly increased numbers of IFN-gamma-producing CD4+ T cells (Th1 cells) and high serum IFN-gamma levels after 12 weeks of age (Fig. 1A). Strikingly, unlike their WT littermates, they also exhibited total loss of splenic CD19+ IgM+ B cells by 12 weeks of age. Similar B cell loss was observed in Ifng−/− MRL+/+ mice but not in Ifng−/− C57BL/6 mice, suggesting a role for IFN-gamma in survival of peripheral B cells in mice with an MRL background. This study aimed to further define roles for IFN-gamma in survival of peripheral B cells and in development of autoreactive B cells in MRL/lpr mice.

Methods: Ifng−/− or Ifng−/Ifng− double-gene knockout MRL/lpr mice were generated by backcrossing with C57BL/6 mice lacking corresponding genes for 8 generations. Expression levels of CD19, IgM, CD21, CD23, and IFNGR1 on splenic B cells were analyzed by flow. Splenic follicular (FO)- and marginal zone (MZ)-B cells were isolated by cell sorting and frequency determined by IFNGR1 expression levels. In vivo, splenic B cells were isolated from Ifng−/− MRL/lpr mice after 12 weeks of age and from WT MRL/lpr mice and MRL+/+ mice shown to be normal in lupus-prone MRL/lpr mice.

Results: The splenic B cell loss observed in Ifng−/− MRL/lpr mice was restored in Ifng−/− Ifngr1−/− MRL/lpr mice even after 12 weeks of age (Fig. 1B).

Fig. 1. Serum IFN-γ levels (A) and splenic CD19+IgM+ B-cell populations (B) of 12 weeks old MRL/lpr mice.

CD21+CD23+ MZ-B cells of WT MRL/lpr and MRL+/+ mice showed high IFNGR1 expression levels compared to their CD21+CD23+ FO-B cells. In contrast, MZ- and FO-B cells of C57BL/6 mice showed minimal IFNGR1 expression (Fig. 2A). MZ-B cells of MRL/lpr mice showed significantly increased frequency of anti-dsDNA IgM-secreting cells compared to their FO-B cells or MZ/FO-B cells of C57BL/6 mice (Fig. 2B).

1947

ProLactin Promotes Survival of Immature B Cells from MRL/lpr Mice. Karina Chavez-Rueda, Rocio Flores-Fernandez, Francisco Blanco-Favela, Maria Legorreta-Haque, Luis Chávez-Sánchez, Rafael Hernández-González and Emiliano Tesoro-Cruz. 1IMSS, Mexico DF, Mexico, 2Instituto Nacional de Ciencias Médicas y Nutrición, Mexico DF, Mexico.

Background/Purpose: Prolactin (PRL) plays an important role in modulating the immune response. PRL is secreted by the pituitary gland as well as many other organs and cells, such as lymphocytes. In B cells, PRL enhances antibody production, including those with self-specificity; as such, PRL has been associated with B cell-triggered autoimmune diseases such as systemic lupus erythematosus (SLE). In this study, our aims were to determine the expression of PRL-receptor during bone marrow B cell development and whether the presence of high PRL serum concentration influences absolute numbers of developing populations and disease outcome in lupus-prone murine models.

Methods: All of the mice experiments were performed in accordance with approved guidelines established by Mexico (Norma Oficial Mexicana NOM-062-SSA1-1999). The NIH Guide for the Care and Use of Laboratory Animals (National Research Council) was followed. Female and male mice were studied. Female C57BL/6 mice were purchased from Harlan, the MRL/MpJ (MRL) and MRL/MpJ FAS+1 (MRL/lpr) mice were purchased from the Jackson Laboratory. The pro-B, pre-B and immature B cells from the bone marrow of mice were purified by flow cytometry and were assessed for the expression of PRL receptor mRNA and protein. The nine weeks old mice were treated with metoclopramide for six weeks to induce high levels of PRL, accelerate SLE disease progression and to determine the expression of PRL-receptor during bone marrow B cell development. The splenic B cell loss observed in MRL/lpr mice was restored in Ifng−/− Ifngr1−/− MRL/lpr mice even after 12 weeks of age (Fig. 1B).

Fig. 1. Serum IFN-γ levels (A) and splenic CD19+IgM+ B-cell populations (B) of 12 weeks old MRL/lpr mice.

CD21+CD23+ MZ-B cells of WT MRL/lpr and MRL+/+ mice showed high IFNGR1 expression levels compared to their CD21+CD23+ FO-B cells. In contrast, MZ- and FO-B cells of C57BL/6 mice showed minimal IFNGR1 expression (Fig. 2A). MZ-B cells of MRL/lpr mice showed significantly increased frequency of anti-dsDNA IgM-secreting cells compared to their FO-B cells or MZ/FO-B cells of C57BL/6 mice (Fig. 2B).

Results: Using real-time PCR and flow cytometry, we observed that the PRL-receptor is expressed in bone marrow early B cells (pro-B, pre-B, immature); in lupus prone mice the highest level of expression was found in pro-Bs and immature cells. Immature cells from lupus-prone strains showed a decrease in the absolute numbers of cells with high PRL-receptor expression in response to PRL. Since immature B cells are permanently being subjected to anti-self-elimination mechanisms, we assessed the survival in immature B cell line and immature B cells from mice. Immature B cells incubated with an anti-IgM antibody have increased survival rates in hyperprolactinemic conditions, in the same way in immature B cells lines the mRNA expression of Bcl-xL was increased.

Conclusion: Taken together, these data indicate an important effect of PRL on B cell development, both favouring positive selection and counter-acting mechanisms against self-specificity. In this scenario, increased PRL levels would result in the maturation of B cell clones with self-reactivity and an increased risk for developing auto-immune diseases.

Disclosure: C. Chappell, None; K. Draves, None; E. Clark, None.

1948
Defective PTEN Regulation and Function Contributes to B Cell Hyperresponsiveness in Systemic Lupus Erythematosus. Xiangni Wu1, Yanxia Ye2, Jingwen Niu2, Yang Li2, Xin Li3, Xin You1, Hua Chen1, Lidan Zhao1, Xiaofeng Zeng1, Fengchun Zhang1, Wei He1, Xuetao Cao1, Xuan Zhang1 and Peter E. Lipsky3.

Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, 3NIH, Charlottesville, VA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease associated with deposition of autoantibodies such as anti DNA antibody. After activation of B cells in lymphoid tissues, B cells circulate in the blood as “plasmablast”, migrate to bone marrow and reside as plasma cells differentiation, and these abnormalities were corrected by anti-IgM which promote antibodies. Specific targeting of circulating plasmablast might be a novel strategy for SLE treatment. Recently, CD19+ CD38+ CD43+ B cell subset from healthy control (HC) are reported to be “pre-plasmablast” phenotype based on gene expression profiling. The clarification of biological properties of CD19+ CD38+ CD43+ B cell subset in SLE patients might provide us a clue to specific targeting to this population. In this study, we analyzed the gene profiling of the circulating B cells in healthy control (HC) and SLE using Agilent based microarray technologies.

Methods: Naïve B cell (CD19+ CD27+ CD38+ CD43+), memory B cell (CD19+ CD27- CD38+ CD43-), and CD19+ CD38+ CD43+ B cell were sorted with FACs Ariall from HC and SLE (n=4, respectively). Total RNA were isolated and labeled, then miRNA was analyzed with Agilent miRNA microarray. Gene profiling data was analyzed with GeneSpring and Ingenuity Pathway Analysis software. Statistical analysis was performed by Fisher’s exact test in upregulator, canonical pathway and gene function analysis; and by modified t-test in comparative analysis between HC and SLE or each B cell subset.

Results: Comparison of gene profiling of CD19+ CD38+ CD43+ B cell and naive/memory B cell showed that genes differentially expressed in CD19+ CD38+ CD43+ B cell were significantly regulated by several transcriptional factors which play roles in cell cycle and proliferation, such as E2F1, E2F3 (p=4.47 x 10^-55), 1.69 x 10^-45, 3.73 x 10^-45, respectively) in addition to XBP-1, PDK1 and PAX5 which are well known to function in differentiation from B cell to plasma cells. In comparison of each B cell subset between HC and SLE patients, 2467 genes were significantly changed in SLE with 1967 genes changed only in SLE. Among them, 1967 genes were significantly regulated by several transcriptional factors which play roles in cell cycle and proliferation, such as E2F1, E2F3, PDK1 and PAX5 which are well known to function in differentiation from B cell to plasma cells.

Conclusion: Defective miR-7 regulation of PTEN contributes to B cell hyperresponsiveness in SLE and could be a new target of therapeutic intervention.
Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease known to be associated with a breakdown of self-tolerance. B-cell hyperactivity and disturbed B-cell homeostasis of peripheral B-cell subsets. To analyze in more detail the extent to which the B-cell antigen receptor (BCR) proximal spleen tyrosine kinase (Syk) contributes to B-cell abnormalities in SLE, comprehensive functional and phenotypic analyses on SLE B-cells were performed.

Methods: B-cells from healthy donors (HD) and SLE patients were analyzed by flow cytometry to assess basal expression of Syk and phosphorylated (p-)Syk. B-cell subsets expressing distinct levels of Syk were identified and characterized phenotypically by flow cytometry, microscopy and molecularly to assess IgVH rearrangements. Their functions were analyzed by in vitro differentiation assays into plasma-cells and Syk induction by cytokines.

Results: A significantly increased frequency of CD27(-)B-cells with enhanced expression of Syk (Syk+++) was found specifically in SLE patients. CD27/Syk- B-cells showed a substantially increased Syk and basal p-Syk expression as well as an increased cytoplasmic Syk accumulation and increased Syk phosphorylation upon BCR engagement compared to CD27(-)Syk+ B-cells. Furthermore, CD27/Syk- B-cells were characterized as CD38- as well as CD19++, CD20++ and mainly CD21- with reduced ABC-B1 transporter activity and exhibited somatically mutated IgVH rearrangements. CD27/Syk++ B-cells showed an enhanced differentiation into Ig secreting plasma-cells in contrast to CD27/Syk+ cells. Finally, Syk+++ B-cells were inducible in vitro by stimulation with IFN-γ, LPS or TNF-α.

Conclusion: SLE patients exhibit an increased frequency of a novel CD27/Syk+++ subset of B-cells with memory B-cell characteristics which candidate as a source of increased plasma-cells characteristic of SLE patients. Moreover, the evidence indicates that the use of intracellular markers, such as Syk, permitted a distinction between naïve and memory B-cell subsets within the CD27+B-cells and and a more precise delineation of the CD27-memory B-cell subset.

Disclosure: S. Fleischer, None; C. Giesecke, None; H. Meißner, None; P. E. Lipsky, None; C. Daridon, None; T. Dönner, None.

1952


Background/Purpose: The advent of B-cell depletion therapy in autoimmune diseases identifies a novel B cell population, referred to as regulatory B cells (Bregs), that exerts regulatory functions via IL-10 production. We previously showed that human Bregs are strongly induced in IgM-memory B cells (Bregs), that exerts regulatory functions via IL-10 production. We aimed to investigate the mechanisms of Breg induction in immune diseases identifies a novel B cell population, referred to as regulatory B cells (Bregs), that exerts regulatory functions via IL-10 production.

Methods: Gene expression and protein production in B cells were assessed by quantitative PCR, ELISA and flow cytometry analysis. Bregs were co-cultured with T cells, and proliferation and IFN-Y production of T cells were assessed. The knockdown vector of Blimp-1 was generated and transfected into B cells.

Results: We first tested the function of Bregs in healthy controls and SLE patients. TLR9-induced Bregs from healthy controls inhibited proliferation and IFN-Y production of T cells, while such Bregs from SLE patients exerted less regulatory effects on the function of T cells. A previous study in the mouse system suggested that Blimp-1 induction is associated with plasma cell differentiation of B cells. In light of a critical role of Blimp-1 in plasma cell differentiation, we generated Blimp-1 knockdown B cells and found that Breg induction is impaired by Blimp-1 silencing. Intriguingly, fleshly-isolated B cells from SLE patients exhibited higher basal levels of Blimp-1 and IL-10 expression, while further induction of Blimp-1 by TLR9 stimulation was significantly abrogated along with less IL-10 production, highlighting the induction of Blimp-1, but not its levels, in Breg induction.

Conclusion: Together, these findings provide not only a better understanding of molecular mechanisms of Breg induction in humans, but also a novel clue to revitalizing Bregs for the treatment of human autoimmune diseases.

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1953

Circulating Plasmablasts from Patients with Systemic Lupus Erythematosus Produce Autoantibodies Reactive to Epstein-Barr Virus. Yang-sheng Yu1, Song Li1, Run Fan1, Yining Y.2, Hongyan Liao1, Zhixin Wang1, Lin Huang1, Qin Wang3, Michelhéne Hort-Hollès1, Amy Cannella1, W. Winn Chatham2, Robert Kimberley3, James O’Dell4, Lynell Klassen1, Robert Carter2, Zhixin Zhang2 and Kiahong Su1. 1University of Nebraska Medical Center, Omaha, NE, 2University of Alabama at Birmingham, Birmingham, AL, 3Shanghai Jiao Tong University, Shanghai, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the over-production of high affinity autoantibodies. It is not clear how such autoantibodies are generated during the course of lupus. The purpose of this study was to analyze the antibody repertoire in circulating plasmablasts in adult SLE patients and explore the molecular basis for the generation of such antibodies in SLE.

Methods: Eight patients with active SLE and seven healthy controls were recruited for the study. A recombinant antibodies were cloned from circulating plasmablasts by single cell RT-PCR analyses. Auto and poly-reactivities of these antibodies were measured by indirect immunofluorescent anti-nuclear antibody assays (IFA-ANA) and ELISAs using a panel of antigens (dsDNA, ssDNA, insulin, and LPS) respectively. Anti-Epstein-Barr Virus (EBV) reactivity of antibodies was examined by ELISAs using EBV viral capsid antigen (VCA) as capturing antigens.

Results: In patients with active SLE, the relative frequencies of circulating plasmablasts were significantly increased compared to those of healthy controls (10.6% vs 1.0%, p=0.0003, n=8). Circulating plasmablasts from SLE patients, but not healthy controls, predominantly produced auto/polyreactive antibodies (auto-reactive: 28.4% vs 4%, p<0.0001, n=8; poly-reactive: 58.3% vs 11.3%, p<0.0001, n=8). Sequence analyses revealed excessive receptor editing and enrichment of antibody replacement products in immunoglobulin (Ig) genes derived from SLE patients (20.6% vs 7.9%, p=0.0002, n=8). Interestingly, 76.7% of the Vh replacement products derived from plasmablasts of SLE patients encoded auto/polyreactive antibodies. Furthermore, about 20% of circulating plasmablast-derived antibodies from SLE patients reacted with EBV VCA antigens. These SLE-derived anti-EBV antibodies cross-reacted with dsDNA and other nuclear antigens. Vh replacement products were also significantly enriched in Ig heavy chain genes encoding anti-EBV antibodies.

Conclusion: The elevated frequencies of auto/polyreactive antibodies, enrichment of Vh replacement products, and production of anti-EBV-VCA antibodies in plasmablasts from SLE patients indicate that autoreactive B cells in active SLE patients are positively selected by EBV antigens. This finding supports the hypothesis that preventing EBV infection is a beneficial intervention to limit active disease in SLE patients.

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1954

Successful Long-Term Depletion of Memory Plasma Cells Requires a Combined Depletion of Plasma Cells and Their Precursors in NZB/W Mouse. Adriano Taddei1, Laleh Kodadadi2, Qingyu Cheng2, Andreas H. Radbruch3, Falk Hiepe1 and Bimta F. Hoyer4. 1Deutsches Rheumaforschungszentrum, Berlin, Germany, 2Charité University Medicine, Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Germany, Berlin, Germany, 3Charité- University Hospital, Berlin, Germany.

Background/Purpose: Autoantibodies contribute significantly to the pathogenesis of systemic lupus erythematosus (SLE). The long-lived plasma cells (LLPC) secreting such autoantibodies are unfortunately refractory to conventional immunosuppressive treatments. A thorough understanding of the mechanisms that control their generation is thus important.

Methods: We first tested the function of Bregs in healthy controls and SLE patients. TLR9-induced Bregs from healthy controls inhibited proliferation and IFN-Y production of T cells, while such Bregs from SLE patients exerted less regulatory effects on the function of T cells. A previous study in the mouse system suggested that Blimp-1 induction is associated with plasma cell differentiation of B cells. In light of a critical role of Blimp-1 in plasma cell differentiation, we generated Blimp-1 knockdown B cells and found that Breg induction is impaired by Blimp-1 silencing. Intriguingly, fleshly-isolated B cells from SLE patients exhibited higher basal levels of Blimp-1 and IL-10 expression, while further induction of Blimp-1 by TLR9 stimulation was significantly abrogated along with less IL-10 production, highlighting the induction of Blimp-1, but not its levels, in Breg induction.

Conclusion: Together, these findings provide not only a better understanding of molecular mechanisms of Breg induction in humans, but also a novel clue to revitalizing Bregs for the treatment of human autoimmune diseases.
**Methods:** BrdU-pulse chase experiments over two weeks in mice of different age were used to analyze the generation of LLPC. Treatments were performed using Bortezomib, cyclophosphamide and a combination of both for very short (36h), short (5 days) and ‘longterm’ treatment (15 and 30 days). Plasma cell numbers were quantified using flowcytometry. Autoreactive plasma cells were analyzed using ELIspot.

**Results:** Autoreactive LLPCs are established in the spleen and bone marrow of lupus-prone mice very early in ontogeny, before week 9 and before the onset of symptoms. The generation of LLPCs then continues throughout life. LLPC counts in the spleen plateaued by week 10, but continued to increase in the bone marrow. After depletion of LLPCs by the proteasome inhibitor bortezomib, their numbers regenerated within two weeks. A persistent, therapeutic depletion of LLPCs was achieved only by combining a short treatment with bortezomib with a longterm depletion of plasma cell precursors.

**Conclusion:** In lupus-prone NZB/W F1 mice, autoreactive LLPCs are generated throughout life. Their sustained therapeutic elimination requires both, depletion of LLPCs and the inhibition of their regeneration by specific depletion of their precursors.

**Disclosure:** A. Taddese, None; L. Kodadadi, None; Q. Cheng, None; A. H. Radbruch, None; F. Hiepe, None; B. F. Hoyer, None.

**1955**

**Disparity in Internalisation of Monoclonal Antibodies Targeting B Cell Antigens and Regulation By Fc Gamma Receptor IIb:**

**Background/Purpose:** Monoclonal antibodies (mAbs) targeting B cell antigens CD20 and CD22 are used to treat patients with SLE either in the clinic or in clinical trials whilst anti-CD19 mAbs have been studied in vitro. The main mechanisms of action of these mAbs are depletion and immunomodulation. Internalisation of antibodies bound to mAbs is key to immunomodulatory action whereas retention of mAbs on cell surface evokes immune effector mechanisms triggering depletion.

**Methods:** We studied internalisation of anti-CD19 mAb (RF89), type1 anti-CD20 mAb (Rituximab), type2 anti-CD20 mAb (BH2H, glycosylated GA101), anti-CD22 mAb (4K12B8) and anti-CD38 mAb (AT13/6h) in 11 patients with SLE. Internalisation of mAbs was assessed using the surface fluorescence-quenching assay on isolated B cells. We used AT10, a mAb against the Fc gamma receptor II (CD32), to assess whether it regulated internalisation of mAbs. Isolated B cells were incubated with mAbs and AT10 for 10 min. Paired t-test or Mann-Whitney U test was used to compare groups.

**Results:** We performed surface fluorescence-quenching assay in 11 patients with SLE, assessed internalisation of mAbs after 6 hours of incubation with mAbs and AT10. Without prior incubation with AT10 (50mcg/mL) in 6/11. The median % of surface accessible mAbs was 68, 48, 71, 23 and 76 for anti-CD19, type1 anti-CD20, type2 anti-CD20, anti-CD22 and anti-CD38, respectively. However, prior incubation with AT10 significantly reduced internalisation of only anti-CD20 antibodies, a mean reduction of 12% and 4% for type1 and type2, respectively (Figure 1A). A remarkable variability between patients in both the extent of internalisation and reduction in internalisation with AT10 was noted for rituximab, but not BH2H (type2-anti-CD20mAb).

**Conclusion:** Internalisation of type1 and type2-anti-CD20mAbs in B cell subpopulations Internalisation of type1, but not type2, anti-CD20mAbs was significantly lower for post-switched cells (IgD-D+C27+) when compared with other B cell subpopulations (naive, IgD-D+C27-, unswitched, IgD-D+C27+ and double negative, IgD-D-C27+) (p<0.05 for all). AT10 reduced internalisation of type1, but not type2, mAbs in all B cell subpopulations (Figure 1B). Internalisation was also 9% greater for IgD+ vs IgD- B cells (p=0.005) suggesting a role for IgD in internalisation of mAbs, probably in synergy with Fc gamma receptor IIb (as B cells predominantly express the inhibitory Fc gamma receptor IIb) (Figure 1C).

**Conclusion:** Disparity in internalisation of mAbs occurs, with a high rate for anti-CD20mAbs, probably related to its high physiological rate of endocytosis and less for type1 anti-CD20 mAbs. Disparity between B cell subpopulations in internalisation of type 1 anti-CD20 mAbs may occur due to differential expression of IgD and Fc gamma receptor IIb. Therefore, internalisation of mAbs poses important therapeutic implications for targeted therapy in SLE.

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**1956**

**Increased IL-6 Production By Effector B Cells in Giant Cell Arteritis and Polymyalgia Rheumatica.**

**Methods:** In newly-diagnosed, non-treated patients with GCA and PMR, and in 44 follow-up samples of GCA and PMR patients receiving corticosteroids for 2 weeks and 3 months, 40 age-matched, healthy controls (HCS) were included. Serum BAFF levels were determined by ELISA and temporal arteries were studied by immunohistochemistry. Intracellular staining for TNF-α, IL-6 and IL-10 was performed after stimulating B cells with PMA and Ca2+ ionophore in the presence of Brefelin A for 4 hours.

**Results:** Newly-diagnosed GCA and PMR patients had decreased numbers of circulating CD19+ B cells when compared to HCs. B cell numbers recovered rapidly in treated GCA and PMR patients in remission. This recovery was not achieved by compensatory hyperproliferation or enhanced bone marrow production. The low B cell counts in newly-diagnosed GCA and PMR patients were associated with an increase in serum levels of the B cell growth factor BAFF. Serum BAFF levels diminished upon the return of B cells during remission. Functional characterization of the B cells showed that circulating numbers of IL-10 producing B effector cells remain normal in GCA and PMR patients, irrespective of disease activity and treatment. In contrast, circulating numbers of TNF-α producing B effector cells were profoundly decreased in newly-diagnosed GCA and PMR patients, but recovered during remission. Moreover, the returning B effector cells in GCA and PMR patients demonstrated an enhanced capacity to produce IL-6. Few B cells were found in temporal artery biopsies of GCA patients.

**Conclusion:** Our combined data indicate that B effector cells, but not B regulatory cells, are redistributed during active disease and quickly return upon remission. These B effector cells are characterized by an enhanced capacity to produce IL-6. The role of these IL-6 producing B effector cells in GCA and PMR warrants further investigation, as B cells and IL-6/IL-6R are potential targets for treatment.

**Disclosure:** K. S. M. van der Geest, None; W. H. Abdulnabah, None; G. Horst, None; A. Rutgers, None; A. M. H. Boots, MSD; J. E. Brouwer, None.
1957

Background/Purpose: Inflammation in the rheumatoid arthritis (RA) synovium is directly associated with inflammation cell migration across microvascular endothelial cells (ECs), and their persistence within the synovium. It has been shown that lymphatic vessel chemokine presentation increases in RA and so should increase the removal of the interstitial fluid containing the invading inflammatory cells which are at significant levels within the fluid. However, dysregulation of chemokine presentation between RA blood vessels and lymphatic vessel ECs may lead to reductions in removal of the ever increasing joint interstitial fluid and persistence of the inflammatory cells.

Methods: Immunohistochemistry was performed on human synovial tissue to using the pan-endothelial cell marker von-Willebrand factor, and the lymphatic EC marker LYVE-1 to assess the presence of CCL7, CCL14, CCL16 and CCL22. The number of vessels positive for each marker and the chemokine were counted to a maximum if 15 vessels over three fields of view (FOV) from 8 RA and 6 non-RA samples. Transmigration of mononuclear cells isolated from RA blood was performed over confluent human dermal lymphatic EC (HDLEC) monolayers in response to human CCL7 and analyzed by FACS analysis. Inflammatory conditions were stimulated by activating overnight with 100ng/mL 100ng/mL TNF-α with 100ng/mL IFN-γ.

Results: Significant increases in CCL14 and CCL22 were observed in RA blood vessels ECs compared to non-RA ECs (P=0.0041 and 0.014 respectively). A significant decrease in CCL7 in RA lymphatic ECs compared to non-RA lymphatic ECs was observed (p=0.011). Furthermore, significant increases in RA monocyte migration were observed in response to CCL7 (p=0.002). The greatest increase to be at 250ng/mL CCL7 (p=0.00313) with a significant increase in monocyte migration also seen at 100ng/mL CCL7 (p=0.037) compared to 0ng/mL.

Conclusion: The significant decrease of CCL7 in lymphatic ECs, combined with it having the greatest chemotactic ability for monocytes for the tested chemokines suggests CCL7 may be of importance in lymphatic removal of infiltrates in the inflamed RA synovium. Reduction in CCL7 may therefore be functional in leukocyte persistence and accumulation in the RA synovium.

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1958
Pyrollopyrimidine Derivatives That Inhibit Binding of BAFF to Its Receptor, BR3, Are Drug Candidates for Primary Sjogren’s Syndrome. Kako Yoshimoto1, Eriko Ishioka2, Katsuya Suzuki3, Takahiro Itu4, Tomohiro Sugano2, Hajime Yamada2, Ayumu Okuda5, Hiroyuki Ishiwata5, Takeshi Doi5, Tatsugumi Hirokawa3 and Tsutomu Takeuchi3.

Background/Purpose: We have been investigating the possible involvement of BAFF (B cell activating factor of TNF family) in the pathogenesis of primary Sjogren’s syndrome (pSS). We found that soluble BAFF (sBAFF) robustly increased IL-6 production in vitro by peripheral monocytes of patients with pSS and that the expression level of a BAFF receptor (BR3) was significantly elevated in pSS monocytes compared to that of normal monocytes. Additionally, the proportion of BR3-positive monocytes to total monocytes was positively and significantly correlated with the sBAFF-induced IL-6 production and the serum IgG level of pSS patients. These data collectively suggest that the elevated expression of BR3 on monocytes is involved in the pathogenesis of pSS. Consequently, our findings suggest that BR3 is a therapeutic target to treat pSS. However, no compounds except antibodies were reported to have inhibitory activities against BAFF signaling so far. In this study, we show some of our latest data about drug discovery for pSS aiming at BAFF signaling pathway.

Methods: High-throughput screening (HTS) of a chemical library was carried out to search for compounds that block binding of sBAFF to BR3. To this end, BR3 expressing CHO-K1 cells were established by transfection of a full-length cDNA of human BR3. Transfectants were cultured in the presence of FMAT Blue-labeled sBAFF and each compound in 384-well plates, and the binding of sBAFF to the cells was monitored by an Applied Biosystems 8200 Cellular Detection System. Hit compounds were further screened as follows: IFN-γ-stimulated THP-1, a human acute monocytic leukemia cell line, was cultured in vitro with sBAFF and each compound for 96 hr, and the cumulative amount of IL-6 produced by the cells was measured by ELISA. Cytotoxicities of the compounds were analyzed by measuring LDH in culture supernatants. The expression level of NF-κB in the cells was analyzed by quantitative PCR.

Results: A total of 18,562 compounds were examined for inhibitory activities of sBAFF binding to BR3. To eliminate false positives, inhibitory activities of the HTS-hits against IL-6 production by sBAFF-stimulated THP-1 were measured. Their cytotoxicities, which result in the reduction of IL-6 production, were also examined. As a result, two pyrollopyrimidine derivatives, BIK12 and BIK13, showed substantial inhibition of sBAFF-binding. IC50 values for BIK12 and 13 were 11 and 6 μM, respectively. sBAFF-induced IL-6 production by THP-1 was significantly suppressed by these compounds in a dose dependent manner, while the compounds had no cytotoxicities. Additionally, the expression of NF-κB in the cells was also repressed by BIK12 and 13. These results collectively suggest that these compounds suppress IL-6 production by THP-1 through an inhibition of binding of sBAFF to its receptor, BR3, and possibly subsequent BAFF signaling pathway.

Conclusion: We have successfully discovered low molecular weight compounds which have inhibitory activities against BAFF signaling. Although IC50 values were not so low, these compounds may provide not only lead compounds for therapeutic drugs of pSS, but also novel tools to explore the pathological mechanism of pSS.

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1959
Interaction of PDE4 and β-Arrestin Reverses Anti-Inflammatory Effects of Catecholamine-Producing Cells in Chronic Arthritis Via Adrenoceptor Switching From G αs to G iα Signalling. Zsuzsa Jene-Laniz1, Janika Zwingenberg1, Torsten Loewin2 and Rainer Straub3.1 Department of Experimental Rheumatology and Neuroendocrinology Immunology, Regensburg, Germany, 2 University Hospital Regensburg, Regensburg, Germany, 3 Laboratory of Experimental Rheumatology and Neuroendocone-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: In recent studies, we confirmed the anti-inflammatory effects of tyrosine-hydroxylase (TH)-positive catecholamine producing synovial cells in chronic arthritis. Other studies described that inhibitors of the cAMP-degrading enzyme, phosphodiesterase 4 (PDE4), exhibit anti-inflammatory effects (see FDA-approved therapy with apremilast). Furthermore, Lefkowitz et al. demonstrated that the interaction of PDE4 with β-arrestin at β-adrenoceptor can result in a catecholamine receptor switching from Gαs to G iα signalling with subsequent ERK1/2 activation. Therefore, the aim of our study was to investigate whether and how PDE4 and catecholamine signalling interact and possibly influence inflammatory responses in chronic arthritis.

Methods: Immunostaining of PDE4 and β-arrestin and visualization of presumed PDE4/β-arrestin interaction (via proximity ligation assay) was performed in synovial tissue and in synovial cell culture of rheumatoid arthritis (RA) and osteoarthritis (OA) patients. Synovial cells were cultivated under normoxic or hypoxic conditions (the microenvironment of inflamed joints is hypoxic) with/without PDE4 inhibitor and/or different concentrations of catecholamine receptor agonists, adenosine receptor agonists, and/or blocker of G iα-mediated pathways (pertussis toxin, ERK1/2 blocker). After 24 hours, supernatants were collected, cytokine concentrations were determined, and activation of ERK1/2 signaling was analyzed.
Results: Both, PDE4 and β-arrestin were detected in the synovial tissue and in synovial cell culture of OA and RA patients. Moreover, the interaction of PDE4/β-arrestin was demonstrated with proximity ligation assay. Under hypoxia, Gαs-coupled adrenergic agonists decreased TNF release in both OA and RA synovial cell culture. In contrast to normoxia, hypoxic incubation with PDE4 inhibitor alone and co-incubation with PDE4 inhibitor and catecholamine receptor agonists with Gαs-protein pathway increased TNF release, which was reversed by pertussis toxin or by ERK1/2 blocker. Western blot analysis demonstrated an increased ERK1/2 activation after treatment with Gαs-coupled adrenergic agonist alone or after co-incubation with PDE4 inhibitor and Gαs-coupled adrenergic agonist.

Conclusion: In summary, this study presents that PDE4 and β-arrestin interact at catecholamine receptors in human arthritic synovial tissue inducing catecholamine receptor switching from Gαs to Gαq signalling, which results in the reversal of catecholamine-induced anti-inflammatory effects at high neurotransmitter concentrations. This phenomenon might be responsible for possible reduced efficacy of PDE4 inhibitor treatment in some chronic arthritic diseases.


Disclosures: Z. Jené-Lenzl, None; J. Zwingenberg, None; T. Lowin, None; R. Straub, None.

1960

NF-κB-Inducing Kinase (NIK) Is Expressed in Synovial Endothelial Cells in Early Arthritis Patients and Correlates with Local Disease Activity and Systemic Markers of Inflammation. K. Aren M. I. Majer, A. E. R. Noort,1 M. Aria, J. H. de Hair,2 Christiaan van der Leij,2 Katinka P. M. van Zoest,2 Danielle M. Gerlag,2 Mario M. Aasa,2 Paul–Peter Tak2 and Sander W. Tas2.

Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.1 Academic Medical Center. University of Amsterdam, Amsterdam, Netherlands.2 Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: The NF-κB family of transcription factors is strongly involved in synovial inflammation. We have previously shown that NF-κB-mediated gene expression in synovial inflammation induces angiogenesis in rheumatoid arthritis (RA) synovial tissue (ST). In this study we investigated the expression of NIK in ST of early arthritis patients and in autoantibody-positive individuals at risk for developing RA, and correlated this with both systemic markers of disease activity (ESR and CRP) and with local disease activity in DMARD-naive early arthritis patients including magnetic resonance imaging (MRI) inflammation scores of the biopsied joint.

Methods: Arthroscopic ST biopsy samples were obtained from 154 early arthritis patients (arthritis duration less than 1 year, disease-modifying anti-rheumatic drug (DMARD) naïve; RA (n=64), unclassified arthritis (UA; n=61), crystal arthropathy (n=11), osteoarthritis (n=4) and spondyloarthritis (n=14)). In addition, a subset of these patients consist enhanced MRI was performed in the same joint and scored for effusion, synovitis, edema, cartilage degeneration and erosions, each in 4–6 compartments. A score of 0–3 for each compartment was given and a total MRI score was calculated (0–81).

Results: In early arthritis patients, NIK was predominantly expressed in endothelial cells (EC) of small blood vessels. No significant difference in NIK expression was observed between baseline diagnosis groups. However, NIK EC were significantly increased in UA patients that remained undifferentiated after 2 years. Furthermore, we observed that NIK EC may correlate better with disease activity than vWF+ EC, since NIK expression correlated with ESR (r=0.184; p=0.024), CRP (r=0.194; p=0.017), swelling of the biopsied joint (r=0.297; p<0.001), MRI effusion (r=0.665; p<0.001), MRI synovitis (r=0.632; p<0.001) and MRI total score (r=0.569; p<0.001). NIK expression did not significantly correlate with edema, cartilage damage and erosion scores (r=0.185; p=0.05). Autoantibody-positive individuals NIK+ EC were present in the synovium before the clinical onset of arthritis, but this did not predict for the development of arthritis.

Conclusion: We demonstrate that NIK EC are already present in the earliest phase of synovial inflammation and may be indicative of high angiogenic activity in the inflamed synovial tissue. Therefore, NIK EC may play an important role in the persistence of synovial inflammation. Collectively, our data underscore the importance of angiogenesis in synovial inflammation and identify NIK as a potential therapeutic target in arthritis to prevent the switch from acute to chronic inflammation.

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1961


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Background/Purpose: Chemokine-like receptor 1 (CMKL1R) is a G protein-coupled receptor (GPCR) expressed by inflammatory monocytes and macrophages in fibroblast-like synoviocytes (FLSs), both of which are pathogenic in osteoarthritis (OA) and rheumatoid arthritis (RA). Its cognate ligand, chemerin, is a chemoattractant for invading inflammatory cells and is present in the synovial lining of arthritis patients. In OA and RA, chemerin/CMKL1R signaling contributes to disease pathogenesis via recruitment of inflammatory leukocytes and stimulates breakdown of cartilage matrix by metalloproteases.

CMKL1R, like most GPCRs, is desensitized by recruitment of G protein receptor kinases (GRKs) and β-arrestins. Due to the significant role of chemerin/CMKL1R interaction in human inflammatory arthritis, we examined the mechanism of CMKL1R regulation by G protein receptor kinases (GRK) 2, 3, and 6 and β-arrestin-2.

Methods: De-identified, healthy, OA, and RA human FLSs were cultured for measurement of relative gene expression by qRT-PCR of CMKL1R, GRK2, GRK3 and GRK6 as compared to housekeeping gene IDUA (ΔCT).

A modified Tango assay was used to measure β-arrestin-2 recruitment to CMKL1R. HTLA cells were over-expressed with CMKL1R and GRK2, GRK3, or GRK6 via calcium phosphate precipitation and stimulated with increasing concentrations of chemerin. After 24 hours, luminescence was measured on a Promega Glomax Multi+ Detection System.

Peritoneal activated monocytes/macrophages from C57BL/6 wildtype (WT) and transgenic mice deficient in GRK2, GRK3, GRK6, or β-arrestin-2 (−/−) were studied ex vivo for CMKL1R receptor internalization and migration. Calcine-labeled monocyte migration to media alone, SDF–1, or chemerin was examined using the FalconTM HTS FluoroBlok 96-Multiwell Insert System (3 μm pore-size) and a Fluoroskan Ascent Microplate Fluorometer. To measure CMKL1R internalization, receptor surface expression was measured by flow cytometry at 30 sec, 1 min, 5 min and 10 min post-stimulation with chemerin and mean fluorescence intensity (MFI) normalized relative to 0 min on F4/80 positive cells.

Results: Relative gene expression of CMKL1R is increased in both OA and RA FLSs compared to normal controls. In addition, RA FLSs showed increased GRK2, -3, and -6 relative gene expression compared to controls. β-arrestin-2 recruitment to ligand-activated CMKL1R is preferentially mediated by GRK6 as compared to GRK2 and -3. Additionally, GRK6−/− and β-arrestin-2−/− murine peritoneal macrophages have enhanced chemotaxis to chemerin, as well as significantly decreased receptor internalization after ligand stimulation when compared to controls.

Conclusion: Chemerin/CMKL1R signaling has an important role in the pathogenesis of OA and RA through the activation of cells within the joint, as well as recruiting proinflammatory monocytes to sites of inflammation. Chemerin-induced migration of proinflammatory monocytes and CMKL1R receptor internalization is predominantly regulated by GRK6 phosphorylation and β-arrestin-2 recruitment.

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1962

**Inflammatory Properties of Inhibitor of DNA Binding 1 As a Unique Fibroblast Derived Nuclear Protein.** Gautham Edhayan1, Christine M. Ha2, Ray A. Ohara3, Takeo Izskaki4, M. A. Aslmin5, Ali Arbab6, Pei-Suen Tsou7, Phillip L. Campbell1, Elena Schiopu3, Dinesh Khanna3, Rachel M. Morgan1, Sean C. Friday1, Todd Fox8 and Jeffrey Ruth9. *1Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, 2Georgia Regents University, Augusta, GA, 3University of Michigan Scleroderma Program, Ann Arbor, MI.

**Background/Purpose:** Inhibitor of DNA binding 1 (Id1) is a nuclear protein containing a basic helix-loop-helix (bHLH) domain that regulates cell growth by selective binding and prevention of gene transcription. Id1 has shown pleiotropic effects: important in vascuogenesis in endothelial progenitor cells (EPCs), and important in angiogenesis in mature endothelial cells (ECs). Our group was the first to report that rheumatoid arthritis (RA) synovial fluid contains elevated amounts of Id1, and histologic analysis of RA synovial tissue (ST) revealed that Id1 is highly expressed in the vasculature of RA. We later found that the primary source of Id1 in STs were activated fibroblasts. Once released, Id1 acts as a potent inducer of angiogenesis, vasculogenesis, and fibrosis. Our data shows that Id1 is not only an important nuclear protein, but also that it can be released from fibroblasts by synovial fibroblasts, as well as the potential importance of Id1 in other rheumatic diseases such as scleroderma (SSc).

**Methods:** Synovial fibroblasts from RA, osteoarthritis (OA), normal (NL), and dermal fibroblasts from NL and SSc patients were plated and cultured without cytokines or stimulated with tumor necrosis factor-α (TNF-α), CXCL16, Interleukin-17 (IL-17), transforming growth factor-β (TGF-β), or platelet-derived growth factor (PDGF). Supernatants were measured for Id1 expression by ELISA. Fibroblast supernatants were subjected to rate zonal centrifugation to isolate and purify exosomes. Whole and lysed (0.5% Triton X-100) exosome fractions were also measured for Id1 by ELISA. For signal transduction analysis, human dermal microvascular endothelial cells (HUVEC), EPCs, and smooth muscle cells were plated and stimulated with human Id1. Western blot analysis was used to determine the kinetics of protein phosphorylation in cell lysates. Finally, we assessed the effects of Id1 signaling on angiogenesis using signaling RNA (siRNA) to inhibit HUVEC signaling pathways in the mouse Matriplugs assay.

**Results:** NL and RA synovial fibroblasts increased Id1 production with stimulation by TGF-β. Similarly, dermal fibroblast supernatants from NL and SSc patients showed a marked increase in Id1 production after stimulation with PDGF and TGF-β. We assessed the role of exosomes to determine the mechanism of Id1 transport outside the cell. We found that Id1 is encapsulated by fibroblast exosomes and that 80% of the Id1 released by RA synovial fibroblasts is contained within exosomes. Cell signaling assays following stimulation by recombinant human Id1 showed the JNK pathway was upregulated in HUVECs, EPCs, and RA synovial fibroblasts, while phospho-phosphorylation was increased in only EPCs. Furthermore, we showed that inhibiting HMVEC associated JNK with siRNA reverses Id1 induced HMVEC vessel formation in the mouse Matriplugs assay.

**Conclusion:** Id1 is a pleotropic molecule that has significant effects on angiogenesis, vasculogenesis, and fibrosis. Our data shows that Id1 is not only an important nuclear protein, but also that it can be released from fibroblasts in exosomes, thus expanding its role in the orchestration of inflammatory lesions.

Disclosure: G. Edhayan, None; C. M. Ha, None; R. A. Ohara, None; T. Izskaki, None; M. A. Aslmin, None; A. Arbab, None; P. S. Tsou, None; P. L. Campbell, None; E. Schiopu, None; D. Khanna, None; R. Morgan, None; S. C. Friday, None; D. A. Fox, None; J. Ruth, None.

1963

**Hierarchical Role of PI3K/Akt/mTOR Signaling Cascade on: Tissue Inflammation, Organization and Angiogenesis in Autoimmune Arthritis.** Sibra Raychaudhuri1, Anupama Mirta2, A nanya Datta Mirta3, Christine Abria2 and Smriti K. Raychaudhuri2. *1Univ California Davis/VA Sac, Davis, CA, 2VA Sacramento Medical Center, Mather, CA.

**Background/Purpose:** The PI3K/Akt/mTOR signaling proteins are pro-survival and thus likely to regulate inflammatory cascades in autoimmune diseases (1). The key pathologic outcome in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) is ‘uncontrolled proliferation’ of synovial fibroblasts (FLS), endothelial cells (EC) and T cells. To identify the regulatory role of the PI3K/Akt/mTOR kinase cascade in FLS proliferation, immune response and neoangiogenesis in PsA and RA, here we investigated the functional role of this kinase cascade in the target pathologic cells (FLS, EC, T cells) of these diseases.

**Methods:** Using the MTT assay we compared the antimitotic effect of Perifosine (Akt inhibitor), GDC-0941 (PI3K inhibitor), Rapamycin, NVP-BEZ235 (PI3K & mTOR inhibitor) and OSI-027 (mTORC1 & mTORC2 inhibitor) on FLS, T cells and human umbilical vein endothelial cells (HUVEC). FLS were derived from synovial tissues and T cells were obtained from the PBMC of PsA (n=5) and RA (n=5) patients. FLS were treated with PDGF and the T cells were treated with anti-CD3/CD28 cocktail. RTPCR was done to determine the effects of these mTOR inhibitors on regulation of genes associated with proliferation (MK167), inflammation (IL-8, MMP3) and T cell activation (IFNG and IL2).

**Results:** All the inhibitors significantly inhibited PDGF induced FLS proliferation in RA and PsA (Figure 1). The dual mTOR inhibitor OSI-027 had a maximum inhibitory effect. In HUVEC and T cells the maximal inhibitory effect was noticed with PI3K inhibitor GDC-0941. RTPCR results showed marked inhibition of the proliferation marker MK167 mRNA in all the cell lines, inhibition of MMP3 gene expression in FLS and inhibition of IFNG and IL2 genes in T cells.

**Conclusion:** Dual inhibitor of mTORC1/mTORC2 and proximal kinase inhibitors (Akt or PI3K) have more potent antimitotic effect on FLS, HUVECs and T cells compared to Rapamycin. These observations open up a new paradigm in respect to the regulatory role of mTOR kinase cascade in inflammatory arthritis and provide novel targets for these diseases. Inhibition of mTORC1 by rapamycin results in an unopposed activation of mTORC2 and thus a positive feedback to the PI3K/Akt pathway and reduces its clinical efficacy. To overcome the therapeutic failure of rapamycin (mTORC1 inhibitor) here we have explored whether an alternative effective therapeutic approach could be a dual inhibition of mTORC1 and mTORC2 or more proximal inhibition of the mTOR cascade by targeting either Akt or PI3K.

Reference:
1. Raychaudhuri SK, Raychaudhuri SP. mTOR Signaling Cascade in Psoriatic Disease: Double Kinase mTOR Inhibitor a Novel Therapeutic Target. Indian J Dermatol 2014;59:67-70.

Disclosure: S. Raychaudhuri, None; A. Mitra, None; A. Datta Mitra, None; C. Abria, None; S. K. Raychaudhuri, None.

1964

**Changes in Soluble CD18 Reflect Latency in the Immune System and Predict Radiographic Progression in Early Rheumatoid Arthritis.** Tue Wenzel Kragstrup1, Babak Jalili1, Kresten Karup Kellers1, Christian Stengaard-Pedersen1, M erete Lund Heltand1, K im Hansiev-Petersen1, Peter Junker2, Mikkel Østergaard2, Ellen Margrethe Hauge2, Malene Hvid2, Thomas Vorup-Jensen3 and Bent Deleur3. *1Aarhus University, Aarhus, Denmark, 2Aarhus University Hospital, Aarhus, Denmark, 3Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, 4Glostrup University Hospital, Glostrup, Denmark, 5Research Unit at King Christian X Hospital for Rheumatic Diseases, Graaesten, Denmark, 6Odense University Hospital, Odense, Denmark.

**Background/Purpose:** In early rheumatoid arthritis (RA), clinical disease characterized by swollen and painful joints is caused by synovitis. However, presence of autoantibodies may precede the clinical onset of RA by several years, and joint damage can progress despite clinical remission. Therefore, early and aggressive synovitis suppression has become the principal goal in ‘treat-to-target’ strategies. However, the temporal changes of immune system abnormalities during therapy and their significance remain poorly understood. Previously, we found a negative consequence of having low levels of the soluble form of CD18 (sCD18) in patients with chronic RA and spondyloarthritides. Here, we study changes in plasma sCD18 levels in patients with early RA during a treat-to-target strategy (the OPERA regimen), during...
arthritogenesis in a murine model of chronic inflammatory polyarthritis (the SKG model) and in RA mononuclear cell cultures.

**Methods:** The level of sCD18 in plasma was analyzed with a time-resolved immunofluorometric assay in a study population of 152 patients with early treatment naïve RA at baseline and after 3, 6, and 12 months of treatment and during induced arthritogenesis in SKG mice. In vitro, synovial fluid mononuclear cells (SFMCs) and peripheral blood mononuclear cells (PBMCs) from 9 RA patients were cultured with either TNFα (40 ng/ml) or adalimumab (500 μg/ml) for 48 hours. Data are expressed as median and IQR.

**Results:** Plasma levels of sCD18 were decreased in early RA patients at baseline (958.7 (766.2–1243) μU/ml) compared with healthy controls (HC) (1001 (872.0–1355) μU/ml) (P < 0.05). The sCD18 plasma levels decreased further by 11% after 3 months (P < 0.05), but after 12 months of treatment the levels returned to those of HC. The sCD18 increment between 3 and 12 months was most pronounced in patients who achieved an early ACR response compared with non-responders (P < 0.05). Changes in plasma sCD18 between baseline and 12 months associated inversely with progression in total Sharpe score (r = −0.18, P < 0.01) at the 24-month radiographic follow-up. Similarly, the serum level of sCD18 was decreased in SKG mice 6 weeks after arthritis induction (249 (151–282) μU/ml) compared with control SKG mice (334 (313–403) μU/ml) (P < 0.05) and exhibited a biphasic course after arthritis induction with an initial increase above baseline (P < 0.05) followed by a decline to levels below baseline (P < 0.05). In vitro, shedding of CD18 from RA SFMC and RA PBMC cultures were increased 2–3 fold by TNFα (both P < 0.01) and decreased by adalimumab (P < 0.05 and P < 0.01, respectively).

**Conclusion:** Concordant biphasic temporal patterns of sCD18 were observed in early RA and in a murine model of chronic inflammatory polyarthritis. The late increase in sCD18 was particularly pronounced in patients who achieved an early ACR response and may reflect latency in immune system restoration pertaining to the course of future radiographic progression.

**References**

**Disclosure:** T. W. Kragstrup, None; J. allian, None; K. K. Kelder, None; K. Stengaard-Pedersen, None; M. Lund Hetland, None; K. Harløv-Petersen, None; P. Junkir, None; M. Østergaard, Abbott/Abbott, Centocor, Merck, Schering-Plough, 2. Abbott/Abbott, BMS, Boehringer-Ingelheim, Eli-Lilly, Centocor, GSK, Jansen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche UCB, Wyeth, S. E. M. Haage, None; M. Hvid, None; T. Vorup-Jensen, None; B. Deleuran, None.

**1965**

**Characterization of the Thyroid Hormone System in Rheumatoid Arthritis.** Anna-Sophia Pörings1, Torsten Lowin2, Luise Rauch3, Tanja Späth3, None; M. Hvid4, None; T. Vorup-Jensen, None; B. Deleuran, None.

**Methods:** Activated ECs, after CTLA4-Ig treatment (10, 100, 500 μg/ml; 24 hrs), decreased their CD86-positivity at FACS by 66%, 59% and 51%, respectively, after 3 and 24 hrs of CTLA4-Ig treatment, the protein expression levels of both ICAM1 and VEGFR-2 were also evaluated by Western blot analysis (WB) and their respective gene expression was evaluated using quantitative real timePCR (qRT-PCR). The statistical analysis was performed using the Mann-Whitney non-parametric t test.

**Results:**Activated ECs, after CTLA4-Ig treatment (10, 100, 500 μg/ml; 24 hrs), decreased their CD86-positivity at FACS by 66%, 59% and 51%, respectively, after 3 and 24 hrs of CTLA4-Ig treatment, the protein expression levels of both ICAM1 and VEGFR-2 were also evaluated by Western blot analysis (WB) and their respective gene expression was evaluated using quantitative real timePCR (qRT-PCR). The statistical analysis was performed using the Mann-Whitney non-parametric t test.

**Conclusion:** Our data demonstrated that thyroid hormones are metabo-
**1967**

**Transforming Growth Factor Beta Is a Major Regulator of Micro-RNA Synthesis in Rheumatoid Arthritis Synovial Fibroblasts.** Anna Engler, E. Karouzakis, Christoph Kolling, Renate E. Gay, Caroline Ospelt.

**Background/Purpose:** Transforming growth factor beta (TGF-β) modulates microRNA (miRNA) biogenesis in a variety of cell types. The expression of miRNAs is deregulated in the synovial fibroblasts from patients with rheumatoid arthritis (RA). However, the role of TGF-β in the regulation of miRNAs in RA is not investigated so far. The aim of the current study was to investigate the role of TGF-β in the regulation of miRNAs and in the inflammatory and matrix-destructive properties of RA.

**Methods:** Synovial tissues were obtained from RA patients undergoing joint replacement surgery. RA (n=6) were stimulated with 10 ng/ml TNF-α or with TGF-β and TNF-α together in cultivation medium supplemented with 5% FCS for 24, 48, or 72 hours. Total RNA was isolated using Qiagen miRNeasy Kit. Global expression of miRNAs was analyzed by human miRNA Array analysis and verified by measurement of single miRNAs using real-time PCR with miRNA-specific TaqMan primers. The levels of interleukins (ILs) and matrix metalloproteinases (MMPs) were detected by Real-time TaqMan and SYBR green PCR.

**Results:** The global miRNA expression profile was altered by stimulation of RA with TGF-β after 48h in all patients. The expression of 29 miRNAs was downregulated by 25-70% whereas the levels of 32 miRNAs were upregulated by 50-800%. TGF-β induced changes in several miRNAs that were previously reported to be deregulated in RA. In particular, the levels of miR-155, miR-221, miR-222 and miR-353 were downregulated, while the expression of miR-18a, miR-22, miR-145 and miR-203 was significantly increased. We then investigated whether TGF-β can modify the effects of TNF-α. Stimulation with TNF-α alone increased the levels of miR-155 by 8.2-fold (p=0.01), while the co-stimulation with TNF-α and TGF-β resulted in only 4.3-fold (p=0.03) increase in miR-155 levels. Treatment with TNF-α decreased the expression of miR-145 by 0.7-fold (p=0.03). However, co-stimulation with TNF-α and TGF-β reversed this effect completely and increased the levels of miR-145 by 2.0-fold (p=0.03). In contrast, TGF-β amplified TNF-α-induced reduction in the expression of miR-222 and miR-335. Stimulation with TNF-α or TGF-β alone already significantly reduced the expression of these miRNAs and co-stimulation with TGF-β and TNF-α together led to a further decrease in the levels of miR-222 (by 0.35-fold, p=0.03) and miR-335 (by 0.4-fold, p=0.02). Moreover, TGF-β mitigated the matrix-destructive activities of RA that were induced by TNF-α by strongly decreasing TNF-α induced MMP1 expression (by 16-fold, p=0.04). In contrast, TNF-α-initiated IL6 production was increased by TGF-β (by 1.7-fold, p=0.03).

**Conclusion:** In the current study we found that TGF-β modulates the expression of miRNAs involved in the pathogenesis of RA. Moreover, TGF-β influences the inflammatory and matrix-destructive activities of RA by reduction of TNF-α-induced MMP1 expression and by enhancement of TNF-α-initiated IL6 production. Thus, TGF-β has dual effects in the regulation of RA and exhibits pro-inflammatory as well as anti-matrix-destructive properties.

**Disclosure:** A. Engler, None; E. Karouzakis, None; C. Kolling, None; R. E. Gay, None; S. Gay, None; C. Ospelt, None.

**1968**

**Highly activated IL-23/T17 axis and JAK2/STAT3 signal pathway in PBMC of active AS patients involve in pathogenesis of AS.** Hongxiao Liu, Peng Chen, Yingyan Zhou, Junya Song, Benyou Liu, Xiaoyan Feng and Xinghua Feng.

**Background/Purpose:** Transforming growth factor beta (TGF-β) has dual effects in the regulation of miRNAs and in the inflammatory and matrix-destructive properties of RA. Moreover, TGF-β influences the inflammatory and matrix-destructive activities of RA by reduction of TNF-α-induced MMP1 expression and by enhancement of TNF-α-initiated IL6 production. Thus, TGF-β has dual effects in the regulation of RA and exhibits pro-inflammatory as well as anti-matrix-destructive properties.
is considered a mesenchymal stem cell marker that is expressed by a small fraction of SF ex vivo. We have analyzed the location and relative proportion of CD271+ cells in synovial tissues from rheumatoid arthritis (RA), osteoarthritis (OA) and normal (N) individuals as well as their ex vivo functional properties in CD271+/− SF sorted cultures.

**Methods:** CD271 expression was analyzed by immunohistochemistry (IHC) in synovial tissues, and by flow cytometry (FC) in SF cultures from RA (n=10), OA (n=10), and normal synovial tissues (n=6). Isolation of CD271+ and CD271- OA SF (n=3) was carried out by magnetic beads sorting in passage 0 from OA explants. Supernatants of sorted CD271+/− SF were analyzed for IL-6, IL-8, MCP-1, MMP-1, MMP-3 and VEGF production by multiplex ELISA array (RayBiotech, Norcross, GA, USA). IL-6 data were confirmed by single specific ELISA. Quantitative data were analyzed by Mann-Whitney or ANOVA test where appropriate.

**Results:** CD271+ cells were observed by IHC in all types of synovial tissues with a perivascular distribution spatially resembling periartericular areas. The number of CD271+ cells per area was significantly increased in both RA and OA tissues compared to normal synovial tissues (772±206, 802±221 and 206±100 per mm² respectively, p<0.0001 ANOVA). The frequency of CD271+ cells in SF cultures was highly variable but a trend towards a higher proportion of CD271+ cells in OA compared to RA and normal established SF cultures was observed (5.1±4.0%, 1.4±0.9% and 1.5±0.8% respectively). In individual OA SF cultures, cell-passageing from passage 0 to 5 induced a progressive decrease in the percentage of CD271+ cells. OA CD271+ SF cultures sorted at passage 0 released significantly more IL-6 (3.1-fold increase) and metalloproteinase MMP-1 (8.1-fold increase) than CD271- SF. A non-significant trend towards more IL-8, MMP-3 and VEGF production in CD271+ SF was also observed. MCP-1 production was similar in both SF subsets.

**Conclusion:** Our results demonstrate an expansion of CD271+ perivascular cells in inflammatory RA and OA synovial tissues. Cultured CD271+ SF showed increased production of proinflammatory factors ex vivo compared to CD271- SF. These data suggest that CD271+ stromal cells could play a proinflammatory role in OA and RA synovium.

**Disclosure:** M. J. Del Rey, None; R. Far, None; G. Criado, None; A. Usategui, None; V. Miranda, None; J. D. Cañete, None; J. L. Pablos, None.

**1970**

T_{H}17 Inflammatory Responses Occur in a Subset of Patients with Erythema Migrans or Lyme Arthritis, but Are Not Predominant Responses in Joints. Klemen Strle, Elise E. Drouin and Allen C. Steere. Massachusetts General Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** Lyme disease usually begins with an expanding skin lesion, erythema migrans (EM), whereas arthritis is a late disease manifestation. The infection usually resolves with appropriate antibiotic therapy, but post-infectious symptoms following EM or persistent synovitis despite antibiotic therapy (antibiotic-refractory arthritis) may occur. Control of the infection in humans is attributed predominantly to innate and adaptive T\_H1 immune responses, whereas the role of T\_H17 responses is not yet well characterized. We recently showed that high levels of IL-23, a T\_H17-associated cytokine, occur in a subset of European patients with EM, and are associated with more frequent post-infectious symptoms and autoantibody responses. Here, we characterized these responses in a large cohort of American patients with EM or Lyme arthritis to elucidate the role of T\_H17-mediated immunity throughout the infection.

**Methods:** The levels of 20 cytokines and chemokines, representative of innate and adaptive T\_H1 and T\_H17 immune responses, were assessed by Luminex in matched acute and convalescent serum samples from 106 culture-positive patients with EM, in matched serum and synovial fluid (SF) samples from 159 patients with antibiotic-responsive or antibiotic-refractory arthritis, and in serum samples from 57 healthy control subjects.

**Results:** Compared with healthy subjects, acute-phase sera from EM patients contained significantly higher levels of the T\_H17-associated mediators (IL-6, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25 and IL-27; P=0.01). With the exception of IL-27, which down-regulates T\_H17 responses, the levels of other T\_H17-associated mediators remained elevated in convalescent sera obtained at the conclusion of antibiotic therapy. The levels of IL-23, the most highly induced T\_H17 cytokine, correlated directly with antibody levels to the B. burgdorferi V\_se antigen (P=0.04) in both acute and convalescent samples, suggesting a role for T\_H17-associated mediators in control of the infection. In patients with Lyme arthritis, the serum levels of IL-23 and other T\_H17-associated mediators were generally lower than in patients with EM, and the levels of these mediators were only minimally concentrated, if at all, in SF. In contrast, innate (IL-8) and T\_H17 mediators (CXCL9 and CXCL10) were 50-fold higher in SF than in serum. Compared with antibiotic-responsive patients, there was a trend toward higher levels of most of the T\_H17-associated mediators, particularly IL-23, in SF in patients with antibiotic-refractory arthritis, and toward a greater frequency of autoantibody responses to human endothelial cell growth factor, the first known target of T\_H17 and B cell responses in this disease.

**Conclusion:** A subset of patients with Lyme disease develops T\_H17 immune responses. T\_H17-associated mediators seem to be highest early in the infection and may play a role in control of the infection. In addition, T\_H17 mediators may be one factor in shaping an immune response early in the illness in which autoantibody responses are more common, thereby contributing to subsequent antibiotic refractory Lyme arthritis.

**Disclosure:** K. Strle, NIH, Arthritis Foundation, 2: E. E. Drouin, None; A. C. Steere, ACR, NIH, Foundation, 2.

**1971**

The Role of the Proinflammatory Mediator High-Mobility Group Box Protein 1 (HMGB1) in Anti-Collagen-Antibody-Induced Arthritis Is Dependent on Vascular Endothelial Growth Factor (VEGF). Federico Biscetti1, Andrea Flex2, Giovanni Pecorini3, Flavia Angelini4, Vincenzo Arena5, Egidio Stigliano6, Barbara Tolusso6, Elisa Gremsie6 and Gianfranco Ferraccioli6. 1Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy. 2Laboratory of Vascular Biology and Genetics, Catholic University School of Medicine, Rome, Italy. 3Department of Pathology, Catholic University School of Medicine, Rome, Italy.

**Background/Purpose:** High-mobility group box 1 (HMGB1) is a non-histone nuclear protein that is released extracellularly and has been implicated in rheumatoid arthritis (RA) and angiogenesis. Although HMGB1 is abundantly expressed throughout the inflamed synovium, the mechanism by which this protein is involved in the development of RA is still not well known. The aim of this study was to better define the role of HMGB1 in the synovial angiogenesis and pathogenesis of RA.

**Methods:** Balb/c mice were injected with monoclonal anti-collagen antibody cocktail followed by lipopolysaccharide. Animals were evaluated every 3 days after the infusion of the antibody cocktail for arthritis incidence and each paw was evaluated and scored individually on a scale of 0–4, with 4 indicating the most severe inflammation. An arthritis index (AI) that expressed a cumulative score for all paws was calculated for each animal. To investigate the role of HMGB1 in pathological synovial angiogenesis in RA, three groups of mice were studied: mice treated with HMGB1, mice treated with HMGB1 inhibitor BoxA and untreated control mice. To further define and clarify the HMGB1 – VEGF interaction, additional groups of mice were treated with BoxA and with vascular endothelial growth factor (VEGF) inhibitor, the sflk-1 plasmid.

**Results:** Immunohistochemical and ELISA analyses confirmed over-expression of HMGB1 and VEGF in the areas of the synovium where more inflammation and neoangiogenesis were present. Interestingly, the selective blockade of HMGB1 or of VEGF alternatively resulted in a lower severity of arthritis evaluated by AI (p=0.003 and p=0.001) (Figure).
increase of the peripheral IL-17A concentration (p < 0.001). ELISA analyses performed on peripheral blood and synovial fluid demonstrated a significant reduction of IL-1b (p < 0.001), IL-6 (p < 0.001) and TNF-a (p < 0.001) in mice where HMGB1 and VEGF pathways were blocked. Interestingly, the selective blockade of HMGB1 and VEGF resulted in an increase of the peripheral IL-17A concentration (p < 0.001).

**Conclusion:** The development of arthritis mediated by HMGB1 and the synovial angiogenesis can be blocked by inhibiting the VEGF activity. The pro-inflammatory and pro-angiogenic cytokine IL-17A is increased when HMGB1 or VEGF are inhibited and the synovial angiogenesis is nevertheless maintained. This model of arthritis. These data confirm that the blood vessels neoformation at the synovial level is dependent on VEGF. Taken together, these findings shed new light on the role of this nuclear protein in the pathogenesis of arthritis in an RA-like model.

**Disclosure:** F. Biscetti, None; A. Flex, None; G. Pecorini, None; F. Angelini, None; V. Arana, None; E. Stigliano, None; B. Toluso, None; E. Gremese, None; G. Ferraccioli, None.

**1972**

**Analysis of Anakinra in Primary Human Cell Systems Reveals an in Vitro Signature for Skin-Related Side Effects.** Ellen L. Berg, Alison O'Mahony and Mark A Polokoff. BioSeek, South San Francisco, CA.

**Background/Purpose:** The therapeutic options for treatment of rheumatic diseases have grown and now include a variety of inflammatory pathway inhibitors, with diverse mechanisms, but having both shared and unique side effects. Understanding side effect mechanisms is important for guiding patient treatment choices and also for developing improved next generation therapies. We have successfully employed high throughput primary human cell-based models of tissue and disease. BioMAP Systems, to study failed and approved drugs and have previously identified in vitro activities that correlate with certain side effects. Here we compare the activity profiles of adalimumab (TNF inhibitor), MTX and anakinra (IL1RA) to test if activities can be correlated with differences in efficacy or safety.

**Methods:** BioMAP system disease biology in early-passage human primary cells and have been used extensively to characterize compounds based on phenotypic signatures. A panel of 12 BioMAP systems, including mono- and co-cultures of vascular, immune, and tissue cell types were used to generate profiles of anakinra, adalimumab, and MTX. Changes in protein-based and clinically relevant endpoints (biomarkers, including inflammatory, immune, tissue remodeling and hemosiderin-related endpoints) as well as other cellular events (e.g., proliferation, cell cytotoxicity) were evaluated. For select activities, a comparison to a large reference database of approved and failed drugs, experimental chemicals, and other agents, was performed to elucidate potential mechanisms.

**Results:** The profiles for both anakinra and adalimumab show anti-inflammatory activities across the panel of BioMAP systems, including reduction in leukocyte recruitment molecules IL-8, E-selectin and MCP-1. Anakinra was more effective in blocking responses in a co-culture system of monocyte-driven (TLR4) vascular inflammation (LPS system) and differentially active in a model of T cell-dependent B cell activation (BT system), reducing IL-17A, IL-17F, and IL-6. In contrast, adalimumab was more effective in co-cultures driven by T cell or macrophage (TLR2) activation (SAg and Mph systems). The profile for MTX was distinct, reducing T cell proliferation (SAg system) and IgG production (BT system). Interestingly, in a fibroblast model of wound healing (HDF3CGF system), anakinra, but not adalimumab or methotrexate increased the levels of V CAM-1 and I-TAC (CXCL11). VCAM-1 and I-TAC (CXCL11) mediate recruitment of inflammatory lymphocytes into sites of inflammation. This combination of activities is an unusual feature shared by Mek and p38 MAPK inhibitors, that we have previously associated with the potential for skin rash side effect.

**Conclusion:** Profiling of anakinra across a panel of primary human cell systems reveals an activity signature that has been correlated with skin side effects, and may be related to the cutaneous side effects observed with anakinra in patients. This signature is shared by inhibitors of Mek and p38 MAPK and suggests a common pathway mechanism. A better understanding of side effect mechanisms can help in the design and selection of novel therapies, or combinations.

**Disclosure:** E. L. Berg, BioSeek; 3; A. O’Mahony, DiscoveRx Corp (BioSeek division); 1, BioSeek; 3; M. A. Polokoff, BioSeek, a division of DiscoveRx, 3.
compared to the normoxic situation. In hypoxic (p=0.005) but not normoxic conditions (p=0.471), RA SFs produce more BAFF when exposed to the same IFN stimulation than OA SFs. IFN leads to a strong phosphorylation of STAT1 but to a reduction in phosphorylated STAT3. However, it has been suggested that concomitant phosphorylation of STAT3 further augments BAFF production. Therefore, we wanted to test if concomitant IL-1 or IL-10, which both lead to phosphorylation of STAT3, further increase IFN-induced BAFF in SFs. However, in the presence of IL-1 or IL-10, IFN-induced BAFF was inhibited in a time- and manner independent of oxygen content in both, OA (p<0.001) and RA (p<0.001) fibroblasts. Furthermore, inhibition of pSTAT3 resulted in further augmentation of IFN-induced BAFF.

Finally, in the presence of dihydrotestosterone and estrogen, IFN-induced inhibition of pSTAT3 resulted in further augmentation of IFN-induced BAFF. BAFF production. Therefore, we wanted to test if concomitant IL-1 or IL-10, STAT1 but to a reduction in phosphorylated STAT3. However, it has been consistent with RA-Inflammation Biology.

1975

Profile 14-3-3η in Human Primary Cell Based BioMAP® Disease Models Reveals a Unique Pro-Inflammatory Phenotypic Signature Consistent with RA-Inflammation Biology. Alison O’Mahony1, Ellen L. Berg2, WP Maksymowycz2, Yuen Guii and Anthony Marotta3. 1BioSeek, South San Francisco, CA, 2University of Alberta, Edmonton, AB, 3Augurex Life Sciences Corp., North Vancouver, BC.

Background/Purpose: 14-3-3 proteins represent a highly conserved seven-member family of ubiquitously expressed intracellular chaperonins that perform a broad range of signaling functions. The 14-3-3 eta (η) protein is an emerging diagnostic and prognostic biomarker for RA driving inflammation and joint erosion. Elevated levels of the η isofrom have been reported in synovial fluid and serum from patients with joint inflammation, but not with other diseases including psoriasis, osteoporosis, SLE, Crohn’s and M.S. Here we evaluate the impact of this RA-associated biomarker on the levels of clinically relevant biomarkers across a panel of human primary cell-based disease models in the BioMAP® platform.

Methods: BioMAP® systems model disease biology in primary human cells cultured alone or with different stimulus combinations and have been used extensively to characterize compounds based on phenotypic signatures. Phenotypic activity profiles were generated for eight concentrations of 14-3-3η observed in RA patients (0.25-50 ng/ml) across a panel of 13 BioMAP systems modeling vascular, immune, inflammation and tissue remodeling biology relevant for various human diseases. Changes in protein-based, clinically relevant endpoints (biomarkers), cell proliferation and cytotoxicity were evaluated to identify activities of 14-3-3η relative to vehicle control. The resultant 14-3-3η BioMAP profile was analyzed and compared in a similarity search with more than 3000 compounds in the BioMAP database to identify common mechanistic signatures using Pearson’s correlation.

Results: 14-3-3η messenger RNA (mRNA) is highly expressed in all BioMAP Diversity Plus Systems with stimulus coupled increases detected in B cell and Fibroblast based systems. The activity profile for 14-3-3η in BioMAP shows highly selective effects in two systems: 1. HPNo, a non-stimulated vascular endothelial cell-PBMC co-culture; 2. BT, a stimulated co-culture of CD19+ B cells plus PBMC modeling T-cell dependent B cell activation. 14-3-3η caused an increase in levels of VCAM-1 and TNFα in HPNo and SLE-6 production in BT, activities consistent with an inflammatory phenotype. Comparison of the profile to the BioMAP database identified mechanistic matches with several pro-inflammatory TLR-like agonists including Pam3CSK4, a TLR-2/1 agonist (r = 0.735), Flagellin, a TLR-5 agonist (r = 0.723) and HKLM, a TLR-2 agonist (r = 0.721). Of interest, the BioMAP profile of 14-3-3η was not similar to LPS, a potential bacterial endotoxin contaminant of biological preparations that also has TLR agonist activity.

Conclusion: The BioMAP profile for 14-3-3η is consistent with activation of B cell responses that correlates with pro-inflammatory activity associated with disease-relevant biomarkers. This data supports the hypothesis that 14-3-3η may serve both as a diagnostic marker in early RA as well as an important target for therapeutic intervention.

References:


1976


Background/Purpose: IFNω is emerging as a clinically validated target in SLE yet it is currently unclear if other type I IFNs are contributing to the IFN signature present in many SLE patients. In this study we analyzed SLE patient sera and plasma for the presence of IFNα and IFNω and compared the biological effects imparted by recombinant IFNα and IFNω on human cells. We further examined the effects of blocking IFNα alone versus dual blockade of IFNα and IFNω using SLE patient-derived IFN stimuli in vitro.

Methods: SLE patient sera and plasma were analyzed for the presence of IFNα and IFNω using a multiplex ELISA. SLE sera or conditioned media from recombinant SLE patient immune complexes were used as stimuli in an ISRE reporter gene assay (RGA) with selectively neutralizing mAbs to IFNα or IFNω or isotype control. To examine the effects of IFNω treatment, PBMCs from 6 healthy human donors were treated with either recombinant IFNα or IFNω and gene and protein expression were analyzed by microarray and, Lumimax or ELISA, respectively. To assess the individual contribution of IFNα and IFNω on the IFN signature, unstimulated SLE whole blood from patients having an elevated IFN signature was treated with neutralizing mAbs to IFNα or IFNω or the combination of both and qPCR analysis was performed. A fully-human monoclonal antibody targeting IFNα and multiple subtypes of IFNω was developed and tested for its ability to neutralize IFNα and IFNω-induced IP-10 release in whole blood.

Results: IFNω and IFNα were found to be elevated in the plasma and serum of a subset of SLE patients. IFNω protein was also detected in conditioned media from SLE patient immune complex-stimulated PBMCs. Combined blockade of IFNα and IFNω resulted in further suppression of IFN activity in comparison to IFNα blockade alone using these endogenous preparations of type I IFN. Microarray data from IFNα- and IFNω-treated PBMCs indicated that 99.25% of genes modulated by IFNα treatment versus untreated control were modulated by IFNα at 24h. IFNω exhibited indistinguishable qualitative gene expression responses as compared to IFNα-treated cells using a 21 gene IFN signature. IFNα and IFNω treatment induced TLR7, IP-10 and BLYS gene expression. IFNω-mediated BLYS and IP-10 induction was confirmed at the protein level. To determine the impact of various IFN inhibitors on the IFN signature present in SLE donor whole blood, neutralizing antibodies targeting IFNα, IFNω, or the combination of both were added to unstimulated blood. Gene expression analysis by qPCR indicated that combined blockade of IFNα and IFNω resulted in greater reduction of multiple IFN inducible genes than IFNα blockade alone. We further demonstrate a fully-human monoclonal antibody capable of dose-dependently inhibiting IP-10 release induced by both IFNα and IFNω.

Conclusion: IFNω antagonism enhanced the ability of IFNα antagonists to suppress IFN activity in SLE patient sera, SLE immune complex-induced preparations of IFN and the IFN signature in SLE patient whole blood in vitro. IFN signatures induced by recombinant IFNα and IFNω were found to be indistinguishable and our current data lends compelling support to the hypothesis that IFNω may contribute to the total type I IFN activity and signature present in some SLE patients.

Disclosure: J. Jordan, Janssen Research and Development, LLC., 3; J. Schreiter, Janssen Research and Development, LLC., 3; H. Liu, Janssen Research and Development, LLC., 3; S. Adhikarakunnathu, Janssen Research and Development, LLC., 3; C. Huang, Janssen Research and Development, LLC., 3; J. Benson, Janssen Research and Development, LLC., 3.
Aim: to functionally characterize the different monocytes subsets in RA patients and analyze their role in the endothelial dysfunction, altered oxidative status and proinflammatory/prothrombotic profile associated to RA.

Methods: Thirty RA patients and 15 healthy donors were included in the study. Endothelial function was measured through post occlusive hyperaemia (PORH) using the Laser-Doppler linear Periflux S5010. Classic, intermediate and non-classic monocytes were characterized by flow cytometry. Different proinflammatory cytokines and peroxides levels were analyzed by flow cytometry in the three different subsets.CD14brightCD16- and CD16+ cells were isolated using immuno-magnetic selection. mRNA expression of inflammatory cytokines, endothelial adhesion markers and oxidative enzymes were analyzed in the two monocytes subsets. Correlation studies between clinical parameters, endothelial function and markers of inflammation and endothelial adhesion expression by the different monocytes subsets were performed.

Results: CD16+ (intermediate and non-classic) monocytes were extended in RA patients. These subsets had increased protein expression of TF, ILK and TNFa and lower peroxide levels compared to CD14brightCD16-. CD16+ monocytes displayed higher mRNA expression of TF, TNFa, TLR4, PPARg and MCP-1. In contrast, CD14brightCD16- cells had increased expression of IL8 and oxidative enzymes. All these parameters were significantly increased in RA patients. RA patients had impaired endothelial function, with a reduced perfusion value after ischemia.

Clinical parameters such as evolution time, CRP, anti-CCPs antibodies and rheumatoid factor levels strongly correlated with endothelial dysfunction, decreased percentage of classic monocytes and increased number of non-classic and intermediate subsets. Furthermore, higher expression of proinflammatory/proangiogenic molecules and endothelial adhesion markers in these CD16+ cells correlated with the alteration in endothelial function and the clinical parameters.

Conclusion: RA patients display an increased number of intermediate and non-classic monocytes directly associated to the autoimmune and inflammatory profile, the progression of the disease and the altered microvascular function. Therefore, CD16+ subpopulation might play a key role in the atherosclerotic pathogenesis of RA.

Funded by CTS7940, PI12/01511, PI2013-0191, SER.

Disclosure: C. Lopez-Pedrera None; P. Ruiz-Limon, None; C. Perez-Sanchez None; R. Carretero None; Y. Jiménez Gómez None; Aguirre Zamorano None; J. calvo-Gutierrez None; E. Collantes-Estevez None; A. Escudero-Contreras None; N. Barbarroja None.

1979

Pseudoestivation By AMPK Activator Therapy Is Associated with Reduced Disease Activity and Downregulation of Pro-Inflammatory Responses in Rheumatoid Arthritis (RA).


Aim: to functionally characterize the different monocytes subsets in RA patients and analyze their role in the endothelial dysfunction, altered oxidative status and proinflammatory/prothrombotic profile associated to RA.

Methods: Thirty RA patients and 15 healthy donors were included in the study. Endothelial function was measured through post occlusive hyperaemia (PORH) using the Laser-Doppler linear Periflux S5010. Classic, intermediate and non-classic monocytes were characterized by flow cytometry. Different proinflammatory cytokines and peroxides levels were analyzed by flow cytometry in the three different subsets.CD14brightCD16- and CD16+ cells were isolated using immuno-magnetic selection. mRNA expression of inflammatory cytokines, endothelial adhesion markers and oxidative enzymes were analyzed in the two monocytes subsets. Correlation studies between clinical parameters, endothelial function and markers of inflammation and endothelial adhesion expression by the different monocytes subsets were performed.

Results: CD16+ (intermediate and non-classic) monocytes were extended in RA patients. These subsets had increased protein expression of TF, ILK and TNFa and lower peroxide levels compared to CD14brightCD16-. CD16+ monocytes displayed higher mRNA expression of TF, TNFa, TLR4, PPARg and MCP-1. In contrast, CD14brightCD16- cells had increased expression of IL8 and oxidative enzymes. All these parameters were significantly increased in RA patients. RA patients had impaired endothelial function, with a reduced perfusion value after ischemia.

Clinical parameters such as evolution time, CRP, anti-CCPs antibodies and rheumatoid factor levels strongly correlated with endothelial dysfunction, decreased percentage of classic monocytes and increased number of non-classic and intermediate subsets. Furthermore, higher expression of proinflammatory/proangiogenic molecules and endothelial adhesion markers in these CD16+ cells correlated with the alteration in endothelial function and the clinical parameters.

Conclusion: RA patients display an increased number of intermediate and non-classic monocytes directly associated to the autoimmune and inflammatory profile, the progression of the disease and the altered microvascular function. Therefore, CD16+ subpopulation might play a key role in the atherosclerotic pathogenesis of RA.

Funded by CTS7940, PI12/01511, PI2013-0191, SER.

Disclosure: C. Lopez-Pedrera None; P. Ruiz-Limon, None; C. Perez-Sanchez None; R. Carretero None; Y. Jiménez Gómez None; Aguirre Zamorano None; J. calvo-Gutierrez None; E. Collantes-Estevez None; A. Escudero-Contreras None; N. Barbarroja None.
In LPS and TNFα-stimulated K4 SF, IL-6 and IL-8 production is decreased in the presence of metformin or phenformin in a dose dependent manner, with phenformin the more potent effect (P < 0.0001). In LPS stimulated HMVEC, the production of IL-6 was also decreased in the presence of metformin or phenformin, dose dependent manner, with phenformin the more potent; 2428 pg/ml (LPS) reduced to 2263 pg/ml (Metformin 0.5 mM). 149 pg/ml (Metformin 1mM, P = 0.0005), 1387 pg/ml (Metformin 2mM, P < 0.0001), 917 pg/ml (Phenformin 0.5 mM, P < 0.0001), 629 pg/ml (Phenformin 1mM, P < 0.0001), and 306 pg/ml (Phenformin 2mM, P < 0.0001). Decreased production of IL-8 was seen with phenformin: 12572 pg/ml (LPS) reduced to 8270 pg/ml (0.5 mM, P < 0.0001), 5731 pg/ml (1 mM, P < 0.0001) and 409 pg/ml (2 mM, P < 0.0001). IL-8 production was not decreased in LPS stimulated cells in the presence of Metformin.

By immunoblot, pAMPK expression was strongly upregulated in the presence of metformin or phenformin (2 mM) compared to unstimulated K4 SF cells indicating a role of both drugs in activating AMPK.

Conclusion: AMPK activation is associated with reduced RA disease activity and down-regulation of pro-inflammatory effector responses. AMPK activating drugs, such as Metformin, may be suitable as an additional therapeutic agent in the treatment of RA.

Disclosure: L. Gallagher, None; U. Fearon, None; D. J. Veale, Abbvie, 2; MSD, 2; Pfizer Inc, 2; Roche, 2; Pfizer, 5; Roche, 5; Abbott, 8; MSD, 8; Pfizer, 6; Roche, 8; D. Kane, None; L. A. O’Neill, None; R. Mullan, None.

1980

Thrombospondin-1 Is Elevated in the Plasma of Patients with Antiphospholipid Syndrome and Is Correlated with Soluble Fas Ligand and Free Active TGF-B Levels

Markos Patsouras, Marina Sikara, Athanasios G. Tzioufas and Panayiotis Vlachoyiannopoulos. School of Medicine, National University of Athens, Athens, Greece.

Background/Purpose: Antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by recurrent thromboembolism and pregnancy morbidity. Thrombospondin (TSP-1) is a matricellular glycoprotein with antiangiogenic and proapoptotic properties, which is secreted by platelets upon activation. It has been described to promote apoptosis through activation of caspases or induction of Fas ligand (sFasL) expression. Furthermore, TSP-1 is considered as the major activator of TGF-beta by releasing it from the Latency Associated Peptide. Herein, we sought to study the involvement of TSP-1 in antiphospholipid syndrome.

Methods: Plasma, serum and platelets obtained from 90 patients fulfilling the diagnostic criteria of APS, 46 healthy individuals (healthy controls: HC) and 26 SLE patients, that served as disease controls were studied.

Human Umbilical Vein Endothelial Cells (HUVECs) were isolated from 2 APS patients and 3 HCs upon full term vaginal delivery by a standard protocol. HC-HUVECs were cultured in the presence of 10% plasma from HC (n = 10) or APS patients (n = 20) for 20 hours. Then, culture supernatants (SPN) were removed, cells were washed twice with HBS and fresh medium was added and left for two hours (hr). The 2 hr SPNs were collected and kept at -20°C till use. Furthermore, HUVECs from APS patients were cultured in medium supplemented or not with their own plasma. TSP-1, soluble Fas, sFasL and active cell-free TGF-B were determined by ELISA in plasma and cell culture SPNs.

Results: APS patients had significantly higher plasma levels of TSP-1, compared to HCs and SLE patients (Mann-Witney U-test): 90.0 (95.90–437.7) in APS patients vs 144.3 (46.3–236.6), P = 0.0001, and: 153.0 (82.2–267.2), P = 0.029 in HCs and SLE patients, respectively. TSP-1 was found to strongly correlate with sFasL and active TGF-B levels (Spearman r = 0.8785, P < 0.0001 and r = 0.827, P < 0.0001, respectively). Significantly higher levels of TSP-1 were detected in culture SPNs obtained from HUVECs treated with plasma from APS patients compared to those from HCs (mean concentration: 139 pg/ml in APS vs 22.8 pg/ml in HCs, P = 0.0009). The analysis of correlations with clinical features, revealed that lower TSP-1 levels (mean value 130.1 ng/ml) were associated with pregnancy morbidity alone, whereas higher levels (403.2 ng/ml) with thromboembolic events with or without miscarriages (P = 0.05).

Conclusion: Our findings implicate TSP-1 in APS pathogenesis, and associate it with the levels of sFasL and active TGF-B in the plasma of patients. Further studies are needed to clarify the exact role of TSP-1.

Disclosure: M. Patsouras, None; M. Sikara, None; A. G. Tzioufas, None; P. Vlachoyiannopoulos, None.

1981

A Qualitative Analysis of Methotrexate Injection Videos on Youtube

Rebekah Rittberg,7 Thairindi Dissanyake6 and Steven J. Katz.5 University of Manitoba, Winnipeg, MB, 5University of Alberta, Edmonton, AB.

Background/Purpose: Methotrexate (MTX) is one of the most commonly prescribed disease modifying antirheumatic drugs for rheumatoid arthritis. While data suggests subcutaneously administered methotrexate is more efficacious, there are many potential patient barriers to its use. Video-assisted teaching has been shown to be an effective supplementary method for subcutaneous MTX education. This review evaluates the quality of video resources available for patients on YouTube for learning to self-administer subcutaneous MTX.

Methods: Using the search term “Methotrexate injection” on YouTube, 2 independent clinical reviewers in 2 different geographic locations analyzed the first 3 pages of search results (60 videos). Discrepancies were evaluated and resolved by a 3rd independent reviewer. Source and search range of videos, audience views video duration and time since video was uploaded to YouTube were recorded. Videos were classified as useful, misleading or a personal patient view. Videos were rated for reliability using the DISCERN reliability tool (0–5, 5 being the most reliable), comprehensiveness (0–4; 1 point each as follows: needle preparation, MTX withdrawal, injection demonstration, needle disposal) & global quality scale (GQS; 1=poor video quality, 5=excellent video quality). Reasons for misleading videos were documented, and personal patient view videos were recorded as being either positive or negative towards MTX injection.

Results: A total of 51 English videos overlapped between the two geographic locations; 10 videos were classified as useful (19.6%), 14 as misleading (27.5%) & 27 as personal patient view (52.9%). Total views of videos were 161,028: 19.2% useful videos, 72.8% personal patient view videos, & 8.0% misleading videos. Mean GQS was 4.2 (± 1.0) for useful videos, 1.6 (± 1.1) for misleading videos & 2.0 (± 0.9) for personal patient view videos (P < 0.0001). Mean reliability was 3.3 (± 0.6) for useful videos, 0.9 (± 1.9) for misleading videos, & 1.0 (± 0.7) for personal patient view videos (P < 0.0001). Comprehensiveness was 2.2 (± 1.9) for useful videos, 0.1 (± 0.3) for misleading videos, & 1.5 (± 1.5) for personal patient view videos (P = 0.0027). Of the personal patient view videos, 77.8% were positive, & 22.2% were negative. No significant correlation was found between the number of video views and quality of the video. The most common reason for a video being misleading was video content being unrelated to MTX injection. Of the 10 videos (19.6%) from university or professional organizations, 80% were useful and 20% misleading, while 72.7% of the 11 medical advertisements/for-profit organizations videos were misleading.

Conclusion: A qualitative review of MTX injection videos posted on YouTube shows a minority of useful videos for MTX injection, with the majority of viewers watching patient created videos. While many of these demonstrate MTX injection positively, this does not necessarily correlate with appropriate and safe technique. While web video may be an additional educational tool available for patients, clinicians need to be familiar with specific resources to help guide and educate their patients to ensure best outcomes.

Disclosure: R. Rittberg, None; T. Dissanyake, None; S. J. Katz, None.

1982

Final Year Medical Students Prefer E-Reading Content to Interactive Case-Based Quizzes in a Pediatric Rheumatology E-Learning Module

Taunton R. Southwood. Institute of Child Health, University of Birmingham and Birmingham Children’s Hospital. Birmingham, United Kingdom.

Background/Purpose: Traditional medical student learning and teaching methods, such as lectures and bedside teaching, maybe inadequate for providing core knowledge and clinical skills in rheumatology, paediatrics and paediatric rheumatology, with reduction in undergraduate time allocated to paediatrics and increasing medical student numbers. To supplement paediatric knowledge and improve access to essential clinical skills, an e-learning module, “paediatric rheumatology”, was developed within a Canvas® learning management system. The design promoted revision of basic sciences (e.g. musculoskeletal anatomy,
way to teach IM residents clinical skills during their busy schedules. Using a validated survey created at Duke University, we found that a short, dedicated MSK exam workshop performed by Rheumatologists improved IM residents’ confidence and ability to perform an MSK exam in statistically significant matter. Limitations were the small size of our study group and poor response rate to the post-survey evaluation. We were also unable to collect a sufficient number of responses from residents who did not participate in the workshop for a control comparison. We hope to perform this workshop on a larger scale with adequate control groups.

Table 1:

<table>
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<th>Post-test Average Ranking</th>
<th>Adjusted p-value</th>
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<td>Question 7: Assessing the following joints for range of motion:</td>
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<td>Question 8: Using information gained from physical exam of the following joint areas to make diagnoses:</td>
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<td>Question 9: Using information gained from physical exam of the following joint areas to guide medical decision making:</td>
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<td>Question 10: Performing and interpreting special diagnostic maneuvers on the following joints:</td>
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Table of contents:

I. Rosenberg, None; X. Mo, None; L. G. Criscione-Schreiber, None; N. Bundy, None.

Tuesday, November 18

Background/Purpose: We developed and conducted an OSCE to assess clinical skills of trainees in rheumatology (TRs) and determine its performance at two consecutive annual evaluations of the National Board of Rheumatology (NCR) certification.

Methods: Thirty-two (in 2013) and 38 (in 2014) TRs, underwent an OSCE and a 300-questions examination (MCQ). MCQ was annually developed by faculty and experienced test questions writers NCRS-certified members, who submitted questions based on pre-specified content areas. Each question was reviewed by a committee of 4 NCR members. OSCE circuits were developed over a 10-month period by a trained NCR committee. At first, NCR members selected and designed stations using public health skills which included history-taking, physical examination, problem solving, studies interpretation, intra-articular injection (using a model) and capillaroscopy test; then, an expert consensus panel of rheumatologists validated each station (≥80% agreement); appropriated consented patients were selected and trained, as were examiners and each one was assigned to a particular station; finally, a pilot OSCE was performed by 3 certified rheumatologists who served as the “gold standard” control participants. Feedback was obtained. Final circuits consisted of 12 (in 2013) and 15 (in 2014) 8-minutes-stations, respectively, with 4 (2013) and 5 (2014) additional rest stations. Stations were scored by the same examiner in a previously validated check-list.

A composite OSCE score was obtained from each participant. Inter-station correlation was calculated using Pearson’s correlation coefficient. Concurrent validity was established by correlating MCQ scores and composite OSCE scores within each TR (Pearson’s correlation coefficient), by comparing OSCE scores between TRs and certified rheumatologists (Student t test) and by comparing distribution of TRs with/without OSCE pass score (Wilcoxon rank sum).

Results: In 2013, mean (±SD) OSCE score in all the participants was 7.1(±0.6) and none received a failing score, meanwhile mean MCQ was 6.5(±0.6) and 7 TRs (21.9%) received a failing score (≤6). In 2014, mean (±SD) OSCE score was 6.7(±0.6) and 3 TRs (7.9%) received a failing score (≤6).

In 2013, there was a significant correlation between MCQ score and composite OSCE score (r=0.44, p=0.006) meanwhile in 2014 correlation was not significant. At both consecutive years, certified rheumatologist had significantly higher OSCE scores than TRs. There were more TRs with a MCQ pass score among TRs with an OSCE pass score than among TRs with an OSCE failing score: 86% vs. 67%, p=0.02. TRs with an OSCE failing score were more frequently distributed in the bottom 2 quartiles on the MCQ (p=0.07).

Nine stations were applied at 2013 and 2014 OSCE circuits, and their (mean ±SD) scores showed good correlation, r from 0.81 to 0.95, p<0.01.

Conclusion: The OSCE was a valid and reliable tool to assess clinical skill competency in TRs.

Disclosure: V. Pascual Ramos, None; G. Medrano-Ramirez, None; E. Solis-Vallejo, None; A. Bernard-Medina, None; D. Flores, None; M. Portela-Hernandez, None; L. Andrade-Ortega, None; O. L. Vera-Lastra, None; R. Espinosa-Morales, None; J. A. Bernard-Limón, None; M. Maldonado-Velázquez, None; L. J. J. Jara, None; L. M. Amezcua-Guerra, None; J. Lopez-Zepeda, None; M. A. Saavedra, None; C. A. Arce, None.

1984

Rheumatology Learning Management System. Rodney Tehrani, Rochella A. Ostrowski and Baltazar Espiritu. Loyola University Medical Center, Maywood, IL.

Background/Problem: A learning management system (LMS) is software that facilitates the development, management, and tracking of training and education. To date, web based learning is a method of teaching that has been under-utilized in medical training. It has the advantage of being an efficient and easily accessible educational tool. We implemented a Rheumatology LMS for Internal Medicine residents. We hypothesized that the LMS would enhance the education and training of Internal Medicine residents in regard to Rheumatology through the use of dynamic and interactive software.

Methods: Five rheumatologic modules were created covering antiphospholipid syndrome, crystal arthritis, giant cell arteritis, myositis and rheumatoid arthritis in the LMS. All first year Internal Medicine residents completed the modules during dedicated educational time. Attendance and completion were mandatory. Modules were completed either in small groups or individually based on the preference of the learner. Residents completed the modules after their first Internal Medicine In-Training Examination (ITE) and prior to their second. We then analyzed the ITE performance of the first year Internal Medicine residents on the Rheumatology subsection to determine whether there was a statistical improvement in their scores compared from previous year residents who did not have access to the LMS.

Results: In the previous 2 years of residents who had not completed the modules, ITE mean examination scores in the rheumatology content changed from 58% to 53% and from 45% to 62%. National percentile rank changes were 16% to 25% and 18% to 16% for the 2 groups respectively. Thirty four residents completed the modules. Mean examination scores improved from 48% correctly answered items on the year 1 ITE to 63% on the year 2 ITE (p value <0.0005). National percentile rank improved from 27% to 46% respectively. All residents in 2014 had a rheumatologic experience trained as a clinic or rotation in rheumatology during their PGY 1 year. Differences in examination scores before and after the module completion remained statistically significant even when stratifying residents according to whether or not they had a clinical rheumatologic experience.

Conclusion: The development and implementation of a LMS can enhance the education and training of Internal Medicine residents to the field of Rheumatology.

Disclosure: R. Tehrani, Rheumatology Research Foundation, 9; R. A. Ostrowski, None; B. Espiritu, None.

1986

Ambulatory Rheumatology Curriculum: Effect of Multimodal Curricular Enhancement. Susan Kroop, Cecilia P. Chung, Mario Davidson, Laura Skaug, D. Alan Johnstone and Charlene M. Dewey. Vanderbilt University School of Medicine, Nashville, TN. *Vanderbilt University, Nashville, TN.

Background/Purpose: Evidence suggests that Internal Medicine (IM) residents are not confident in basic rheumatologic skills (history taking, exams, and procedures). To improve IM residents’ confidence in rheumatologic skills, we implemented and evaluated a multimodal simulation training session (MSTS) using standardized patients and manipulatives to enhance Post Graduate Year (PGY) 1 IM residents’ rheumatologic skills. To assess the utility and effectiveness of the MSTS enhancement, we conducted pre/post self-assessment of residents completing the curriculum.

Methods: We developed and implemented our MSTS for all PGY 1 IM residents rotating on the 1 year hematology/oncology block during the 2014 academic year. The two-part training consisted of a live standardized patient (SP) and deliberate practice with a mannequin for knee aspirations with feedback for both. PGY 1 residents performed a rheumatologic history and exam on a SP presenting with monarthritic inflammatory knee arthritis and practiced knee joint aspiration using a mannequin under the direct supervision of an attending rheumatology faculty member.

All PGY 1 residents completed an online, self-assessment survey on self-confidence (0=not confident, 100=extremely confident) in performing a rheumatologic history, physical examination and common rheumatologic procedures pre/post their rheumatology block as well as a separate MSTS evaluation form. Pre/post-rotation assessments were analyzed and 2014 results compared to the 2013 academic year, a historical control using the Wilcoxon Signed Rank test. IRB approval and consent was obtained prior to completing the survey.

Results: In 2013 and 2014, 22/27(81%) and 39/43 (91%) of PGY 1 IM residents completed pre/post surveys respectively. Both cohorts significantly increased (p<0.05) their self-assessed confidence ratings from pre to post rotation in all variables other than trochanteric bursa injection in the 2013 cohort (Table 1). The 2014 cohort had significantly greater changes in self-assessed confidence ratings than the 2013 historical controls. The difference in the median in rheumatology history was 12, exam was 11, knee aspiration was 37 and knee injection was 34 (Table 1). 35/43 (81%) PGY 1 IM residents strongly agreed and 8/43 (19%) agreed that the MSTS was a valuable training exercise.
**Conclusion:** Our results indicate that our MSTS enhanced curriculum improves residents’ self-confidence in performing a rheumatologic history and exam and knee injection and aspiration techniques when compared to an unenhanced prior curriculum. Further study is required to assess if these results are sustained over time and whether this translates into IM residents performing more procedures competently during their training.

| Table 1. Median Self-Assessed Confidence Levels for PGY 1 Residents with and without MSTS |
|-------------------------------------------------|-------------------------------------------------|
| Self-Assessed Confidence in Performing | 2013 Median (IQR)* Historical | 2014 Median (IQR)* MSTS |
| Rheumatology History Taking | Pre-Rotation | Median (IQR) | P Value | Post-Rotation | Median (IQR) | P Value | Difference Pre-Post Rotation | P Value |
| 50 (27–62) | <0.001 | 34 (19–49) | 70 (61–81) | <0.001 | 12 (22) |
| Rheumatologic Exam | 36 (5–55) | <0.001 | 31 (12–39) | 71 (65–83) | <0.001 | 11 (22) |
| Knee Injection | 10 (2–13) | <0.001 | 9 (2–30) | 60 (55–74) | <0.001 | 34 (20–44) |
| Knee Aspiration | 13 (10–20) | <0.005 | 9 (0–30) | 63 (65–75) | <0.001 | 37 (25–49) |
| Shoulder Injection | 7 (5–12) | <0.005 | 7 (0–10) | 27 (16–42) | <0.001 | 6 (1–10) |
| Trochanteric Bursa Injection | 7 (5–14) | <0.01 | 7 (5–10) | 25 (18–32) | <0.001 | 9 (0–10) |

*Visual Analog scale (0, not confident-100, extremely confident). P<0.05 = Interquartile Range.

**Discussion:** S. Kroop, None; C. P. Chung, None; M. Davidson, None; L. Skaug, None; D. A. Johnstone, None; C. M. Dewey, None.

**1987 Simulation in Continuing Education: Improving Evidence-Based Decisions for Rheumatoid Arthritis Management.** N. Mehta1, M. Warters2 and Douglas Blevins2. 1Medscape, LLC, New York, NY, 2Ther Sat, Durham, NC.

**Background/Purpose:** In many patients with rheumatoid arthritis (RA), the disease is not adequately controlled, and only a minority of patients attain the goal of consistent remission or low disease activity. Underlying clinical practice gaps and educational needs were identified and a study was conducted to determine if online, simulation-based educational interventions could improve competence and performance of rheumatologists in managing patients with RA.

**Methods:** A cohort of US-practicing rheumatologists who participated in simulation-based educational interventions was evaluated. The interventions consisted of four cases presented in a platform that allowed physician learners to choose from numerous lab tests and assessment scales as well as thousands of diagnoses, treatments, and procedures. The clinical decisions made by the participants were analyzed using an artificial intelligence technology, and instantaneous or delayed clinical guidance was provided employing current evidence-based and expert faculty responses. Participant decisions were collected after clinical guidance and compared with each user’s baseline data using a 2-tailed paired T-test to provide P values for assessing the impact of simulation-based education on the clinical decisions made by participants.

**Results:** The assessment sample consisted of 185 rheumatologists who made at least one clinical decision within the simulation and proceeded to the end. Clinical guidance was provided in 125/185 (67%) of cases. A result of clinical guidance provided through simulation, significant improvements were observed in several areas of management of patients with RA, specifically:

- 32% improvement in the selection of a biologic agent in a patient with inadequate response to methotrexate (62% post intervention vs 30% baseline, P<0.001)
- 11% improvement in recommendations for corticosteroids (77% post intervention vs 66% baseline, P=0.044)
- 10% more participants correctly ordered clinical disease activity index and C-reactive protein to determine the level of disease activity (84% post intervention vs 74% baseline, P<0.03)
- 16% improvement in selection of non-TNF biologic agent in a patient with RA not adequately controlled on methotrexate plus trials of etanercept and then adalimumab (60% post intervention vs 44% baseline, P=0.004)
- 21% more participants selected an appropriate biologic in a patient failing an initial anti-TNF agent (57% post-intervention vs 36% baseline, P<0.001)

**Conclusion:** This study demonstrated the success of simulation-based educational interventions on improving the evidence-based practice patterns of rheumatologists in the management of patients with RA. Simulation-based interventions that lead to improvement in physician performance in a consequence-free environment can result in more evidence-based clinical decisions for RA and improvement in patient outcomes.

Disclosure: N. Mehta, None; M. Warters, None; D. Blevins, None.

**1988 Process Outcomes and Community-Wide Efficacy of the Amigo Inter-Institutional M entoring Initiative within Pediatric Rheumatology.** Lakshmi N. Moorthy1, Eyal Muscal1, Meredith P. Riebschleger1, Kelly A. Rouster-Stevens2, Polly J. Ferguson2, Rayfel Schneider3, Maria Klein-Gitelman4, Termine I. Brueggemeier2, A. Huttertloccher5, and Peter A. Nigrivic6.

1Robert Wood Johnson Medical School-Rutgers University, New Brunswick, NJ, 2Texas Children’s Hospital, Houston, TX, 3University of Michigan, Ann Arbor, MI, 4Emory University School of Medicine, Atlanta, GA, 5University of Iowa Carver College of Medicine, Iowa City, IA, 6The Hospital for Sick Children, Toronto, ON. 

**Background/Purpose:** Mentoring is considered a critical contributor to career success in academic medicine. Recognizing that pediatric rheumatologists may experience limited access to mentoring due to the small size of most clinical programs, the American College of Rheumatology (ACR) and Childhood Arthritis and Rheumatology Research Alliance (CARRA) cooperatively developed a sub-specialty-wide inter-institutional mentoring program, entitled the ACR/CARRA Mentoring Interest Group (AMIGO). We report outcomes of this initiative three years after its inception as a small pilot program in 2011.

**Methods:** Two distinct sets of surveys were conducted: (1) AMIGO participants in the pilot phase were surveyed 17 months after matching to characterize mentor-mentee contact, and results compared with a subsequent cohort of participants following full implementation of AMIGO (2) All US/Canadian pediatric rheumatologists were surveyed before and after implementation of AMIGO to identify global changes in mentorship over this interval.

**Results:** (1) Participants in the pilot phase (19 dyads) and general implementation phase (112 dyads) reported comparable experiences with AMIGO, including success in establishing contact and suitability of mentorship partners. (2) Participants in the overall intervention phase (112 dyads) reported similar anticipated benefit from the program. (2) Respondents in the community wide surveys included 180 pediatric rheumatologists in 2011 and 177 in 2014, with comparable demographics. A mong survey respondents, 31/36 fellows (86%), 17/58 junior faculty (29%), and 37/61 (61%) senior faculty reported participation in the AMIGO program. Over the interval from 2011 to 2014, overall satisfaction with mentoring increased for fellows (p=0.01) but not junior faculty. AMIGO mentees reported that participation in AMIGO provided benefit in the domains of research/scholarship (30/51, 61%), career development (35/51, 71%), work-life balance (21/51, 43%), and connectedness to the pediatric rheumatology community (33/61, 56%).

**Conclusion:** The AMIGO program has expanded successfully from its pilot phase and now serves the large majority of US and Canadian pediatric rheumatologists as well as many junior faculty members. AMIGO mentees reported benefit in the domains of research, career development, and work-life balance. Institution of AMIGO was associated with improved satisfaction with mentoring among fellows, where program penetration was greatest. These results confirm that a subspecialty-wide inter-institutional mentoring program is feasible and can translate into concrete gains measurable at the level of the whole community.

Disclosure: L. N. Moorthy, None; E. Muscal, None; M. P. Riebschleger, None; K. A. Rouster-Stevens, None; P. J. Ferguson, None; R. Schneider, None; M. Klein-Gitelman, None; H. I. Brunner, None; A. Huttertloccher, None; P. A. Nigrivic, None.

**1989 Application of an Experiential Learning Framework for Clinician Scholar Educator Training in a Rheumatology Fellowship.** Rhea Hanley1, Jessica Berman1, Stephen A. Pagel2, Anne R. Bass3, and Juliet Aizer4. 1Hospital for Special Surgery, New York, NY, 2Hospital for Special Surgery, W eill Cornell Medical College, New York, NY.

**Background/Purpose:** Rheumatology training programs rely on capable clinician-scholar educators to sustain the rheumatology workforce. No program for rheumatology fellow clinician-scholar educator (CSE) training has been described in the literature. The goals of this program are to model and cycles of Kolb’s experiential learning in a mentored rheumatology fellow CSE experience as a proof-of-concept model.

**Methods:** With mentorship from a faculty CSE, a second year rheumatology fellow at Hospital for Special Surgery contributed to implementation...
of a learning module on fracture risk for New York Presbyterian Hospital (NY PH) internal medicine (IM) residents. A applying an experiential framework (learning through experience), the fellow refined the fracture risk module through cycles of Reflective Observation (review of faculty-led sessions), Abstract Conceptualization (identification of effective techniques), Active Experimentation (enactment of proposed teaching vignettes), and Concrete Experience (teaching parts of sessions). The fracture risk module itself was built on the same experiential framework; IM residents recalled patients with fractures, identified fracture risk factors, formed clinical approaches, and estimated fracture risk. From July 2013-June 2014, IM residents completing a rheumatology rotation participated.

Following sessions, the fellow and faculty CSE reflected module content and format, and on the teaching experience. Verbal and written prompts elicited impact, challenges, and key elements.

**Results:** The fellow attended 24/36 (66.7%) sessions, and taught in 21/24 (87.5%) of attended sessions.

The fellow found the experience valuable and feasible. Confidence related to clinical mastery and self-efficacy regarding curricular design and teaching abilities increased. The fellow cited increasing comfort and ease preparing to teach sessions and answering questions from IM residents.

The fellow's suggestions were consistent with experiential learning techniques, demonstrating application of new knowledge. Greater knowledge of the clinical subject (fracture risk) was evident in increased ability to respond to residents' questions. The fellow's knowledge and scholarly approach resulted in publication of a review article.

Challenges included competing clinical and research demands. Key elements identified for the fellow's learning included longitudinal faculty mentorship, establishment of fellow's content expertise, shared curricular development, explicit application of an educational framework, iterative learning cycles around a recurring teaching module, and flexibility in involvement to allow for other research experiences.

**Conclusion:** This descriptive analysis demonstrates the utility and feasibility of the fracture risk module. A application of an experiential framework to fellow teaching in a recurring teaching module promoted iterative cycles of learning. Fellow self-efficacy and knowledge related to both rheumatology and education increased. This model may be adapted to support rheumatology fellow CSE development more broadly and systematically as a programmatic element.

**Disclosure:** R. Khianey, None; J. Berman, None; S. A. Paget, None; A. R. Bass, None; J. Alzer, None.

**1990**

Pilot M usculoskeletal W orkshop for I nternal M edicine Residents. Sonali Khandewal, Narenader Amapunreddy, Joel A Block, Andem Eykpenny and Richard I Abrams. Rush University Medical Center, Chicago, IL.

**Background/Purpose:** M usculoskeletal (MSK) complaints in primary care are common but often underemphasized in residency training. There are few reports of methods residency programs have reported to address this need. Wilcox et al reported an intervention for residents consisting of a monthly experience, and Houston et al reported the experience of residents in a community clinic precepted by general internists. Both of these interventions were scheduled as multi-week curricula. With limitation of work hours, residents spend less time on sub-specialty rotations such as Rheumatology, and so it becomes challenging to incorporate adequate exposure to the MSK examination. To address this need for more dedicated MSK teaching while maintaining sensitivity to the constraints of limited contact hours, a pilot MSK workshop consisting of a single 90 minute session was initiated.

**Methods:** As part of the ambulatory medicine curriculum for medicine residents at Rush University a MSK workshop was initiated. The workshop consisted of a lecture followed by assessment of preselected patients with MSK complaints. The residents assessed each patient through a focused examination. To address this need for more dedicated MSK teaching while maintaining sensitivity to the constraints of limited contact hours, a pilot MSK workshop consisting of a single 90 minute session was initiated.

**Results:** In our institution there are 12 pediatric and adult rheumatology fellows. Response rates were 100%, 83% and 75% at the 1st, 2nd and 3rd timepoints respectively. At all time points 100% of fellows noted interest or strong interest in learning NCF techniques. After the course 67% felt confident in their ability to perform NCF while before the course only 17% felt confident, p = 0.03. Prior to the completion of the curriculum 28% of fellows responded that they used NCF frequently when they performed rheumatologic consultation compared to 67% after the course, p = 0.09.

Before and after the one-day course participants were asked to look at photographs of normal and abnormal NCF using a web-based application via
SurveyMonkey. Response rates were 36/70 (51%) prior and 19/70 (27%) after. In the pre-test 74% answered all questions correctly and 95.5% answered all questions correctly in the post-test. Improved identification of normal NFC was observed: 18/36 (50%) before the course and (18/18) 100% after the course on one question, p<0.001. Improved identification of neoangiogenesis was observed, 18% pre versus 77% post, p<0.001.

Conclusion: NFC is an area of interest for rheumatology trainees and attendings. This curriculum was feasible and led to improved ability of learners to distinguish normal from abnormal and to recognize and describe SSC-specific NFC changes that identify validated patterns of disease progression. This curriculum also led to improved confidence in examining nailfold capillaries and increased use of this skill in rheumatologic consultation.

Disclosure: D. Lerner. None; S. A. Paget. None; M. Cutolo. None; V. Smith. None; R. F. Spiera. None; J. K. Gordon. None.

Resident’s Guide to Rheumatology Mobile Application: An International Needs Assessment. Evelyn V. Rozenblyum1, Niraj Mistry2, Tania Celucci1, Tina Martimianakis3 and Ronald M. Laxer4. 1University of Toronto, Toronto, ON, 2McMaster Children’s Hospital, Hamilton, ON, 3Hospital for Sick Children, Toronto, ON, 4The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: “A Resident’s Guide To Pediatric Rheumatology” (the Guide) is a widely accepted resource for pediatric rheumatologists and trainees. In preliminary assessments, uptake of the Guide was broader than intended and it was used by trainees to help with clinical decision-making, learning and teaching. Users of the Guide suggested that it be developed into a mobile application (app).

The Technology Acceptance Model (TAM) provides a framework to assess the perceived usefulness and ease of use of a tool to predict future acceptance and use.

Objectives: (1) To determine the International demand amongst pediatric professionals and current trainees for a mobile app format of the Guide.

(2) To determine user preferred features, functions, and format to be included in a mobile app using the TAM.

Methods: An electronic survey was developed and distributed to pediatric residents at SickKids hospital and to both faculty and trainee members of the International Pediatric Rheumatology list server. The survey included respondent demographics, perceived usefulness, perceived ease of use, and behavioral intention to use the app based on the TAM. Data were analyzed using descriptive statistics.

Results: The survey was distributed to 75 pediatric residents and 1132 members of the Pediatric Rheumatology litserver and 135 (12% response rate) completed the survey. The majority of respondents were rheumatologists (53%), while the remainder consisted of Fellows (17%), Pediatric Residents (16%), and other allied health professionals (5%). 93% owned a smartphone and 58% owned a tablet. Most had medically related apps (75%) compared to e-books (38%), but had similar use for each—one to several times per week for 1–15 minutes each time on average.

The most useful features of an app would be clinical pictures (e.g. skin rashes), radiology images (e.g. joint x-rays), and definitions of key terms. Least useful features were games and multiple-choice questions. Additional features included a searchable index and links to journal articles.

Looking at the TAM, the vast majority of respondents thought that the mobile app would enhance trainees’ learning and teaching effectiveness. Greater than 80% of respondents consistently supported its perceived ease of use, 55% stated that they were likely to use the app often.

86% felt it was important for the app to be developed. If the app was not available for free, a majority (43%) of respondents were willing to pay for the app with a most willing to pay up to $5.00, and 10% willing to pay up to $10 for access to the app.

Conclusion: Development of the Guide app was well supported with adding features such as clinical photographs, radiology images, definitions and search function. TAM showed the intention to use the app and the future will be most determined by the perceived ease of use which was consistently high in the survey. Interestingly, users were willing to pay for the app if it was not free.

Future steps include a qualitative study utilizing focus groups to assess the perceived functionality, usability, facilitators and barriers in using the Guide app prototype to create the most targeted, user friendly app.

Disclosure: E. V. Rozenblyum. None; N. Mistry. None; T. Celucci. None; T. Martimianakis. None; R. M. Laxer. None.

Does Psychological Safety Impact Learning Environments among Rheumatology Fellows: Findings from Veterans Affairs Learners’ Perception Survey. Joe Gamboa1, Karina Maraariane D. Torralba2, Chau Nguyen3, Grant W. Cannon4, Samuel Baz5 and T. Michael Kashner6. 1Loma Linda University, Loma Linda, CA, 2Salt Lake City VA and University of Utah, Salt Lake City, UT, 3Loma Linda University Medical Center, Loma Linda, CA, 4Office of A cademic Affiliation, VA Loma Linda Healthcare System, Loma Linda, CA.

Background/Purpose: Each year, over 35% of all U.S. residents will rotate through a U.S. Department of Veterans Affairs (VA) medical center as part of their clinical training. The VA Learners’ Perceptions Survey (LPS) was created to assess VA’s performance in furthering its professional education training mission.

Objective: The purpose of our research is to assess how Rheumatology fellows rate psychological safety (PS) and their experiences with VA faculty/preceptor, along with clinical, learning, working, and personal environments.

Methods: The LPS is a validated instrument that measures health professions trainee satisfaction with clinical programs. We explored data from 70 Rheumatology fellows who responded to the LPS from July 2011 to January 2014 at 29 VA medical centers across the US. PS was assessed on a 5-point Likert scale (“strongly disagree” “agree,” “neither,” “disagree,” and “strongly agree”) with: “members of the clinical team of which I was a part are able to bring up problems and tough issues.” This question accounted for 85% of the cumulative variance with other question formats: “I feel free to question decisions or actions of those with more authority,” and “It is safe to take a risk on this clinical team.”

Results: There were 44 (67%) of 66 respondents who were female. 36 (52%) of 69 were international medical school graduates, 37 (53%) of 70 were PGY 4. Among all 70 fellows, 66 (94%) reported satisfaction with their clinical learning environment, 65 (93%) with preceptors, and 64 (91%) with working, 65 (93%) personal, 66 (94%) clinical, and 61 (87%) medical systems environments. Of the 70 fellows, 67 (96%) agreed or strongly agreed that members of the fellow’s clinical team could bring up problems and tough issues. Among those strongly agreeing their VA experience was psychologically safe. 35(79%) of 45 agreed being very satisfied with their clinical learning (versus 8 (32%) of 25 otherwise, x2(4)=16.272, p=0.003); 35 (80%) of 44 with the preceptors (versus 31% otherwise, x2(4)=20.089 p=0.001); 36 (84%) of 43 with working (versus 26%, x2(4)=24.364 p=0.001), 38 (81%) of 47 personal (versus 21%, x2(4)=22.993 p<0.001), 36 (82%) of 44 clinical environment (versus 27%, x2(3)=21.145 p<0.001), and 36 (84%) of 43 medical systems (versus 20%, x2(3)=27.044 p<0.001).

Conclusion: Our data suggests that Rheumatology fellows were satisfied with their VA clinical learning experience, and that psychological safety was strongly associated with the fellow’s satisfaction of their VA learning, working, and clinical training environments.

Table 1. Overall ratings at VA facility by Rheumatology fellows 2001-2014 across major domains in LPS survey

<table>
<thead>
<tr>
<th>Domain</th>
<th>Total N</th>
<th>Very Satisfied N (%)</th>
<th>Somewhat Satisfied N (%)</th>
<th>Not Satisfied N (%)</th>
<th>x2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning environment</td>
<td>45</td>
<td>35 (78%)</td>
<td>21 (46%)</td>
<td>9 (20%)</td>
<td>24.364</td>
</tr>
<tr>
<td>Preceptors</td>
<td>44</td>
<td>35 (80%)</td>
<td>21 (48%)</td>
<td>9 (20%)</td>
<td>24.266</td>
</tr>
<tr>
<td>Clinical environment</td>
<td>44</td>
<td>36 (82%)</td>
<td>22 (62%)</td>
<td>7 (16%)</td>
<td>21.145</td>
</tr>
<tr>
<td>Physical environment</td>
<td>37</td>
<td>32 (87%)</td>
<td>21 (59%)</td>
<td>1 (3%)</td>
<td>12.224</td>
</tr>
<tr>
<td>Working environment</td>
<td>43</td>
<td>36 (84%)</td>
<td>21 (62%)</td>
<td>6 (14%)</td>
<td>22.993</td>
</tr>
<tr>
<td>Personal experience</td>
<td>47</td>
<td>28 (60%)</td>
<td>18 (42%)</td>
<td>11 (23%)</td>
<td>21.145</td>
</tr>
<tr>
<td>Reliability of staff and</td>
<td>40</td>
<td>35 (88%)</td>
<td>24 (60%)</td>
<td>1 (3%)</td>
<td>24.364</td>
</tr>
<tr>
<td>Quality of staff and</td>
<td>41</td>
<td>31 (80%)</td>
<td>28 (72%)</td>
<td>2 (5%)</td>
<td>24.266</td>
</tr>
<tr>
<td>System and process dealing</td>
<td>43</td>
<td>36 (84%)</td>
<td>18 (55%)</td>
<td>1 (2%)</td>
<td>27.044</td>
</tr>
</tbody>
</table>

Disclosures: J. Gamboa. None; K. M. D. Torralba. None; C. Nguyen. None; G. W. Cannon. None; S. Baz. None; T. M. Kashner. None.
Incorporation of Musculoskeletal Ultrasound Curriculum and 6-Month Assessment of Knowledge Retention into the 2nd Year of Medical Student Training. Kiley Toder, William Rennie, Ruth L. Marder and Maria L. Barilla-Labarda. 1 Northshore LIJ, Great Neck, NY, 2 Hofstra North Shore LIJ School of Medicine, Hempstead, NY, 3 North Shore LIJ Health System, Great Neck, NY, 4 Hofstra North Shore LIJ Health System, Great Neck, NY.

Background/Purpose: Few medical schools offer a formal curriculum in musculoskeletal ultrasound (USMUS); the success of such a program in terms of skills and knowledge acquisition and durability of response has not been clearly documented. The purpose of this study was to assess second year students’ ability to identify the presence of pre-loaded suprapatellar effusions using a cadaver model following a formal USMUS curriculum and assess their skill and knowledge retention rate at 6 months.

Methods: A part-of a longitudinal USMUS curriculum at Hofstra NSLIJ SOM, 3 sessions were reserved for USMUS during the 2nd year of study. There were pre-assigned readings prior to each session. The 1st session reviewed probe selection, patient positioning, and recognition of tissues (tendon, muscle, bone, cartilage, etc). The 2nd session demonstrated normal and pathologic knee anatomy on a cadaveric model. Multiple choice question style pre-assessment was given prior to this session. In the 3rd session, students performed a standard knee US exam with the guidance of MSUS-trained faculty. The summative assessment evaluated the students’ ability to perform a standard knee exam, label knee anatomy on acquired images, and identify a suprapatellar “effusion” in a cadaver preinjected with a gelatin mixture. This exercise was repeated 6 months later in a smaller, voluntary group of students to assess retention of skills and knowledge.

Results: In the pre-assessment 22/57 (38.5%) students correctly identified the US image with a knee effusion although only 2 students could label it correctly compared to 37/57 (67%) in the summative assessment (p<.003 correct answer and p<.0001 labeling). Thirteen students volunteered to participate in the 6 month extension; they did not prepare in advance nor have significant exposure to USMUS during the intervening months. Twelve of these students (84.6%) had identified the anatomy and 10 (76.9%) had identified the effusion during the summative assessment in December. In June, a decrease in both knowledge (table) and skills (84.6% of images were of poor quality or taken in non-standard locations) was found although the majority (61.5%) was still able to identify the pathology.

Conclusion: Following a formal USMUS curriculum, the majority of the 2nd year medical students were able to demonstrate their skill at acquisition of images, distinguish pathologic from normal findings, and identify knee structures by US. However, the retention rate for quality images and identifying anatomical structures decreased at 6 months. Yet, a majority of students identified fluid and bone in the knee that helped to obtain their respective images and assess the location and nature of the effusion. Thus, although anatomy would have to be further reinforced, student’s identification of effusions was durable at 6 months.

Disclosure: K. Toder, None; W. Rennie, None; R. L. Marder, None; M. L. Barilla-Labarda, None.

Design and Implementation of a Clinical Teaching Tool for Approach to Children with Suspected New Rheumatologic Diagnosis. Kristen Hayward and Jennifer Hrachovec. Seattle Children’s Hospital, Seattle, WA.

Background/Purpose: Approximately 1 in 1000 children suffer from a rheumatologic disorder. Despite the relative frequency of these conditions, there is a shortage of pediatric rheumatologists and many children with rheumatologic conditions will present to primary care providers for initial evaluation and management. Unfortunately, there is strong evidence that graduating pediatric residents are ill equipped to recognize and treat these children. In the University of Washington Pediatric Residency Program, only one in three students have exposure during a 3-day intensive musculoskeletal mini-residency, which is planned to assess the impact of the tool on trainee knowledge of and comfort with evaluation of children with rheumatologic conditions as well as potential for dissemination to additional institutions.

Disclosure: K. Hayward, None; J. Hrachovec, None.

Improvement in Basic Bone Health Knowledge Among VA Primary Care Practitioners during a Focused Musculoskeletal Mini-Residency. Mathilde Pioro, Nancy Fisher, Marissa Grotzke, Grant W. Cannon and Michael Battiston. 1 Cleveland Veterans Affairs Medical Center, Cleveland, OH, 2 Salt Lake City Veterans Affairs Medical Center, Salt Lake City, UT, 3 Salt Lake City VA and University of Utah, Salt Lake City, UT, 4 University of Utah Health Sciences Center, Salt Lake City, UT.

Background/Purpose: Osteopenia and osteoporosis are common yet underrecognized in the veteran population. The teaching needs, methods, and outcomes of an educational intervention designed to teach VA primary care providers novel concepts involved in initial diagnosis and treatment of childhood rheumatologic disorders, this teaching tool offers a foundational model which can be translated to future patient encounters. Additional work is planned to assess the impact of the tool on trainee knowledge of and comfort with evaluation of children with rheumatologic conditions as well as potential for dissemination to additional institutions.

Disclosure: K. Toder, None; W. Rennie, None; R. L. Marder, None; M. L. Barilla-Labarda, None.
FRAX screening algorithm.

Conclusion: A comprehensive structured curriculum with consistent information for rheumatology helps to improve core content knowledge of rheumatic diseases and aids in consolidation of the clinical experience for medical students and residents during their rheumatology elective.

Figure 1: Rheumatology Elective Pre-test vs. Post-test Scores

Disclosure: S. Manocha, None; I. Cobb, None; S. Hassan, None; S. P. Ballou, None; M. N. Magrey, None.

1998

pGALS Training Increases Kenyan Pediatric Residents’ Confidence in Performing a Musculoskeletal Exam.

Tanya Glushko1, Ines Colmegna2, Helen Foster3, Sasha Bernatsky1, Carol Hitchon1 and Rosie Scuccimarro1.

1McGill University, Montreal, QC, 2McGill University - Royal Victoria Hospital, Montreal, QC, 3Newcastle University - Royal Victoria Hospital, Montreal, QC, 4Newcastle University, Newcastle, United Kingdom, 5University of Manitoba, Winnipeg, MB.

Background/Purpose: Musculoskeletal (MSK) manifestations are a common reason for outpatient consults accounting for 6–9% of pediatric clinic visits in developed countries. Patients are initially evaluated by primary care practitioners, general pediatricians and emergency physicians. It has been suggested that low confidence in pediatric MSK assessment is a key factor contributing to diagnostic delays and poor outcomes.

pGALS (pediatric Gait, Arms, Legs, Spine) is a simple tool for MSK assessment, which facilitates early recognition and prompt referral of patients with joint problems. When performed by non-pediatric specialists and compared with pediatric rheumatologists, pGALS has been shown to have excellent sensitivity (97–100%) and specificity (98–100%) for detecting abnormal joints.

We undertook this study to evaluate pediatric residents’ confidence in conducting an MSK evaluation and the effect that a pGALS training session had on enhancing this perception.

Methods: Pediatric residents working at the two training centers in Nairobi, Kenya (Aga Khan University Hospital and Kenyatta National Hospital) participated in a 60 minute hands-on session on pGALS given by a pediatric rheumatologist. Written anonymous questionnaires performed prior and post training assessed the participants’ level of confidence in examining the MSK system.

Results: Sixteen residents with an average of 2.9 ± 0.8 years of training completed the survey. Ten out of 16 (63%) reported previous MSK exam training. None of the participants had been trained in pGALS before. A third of residents (31%) were not comfortable examining the MSK system, while the remaining felt comfortable in some aspects only. The level of confidence in examining the MSK system was significantly lower than that for all of the following systems: cardiovascular, respiratory, abdominal and neurological (p<0.0005).

Ninety four percent of the residents reported increased level of confidence (p<0.001) following the pGALS training session. Most physicians considered the training session extremely beneficial (75%) or very beneficial (25%). Ten residents (63%) reported planning to use this tool for all patient visits, 4 (25%) in patients with minimal joint complaints and 2 (12%) in those with
obvious joint concerns. In their clinical setting, the residents thought that office posters (63%) and pocket cards (63%) would be more useful than web-based video demonstrations (25%) to facilitate the use of the pGALS in clinical practice. They felt that the best way to increase confidence in the MSK exam was with one-on-one bedside coaching (81%) rather than web-based video demonstrations (50%) and workshops (44%).

Conclusion: pGALS training together with routine reminders to facilitate pGALS incorporation into the regular exam translates into increased physician confidence, which may lead to earlier recognition of rheumatic diseases in children. pGALS teaching materials may need to be tailored to the clinical setting that they will be used in.

Disclosure: T. Glushko, None; I. Colmegna, None; H. Foster, None; S. Bernatsky, None; C. Hitchon, None; R. Scuccimarra, None.

1999

Internal Medicine Resident Confidence in Rheumatologic and Musculoskeletal Diseases: A Needs Assessment Survey. Cristina Savasta, Deborah Korenstein and Yusuf Ali. Icahn School of Medicine at Mount Sinai, New York, NY.

Background/Purpose: Small studies have demonstrated a lack of confidence and competency in the areas of rheumatology and musculoskeletal diseases among internal medicine physicians at various levels of training. This can lead to a delay in the diagnosis of rheumatologic disease and may result in suboptimal patient outcomes and increased morbidity. Increasing time devoted to teaching the subject has been shown to increase resident confidence, suggesting that an intervention could have a significant impact on residents' ability to diagnose and manage rheumatologic diseases. We aim to assess resident confidence in rheumatologic and musculoskeletal topics and skills in order to evaluate the need for an educational intervention.

Methods: We emailed a survey to the 137 residents in the Department of Medicine at a large, urban university hospital. The survey included 6 questions on a 5-point Likert scale measuring self-assessed knowledge of rheumatology topics and confidence in musculoskeletal exam questions. Questions regarding non-rheumatologic topics were included to control for rheumatology topics and confidence in musculoskeletal exam skills. Questions assessing residents' ability to diagnose and manage rheumatologic diseases were performed using 5 points, assessment (2 points) and management (2 points). They attended rheumatology clinic for an average of 3 sessions weekly for 4 weeks. The other residents viewed videos on arthrocentesis and MSK physical examination.

Fifty medical records from Primary Care continuity clinic were analyzed for evaluation of MSK complaints. The selected outpatient records had MSK-related chief complaints and were completed within 18 months from the writers' rheumatology teaching in both groups. The performance of the residents was assessed using a predetermined grading system by two blinded evaluators. Evaluators reviewed specifics regarding history (10 points), physical examination (5 points), assessment (2 points) and management (2 points) for a possible total of 20 points. Evaluators also gave each record a summary score for documentation of history, physical examination, assessment or plan (possible total of 4 points) regarding the chief complaint.

Results: Results are displayed in Table 1. A 2-tailed T-test was performed comparing the total scores by evaluator 1 and evaluator 2; p values were 0.14 and 0.28 respectively.

Table 1. Mean scores with +/- standard deviation for chart review by evaluator 1 and evaluator 2

<table>
<thead>
<tr>
<th>Resident assignment</th>
<th>Rheumatology</th>
<th>Non-Rheum</th>
<th>Rheumatology</th>
<th>Non-Rheum</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>4.2 (2.0)</td>
<td>4.7 (2.0)</td>
<td>4.3 (2.1)</td>
<td>4.4 (2.4)</td>
</tr>
<tr>
<td>Exam</td>
<td>1.2 (1.3)</td>
<td>1.8 (1.2)</td>
<td>1.2 (1.2)</td>
<td>1.9 (1.0)</td>
</tr>
<tr>
<td>Assessment</td>
<td>1.8 (0.9)</td>
<td>1.4 (0.9)</td>
<td>0.8 (0.6)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>Management</td>
<td>1.8 (0.5)</td>
<td>1.6 (0.7)</td>
<td>1.7 (0.5)</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>8.1 (3.2)</td>
<td>9.5 (3.3)</td>
<td>8.0 (3.1)</td>
<td>8.9 (3.3)</td>
</tr>
<tr>
<td>Summary score</td>
<td>3.2 (0.7)</td>
<td>3.6 (0.7)</td>
<td>3.2 (1.0)</td>
<td>3.5 (0.8)</td>
</tr>
</tbody>
</table>

Conclusion: We found no significant difference in documentation of medical care for MSK complaints between medical residents who had a rheumatology elective with active learning and medical residents who had passive learning for rheumatology. These results indicate that passive learning through reading and videos is as effective as small group teaching, at least for 4 week long elective experiences. Improvement in outcomes may require reinforcement over a longer period of time and in different clinical settings.

Disclosure: D. M. Lazaro, None; D. Ozeri, None; J. Chechi Gobilaro, None; D. Hassana, None.

2000

The Effect of a Rheumatology Ambulatory Rotation for Medical Residents on Documentation of Musculoskeletal Complaints. Deana M. Lazaro1, David Ozeri1, Jenna Chechi Gobilaro2 and Deena Hassana2.

1Brooklyn VA, Brooklyn, NY; 2SUNY Downstate Medical Center, Brooklyn, NY; 3SUNY Downstate Medical Center, Brooklyn, Algeria.

Background/Purpose: Musculoskeletal (MSK) complaints are commonly the reason for visits to Primary Care offices. Therefore, it is important to teach residents to recognize and manage them. Passive learning techniques such as reading may improve knowledge but do not necessarily teach residents to synthesize and apply that knowledge in a clinical encounter. The purpose of this study is to determine if an enriched rheumatology curriculum, using active learning techniques, leads to better assessment and management of MSK complaints in a primary care setting among medical residents.

Methods: This pilot study is a blinded, retrospective, case-controlled trial comparing residents who participated in a rheumatology elective in comparison to residents who had passive learning about rheumatology. Medical residents were assigned to rheumatology or another subspecialty elective. All residents were assigned rheumatology reading in preparation for a post-test and objective structured clinical examination (OSCE). Rheumatology elective residents were taught using active learning techniques such as arthrocentesis simulation and small group teaching for MSK examination. They attended rheumatology clinic for an average of 3 sessions weekly for 4 weeks. The other residents viewed videos on arthrocentesis and MSK physical examination.

Conclusion: The Effect of a Rheumatology Ambulatory Rotation for Medical Residents on Documentation of Musculoskeletal Complaints. Deana M. Lazaro1, David Ozeri1, Jenna Chechi Gobilaro2 and Deena Hassana2.

1Brooklyn VA, Brooklyn, NY; 2SUNY Downstate Medical Center, Brooklyn, NY; 3SUNY Downstate Medical Center, Brooklyn, Algeria.


1Salt Lake City VA and University of Utah, Salt Lake City, UT; 2San Diego VA, San Diego, CA; 3Denver VA Medical Center, Denver, CO; 4Louisville VA, Kentucky, KY.
Background/Purpose: To address the problem of insufficient training in Musculoskeletal (MSK) diseases by practicing primary care providers (PCPs), the Veterans Affairs (VA) Office of Specialty Care Transformation provided pilot funding through a competitive, peer-reviewed process to develop and support a “MSK Mini-Residency” to train PCPs in evaluation and management of common MSK diseases.

Methods: The 3 day MSK mini-residency curriculum intersperses didactic lectures with small group workshops, as well as case based interactive small-group practice sessions and technology-enhanced simulation (see full schedule, Table 1). Participants’ competency in performing and interpreting the physical examination of the shoulder and knee is evaluated by a 2-station Objective Structured Clinical Examination (OSCE), to ensure sufficient preparation for assessing patients in clinic. Course evaluation was conducted using the Kirkpatrick’s model of assessing educational effectiveness, and Phillip’s concept of Return on Investment. Table 1

Results: From 2012–2014, the 3-day MSK Mini-Residency course has been presented at 12 VA medical centers, serving catchment areas centered in Los Angeles, San Francisco, Denver, Omaha, Louisville, Cleveland, Philadelphia, Tampa, Orlando, and Boston. Table 2 shows the distribution of participants by their ability and preparation to evaluate and manage shoulder and knee pain in their clinics.

Table 2

<table>
<thead>
<tr>
<th>MSK Mini-Residency Participants</th>
<th>Total</th>
<th>Physician</th>
<th>NP</th>
<th>PA</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, %</td>
<td>241 (100)</td>
<td>148 (61)</td>
<td>75 (32)</td>
<td>15 (6)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Post course competency in examining the shoulder and knee, and in reporting, interpreting, and managing the cases using a framework of high-value care, was confirmed with 2-station OSCE. Course evaluations were extremely positive across all sites; over 95% of participants anticipate that the training will impact their job performance and would recommend the course to others.

Conclusions: The MSK Mini-Residency is an effective model for training and evaluating primary care providers in the diagnosis and management of common musculoskeletal diseases.

Disclosure: M. J. Battistone, None; A. M. Barker, None; M. P. Groztko, None; J. P. Beck, None; A. Quan, None; M. Hose, None; V. Seligman, None; R. Ravendell, None; P. Pavuluri, None; W. N. Roberts, None; M. Pioro, None; N. Fisher, None; V. Osting, None; B. Prihar, None; J. Hackman, None; S. Kirsh, None; G. W. Cannon, None.

2002

Implementation of a Collaborative Rheumatology and Physical Therapy Musculoskeletal Ultrasound Training Program. Minna J. Kohler1, Chloe Sculom2, Imran Siddiqui3, Keviin O’Connor4 and Marcy B. Bolster1, 2Massachusetts General Hospital/Harvard Medical School, Boston, MA; 2, 3Spaulding Rehabilitation Hospital/Harvard Medical School, Charlestown, MA.

Background/Purpose: Rheumatology musculoskeletal ultrasound (MUS) certification has been established and MUS teaching is rapidly being incorporated into U.S. rheumatology fellowship training programs. Similarly, MUS use by physiatrists is growing, and exposure to MUS and rheumatology teaching is now mandatory in physical medicine and rehabilitation (PM&R) residency programs. At this time, no standardized rheumatology MUS curriculum is required, but competency criteria are currently under discussion.

Methods: We describe the implementation of a novel, collaborative rheumatology/physiatry MUS training program at a single academic center. The program was developed by a rheumatology MUS expert in conjunction with the program directors of both rheumatology fellowship and PM&R residency to adequately expose fellows to MUS, and fulfill both rheumatology and MUS training requirements for residents. A self-assessment survey of the participating fellows and residents was obtained post-implementation, using a 3-point Likert formatted scale (1 = no knowledge to 3 = extensive knowledge).

Results: All first year rheumatology fellows (n = 2) were required to participate in a twice monthly half day faculty-mentored, MUS clinic over one year. For the second year rheumatology fellows with a demonstrated interest in MUS (n = 1), additional training included longitudinal, weekly, faculty-mentored MUS clinics, participation in the USSONAR program, and MUS research. All PGY-3 PM&R residents (n = 9) were required to participate in a 1-month rotation of faculty-mentored MUS clinics, 3 days per week. All rheumatology fellows and PM&R residents (n = 12) participated in an introductory MUS lecture to review basic knowledge, image acquisition, and reasonable use of MUS. Every other month, hands-on sessions reviewed anatomy and scanning protocols. Both groups had access to US equipment for self-directed learning. In the clinic, fellows/residents evaluated patients referred for musculoskeletal pain in a one-stop approach where MUS and guided injections may be performed, as indicated. All fellows and residents completed the survey (Table 1). Post-curriculum, 100% of participants felt they had adequate exposure to MUS and adequate MUS knowledge. Ten of the 12 trainees (83%) continued participating in self-directed learning. The average range of MUS exams performed by all participants was 11-20; MUS-injections also ranged from 11-20. Six of the 12 trainees (50%) participated in MUS research activities.

Conclusion: Implementation of a collaborative MUS training program is beneficial to the education of both rheumatology fellows and PM&R residents. Improvement in MUS knowledge and ability was shown in both groups. A combined program can adequately fulfill the educational and research needs for both specialties, especially when the number of trained MUS instructors may be limited.

Disclosure: M. J. Kohler, None; C. Sculom, None; I. Siddiqui, None; K. O’Connor, None; M. B. Bolster, Johnson and Johnson, 1, Eli Lilly and Company, 2, ABIM

Table 1. Post-Implementation Survey (3-point Likert Scale)

<table>
<thead>
<tr>
<th>Fellow/Resident Self-Assessment</th>
<th>Pre-curriculum (mean)</th>
<th>Post-curriculum (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic MUS anatomy knowledge</td>
<td>1.36</td>
<td>2.55</td>
</tr>
<tr>
<td>Level of ability to optimally image structures</td>
<td>1.27</td>
<td>2.36</td>
</tr>
<tr>
<td>Level of ability to interpret MUS images</td>
<td>1.18</td>
<td>2.09</td>
</tr>
<tr>
<td>Ability to perform MUS-guided procedures</td>
<td>1.18</td>
<td>2.27</td>
</tr>
<tr>
<td>Understanding of indications for reasonable use of MUS</td>
<td>1.45</td>
<td>2.33</td>
</tr>
</tbody>
</table>

Tuesday, November 18
2003

Pilot Study of a Web-Based Module on Gout. Bernadette Siaton, Elizabeth Clayton, Alexandra Kueider and Matthew Rietschel. 1University of Maryland Medical System, Baltimore, MD, 2University of Maryland, Baltimore, MD, 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 4University of Maryland School of Nursing, Baltimore, MD.

Background/Purpose: The majority of internal medicine trainees complete residency with little exposure to rheumatology. We aimed to create a validated, self-directed, web-based, core curriculum in rheumatology for residents. The first module focused on gout. We also aimed to assess the efficacy of this educational product utilizing the script concordance testing (SCT) method. SCT assesses clinical data interpretation and decision making.

Methods: We obtained IRB exemption to perform this study that included internal medicine trainees at the University of Maryland Medical Center. Pre-test and post-test questions were examined for item validity. Pre- and post-test scores were compared to the scores of the expert panel, which was made up of 2 rheumatology fellows, 9 academic rheumatologists, and 1 community rheumatologist. Baseline knowledge was assessed via a pre-test on the Blackboard learning management system, followed by the educational intervention, an interactive didactic presentation on gout. The module included gout pathophysiology, clinical presentation, and therapeutic management. Immediate post-testing was performed. An ANOVA was used to compare trainee and expert groups as well as pre- and post-test scores. Cronbach’s alpha was used to calculate test reliability. An effect size was calculated using Cohen’s d.

Results: Ten trainees completed pre-and-post-tests for analysis. The 20-case SCT achieved high reliability (Cronbach alpha for all 20 cases > 0.75). At a baseline, the trainees’ average SCT score was 32 points (M = 32.45, SD = 1.99); whereas the experts’ average SCT score was 40 points, (M = 40.65, SD = 1.72). After the didactics, trainees’ SCT scores increased by an average of 2.83 points F (1, 18) = 9.33; (p < 0.01). Cohen’s d showed a strong effect size (d = 1.13). Expert SCT scores were an average of 8.2 points (SD = 0.81) higher than trainee pre-test scores. Expert SCT scores were an average of 5.4 (SD = 0.84) points higher than trainee post-test scores. Both of these differences were statistically significant (p < 0.0001).

Conclusion: Trainee test scores significantly increased after the educational intervention in this pilot study. Expert SCT scores were higher at baseline and remained higher after the didactics, which lends support to the construct validity of the tool as the experts had higher clinical competence. The effect of the educational intervention will be tested on a larger group of internal medicine trainees. Future plans include subgroup analysis by post-graduate year, implementation of self-efficacy evaluations, and possible re-testing at 6 or 12 month intervals to assess durability of knowledge. Additional modules for the core curriculum will be developed.

Disclosure: B. Siaton, None; E. Clayton, None; A. Kueider, None; M. Rietschel, None.

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Osteoporosis Screening and Fracture Risk Assessment Tool Usage Among House Staff. Jordan Brodsky, Meghan Greenfield and Erin Patton, Albert Einstein College of Medicine, Woodmere, NY, 2Beth Israel Medical Center, New York, NY.

Background/Purpose: Despite increased awareness of the magnitude and consequences of osteoporosis and the availability of recommendations for screening and treatment by multiple organizations, osteoporosis is still under diagnosed and inadequately managed in the United States. Identifying patients at risk, making a timely diagnosis, implementing prevention measures and initiating pharmacologic therapy for appropriate patients can all help to minimize fracture risk. A cademic hospitals with resident-led outpatient primary care providers are an area where there may be under-utilization of evidence-based fracture risk assessment tools, such as the Fracture Risk Assessment Tool (FRACT).

Methods: House staff of the Internal Medicine department at Beth Israel Medical Center where given an anonymous questionnaire. The goal was to assess the resident’s knowledge of current practice guidelines and recommendations for osteoporosis and the utilization of the FRACT score.

Results: 48 residents of Internal Medicine, levels PGY 1, 2 and 3, filled out the questionnaire. 63% of residents estimated their female patient population was greater than 65 years old and 31% of their male patient population was greater than 70 years old. 77% of residents had knowledge of what the FRAX score was and 48% of resident knew the appropriate use in patient care. 62% used the FRAX score to identify patients who met criteria for the initiation of treatment for osteoporosis. 29% could identify the modifiable risk factors and 31% identified the non-modifiable risk factors. Although 33% of residents calculated the FRAX score, 33% said they would use the FRAX score on woman less than 65 years old. 79% of residents wanted to receive more information on the FRAX score and its appropriate applications.

Conclusion: A proper identification and prevention are imperative to reducing the risk of osteoporosis and osteoporosis-related fractures in individuals. Our study concluded that internal medicine residents at one academic medical center are following the current guidelines for screening for osteoporosis with DEXA scans, however, the use of the FRAX score for the identification of patients at high risk for fracture requiring the initiation of treatment for osteoporosis, is highly underutilized. There was also a discrepancy between the resident’s knowledge of the FRAX score and its application in clinical practice. Further training and education regarding osteoporosis screening and the use of the FRAX score in a resident led outpatient primary care setting will be beneficial to resident providers and their patients.

Disclosure: J. Brodsky, None; M. Greenfield, None; E. Patton, None.

2005

Multimedia Patient Education Tool for Patients with Osteoporosis. Maria A. Lopez-Olivo, Aparna Ingleshwar, Robert Volk, Andrea Barbo, Mary Ellen Weiss, Heather Park and Maria E. Suarez-Almazor. 1The University of Texas at Houston, MD Anderson Cancer Center, Houston, TX, 2Baylor College of Medicine, Houston, TX.

Background/Purpose: Patient education materials incorporating video modelling can be effective in improving patients’ outcomes. We conducted a randomized control trial to test the efficacy of a multimedia-patient education tool (MM-PiET) for patients with osteoporosis, including storyline and narratives.

Methods: 224 patients were recruited from three outpatient clinic systems and through advertisement. Inclusion criteria were: (i) diagnosis of osteoporosis/osteopenia, (ii) female gender, (iii) age =50 years (iv) at least 3 years post-menopausal, (v) adequate cognitive status, and (vi) ability to communicate in English or Spanish language. Participants were given materials to review based on randomization (Intervention = MM-PiET; Control = written booklet with same content as MM-PiET). All participants completed pre-post self-report questionnaires. Primary outcome measures included: a) Disease knowledge and b) Decisional Conflict Scale- “Informed” and “Values clarity” scales. Secondary outcomes included: a) Ottawa Acceptability Instrument and b) Evaluation of the educational tool. Baseline demographic information and health literacy level were also obtained. Mann differences in knowledge scores (pre-post randomization) and between group differences in the Ottawa Acceptability tool evaluation measures were analyzed.

Results: 111 patients were randomly allocated to the MM-PiET intervention and 113 to the control booklet. Mean age of participants was 64±9 years and 82% had adequate health literacy. Knowledge scores significantly increased in both groups, post randomization (MM-PiET: 9.5±4.2 vs 12.8±3.2 and Control: 9.1±4.2 vs 12.5±3.2; p<0.05 for both groups). Post randomization, participants in both groups had significantly lower “Informed” scores which calculate the FRAX score (pre vs post: Intervention: 55.3±38.7 vs 15.8±25.6 and Control: 54.0±38.1 vs 17.7±30.8; p<0.05 for both groups; lower scores = more informed) and “Values clarity” scores (pre vs post: Intervention: 49.8±40.9 vs 16.9±30.6 and Control: 55.1±40.8 vs 18.6±29.3; p<0.05 for both groups; lower scores = more values clarity). Compared to controls, participants in the MM-PiET group rated better explanation of the medical facts (p<0.03), and the understanding of the potential side effects (p<0.03). When asked about the balance of the material (slanted towards self-care/lifestyle options, slanted toward medical therapies, balanced), higher number of intervention group participants found the material to be “balanced” (p<0.004).

Conclusion: The results of our study indicate that, when compared to standard written materials, the MM-PiET was better rated and was comparable in improving knowledge in women with osteopenia/osteoporosis.

Disclosure: M. A. Lopez-Olivo, None; A. Ingleshwar, None; R. Volk, None; A. Barbo, None; M. J. Ibaja-Weiss, None; H. Lin, None; M. E. Suarez-Almazor, None.
Multiple Joint Osteoarthritis: Patient Preferences for a Generic Exercise and Self-management Programme. Nicola E. Walsh¹, Geeta Patel² and Rachael Gooberman-Hill³. ¹University of the West of England Bristol, Bristol, United Kingdom, ²University of the West of England, Bristol, Bristol, United Kingdom, ³University of Bristol, Bristol, United Kingdom.

Background/Purpose: In the UK approximately 1.75 million people aged 45 and over are diagnosed with multiple, peripheral joint osteoarthritis (OA), a figure that would increase significantly with the inclusion of degenerative spinal pain. Exercise and self-management are recommended core treatment strategies for OA, but evidence is generally limited to single-site osteoarthritis clinical trials and interventions. In clinical practice patients frequently consult with either pain in more than one joint, or re-consult over time when symptoms manifest in other joints. We developed a 6-week group programme to Facilitate Activity and Self-management in Arthritis (FASA) for people with multisite OA of the hip, knee and/or lower back. The aim of FASA was to teach an exercise programme for these joints, and provide education regarding multiple joint pain management. This qualitative study, embedded within a randomised controlled trial (RCT), presents data from a focus group analysis to determine perceived benefits and acceptability of the intervention.

Methods: Nine semi-structured, focus group interviews facilitated by a researcher independent of the RCT were conducted with patients with OA who had participated in the FASA programme, and had completed their primary end point assessment at 6 months post-intervention. The interviews were audio-recorded, transcribed and analysed using thematic analysis. A second researcher independently coded a selection of transcripts to establish accuracy of interpretation.

Results: Forty-five participants (28 female), age 53–85 years (mean = 68 years) with multisite OA joint pain participated in the focus groups. Thematic analysis demonstrated that individuals reported benefits from gaining confidence and knowledge of how to self-manage pain in other joints should it manifest. They also found it beneficial to undertake exercises that took into account their multisite presentations. Gaining insight of how others coped with their pain, irrespective of site, was also considered positive; participants also talked about valuing the shared pain experience. Whilst the majority of participants valued the more general joint pain approach, three people with lower back pain found it difficult to relate to those who did not experience back pain, and expressed a preference for a specific intervention tailored to their presentation.

Conclusion: An exercise and self-management intervention for multisite OA was perceived as beneficial and acceptable to the majority of participants, who reported increased confidence and knowledge for self-management. Further consideration regarding the suitability of integrating back pain patients into these generic sessions may be necessary. Embedding a qualitative analysis into an RCT enhances our understanding of interventions and provides valuable insight from a patient perspective.

Disclosure: N. E. Walsh, None; G. Patel, None; R. Gooberman-Hill, None.


Background/Purpose: Lupus through the Lens is a photography project for people with lupus to capture, in pictures, what it means to live with lupus. Created by the S.L.E. Lupus Foundation, it borrows from photovoice, a socially-engaged photography technique based on community-based participatory research and visual narrative inquiry. To our knowledge, photovoice has not been used within the lupus community. The Foundation’s goals for the program were: 1. create public awareness about the shared lived experience of lupus since it is often misunderstood by both lay people and healthcare professionals, 2. aid participants in coping with their illness, and 3. aid viewers with lupus to feel less isolated and more validated in their experience through identification with photos and respective captions.

Methods: This was a 7-week workshop that met over 4 months with 6 participants, all with lupus. Participants were integral in developing project content: through group discussions, they chose the program title and photos to include on the project website; they developed captions, which further defined the meaning of their work. Participants were loaned cameras, and a participant with photography experience gave lessons on camera use and photography techniques. To create public awareness, photos were displayed on a dedicated website and via social media.

Results: Of 803 photos, 53 were selected for the project website. The Foundation’s goals were met. Awareness is measured by website traffic; within its first 6-weeks, there were 26,000 views. Participants were aided in coping with their illness, as reported in their final evaluation indicated by a sense of pride, camaraderie, socialization, and self-expression; a new way to share lupus with others; and a deeper understanding of the personal impact of one’s own lupus. Based on responses on the project website, Facebook, email and in-person communication, viewers shared that the project gave their experience a voice and they related to the photos on an emotional level.

Conclusion: The project resulted in powerful images and new ways to convey what it is like to live with lupus. The participants themselves defined it as a success. While the program is time-intensive, it is an inexpensive program that can be replicated by other lupus groups. The Foundation will continue in-person workshops, and the project will also grow through online submissions. Based on participants’ feedback, the program has the potential to help reduce feelings of isolation and depression, and increase self-esteem and a sense of self-efficacy. More data are needed to confirm participants’ reported outcomes. In the future, variables like self-efficacy, self-esteem, depression, and quality of life will be incorporated into the evaluation.

Disclosure: J. Rowshandiel, None; D. Gross, None.

Personalized Risk Education for Rheumatoid Arthritis Improves Self-Perceived Risk Accuracy and Risk Factor Knowledge in First-Degree Relatives. Jeffrey A. Sparks¹, Mauria D. Iversen², Rachael Miller Kroouze³, Nellie A. Friedman¹, Taysr G. Mahmoud³, Sarah S. Kalia³, Michael L. Atkinson³, Robert C. Green³ and Elizabeth W. Karlson¹. ¹Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, ²Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Having a first-degree relative (FDR) with RA increases personal RA risk by four-fold. Other RA risk factors include demographics, genetics, auto-antibodies, and behaviors. We aimed to develop a personalized RA risk tool incorporating these risk factors, suitable for use in RA education trials. We explored changes in self-perceived RA risk and RA knowledge after personalized RA risk education among a group at increased RA risk due to having a relative affected with RA.

Methods: We conducted a pilot study on RA self-perceived risk, knowledge, and attitudes among FDRs recruited at a large academic hospital. Eligible participants had a FDR with RA. We developed a web-based interactive tool, the Personalized Risk Estimator for RA (PRE-RA), which provided RA education and calculated lifetime RA risk based on demographics, genetics (HLA shared epitope), auto-antibodies (RF and ACPA), and...
behaviors (smoking, overweight/obesity, low fish intake, and dental health). RA knowledge and attitudes were assessed before and 6 weeks after the intervention: PRE-RA and health education. RA risk factor knowledge was evaluated by whether subjects agreed that an established risk factor, supported by literature, increased RA risk. An RA knowledge index was calculated by the total number of established factors agreed to increase RA risk. Self-perceived lifetime RA risk before and after the intervention was compared to the PRE-RA calculated lifetime RA risk using Wilcoxon rank-sum test. RA knowledge and attitudes before and after intervention were compared by Fisher's exact or Wilcoxon rank-sum tests.

**Results:** A total of 37 subjects enrolled in the study and 14 completed the PRE-RA tool with health education. Median age was 44 years (range 20–70) and 76% were female. Using demographics, behaviors, genetics, and auto-antibodies, the median personalized lifetime calculated RA risk was 5% (range 1–56, mean 12.4, SD 14.7; Table) and was significantly lower than self-perceived risk at baseline (median 50%, range 0–85, mean 38.6, SD 23.7; p = 0.002). After intervention, self-perceived risk approached the calculated PRE-RA risk but remained significantly higher (median 14%, range 1–80, mean 25.1, SD 26.5; p = 0.04). RA knowledge index significantly improved after the PRE-RA tool (median 8, mean 8.6, SD 0.5) compared to baseline (median 6, mean 5.4, SD 1.6; p < 0.0001). Only 20% agreed that smoking was a risk factor for RA at baseline, but 100% agreed after the intervention (p < 0.0001).

**Conclusion:** We developed an interactive RA risk education tool, PRE-RA, personalized to demographics, behaviors, genetics, and auto-antibodies suitable for use in RA risk education trials. Subjects in our study had high self-perceived RA risk, compared to calculated risk, that became more accurate after personalized RA risk education. Knowledge of RA risk factors was low prior to intervention and significantly increased after the PRE-RA tool and health education.

<table>
<thead>
<tr>
<th>Table. RA risk self-perception, knowledge, and attitudes at baseline and after the Personalized Risk Estimator for RA (PRE-RA) tool and health education among RA first-degree relatives.</th>
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<tbody>
<tr>
<td><strong>Self-perceived vs. calculated lifetime RA risk</strong></td>
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<tr>
<td><strong>Baseline lifetime % RA risk, median (range)</strong></td>
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<tr>
<td>50 (0–85)</td>
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<tr>
<td><strong>Post-intervention lifetime % RA risk, median (range)</strong></td>
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<td><strong>Baseline vs. 6-weeks after intervention</strong></td>
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<td><strong>Lifetime % RA risk, median (range)</strong></td>
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<tr>
<td>50 (0–85)</td>
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<tr>
<td>Smoking is a risk factor for RA, % agree</td>
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<tr>
<td>Diet is a risk factor for RA, % agree</td>
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<tr>
<td>Dental health is a risk factor for RA, % agree</td>
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<tr>
<td>Obesity is a risk factor for RA, % agree</td>
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<tr>
<td>RA knowledge index, median (range)</td>
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<tr>
<td>&gt;45% lifetime RA risk for average person, % agree</td>
</tr>
<tr>
<td>18% lifetime risk of RA is low or very low, % agree</td>
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</tbody>
</table>

*A total of 14 subjects provided self-perceived risk after the PRE-RA tool and health education.

**Disclosure:** J. A. Sparks, None; M. D. Iversen, Pfizer Inc; 2. R. Miller Kroouze, None; N. A. Friedman, None; T. G. Mahmoud, None; S. S. Kalia, None; M. L. Atkinson, None; R. C. Green, None; E. W. Karlson, None.

**Development of Multimedia Patient Education Tools (MM-PET) for Osteoarthritis (OA), Osteoporosis (OP) and Rheumatoid Arthritis Patients (RA).** Maria A. Lopez-Olivo, Aparna Ingleshwar, Robert Volk, Andrea Barro, Maria Libaja-Wassis and Maria E. Suarez-Almazor. 1The University of Texas, MD Anderson Cancer Center, Houston, TX, 2The University of Texas MD Anderson Cancer Center, Houston, TX, 3Baylor College of Medicine, Houston, TX.

**Background/Purpose:** The purpose of our study was to develop and perform usability testing of Multimedia Patient Education Tools (MM-PET) for patients with knee osteoarthritis, osteoporosis and rheumatoid arthritis.

**Methods:** We developed three MM-PETs following an Edutainment Model (one for each disease). The goals were designed to make the programs both didactic and entertaining and the navigation and graphical user interface as simple as possible. Entertainment education was provided via a storyline with several episodes linked to the consecutive learning modules which emphasized the content of the episodes. Learning objectives were drafted for each MM-PET topic. After segments of the scenes were developed, we pre-tested them to ascertain that the stories had the appropriate cultural context and lifestyle. Refinements were made to the program after pre-testing to ensure accuracy. Ten cognitive interviews per disease were conducted to identify potential language and imagery issues in the MM-PETs. Once the MM-PET was finalized, patients (20 per disease) were shown the tool and were interviewed. Their disease knowledge was tested with a self-report questionnaire (before and after viewing the MM-PET).

**Results:** The general sequence of content was: i) overview of the disease, ii) description of treatments, iii) testimonial i, (iii) description of the harms and benefits of each option iv) testimonial ii, h) review of key facts and suggestions for questions to ask of the patient's doctor, and vi) testimonial iii. Both the content and the instructions were narrated, and visual cues were provided to reach patients who are poor readers or who cannot read. We created both English and Spanish-language versions. After cognitive interviewing, 4 of the 10 patients suggested adding more content: for knee osteoarthritis, information on knee replacement and rehabilitation after surgery; for osteoporosis, providing more information on the difference between osteoporosis and osteoarthritis; and for rheumatoid arthritis: i) including more information on nutrition to prevent anemia and bone decalcification and ii) exercises to help with the stiffness. In the pilot testing, 60 participants were interviewed and in terms of acceptability, most patients in all disease groups found the length and amount of information presented in the MM-PETs to be "just right", and the presentation as "balanced". In terms of comprehension, all participants provided a favorable evaluation of the MM-PET; all found the video easy to use, the vocabulary easy to understand and the material to be well organized. A ll participants felt they gained "clarity" on disease education, symptoms, and time medication takes to start acting. 2. We were encouraged to see their doctor regularly", and 3) were more aware about taking their medications. Statistically significant differences were observed in pre-post knowledge questionnaire scores (OA, p = 0.03; OP, p = 0.001; RA, p < 0.0001).

**Conclusion:** Multimedia tools that incorporate video modeling can help patients better understand and manage their disease. Patient involvement in the development process is essential to ensure relevant content and usability.

**Disclosure:** M. A. Lopez-Olivo, None; A. Ingleshwar, None; R. Volk, None; A. Barro, None; M. Jibaja-Weiss, None; M. E. Suarez-Almazor, None.

**2010**

**Reaching out to Physical Therapists: Results of a Survey on Physical Therapists Preferences for Learning about Evidence-Based Community Programs.** Jennifer Heffring1, Teresa J. Brady2, Jennifer Bertoldi, M. arc Goldstien1, Erika Bonilla, Mari Brick3, Erica Odom4, Angela Oliver5 and Frederick6. 1University of Texas, MD Anderson Cancer Center, Houston, TX, 2The University of Texas, MD Anderson Cancer Center, Houston, TX, 3The University of Texas, MD Anderson Cancer Center, Houston, TX, 4American Physical Therapy Association, Atlanta, GA, 5Centers for Disease Control and Prevention, Atlanta, GA, 6Westat Inc, Rockville, MD, 7American Physical Therapy Association Association, Alexandria, VA, 8Westat Inc, Rockville, MD, 9American Association of Chronic Disease Directors, Voorheesville, NY, 10American Chronic Pain Association, Rocklin, CA.

**Background/Purpose:** Community resources such as evidence-based physical activity (PA) and self-management education (SME) programs, with their documented health benefits, can complement clinical care. These clinical-community linkages can be strengthened by Physical Therapists (PTs) awareness and recommendation of these resources to their patients. The purpose of this study was to explore PTs awareness of, and attitudes towards the use of arthritis-appropriate PA and SME programs, and factors that would influence their decision and facilitate a recommendation of these programs to their patients.

**Methods:** A stratified random sample of 10,000 members from the geriatrics, home health, orthopedics, and private practice sections of American Physical Therapy Association (APTA) received e-mail invitations to participate in an on-line survey exploring awareness of and preferences related to evidence-based community PA and SME programs. Inclusion criteria included PTs in clinical practice with > 50% adult patients. The survey questions and response options were based on earlier qualitative interviews and refined through pilot-testing.

**Results:** 1180 PTs responded to the invitation (response rate 11.6%), 84% of respondents met eligibility criteria; a total of 973 PTs participated in the survey. 67% of PTs surveyed were aware of some PA programs in the community; only 22% were aware of community SME programs. Willingness to refer to evidence-based programs was high (over 90% were somewhat or very likely to refer to PA and SME programs). PTs preferred to learn about these resources via means they can access at their convenience (e-mail-82%,
Arthritis affects > 1 in 5 American adults, and is the most common cause of disability. Nearly 1/3 of people with diabetes or heart disease also have arthritis. Public health interventions such as community-based physical activity (PA) and self-management education (SME) programs have demonstrated health benefits among people with arthritis, yet availability is limited. State legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority.

**Conclusion:** Although awareness of PA and SME programs differed by program type, large number of PTs expressed willingness to recommend arthritis-appropriate evidence-based programs in the community, both during therapy and at discharge. PTs need patient materials to facilitate these recommendations, preferably brochures, flyers, or website. Preferred channel to receive program information was via website. These results can be used to shape messages, materials, and messages to encourage PTs to recommend evidence-based community programs and improve patient outcomes.

**Disclosure:** J. Hefelfinger, None; T. J. Brady, None; J. Berkold, None; M. Goldstein, None; E. Bonilla, None; M. Brick, None; E. Odom, None; A. Oliver, None; P. Cowan, None.

**Background/Purpose:** To increase awareness of and promote the use of evidence-based physical activity (PA) and self-management education (SME) programs for arthritis through social media. The National Conference of State Legislatures (NCSL) invited State Legislators to participate in focus groups (FGs) that preceded the NCSL 2013 Legislative Summit. Selection criteria included: leadership of an NCSL’s Health Committee, appointment to an NCSL’s committee on PA, no previous participation in an arthritis education session at the 2012 Legislative Summit, and previous education session attendance.

**Methods:** The NCSL invited 20 state legislators and 2 legislative staff to participate in focus groups (FGs) that preceded the NCSL 2013 Legislative Summit. Selection criteria included: leadership of an NCSL’s Health Committee, appointment to an NCSL’s committee on PA, no previous participation in an arthritis education session at the 2012 Legislative Summit, and previous education session attendance.

**Results:** 16 Legislators and 2 staff participated (82% response rate). The legislators were: 56% Democrat, 38% Republican, and 1% Independent. Legislators were both interested in and surprised by the arthritis-affected health status of people with arthritis, yet availability is limited. State legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislatures address other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority. Some state legislation addresses other chronic diseases, yet arthritis receives low priority.

**Conclusion:** Results suggest that in addition to being an effective platform for health promotion and education, social media may also serve as an informal support system by providing validation of experiences and symptoms. Future studies will target specific health behaviors, measure outcomes of interest through pre and post testing, and potentially include an off-line component to promote high level of engagement.
Quality Appraisal of Educational Websites on Osteoporosis and Bone Health. Maria A. Lopez-Olivo, Noha A. Abdel-Wahab, Abhinav Dodeja, Gregory Pratt and Maria E. Suarez-Almazor. The University of Texas, MD Anderson Cancer Center, Houston, TX, The University of Texas Health Science Center, School of Public Health, Houston, TX.

Background/Purpose: Osteoporosis, like many other chronic diseases, can have better outcomes when informed patients get involved in self-management, resulting in better outcomes. Bone health education publicly available through the Internet, if evidence-based and unbiased, could help patients deal with issues such as decision making, maintaining healthy lifestyles, using medications correctly, and improving their communication with health professionals. The current study aimed to assess the quality of websites providing bone health-related information on the Internet.

Methods: We performed an environmental scan of the currently available osteoporosis and bone health patient education information on the World Wide Web. The sample websites were identified by using three separate search tools: Google Advanced, Bing, and Ask.com. We used the phrases “bone health” and “osteoporosis” in titles of Web pages and reviewed the first 100 results in each of the following domains: gov, .org, .com, plus links to .edu websites. Only patient education websites were included. Websites that were part of clinical guidelines were excluded. Two independent investigators collected data regarding: information provided (accuracy and completeness); design, disclosures and references provided. Literacy was evaluated using the Flesch Grade Level readability formula.

Results: We identified 29 websites (92% non-profitable). Most websites were focused on risks factors of osteoporosis, preventive measures, screening recommendations, and topics to discuss with the physician. All websites provided adequate information describing treatment options; however, only 10.5% had information addressing duration of treatment, what happens when treatment stops, and the benefits and risks of various treatments. Only 50% of the websites had their content updated to 2014. Reading levels ranged from 7.8 to 14.8 (higher than the recommended 6-grade level). Ninety percent of the sites were static websites with no interactive features in their design. Only 33% included an adequate disclosure statement and 25% cited their sources of information to support their content.

Conclusion: Websites with information about bone health and osteoporosis commonly fail to report adequate disclosure statements and sources of information. While they commonly present information about initial treatment choices, most fail to address risk-benefit issues, and common barriers that can occur throughout the course of the disease. In addition, most websites are written at a 9-grade level or above, rendering them unsuitable for low-literacy populations.

Disclosure: M. A. Lopez-Olivo, None; N. Abdel-Wahab, None; A. Dodeja, None; G. Pratt, None; M. E. Suarez-Almazor, None.

ACR/ARHP Poster Session C
Epidemiology and Public Health: Rheumatoid Arthritis
Pathogenesis and Treatment
Tuesday, November 18, 2014, 8:30 AM – 4:00 PM

Performance of Self-Reported Measures for Periodontitis in Rheumatoid Arthritis and Osteoarthritis. Brian Coburn, Harlan Sayles, Robert Redman, Jeffrey Markt, Mark Beatty, Garth Griffiths, David McGowan and Ted R. Mikuls. University of Nebraska Medical Center, Omaha, NE, Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, University of Nebraska Medical Center, Lincoln, NE, Veterans Affairs Medical Center (VAMC), Washington, DC, Dallas VA and University of Texas Southwestern, Dallas, TX, George E. Wahlen VA Medical Center, Salt Lake City, UT.

Background/Purpose: Periodontitis (PD) is associated with many chronic health conditions including rheumatoid arthritis (RA). Affecting one-third to one-half of the US population, the high prevalence of PD underscores its potential impact. PD may play a role in initiating or worsening RA. Yet, studies are often hindered by reliance on intensive full-mouth exams required for PD diagnosis whereas new self-report methods can reduce cost. Many studies indicate that PD has a different presentation in RA patients. It is unknown whether this difference affects performance of self-report measures. The purpose of this study was to evaluate self-report against the reference standard of clinically-defined PD in RA and osteoarthritis (OA) patients after accounting for factors associated with PD.

Methods: Six self-report PD questions were evaluated in RA and OA patients. All RA patients met ACR criteria and OA patients were classified based on physician diagnosis or corresponding x-ray results. Self-report questions were validated against a reference standard of severe or moderate-to-severe PD based on full-mouth examination. M ultivariable logistic regression was used to evaluate the performance of: 1) self-report alone; 2) age, sex, education, and smoking status; and 3) a combination of the above. Model performance was assessed using the c-statistic. Convergent validity of self-reported “bone loss or deep pockets” and “loose teeth” was assessed; associations of self-report with RA disease characteristics were explored.

Results: Self-report performed similarly in RA and OA, with individual specificity for PD ≥ 68% and sensitivity between 10% and 45%. Question-only models yielded c-statistics of 0.66–0.72 while risk factor-only models yielded c-statistics of 0.74–0.79. The best performing models incorporated both self-report questions and PD risk factors with c-statistics ≥0.79. Greater radiographic alveolar bone loss was observed among participants reporting ‘bone loss or deep pockets’ (p = 0.001) and ‘loose teeth’ (p = 0.001). Among RA patients, ‘loose teeth’, but not other self-report factors, was associated with rheumatoid factor positivity (p = 0.047) and higher disease activity (p < 0.001).

Table 1. Logistic Regression for Final Models after Backward Stepwise Selection

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 592)</th>
<th>RA (n = 275)</th>
<th>OA (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>PD</td>
<td>Mod-Sev PD</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>1.05 (1.03–1.08)</td>
<td>1.05 (1.03–1.08)</td>
<td>1.05 (1.03–1.08)</td>
</tr>
<tr>
<td>Male (Female)</td>
<td>2.43 (1.86–3.17)</td>
<td>1.37 (1.24–1.52)</td>
<td>1.46 (1.26–1.70)</td>
</tr>
<tr>
<td>Smoke Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1.46 (1.24–2.80)</td>
<td>1.44 (1.20–1.72)</td>
<td>1.39 (1.20–1.64)</td>
</tr>
<tr>
<td>Current</td>
<td>3.13 (1.79–5.43)</td>
<td>2.78 (1.28–6.21)</td>
<td>2.75 (1.28–5.97)</td>
</tr>
<tr>
<td>Questions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gum Bled</td>
<td>2.01 (1.72–4.22)</td>
<td>2.22 (1.79–2.91)</td>
<td>2.07 (1.68–2.57)</td>
</tr>
<tr>
<td>Bone Loss/Deep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pocket</td>
<td>5.09 (3.89–6.64)</td>
<td>4.97 (3.78–6.48)</td>
<td>4.44 (3.02–6.43)</td>
</tr>
<tr>
<td>Periostal/Treatment</td>
<td>2.74 (1.73–4.62)</td>
<td>2.19 (1.30–3.72)</td>
<td>2.75 (1.83–4.17)</td>
</tr>
<tr>
<td>See Periodontist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose Teeth</td>
<td>3.08 (1.93–4.95)</td>
<td>2.84 (1.82–4.44)</td>
<td>2.80 (1.60–4.94)</td>
</tr>
<tr>
<td>Periodontist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Model AUC</td>
<td>0.52 (0.46–0.58)</td>
<td>0.52 (0.46–0.58)</td>
<td>0.52 (0.46–0.58)</td>
</tr>
</tbody>
</table>

All odds ratios displayed have a p-value less than 0.05. Separate models are presented for each group: rheumatoid arthritis (RA), osteoarthritis (OA) and overall. Each group is analyzed by the severe and moderate-to-severe PD (Mod-Sev) definitions. Area under the curve (AUC). AUCs for question-only models: Overall & Severe PD – 0.78; Overall & Severe Mod-Sev PD – 0.70; RA and Severe PD – 0.74; OA and Severe PD – 0.72; OA and Mod-Sev PD – 0.68. AUCs for risk factor-only models: Overall & Severe PD – 0.79; Overall & Severe Mod-Sev PD – 0.70; RA & Severe PD – 0.74; RA and Mod-Sev PD – 0.72; OA & Severe PD – 0.76; OA and Mod-Sev PD – 0.77.

Conclusion: Patient self-report, when combined with other risk factors, performs well in identifying PD among patients with RA and OA. Self-report questions related to alveolar bone loss exhibit excellent convergent validity in these patient subsets.

Disclosure: B. Coburn, None; H. Sayles, None; J. Payne, None; R. Redman, None; J. Markt, None; M. Beatty, None; G. Griffiths, None; D. McGowan, None; T. R. Mikuls, None.

2015
Fine Particulate Air Pollution and Systemic Autoimmune Rheumatic Disease in Two Canadian Provinces. Sasha Bernatsky, Audrey Smargiassi, Cheryl Barnabe, Lawrence W. Svensson, Allan Brand, Marie Hudson, Steven M. Edworthy, Ann E. Clarke, Paul R. Fortin, Patrick Belisle and Lawrence Joseph. McGill University Health Centre, Montreal, QC, University of Montreal, Montreal, QC, University of Calgary, Calgary, AB, Instutit national de santé publique du Québec, Montreal, QC, Lady Davis Institute for Medical Research and Jewish General Hospital, Montreal, QC, The University of Calgary, Calgary, AB, LaPaval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC, Research Institute of the McGill University Health Centre, Montreal, QC, McGill University, Montreal, QC.
Background/Purpose: To estimate the degree to which fine particulate (PM2.5) air pollution is associated with systemic autoimmune rheumatic diseases (SARDs).

Methods: We used population-based administrative data from Alberta (1993–2007) and Quebec (1989–2010). The SARD case definition was based on at least 2 physician billing claim codes, or at least 1 rheumatology billing code, or at least 1 hospitalization diagnostic code (for systemic lupus, Sjögren's Syndrome, scleroderma, polymyositis, dermatomyositis, or undifferentiated connective tissue disease). Bayesian hierarchical latent class regression models estimated the probability that any given resident was a SARD case, given our three case definitions. Mean 2001–2006 residential exposures to ambient PM2.5 levels were assigned using satellite-derived data for Dissemination Area regions in Alberta, and Local Community Services Centre (CLSC) regions in Quebec (both assigned from postal code of residence). The sum of individual level probabilities provided the total cases per region in each province, according to age, sex, urban-versus-rural residence, income, and PM2.5 levels. In Alberta, we also stratified by First-Nations (FN) status, which in Alberta represents about 3% of the population (Blackfoot, Cree, Chipewyan, Dene, Saree, Stoney/Nakoda Sioux, and others). The hierarchical model generated odds ratios for estimating the probability of a SARD case, based on age, sex, urban-versus-rural residence, income, and PM2.5 levels. The model accounted concurrently for these characteristics, as well as an interaction term between age and sex. The model generated Bayesian 95% credible intervals (CrI), which are similar to the non-Bayesian confidence interval for the OR estimates.

Results: The probability of being a SARD case was higher among females versus males and for residents aged 45 versus younger, with the highest ORs for older females. Independently, the odds of being a SARDS case increased with PM2.5 levels. In Alberta, the effect was slightly greater for FN residents. Specifically, in Alberta, when we used a continuous variable for PM2.5, the adjusted OR (interpreted as increase in SARDS per unit increase in PM25) in FN residents was 1.38 (95% CrI 1.14, 1.68) whereas in non-FN Alberta residents the adjusted OR was 1.05 (95% CrI 1.01, 1.08). In Quebec, where information on FN status (1% of the Quebec population) was not available, the adjusted OR for PM2.5 as a continuous variable, was 1.05 (95% CrI 1.00, 1.08).

Conclusion: Adjusting for demographics, exposure to PM2.5 is associated with an increased risk of SARDs. Our data suggest that FN populations may be particularly vulnerable to this effect. Improving air quality across the continent appears to be an important way to reduce chronic disease burden, not only for respiratory and cardiac disease, but also systemic autoimmune rheumatic diseases.

Disclosure: A. Ilar, None; P. Wiebert, None; L. Klar eskog, None; L. Alfredsson, None; C. Bengtsson, None.

2017

Fish Consumption and Risk of Rheumatoid Arthritis Among Women in Large Propective Cohorts. Jeffrey A. Sparks, Shun-Chao Chang, Bing Lu, Susan M. Aspnes, Karen H. Costenbader and Elizabeth W. Karlson. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Prior studies have suggested a protective effect of fish intake on RA. However, these studies were limited by potential recall bias, short follow-up, and small sample sizes. We aimed to evaluate the effect of fish consumption on RA development in two large cohorts, the Nurses' Health Study (NHS) and NHSII.

Methods: We examined the effect of fish consumption on RA risk among women in two large, prospective cohorts. NHS is composed of 121,700 US nurses followed since 1976; NHSII is composed of 116,430 nurses followed since 1989. Lifestyle and environmental exposures were collected through biennial questionnaires. Diet and fish intake were assessed by a semi-quantitative food frequency questionnaire completed every 4 years. Participants who provided fish data at baseline in each cohort were analyzed. Incident RA cases were identified by screening questionnaire and validated by medical record review according to the 1987 ACR RA criteria. Cumulative average fish intake prior to RA development was used to represent long-term fish intake. Cox regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) of fish intake and RA risk, adjusted for confounders, including age, total energy intake, smoking, body mass index, alcohol, and soda intake. HRs from the two cohorts were meta-analyzed using a random effects model.

Results: We validated 652 incident RA cases among 86,135 women in NHS and 322 incident RA cases among 92,984 women in NHSII with diet data. For women in NHSII, modest fish consumption (1–2 servings per week) was associated with a protective effect on RA (age-adjusted HR 0.63, 95% CI 0.42–0.96, Table 1) compared to never/rare fish consumption that was nearly significant in the multivariable model (HR 0.66, 95% CI 0.44–1.01). However, for women in NHS, modest fish consumption was not associated with RA (HR 0.86, 95% CI 0.57–1.32) compared to never/rare fish intake. In meta-analysis of the results, there was a suggestion of a protective effect for modest fish intake that was statistically significant (HR 0.76, 95% CI 0.56–1.02). More frequent fish consumption was not statistically associated with RA (HR 0.94 for 2 to ≤3 servings/week; HR 0.88 for >3 servings per week compared to never/rare intake) and there was no statistically significant trend for fish consumption on RA risk.

Conclusion: In these large prospective studies of nearly 180,000 women, there was a suggestion of a protective effect of modest fish consumption (1–2 fish servings per week) on RA development compared to never/rare fish intake. This protective effect of fish intake on RA risk was more pronounced in NHSII than NHS, but was not statistically significant in meta-analysis of both cohorts. Cohort differences, such as age, secular diet trends, and age at RA onset, may explain these results or they may be due to chance. Further studies of nutritional components of fish, such as omega-3 fatty acids, may clarify the effect of fish intake on RA risk.
Table. Hazard ratios for RA development by categories of cumulative average updated fish intake serving frequency in NHS (n = 86,133), NHS II (n = 92,984), and meta-analysis of both cohorts.

<table>
<thead>
<tr>
<th>NHS II</th>
<th>Age-adjusted HR</th>
<th>Person-years</th>
<th>NHS II</th>
<th>Age-adjusted HR</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>29</td>
<td>88</td>
<td>107</td>
<td>56</td>
<td>42</td>
</tr>
<tr>
<td>Person-years</td>
<td>125,680</td>
<td>453,864</td>
<td>663,142</td>
<td>242,353</td>
<td>225,015</td>
</tr>
</tbody>
</table>

K. H. Costenbader

Table. Mediterranean or vegetarian diet and risk of RA, stratified by ACPSA and RF-status.

<table>
<thead>
<tr>
<th>Case (n expressed/unexposed)</th>
<th>Controls (n expressed/unexposed)</th>
<th>Mediterranean Diet</th>
<th>OR (95% CI)</th>
<th>OR (95% CI) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPSA</td>
<td>RF</td>
<td>ACPSA</td>
<td>RF</td>
<td>ACPSA</td>
</tr>
</tbody>
</table>

Table. Mediterranean or vegetarian diet and risk of RA, stratified by ACPSA and RF-status.

<table>
<thead>
<tr>
<th>Case (n expressed/unexposed)</th>
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<th>OR (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ACPSA</td>
<td>RF</td>
<td>ACPSA</td>
<td>RF</td>
<td>ACPSA</td>
</tr>
</tbody>
</table>

Discipline: K. Johansson1, M. Sandberg2, S. Saevarsdottir3, M. Neovius4, L. Alfredsson5, J. Askling1, and C. Bengtsson6. 1Clin-
cial Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 2The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, 3Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Lifestyle factors are of major importance for development of RA. Yet, regarding the role of diet, surprisingly little is known. The Mediterranean diet, rich in fish, plant food, mon- and poly-
unsaturated fat, and including moderate wine consumption, has been suggested to protect against e.g. cardiovascular disease, but its effect on RA development has only been studied to a limited extent. The aim of this study was to investigate whether Mediterranean or vegetarian (vs. Western) diet influences the risk of developing RA.

Methods: In the Swedish case-control study Epidemiological Investigation of Rheumatoid Arthritis (EIRA), 1296 incident RA cases and 2661 randomly selected controls matched by age, sex and residential area were enrolled between 2005 and 2012. Type of diet the year before enrolment was ascertained by a single question in a food-frequency questionnaire, including Western diet, Mediterranean diet, vegetarian diet, vegan diet, or other specified diet. Odds ratios (OR) were estimated for RA overall, and also stratified for anti-citrullinated peptide autoantibodies (ACPSA) and rheumatoid factor (RF) status. Adjustments were made for the matching factors in the crude model and additionally for BMI, smoking, formal education and, physical activity in the adjusted model.

Results: 9% of the RA-cases (n=122/1269) reported to consume a Mediterranean diet the year before enrolment compared with 12% (309/2661) of the controls, 91% (n = 247/269) of the RA-cases and 93% (80/2661) of the controls reported to consume a vegetarian diet. After adjustment for the matching factors, a Mediterranean diet was associated with a statistically significant decreased risk of RA compared with Western diet (OR 0.76; 95% CI 0.62–0.97; Table). However, after additional adjustment the association did not remain statistically significant (OR 0.96; 95% CI 0.86–1.08). The results did not change when stratifying by ACPSA or RF-status, although there was a tendency towards lower risk with Mediterranean diet in ACPSA+ and RF+ patients. Vegetarian diet was not associated with development of RA, neither in the crude model nor the adjusted model.

Conclusion: Self-reported Mediterranean diet is in itself associated with a lower risk of RA, but this association disappeared after adjustment for the selected potential confounders. A tendency towards lower risk with Mediterranean diet in ACPSA+ and RF+ patients was observed. No association was observed for a vegetarian diet.

Discussion: K. Johansson, None; S. C. Chang, None; B. L. Lu, None; S. Malspeis, None; K. H. Costenbader, None; E. W. Karlson, None.

2018

Do Mediterranean or Vegetarian Diets Influence Risk of Rheumatoid Arthritis? Kari Johansson1, Maria Sandberg2, Saedis Saevarsdottir3, Martin Neovius4, Lars Alfredsson5, Johan Askling1, and Camilla Bengtsson6. 1Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 2The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, 3Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Hypertension is common in rheumatoid arthritis (RA), but it is unclear whether this prevalence is due to RA-related medications or to the disease process itself. Prior work in first-degree relatives (FDR) of RA patients without clinically apparent RA, and thus without RA-related medications, has shown that markers of endothelial dysfunction were associated with antibodies to citrullinated protein antigens (ACPSA), suggesting that ACPSA may be involved in vascular injury. Thus, we sought to investigate associations between ACPSA and systolic and diastolic blood pressure in FDRs.

Methods: In the Studies of the Etiology of Rheumatoid Arthritis (SERA) (a multicenter prospective study of preclinical RA), we evaluated associations between ACPSA and systolic (SBP) and diastolic blood pressure (DBP) in 89 FDRs of RA patients. A panel of 15 ACPSA were measured using a Bio-Plex bead-based assay, and were dichotomized as positive/negative based on pre-specified cut-offs in 200 RA patients and 98 blood bank controls. These cutoffs were developed using receiver operating characteristic (ROC) curves giving ≥90% specificity. Seventeen FDRs lacked ACPSA measurements and were excluded, leaving 72 FDRs for analysis. SBP and DBP were measured 3 times and averaged. ANCOVA was used to evaluate associations between ACPSA positivity and SBP and DBP, adjusting for age, sex, race, body mass index (BMI), and smoking. ANCOVA was used to evaluate associations between ACPSA positivity and SBP and DBP, adjusting for age, sex, race, body mass index (BMI), pack-years of smoking, high sensitivity C-reactive protein (CRP), and current use of anti-hypertensive medications.

Results: Averag age was 51 years, and 69% were female. Mean SBP was 119 ± 18 mmHg and DBP was 74 ± 9 mmHg. 46% of FDRs were positive for any ACPSA; these individuals were younger and had lower BMI, more pack-years of smoking, and higher levels of hsCRP, and had marginally higher DBP. (Table) Positivity for antibodies to cit-fibrinogen A (211–230) was associated with 11.52 mmHg higher SBP; to cit-filaggrin was associated with 13.9 mmHg higher SBP; to cit-clusterin, cit-filaggrin, and cit-vimentin were associated with 7–8 mmHg higher DBP. Positivity for each additional ACPSA was significantly associated with a 0.98 mmHg increase in SBP, and a 0.58 mmHg increase in DBP.

Conclusion: In FDRs without RA, ACPSA positivity is associated with higher SBP and DBP, independent of risk factors and medications for hypertension. While cit-fib and cit-vimentin have been implicated in subclinical CVD in RA, these findings suggest ACPSA play a role in the vascular changes leading to hypertension prior to RA.
Conclusion: Circulating carotenoid metabolites were associated with a reduced risk of seronegative RA, but not seropositive RA, suggesting different mechanisms for development of these two RA phenotypes. Further studies are needed to confirm our finding.

Table. The association between circulating carotenoids (quartiles) and risk of seropositive and seronegative RA (Odds ratio and 95% confidence interval)∗

<table>
<thead>
<tr>
<th>Carotenoid Metabolite</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein/zeaxanthin</td>
<td>1.00</td>
<td>1.08</td>
<td>0.62 (0.39,2.78)</td>
<td>1.36</td>
<td>0.79 (0.27,0.37)</td>
</tr>
<tr>
<td>β-carotxin</td>
<td>0.87</td>
<td>0.85 (0.51,1.49)</td>
<td>1.00</td>
<td>0.58 (0.17,1.12)</td>
<td>1.17</td>
</tr>
<tr>
<td>Lycopene</td>
<td>1.00</td>
<td>1.04 (0.81,2.17)</td>
<td>1.53</td>
<td>0.90 (0.62,2.20)</td>
<td>1.20</td>
</tr>
<tr>
<td>α-carotene</td>
<td>1.00</td>
<td>0.96 (0.56,1.67)</td>
<td>1.09</td>
<td>0.63 (0.31,1.28)</td>
<td>1.28</td>
</tr>
<tr>
<td>β-carotene</td>
<td>1.00</td>
<td>1.50 (0.82,2.59)</td>
<td>1.06</td>
<td>0.61 (0.32,0.99)</td>
<td>1.72</td>
</tr>
<tr>
<td>Total carotenoids**</td>
<td>1.00</td>
<td>1.08</td>
<td>0.62 (0.39,2.78)</td>
<td>1.36</td>
<td>0.79 (0.27,0.37)</td>
</tr>
</tbody>
</table>

S887
vs. 72.3 mmHg), cholesterol ratio (3.7 vs. 3.4), HbA1c (5.9 vs. 5.5%), FBG (108 vs. 99 mm/dl), CRP (0.19 vs. 0.12 mm/dl). Health history was also suboptimal in the CVD group, including ever-smoking (57.8 vs. 40.0%); history of CVD risk factors such as DL, DM and HTN (22.3 vs. 4.4%, 2.4 vs. 0.3% and 35.9 vs. 7.1%, respectively); and family CVD history (37.1 vs. 22.2%), p < 0.001 for all.

On multivariate analysis, however, RF positivity was not correlated with CVD (1.06, 95%CI 0.91–1.22), in either men (1.03, 95%CI 0.85–1.23) or women (1.10, 95%CI 0.86–1.42) after adjustment for clinically established risk factors.

Conclusion: Despite its association with CVD in individuals with RA, RF does not appear to be correlated with CVD and appears to be inappropriate for use as a CVD screening test in apparently healthy individuals. Further investigations to clarify the reason for this discrepancy between RA patients and general population are warranted in the future.

Disclosure: C. Min, None; M. Kishimoto, None; G. A. Deshpande, None; S. Kaneshita, None; M. Suda, None; Y. Ohara, None; Y. Haji, None; R. Rokutanda, None; Y. Suyama, None; H. Shimizu, None; T. Tsuda, None; K. I. Yamaguchi, None; A. Takeda, None; Y. Matsui, None; M. Okada, None.

2022


Background/Purpose: High global prevalence rates of rheumatoid arthritis (RA) have been reported in First Nations (FN). For our regional population of 1.2 million, health care is universally covered, and health services and diagnoses based on International Classification of Disease codes (ICD-9-CA) are recorded in the Population Health Research Database (PHRD) from 1984. As a first step to addressing RA care in FN, we validated case definitions for RA for use with the PHRD and described the incidence, prevalence, and health care use for RA.

Methods: Records from April 1, 1995 to March 31, 2010 were accessed. FN people were identified using linkage with the Federal Indian Registry File (FIRF) which records all registered FN for the purposes of entitlement. Identification was expanded to include non-status Indians otherwise eligible (Metsis, Inuit). Residents who resided in the province for >2 years were identified as having RA if they had ≥5 physician visits or hospitalizations with ICD-9-CM/ICD-10 codes 714/M05/M06.06 recorded. Persons resident for <2 years were identified as having RA if they had ≥3 such claims. This definition was validated for the years 2000-2010 by linkage with the A-rthritis Centre database (includes self-identified nonFN, FN, Metsis; RA n = 2281; nonRA n = 7044; definition sensitivity 77.12, specificity 90.30 Y ouden statistic 67.42). Crude and age standardized prevalence rates for FN and nonFN in 2000–2010 were determined. Onset age (age at first RA code), was compared in prevalent cases. Using a 5-year run-in time to eliminate prevalent cases, incident RA cases were identified and compared between FN and non-FN using logistic regression and odds ratios with 95% CI reported. Physician visits and hospitalizations were compared between FN and nonFN from 2000–2010.

Results: While both crude and age standardized overall prevalence rates of RA increased from 2000–2010 (crude prevalence 0.34% to 0.65%), FN had higher rates than nonFN in each year. In 2009–2010, crude rates were 0.63% vs. 0.63% for FN vs. nonFN, while age adjusted rates were 1.0% vs. 0.4%; for a rate that was 2.48 times higher in FN than non-FN in 2009–2010 (95% CI 2.471–2.472; p < 0.0001). The age standardized annual incidence of RA decreased from 0.07% in 2000 to 0.02% in 2010. The overall incidence of RA was higher in FN than nonFN at most years with FN having 2.23 times higher incidence of RA in 2009–2010 (CI 2.22–2.23; p < 0.0001). RA onset age was earlier in FN than non-FN (41 vs. 55 years; p < 0.0001). Despite greater physician visits (110 vs 99; p < 0.0001) (all rates are per person over 10 years) and more hospitalizations (3.4 vs 1.9; <0.0001), FN had fewer rheumatologist visits (6.9 vs 8.2 p < 0.0001), non-rheumatology specialist visits (15 vs 23 p < 0.0001) and surgeries (3.7 vs 5.3 p < 0.0001) than non-FN.

Conclusion: While overall provincial RA incidence is decreasing, FN have more than twice the risk of developing RA, with a prevalence of 1% in 2009–2010, as well as an onset age 10 years earlier than the general population. When combined with generally more severe disease in FN and fewer rheumatology visits this demonstrates a significant care gap highlight-
2024

Prevalence of Rheumatoid Arthritis in French West Indies, an African Ancestry Population. The Epissa Study. Michel De Bandt, Rishika Banydeen, Lauren Brunier, Kallen Polomat, Veronique Delhinger, Serge Arn, Christophe Deligny, Benedicte Garnery, Helene Cormier, Fabienne Dubrecq, Pascal Dubreuil, Daniela Durif, Sabine Molcard, Loic Braithe, Olivier Furet, Lucien Louisjoseph, Sylvie Merle and Georges Jean-Baptiste. 1Unit of rheumatology, Fort de France, France, 2Unit of epidemiology and biostatistics, Fort de France, France, 3Unit of rheumatology, CHUM, 97200 Fort de France, France, 4Unit of internal medicine, Fort de France, France, 5Unit of rheumatology, CHUM, Fort de France, France, 6Unit of internal medicine, Fort de France, France, 7Unit of rheumatology, Fort de France, France, 8Unit of rheumatology, Fort de France, France.

Background/Purpose: Rheumatoid arthritis (RA) is a disabling chronic disease, regarded as the most frequent inflammatory rheumatism in adults, with a prevalence estimated between 0.3 and 1%, and a feminine ascendency. In metropolitan France this prevalence is estimated from 0.3% to 0.5% of the general population. No precise data is available for French West Indies, and the prevalence of RA in this population of African ancestry is poorly evaluated.

Methods: The objective of the study is to estimate RA prevalence in the FWI by a census forward-looking epidemiological survey in the hospital and liberal sectors for one year duration. It is a unique tour with clinical examination, self-administered questionnaires and declaration. Secondary objectives are description of clinical and socio economical aspects of RA and cardiovascular comorbidities. We present the results for Martinique. Our survey included patients’ characteristics and a questionnaire, to ensure a good completeness. Data were analysed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Thorough descriptive analysis of collected variables was conducted. Crude prevalence rates were adjusted to a standard population of Martinique (nationwide census in 2010). The 95% CIs were calculated using the Poisson distribution.

Results: Our completeness is good. 538 RA were collected, giving a prevalence in Martinique of 0.28% of the adult population (290 000), respectively 0.049 for men and 0.29% for women. 44% of these patients are treated in private practice and 56% in hospital. This cohort is composed of 88% women and 12% men; 92% were born in Caribbean and 7.7% of African origin. Some characteristics as: reduced prevalence, strong female factors were noticed in 89.4% with a mean of 2 CVRF beside RA. The prevalence in Martinique of 0.184% of the adult population (290 000), standard population of Martinique (nationwide census in 2010). The 95% CIs were calculated. Crude prevalence rates were adjusted to a standard population of Martinique (nationwide census in 2010). The 95% CIs were calculated using the Poisson distribution.

Conclusion: The study clarifies the prevalence of RA in this population of African origin. Some characteristics as: reduced prevalence, strong female representation, strong seropositivity, high levels of anti-CCP, no tobacco, differentiate our patients from other populations and evoke another etiology.

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2025

Factors Associated with Time to Diagnosis from Symptom Onset in Early Rheumatoid Arthritis Patients. Yoon-Kyoung Sung, Soo-Kyung Cho, Dam Kim, Soyoung Won, Jiyoung Lee, Jung-Yoon Choe, Chan-Bum Choi, Seung-Jae Hong, Jae-Bum Jun, Tae-Hwan Kim, Eunmi Koh, Hye-Soon Lee, Jisoo Lee, Daehyun Yoo, Bo Young Yoon, and Sang-Chool Bae. 1Clinical Research Center for Rheumatoid Arthritis (CRCA), Seoul, South Korea, 2Catholic University of Daegu School of Medicine, Daegu, South Korea, 3Kyung Hee University, Seoul, South Korea, 4Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 5Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 6Hanyang University Guri Hospital, Guri, South Korea, 7Ewha Womans University School of Medicine, Seoul, South Korea, 8Yonsei University Ilan Paik Hospital, Goyang, South Korea.

Background/Purpose: Early diagnosis and treatment is an optimal target for better outcomes in rheumatoid arthritis (RA) in clinical practice. To make an early diagnosis, it would be helpful to know the sociodemographic or clinical factors for recognition of disease. On this study, we aimed to identify the factors associated with time to diagnosis after symptom onset in early RA patients.

Methods: Early RA patients with less than 1 year of disease duration in the Korean Observational Study Network for Arthritis (KORONA) database were included in this analysis. The time to diagnosis was defined as the duration between symptom onset and the diagnosis of RA in each patient. Early RA patients were further divided into two groups according to the time to diagnosis: early diagnosis group (time to diagnosis < 3 years), and late diagnosis group (time to diagnosis ≥ 3 years). Using the multivariate regression model, we identified the factors associated with the early diagnosis. We also compared the disease status such as disease activity, hand radiographic change and functional disability on the point of RA diagnosis between early diagnosis group and late diagnosis group.

Results: Among the 714 early RA patients, 401 patients (56.2%) and the other 313 patients (43.8%) were classified as early diagnosis group and late diagnosis group, respectively. In multivariate analysis, older onset age (OR 1.03, 95% CI 1.02–1.05), higher education level (OR 1.72, 95% CI 1.15–2.57) and higher income (OR 1.47, 95% CI 1.03–2.10) were identified as associating factors for early diagnosis (See table). Disease activity scores (DAS) using 28 joints on diagnosis (3.81 ± 1.44 vs. 3.82 ± 1.42, p = 0.92) and functional disability (0.65 ± 0.61 vs. 0.57 ± 0.62, p = 0.07) were not different between two groups. However, joint erosions on X-ray (37.8% vs. 26.5% p<0.01) was common in late diagnosis group than early diagnosis group.

Conclusion: Old age at symptom onset, higher education level or income were the factors associated with short time to diagnosis in early RA patients. Hand joint erosion was more common in late diagnosis group when they diagnosed as RA.

Table. Factors associated with time to diagnosis in early RA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>Multi-adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age</td>
<td>1.03 (1.00–1.03)</td>
<td>1.03 (1.02–1.05)</td>
</tr>
<tr>
<td>Male</td>
<td>0.92 (0.64–1.32)</td>
<td>0.78 (0.52–1.15)</td>
</tr>
<tr>
<td>Family history of RA</td>
<td>0.82 (0.52–1.31)</td>
<td>0.85 (0.52–1.36)</td>
</tr>
<tr>
<td>Body Mass Index ≤18.5 kg/m²</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Body Mass Index &gt;18.5 kg/m²</td>
<td>1.36 (0.70–2.62)</td>
<td>1.13 (0.56–2.30)</td>
</tr>
<tr>
<td>Body Mass Index &gt;23.0 kg/m²</td>
<td>1.02 (0.53–1.97)</td>
<td>0.84 (0.41–1.73)</td>
</tr>
<tr>
<td>Income &lt;2 million won</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Income ≥2 million won</td>
<td>1.38 (1.02–1.86)</td>
<td>1.47 (1.03–2.10)</td>
</tr>
<tr>
<td>Exercise</td>
<td>1.12 (0.97–1.78)</td>
<td>1.18 (0.86–1.65)</td>
</tr>
<tr>
<td>Exercise in first small joint</td>
<td>1.37 (0.99–1.89)</td>
<td>1.31 (0.93–1.85)</td>
</tr>
<tr>
<td>Number of comorbidity</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.12 (0.80–1.57)</td>
<td>0.99 (0.69–1.43)</td>
</tr>
<tr>
<td>Exercise</td>
<td>1.11 (0.75–1.66)</td>
<td>0.94 (0.61–1.46)</td>
</tr>
<tr>
<td>Rheumatoid factor positivity</td>
<td>1.17 (0.73–1.89)</td>
<td>1.29 (0.77–2.15)</td>
</tr>
</tbody>
</table>

This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI11C0200).

Disclosure: Y. K. Sung, None; S. K. Cho, None; D. Kim, None; S. Won, None; J. Lee, None; J. Y. Choe, None; C. B. Choi, None; S. J. Hong, None; B. J. Jun, None; H. H. Kim, None; E. Koh, None; H. S. Lee, None; J. Lee, Basic Science Research Program through the National Research Foundation (NRF) funded by the ministry of Education and Technology 2010-0010589, 2; D. H. Yoo, None; B. Y. Yoon, None; S. C. Bae, None.

2026

Treatment Delays and Worse Outcomes Associated with Lower Socio-economic Status in Rheumatoid Arthritis. Emily M. olina, Jose Felix Restrepo, Inmaculada del Rincon, Daniel Battafarano and Agustín Escalante. 1University of Texas Health Science Center, San Antonio, TX, 2University of Texas Health Science Center at San Antonio, San Antonio, TX, 3San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.
Background/Purpose: Prompt and routine care in rheumatoid arthritis (RA) is critical for best outcomes. Low socioeconomic status (SES) RA patients use fewer health services and have higher disease activity. We sought to examine the role of SES, distance to the rheumatologist (DTR), and delays in DMARD treatment as determinants of outcome in RA.

Methods: RA outpatients were recruited from public, private, military, and Veteran’s Affairs rheumatology clinics. The recruitment period spanned nearly 15 years. We assessed SES based on education, occupation, and income using the Nam & Powers scale. The time from RA symptom onset to DMARD initiation (DMARD lag) was determined by self-report of the two dates. The distance from a patient’s address to the rheumatologist was obtained using Google Maps. We examined three specific clinical outcomes in RA: disease activity, determined by DAS28ESR; joint damage, determined from hand radiographs using the Sharp score; and physical disability, determined by the Modified Health Assessment Questionnaire (M HAQ). We used linear regression models to examine the association of the clinical outcomes with SES, DTR, and DMARD lag, adjusting for other confounders such as age, sex, ethnicity and duration of RA.

Results: We recruited 1,209 RA patients, 1159 of whom had received DMARD treatment. Average DMARD lag was 6.9 ± 8.9 years. Greater DMARD lag was associated with older age (P = 0.001), longer disease duration (P ≤ 0.001) and worse status on all three clinical outcomes (P ≤ 0.001). Lower SES was associated with a longer DMARD lag (beta coeff. -0.120, P = 0.001) and a shorter DTR (beta coeff. 0.261, P = 0.001). On average, patients with lower SES waited 8.5 ± 10.2 years after onset of RA symptoms to begin DMARD treatment, which was significantly longer than those in middle and upper SES tertiles who waited 6.1 ± 7.9 years (P = 0.002) and 6.1 ± 8.6 years (P = 0.009), respectively. Adjusting for confounders including DTR and DMARD lag, SES remained inversely associated with DAS28ESR (beta coeff. -0.282, P = 0.001), Sharp score (beta coeff. -0.135, P ≤ 0.001) and M HAQ (beta coeff. -0.296, P ≤ 0.001).

Conclusion: Low SES RA patients experience a significantly greater delay in DMARD treatment. Low SES and greater DMARD lag were independently associated with worse clinical outcomes, despite adjusting for potential barriers to care such as distance to the rheumatologist and other confounders. Strategies to reduce treatment delay in low SES RA patients are needed.

Disclosure: E. Molina, None; J. F. Restrepo, None; I. del Rincon, None; D. Battafarano, None; A. Escalante, None.

2027

Higher Educational Level Correlates with Retarded Onset and Less Severe Disease in Rheumatoid Arthritis Patients. Michael Zaenker1, Udo Schwill1, Petra Reutermann2, Joachim Listing3, and Christel Kordbarlag4. 1Purpan University Hospital, Toulouse, France; 2UPMC GRC08, Paris 06 University, Pitie Salpetriere Hospital, Paris, France; 3INSERM - UMR S 938, Paris, France; 4CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France; 5Purpan University Hospital, Toulouse Cedex 9, France.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease with peak incidence in the fourth and fifth decades of age. To investigate whether age at disease onset determines clinical, radiographic or functional outcomes in a cohort of RA patients, taking into consideration possible age-related differences in treatment modalities.

Methods: The ESPOIR cohort is a longitudinal, prospective, multicenter, observational study of adult patients with early arthritis. For this study, we selected data for patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA during the first 3 years of follow-up. Patients were pooled into 3 groups by age at disease onset: young-onset RA (YORA) [< 45 years], intermediate-onset RA (IORA) [45 to 60 years], and late-onset RA (LORA) [> 60 years].

Results: We included 698 RA patients (median [interquartile range] age 50.3 [39.8–57.2] years; female 78.2%), 266 YORA, 314 IORA, and 118 LORA. The median SDAI was 28.5 [20.6–38.6] and median
HAQ-DI score 1 (0.5–1.5). At 1 year, SDAI remission was greater for patients with YORA than IORA and LORA (<0.0001). Having at least one additional erosion was greater for LORA and IORA than YORA patients after 1 year (41.1% [39/95] and 29.7% [81/272] vs 23.8% [51/214], p = 0.009) and 3 years (48.2% [41/85] and 43.4% [105/237] vs 32.81% [63/192], p = 0.017). The proportion of patients with HAQ score < 0.5 was greater for YORA than IORA and LORA at 1 year (p = 0.007) and remained significant at 2 and 3 years. The first DMARD survival rate was lower for YORA than IORA and LORA patients during the 3 years (p = 0.005). On multivariate analysis, young age at RA onset was independently associated with SDAI remission at 1 year, no additional erosion at 3 years and HAQ score < 0.5 at 1, 2 and 3 years.

Conclusion: In a cohort of early RA, young age at disease onset is associated with high rate of remission at 1 year, low radiographic progression at 3 years and low functional score during 3-year follow-up. Young age at disease onset is associated with low first DMARD survival rate over 3 years, which suggests that late-onset RA patients may receive less aggressive treatment strategies than younger patients.

Disclosure: T. Krans, None; A. Ryussen-Witrand, None; D. Nigon, None; B. Fautrel, None; F. Berenbaum, Merck, Pfizer Inc, Roche, Bristol-Myers Squibb, and UCB, 2, Abbott, Roche, and UCB, 5; A. G. Cantagrel, None; A. Constantin, None.

2029

Treatment Patterns of Multimorbidity Rheumatoid Arthritis Patients: Results from an International Cross-Sectional Study. Helga Radner1, Kazuki Yoshida2, Ihsane Hmamouchi3, Maxime Dougados4, Josef Smolen5, Ib Karsten Christensen4, Trine Bay Laurberg4, Karoline Reinholt8, K. Yoshida, None; I. Hmamouchi, None; M. Dougados, None; J. Smolen, None; D. H. Solomon, None.

Background/Purpose: The presence of multimorbidity could lead to less intensive treatment of RA. This can increase RA disease activity and worsen outcomes such as function, quality of life and mortality.

The aim of the study is to describe the treatment profile of multimorbidity RA patients in contrast to patients with RA only, and compare it across different international regions.

Methods: COMORA is a cross-sectional study assessing morbidities, RA related outcomes and treatment of RA patients, recruited in 17 countries worldwide. Patients were grouped according to their multimorbidity profile assessed by a counted multimorbidity index (cMMI), enumerating the number of previous medical conditions. Adjusted logistic regression models were examined to determine the odds ratio (OR) and 95% confidence interval (CI) of use of bDMARD, TNFi, sDMARD, NSAIDs or steroids, based on a patient’s cMMI and global region, after adjusting for age, disease activity, disease duration, and previous DMARD therapy.

Results: The study cohort consisted of 3920 patients, and 2563 (65.4%) were DMARD naive. Overall, 92.6% of the patients were on DMARD therapy, 32.7% received bDMARD; 59.2% sDMARD only; 51.1% NSAIDs and 54.8% corticosteroids. Regional differences could be observed with the most frequent use of bDMARDs in US (46.5%) and lowest frequency in North Africa (9.0%) (Figure). After adjusting for confounders in logistic regression analyses, the OR for use of bDMARDs was reduced for each additional morbidity (OR 0.90, 95%CI 0.83–0.97). Similarly, the probability for use of TNFi was also reduced (OR 0.92, 95%CI 0.84–0.99), whereas the OR for use of sDMARD was increased (OR 1.12, 95%CI 1.04–1.21). No change of OR was found for NSAID or steroid use (Table).

Conclusion: In our cohort, differences in bDMARD prescribing exist across global regions. After adjusting for covariates, the OR of bDMARD and TNFi use decreases 10% for each additional chronic morbidity condition as assessed by cMMI, whereas the OR of sDMARD use increased, probably reflecting rheumatologists’ greater comfort using these agents in patients with a greater multimorbidity burden.

Table: Logistic regression models

<table>
<thead>
<tr>
<th>Covariates</th>
<th>bDMARD</th>
<th>TNFi</th>
<th>sDMARD</th>
<th>NSAIDs</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counted multimorbidity index</td>
<td>0.90 (0.83–0.97)*</td>
<td>1.12 (1.04–1.21)*</td>
<td>1.06 (0.99–1.13)*</td>
<td>1.01 (0.98–1.04)*</td>
<td>1.01 (0.98–1.04)*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99 (0.98–1.00)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.99 (0.98–1.00)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.97–0.99)</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>1.13 (1.10–1.16)</td>
<td>1.07 (1.04–1.10)</td>
<td>1.03 (1.00–1.06)</td>
<td>1.03 (1.00–1.06)</td>
<td>1.03 (1.00–1.06)</td>
</tr>
<tr>
<td>Clinical disease activity index</td>
<td>0.97 (0.99–0.99)</td>
<td>0.99 (0.99–0.99)</td>
<td>0.97 (0.99–0.99)</td>
<td>0.97 (0.99–0.99)</td>
<td>0.97 (0.99–0.99)</td>
</tr>
<tr>
<td>Regional US reference</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Region Europe</td>
<td>0.58 (0.55–0.60)</td>
<td>0.58 (0.55–0.60)</td>
<td>0.58 (0.55–0.60)</td>
<td>0.58 (0.55–0.60)</td>
<td>0.58 (0.55–0.60)</td>
</tr>
<tr>
<td>Region Asia</td>
<td>0.35 (0.32–0.39)</td>
<td>0.35 (0.32–0.39)</td>
<td>0.35 (0.32–0.39)</td>
<td>0.35 (0.32–0.39)</td>
<td>0.35 (0.32–0.39)</td>
</tr>
<tr>
<td>Region South America</td>
<td>0.56 (0.53–0.60)</td>
<td>0.56 (0.53–0.60)</td>
<td>0.56 (0.53–0.60)</td>
<td>0.56 (0.53–0.60)</td>
<td>0.56 (0.53–0.60)</td>
</tr>
<tr>
<td>Region North Africa</td>
<td>0.06 (0.03–0.11)</td>
<td>0.06 (0.03–0.11)</td>
<td>0.06 (0.03–0.11)</td>
<td>0.06 (0.03–0.11)</td>
<td>0.06 (0.03–0.11)</td>
</tr>
<tr>
<td>OR &lt; 0.05</td>
<td>0.03 (0.01–0.08)</td>
<td>0.03 (0.01–0.08)</td>
<td>0.03 (0.01–0.08)</td>
<td>0.03 (0.01–0.08)</td>
<td>0.03 (0.01–0.08)</td>
</tr>
</tbody>
</table>

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Predicting Failure of Conventional Disease Modifying Antirheumatic Drugs in Treatment Naive Early Rheumatoid Arthritis Patients: A Single Centre Inception Prognostic Factor Cohort Study. Mette Axelsen1, Trine Bay Laurberg2, Robin Christensen2, Ulrich Fredberg3, and Torkel Ellingsen4. 1Silkeborg Hospital, Silkeborg, Denmark, 2MSU, The Parking Institute, Copenhagen University Hospital, Frederiksborg, Denmark, 3Diagnostic Centre Region Hospital Silkeborg Denmark, Silkeborg, Denmark, 4Diagnostic Centre Region Hospital Silkeborg Denmark, Odense, Denmark.

Background/Purpose: Finding prognostic factors for treatment failure on synthetic disease modifying antirheumatic drugs (DMARD) in early treatment naive rheumatoid arthritis (RA) is a challenge. The purpose of this study is to investigate whether baseline characteristics and disease activity variables add value to predict failure of classical DMARD treatment in a multivariable model.

Methods: The study included DMARD naive patients consecutively diagnosed with RA according to the ACR/EULAR criteria 2010. The patients were enrolled between 1.10.2009 and 1.11.2012. They were followed for one year. Disease activity was registered in the DAnBIO registry: number of swollen joints (NSJ)/38 joints), number of tender joints (NTJ)/40 joints), Health Assessment Questionnaire (HAQ), visual analog scales (VAS) 0–100 were used to assess pain, fatigue, patient and physician global assessment and DAS28-CRP, CRP, IgM-RF and anti-CCP. Treatment was oral methotrexate 15 mg per week initiated at time of diagnosis increased to 20 mg per week at week 6. If DAS28-CRP at this point was higher or equal to 3.2 and one or more swollen joints were present, treatment was intensified according to guidelines aiming at triple therapy (if tolerated). Intravenous glucocorticoid injections were given in swollen joints. Treatment with biologics was applied according to guidelines. COX regression analysis was used to investigate if

Figure: Regional differences of current treatment status
Tuesday, November 18

showed that young age and high CRP was significantly associated with failure of ACR/EULAR 2010 criteria for the diagnosis of early RA, regression analyses had initiated biologic therapy (DAS28CRP: 2.3).

significant differences in disease activity was found between the patients still significantly associated (HR 0.95 (95% CI: 0.91 to 0.98), p = 0.002). After one year of follow-up no significant differences in disease activity was found between the patients still on DMARD treatment (DAS28CRP: 2.1) compared to the 16 patients that had initiated biologic therapy (DAS28CRP: 2.3).

Conclusion: In a pragmatic, single centre inception cohort, using the ACR/EULAR 2010 criteria for the diagnosis of early RA, regression analyses showed that young age and high CRP was significantly associated with failure on initial classical guideline applied DMARD strategy (p = 0.002).

Disclosures: M. Axelsen None; T. Bay Laarberg None; R. Christensen None; U. Fredberg None; T. Ellingsen None.

2031

Early Adherence to Methotrexate in Rheumatoid Arthritis (RA) is High: a Prospective Longitudinal Study of New Users. Holly Hope1, Kimme Hyrich2, James Anderson3, Lis Cordingley4 and Suzanne Verstappen5.

Background/Problem: Methotrexate (MTX) is the recommended first-line DMARD for rheumatoid arthritis (RA) in most countries, however response is not universal. Non-adherence may explain this to some degree. The aim of this analysis was to describe patient self-reported adherence to MTX over the first 6 months of therapy and identify factors associated with non-adherence.

Methods: Patients were enrolled in the Rheumatoid Arthritis M etadiction Study (RAMS) a 1 year prospective study of MTX new-users for RA in the UK. At baseline, data was collected on demographic factors, alcohol and smoking history, disease activity (DAS28) and disease duration. In addition patients completed the Health Assessment Questionnaire (HAQ), visual analogue scales (VAS) for pain and fatigue, The Beliefs about Medicines Questionnaire (BMQ), Brief Illness Perceptions Questionnaire (B-IPQ), Hospital Anxiety and Depression Scale (HADS), the EQ-5D quality of life questionnaire, Food Compliance Questionnaire-Rheumatology (FCQ-R), a compliance self-report adherence measure. To measure adherence during the first 6 months after MTX commencement patients completed a weekly MTX diary detailing any missed doses including reasons. Proportional adherence was determined using number of non-adherent weeks compared to total number of eligible weeks. Non-adherence was defined as ≥1 dose missed against medical advice. The associations between patient characteristics, measures of illness and medicine cognitions, and adherence were assessed applying adjusted (age, sex, disease duration and disease activity) univariate logistic regression analysis.

Results: Analyses included the first 392 patients recruited to RAMS who completed the 6 month diary (median age 61 years, 70% female, mean DAS28 = 4.3 [sd 1.3]). In total, 20% (n = 80) of patients reported 174 non-adherent weeks. Reasons for non-adherent weeks included (% weeks): no reason given (30%), adverse effects (28%), feeling unwell/ suspected infection (18%), forgetting (12%), taking a drug holiday (9%) or delayed prescription refill (3%). Overall mean proportional adherence was very high (98%). Of adherent patients, 19% missed at least one dose under medical advice. Factors associated in adjusted analyses with being ever non-adherent included higher baseline DAS28 score (OR 1.31 per unit DAS28 (95%CI:1.06, 1.61) and lower baseline CQ-R score (0.95 per unit CQ-R 95%CI:0.92, 0.99). BMQ concern and necessity scores, HADS depression score, illness perceptions and other patient characteristics were not associated with adherence.

Conclusion: Over 20% of individuals were nonadherent although as many patients missed doses under medical advice. The effects of relatively low levels of non-usage of MTX, either due to non-adherence or to advised withdrawal, on disease outcomes is yet to be evaluated, however, these data suggest that levels of overall adherence to MTX over the first 6 months of therapy were very high.

Table 1: Baseline characteristics of cohort and association with nonadherence

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>n</th>
<th>Adherent</th>
<th>Nonadherent</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>304</td>
<td>63 (51.7-70)</td>
<td>79</td>
<td>59 (46.6-69.0)</td>
<td>0.98 (0.96-1.00)</td>
</tr>
<tr>
<td>Gender-female</td>
<td>307</td>
<td>210 (68.4%)</td>
<td>79</td>
<td>60 (75.9%)</td>
<td>1.19 (0.65-2.18)</td>
</tr>
<tr>
<td>Currently drinks</td>
<td>292</td>
<td>213 (72.9%)</td>
<td>83</td>
<td>53 (63.9%)</td>
<td>0.63 (0.37-1.12)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>305</td>
<td>49 (16.1%)</td>
<td>80</td>
<td>19 (23.8%)</td>
<td>1.50 (0.79-2.41)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>304</td>
<td>9.6 (4.5-31.4)</td>
<td>80</td>
<td>12.9 (5.4-28.9)</td>
<td>1.00 (1.00-0.71)</td>
</tr>
<tr>
<td>1 current co morbidity</td>
<td>312</td>
<td>99 (31.7%)</td>
<td>80</td>
<td>25 (31.3%)</td>
<td>1.01 (0.55-1.85)</td>
</tr>
<tr>
<td>≥1 current co morbidity</td>
<td>312</td>
<td>49 (15.7%)</td>
<td>80</td>
<td>17 (21.3%)</td>
<td>1.15 (0.75-2.23)</td>
</tr>
<tr>
<td>VAS-pain</td>
<td>302</td>
<td>49 (28-70)</td>
<td>79</td>
<td>49 (25-73)</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>VAS-fatigue</td>
<td>304</td>
<td>50 (23-71)</td>
<td>79</td>
<td>59 (26-77)</td>
<td>1.00 (0.99-1.00)</td>
</tr>
<tr>
<td>Disability (HAQ)</td>
<td>303</td>
<td>1.0 (0.5-1.6)</td>
<td>80</td>
<td>1.1 (0.4-1.8)</td>
<td>0.89 (0.58-1.37)</td>
</tr>
<tr>
<td>HOOL (EO-SD)</td>
<td>291</td>
<td>0.74 (0.62-0.80)</td>
<td>78</td>
<td>0.71 (0.62-0.80)</td>
<td>0.59 (0.20-0.40)</td>
</tr>
<tr>
<td>Depression (HAD)</td>
<td>300</td>
<td>8 (7-9)</td>
<td>78</td>
<td>8 (7-9)</td>
<td>1.12 (0.89-1.41)</td>
</tr>
<tr>
<td>Anxiety (HAD)</td>
<td>295</td>
<td>13 (12-15)</td>
<td>77</td>
<td>14 (12-15)</td>
<td>1.13 (0.95-1.34)</td>
</tr>
<tr>
<td>Necessity beliefs (BMQ)</td>
<td>288</td>
<td>19 (17-23)</td>
<td>76</td>
<td>20 (17-25)</td>
<td>0.99 (0.91-1.06)</td>
</tr>
<tr>
<td>Concerns (BMQ)</td>
<td>291</td>
<td>15 (12-17)</td>
<td>77</td>
<td>16 (14-18)</td>
<td>1.02 (0.95-1.10)</td>
</tr>
<tr>
<td>B-IPQ</td>
<td>280</td>
<td>46 (38-53)</td>
<td>71</td>
<td>47 (39-55)</td>
<td>1.00 (0.97-1.03)</td>
</tr>
<tr>
<td>CQ-R</td>
<td>142</td>
<td>75.4 (66.7-84.2)</td>
<td>36</td>
<td>69.3 (62.7-76.3)</td>
<td>0.95 (0.92-0.99)</td>
</tr>
</tbody>
</table>

All values n (%) or median(IQR) unless stated.

*p < 0.05 † † adjusted for age, DAS28, disease duration

Disclosures: H. Hope None; K. Hyrich None; J. Anderson None; L. Cordingley None; S. Verstappen None.

2032

Psychological Factors Predict Adherence to Methotrexate (MTX) in Rheumatoid Arthritis (RA): Findings from a Systematic Review of Rates, Predictors and Associations with Patient Outcomes. Holly Hope1, James Bluett2, Kimme Hyrich3, Lis Cordingley4 and Suzanne M. Verstappen5.

Background/Problem: Methotrexate (MTX) is a first line therapy for Rheumatoid Arthritis (RA). Treatment response to MTX is not universal, and nonadherence may partially explain poor treatment response to MTX, therefore it is imperative to investigate adherence to MTX specifically. Previous systematic reviews have evaluated adherence to all DMARDs. The aims of this systematic review were: 1) to summarise existing rates of adherence to MTX, 2) to identify predictors of adherence and 3) assess the association between non-adherence with patient outcomes.

Methods: A systematic search of papers published between January 1980 to 2014 was conducted in PubMed, PsyCINFO, EMbase and CINAHL databases. Studies were eligible for inclusion if; 1) MTX was used as monotherapy or in combination with other therapies, 2) MTX was used in an RA or inflammatory polyarthritis population, 3) adherence was defined and measured as the extent to which patients follow the guidelines in the period of the prescription, and 4) it was an original piece of research. Papers were reviewed by two researchers and consensus agreed with a third. A quality assessment (QA) tool formally assessed each included article.

Results: In total, ten studies met the inclusion criteria and eight were evaluated high quality using the QA tool. Rates of adherence ranged widely from 59% to 107%, and exposed differences in definitions of adherence, study methodologies and sample heterogeneity. The methods used to assess adherence included; Medication Event Monitoring Systems (n = 2), Pharmacy Refill (n = 5), validated self-report questionnaire (n = 2) and 7 day diary (n = 1) (Table 1). Twenty-one potential predictors of MTX adherence were identified; the strongest evidence occurred for beliefs in the necessity and efficacy of MTX, absence of low mood, mild disease and MTX as a monotherapy. Disease activity was the only patient outcome where the effect of nonadherence...
ience was assessed. Three studies tested this association and each found nonadherence associated with poor treatment response.  

**Conclusion:** Psychological factors were the strongest predictors of adherence rates in this first systematic review specific to MTX. It was the first to include synthesis of evidence on patient outcomes and show nonadherence to MTX affects treatment response in RA.

Table 1. Comparison of MTX rates of adherence across studies

<table>
<thead>
<tr>
<th>Author</th>
<th>QA score</th>
<th>High-low quality</th>
<th>Measurement used</th>
<th>Definition of MTX adherence</th>
<th>n</th>
<th>MTX adherence</th>
<th>95% CI/SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contreras-Yanez et al. (2013)</td>
<td>15</td>
<td>High MERS</td>
<td>% of correctly taken doses</td>
<td>76</td>
<td>80%</td>
<td>62%</td>
<td>20%</td>
</tr>
<tr>
<td>de Cock et al. (2003)</td>
<td>12</td>
<td>Low MERS</td>
<td>% of correctly taken doses</td>
<td>23</td>
<td>80%</td>
<td>10%</td>
<td>98-117</td>
</tr>
<tr>
<td>Pharmacy refill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannon et al. (2010)</td>
<td>14</td>
<td>High MPR</td>
<td>≥80% prescriptions filled</td>
<td>85</td>
<td>80%</td>
<td>5%</td>
<td>NP</td>
</tr>
<tr>
<td>de Thierry et al. (2010)</td>
<td>14</td>
<td>High CMG</td>
<td>% of treatment gaps filled</td>
<td>941</td>
<td>87.7%</td>
<td>8.6-88.3%</td>
<td></td>
</tr>
<tr>
<td>Grilz et al. (2010)</td>
<td>9</td>
<td>High MPR</td>
<td>% of treatment prescriptions filled</td>
<td>370</td>
<td>80%</td>
<td>5%</td>
<td>NP</td>
</tr>
<tr>
<td>Halley et al. (2004)</td>
<td>8</td>
<td>High MPR</td>
<td>% of treatment prescriptions filled</td>
<td>1668</td>
<td>63.7%</td>
<td>23.8-102</td>
<td></td>
</tr>
<tr>
<td>Grilz et al. (2007)</td>
<td>8</td>
<td>High MPR</td>
<td>% of treatment prescriptions filled</td>
<td>2933</td>
<td>80%</td>
<td>5%</td>
<td>NP</td>
</tr>
<tr>
<td>Self report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Thierry et al. (2010a)</td>
<td>14</td>
<td>High C.Q.R</td>
<td>C.Q.R score &gt;75th percentile</td>
<td>85</td>
<td>81%</td>
<td>23.5%</td>
<td>NP</td>
</tr>
<tr>
<td>Contreras-Yanez et al. (2010)</td>
<td>11</td>
<td>Low 7 day DRR</td>
<td>% of correct doses taken across 7 time points</td>
<td>65</td>
<td>9 mo.</td>
<td>23.1%</td>
<td>NP</td>
</tr>
<tr>
<td>Salt &amp; Frazier (2011)</td>
<td>9</td>
<td>Low MARS</td>
<td>MARS score &gt;7.9</td>
<td>77</td>
<td>92%</td>
<td>10%</td>
<td>NP</td>
</tr>
</tbody>
</table>

**Table 2. Associations with patient outcomes**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size</th>
<th>Predictor</th>
<th>Outcome</th>
<th>Descriptive statistics</th>
<th>Unadjusted effect size (95% CI)</th>
<th>Adjusted effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campos et al. (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full cohort</td>
<td>455 (15 non-adherent 340 adherent)</td>
<td>M PR = 80%</td>
<td>Mean difference</td>
<td>Linear</td>
<td>-0.24 (0.08, -0.42)</td>
<td>-0.17 (0.08, -0.26)</td>
</tr>
<tr>
<td>First time user cohort</td>
<td>85 (18 non-adherent 67 adherent)</td>
<td>M PR = 80%</td>
<td>Mean difference</td>
<td>Linear</td>
<td>-0.56 (0.09, -1.02)</td>
<td>-0.50 (0.06, -1.05)</td>
</tr>
<tr>
<td>Established cohort</td>
<td>298 (13 non-adherent 385 adherent)</td>
<td>M PR = 80%</td>
<td>Mean difference</td>
<td>Linear</td>
<td>-0.54 (0.09, -1.02)</td>
<td>-0.50 (0.06, -1.05)</td>
</tr>
<tr>
<td>Warrington et al. (2010)</td>
<td>302</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients prescribed at 2 years</td>
<td>0% (1.0)</td>
<td>Mean difference (95% CI)</td>
<td>Linear</td>
<td>-0.52 (-1.08, 0.04)</td>
<td>-0.50 (-1.05, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Contreas-Yanez et al. (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expanded cohort</td>
<td>56 (45 maintained in disease flare)</td>
<td>M PR = 80%</td>
<td>Mean difference</td>
<td>Linear</td>
<td>-0.35 (0.05, -0.65)</td>
<td>-0.33 (0.03, -0.64)</td>
</tr>
<tr>
<td>Marder et al. (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**20134**

A Treat-to-Target Strategy Preserves Work Capacity in Early Rheumatoid Arthritis (RA). M i h r D. Wechalekar1, Steve Quinn2, Susan Lester3, Ella Shahanah4, Robert Mctaf5, E. Michael Shahanah5 and Susanna Proudman6. 1 Flinders University School of Medicine, Adelaide, Australia, 2 Flinders University, Adelaide, Australia, 3 Queen Elizabeth Hospital, Woodville South, Australia, 4 Discipline of Medicine, Adelaide, Australia, 5 University of Adelaide, Adelaide, Australia, 6 Flinders University, Bedford Park, South Australia, Australia.

**Disclosure:** R. J. Black, None; R. Joseph, None; B. Brown, None; M. M. Mvahedi, None; M. Lunt, None; W. G. Dixon, None.

**2034**

A Treat-to-Target Strategy Preserves Work Capacity in Early Rheumatoid Arthritis (RA). Mihir D. Wechalekar, Steve Quinn, Susan Lester, Ella Shahanah, Robert Mctaf, E. Michael Shahanah and Susanna Proudman. Flinders University School of Medicine, Adelaide, Australia, Queen Elizabeth Hospital, Woodville South, Australia, Discipline of Medicine, Adelaide, Australia, University of Adelaide, Adelaide, Australia, Flinders University, Bedford Park, South Australia, Australia.

**Background/Purpose:** Historical data 4 indicate a third of patients with RA are unable to work within the first 5 years of diagnosis. Our aim was to quantify work disability in an inception cohort of patients with early (<12 months) RA (fulfilling ACR 1987 revised classification criteria) receiving treat-to-target combination DMARD therapy.

**Methods:** Patients received initial triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) with escalation (using other DMARDS or biologic DMARDS) to achieve DAS28 (ESR) remission. Patients completed an annual validated work and arthritis questionnaire. Random effect mixed modelling was used to assess associations between the primary outcome, average hours worked per week, and baseline prognostic factors, with subject entered as a random effect to account for correlated observations. Hours worked per week (HWPW) were compared with age, gender and period matched population averages.

**Results:** There were 341 observations on 139 patients. Patients were included in the analysis if they had complete data and were working at any time point, that is, those with at least one positive value for hours worked; this included 67 patients with 313 observations. The mean (SD) age at disease onset was 42.8 (15.0) years; 55/67 (82%) were women; median (IQR) duration of polyarthritis was 16 (12–28) weeks. The median (IQR) follow up time was 3 (2.0–5.2) years. At baseline, the proportion of patients in work at baseline was 67% and this did not significantly change with time (73% at the end of the follow-up period).

**Discussion:** Males worked more hours; there was no significant loss of working hours over the mean follow-up period (Table 1). Anti-cyclic citrullinated peptide antibody positivity was associated with loss of working hours; there was no relationship between baseline or area-under-the-curve DAS28 and HWPW and working hours lost. When examined by profession 50% working as labourers including: Demographics, Inflammatory comorbidities, GC-associated comorbidities and DMARDS.
on enrolment gave up work on follow up as compared to only 7% of those in managerial roles. For the matched population averages HWPV increased by 3.7 over a comparable follow-up period (p=0.001).

**Table 1.**

<table>
<thead>
<tr>
<th>p-value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males worked 14.5 (95% CI 6.4, 22.6) hours/ week more than females</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with anti-cyclic citrullinated peptide (CCP) positivity were more likely (7.4 (95%CI 1.3, 13.7)) to reduce working hours</td>
<td>0.017</td>
</tr>
<tr>
<td>Loss of working hours over mean follow-up period was 0.85 (95% CI</td>
<td>1.05, 3.4)</td>
</tr>
</tbody>
</table>

**Conclusion:** In contrast to the era before the advent of more intensive treatment approaches, a treat-to-target strategy mainly using conventional DMARDs preserves work capacity in patients with RA over the first few years of disease. Patients with ACPA or in manual labouring roles were more likely to reduce working hours.


Disclosure: M. D. Wechalekar, None; S. Quinn, None; S. Lester, None; E. Shanahan, None; R. Metcalf, None; E. M. Shanahan, None; S. Proudman, None.

**2035**

**Joint Distribution and Outcome in 350 Patients with Monoarthritis of the Knee:**

Of 350 patients with monoarthritis of the knee, 111 patients (31.7%) fulfilled the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA). Among these, 64 patients (57.1%) had arthritis due to trauma. 364 patients (33%) had monoarthritis of the ankle. In 261 patients (74.6%) the arthritis had resolved without DMARD treatment at last follow-up. 49 patients (14.0%) were prescribed with DMARDs, 188 (53.7%) received intra-articular corticosteroids, and 80 (22.9%) systemic corticosteroids.

Baseline and follow-up data according to joint distribution in 350 patients with monoarthritis

<table>
<thead>
<tr>
<th>Joint Distribution</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hand</strong>*</td>
<td>23 (6.6%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Wrist</td>
<td>49 (14.4%)</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td>Elbow</td>
<td>5 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Shoulder</td>
<td>9 (2.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hip</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Knee</td>
<td>172 (49.1%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Ankle</td>
<td>59 (16.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Foot</td>
<td>30 (8.6%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Other***</td>
<td>3 (0.9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2010 ACR/EULAR classification criteria for rheumatoid arthritis

**Conclusion:** Few patients with acute or recent onset monoarthritis seem to develop chronic inflammatory joint disease over two years. The likelihood of developing RA or other chronic rheumatic diseases was lowest in patients with monoarthritis of the ankle.

Disclosure: E. S. Norll, None; G. H. Brinkmann, None; T. K. Kvien, None; O. Bjørneboe, None; A. J. Haugen, None; H. Nygaard, None; C. Thunem, None; E. L. Lie, None; M. D. Mjaa-vann, None.

**2036**

**Biologic Disease-Modifying Antirheumatic Drugs and Risk of High-Grade Cervical Dysplasia and Cervical Cancer in Women with RA.**

Se-young C. Kim1, Sebastian Schneeweiss2, Jun Liu3, Elizabeth W. Karl-son4, Jeffrey N. Katz5, Sarah K. Kitz6, Sarah E. Shanahan7, and Daniel H. Solomon8. 1) Brigham and Women’s Hospital, Boston, MA, 2) Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

**Background/Purpose:** Human papillomaviruses (HPV) are causes of high-grade cervical dysplasia and cervical cancer. Persistent HPV infection, the major risk factor for cervical cancer, is associated with several factors including HPV genotype, sexual partners, history of sexually transmitted disease (STD) and immunosuppression. A recent large cohort study found a higher risk of high-grade cervical dysplasia and cervical cancer in patients with rheumatoid arthritis (RA) compared to non-RA patients. The objective of this study was to assess the risk of high-grade cervical dysplasia or cervical cancer related to use of biologic disease-modifying antirheumatic drug (DMARD) versus only non-biologic DMARDs for RA.

**Methods:** Using U.S. commercial insurance claims data (2001-12), we conducted a cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia or cervical cancer in women who initiated biologic or non-biologic DMARDs for RA. The index date was defined as the date of the first biologic or non-biologic DMARD after ≥2 diagnoses of RA. Patients were required to have an enrollment period of ≥365 days prior to the index date for baseline covariate assessment. High-grade cervical dysplasia or cervical cancer was defined by a validated claims-based algorithm with a positive predictive value of ≥81%. The number of gynecologic (Gyn) visits or procedures during follow-up was also assessed. To control for potential confounders such as age, being sexually active, comorbidities including STD, medications, prior Papanicolaou test, and healthcare utilization, biologic DMARD initiators were matched to non-biologic DMARD initiators on the propensity score (PS) with a 1:1 ratio.

**Results:** 7,539 PS-matched pairs of biologic and non-biologic DMARD initiators were included with a mean age of 50 years. 39% had a Papanicolaou test at baseline. During a mean (SD) duration of active treatment of 1.4 (1.5) years, 20 developed high-grade cervical dysplasia or cervical cancer. The IR of high-grade cervical dysplasia or cervical cancer per 1,000 person-years was 1.12 in biologic DMARD initiators and 0.70 in non-biologic DMARD initiators. The hazard ratio was 1.63 (95%CI 0.62–4.27) for biologic DMARD compared to non-biologics (Table). The number of outpatient Gyn visits (Rate ratio [RR] 0.96, 95%CI 0.88–1.04) and Gyn procedures (RR 0.94, 95%CI 0.86–1.02) was not different between the groups.

**Conclusion:** A women with RA, initiation of biologic DMARDs may be associated with a moderately increased, albeit not statistically significant, risk of high-grade cervical dysplasia or cervical cancer, although the absolute risk was low. Both biologic and non-biologic DMARD initiators had a similar number of Gyn visits and procedures during follow-up.

Disclosure: M. D. Wechalekar, None; J. Barrett, None; S. Quinn, None; S. Lester, None; E. Shanahan, None; R. Metcalf, None; E. M. Shanahan, None; S. Proudman, None.
research should determine the need for more intensive cervical cancer screening strategy in RA patients.

### Table
**Risk of high-grade cervical dysplasia or cervical cancer associated with initiation of biologic versus non-biologic DMARDs: 1** property score matched as treated analysis

<table>
<thead>
<tr>
<th>Biologic DMARD (N=7,538)</th>
<th>Non-biologic DMARD (N=2,134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Person-years</td>
<td>IR (95% CI)</td>
</tr>
<tr>
<td>High-grade cervical dysplasia or cervical cancer</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>12,452</td>
</tr>
</tbody>
</table>

**Disclosure: S. C. Kim, S. Schneeweiss, Pfizer Inc, 2; S. Schneeweiss, Pfizer Inc, 2, Amgen, Inc., 1, Amgen, Inc., 3.**

**2037**

**Incidence and Prevalence of Myasthenia Gravis in Rheumatoid Arthritis Patients with and without Treatment Compared with the General Population.**

Neil Accortt1, Mary Anthony, Jennifer Schenfeld, Travis Wheeling2, Anna Hasebroek, Cynthia O'Malley and Michael Sprafka1,2.

**Amgen, Inc., Thousand Oaks, CA; 2Docs Global, Inc, North Wales, PA.**

**Background/Purpose:** There is a dearth of information on the incidence rate of myasthenia gravis (MG) in the US and specifically among rheumatoid arthritis (RA) patients. RA patients have been shown to be at risk for other autoimmune diseases so we sought to describe the rate of MG among RA patients, with and without treatment.

**Methods:** We conducted a retrospective cohort study using an administrative claims database. There were 8 study cohorts; General population (GP): incident RA population regardless of treatment; and 6 RA sub-cohorts defined by treatment exposure. Inclusion criteria included a minimum of 2 years of continuous enrollment with pharmacy coverage between 01/01/2005 - 12/31/2011. To ensure incident RA, patients could not have any RA claims during the first 12 months of enrollment. RA patients were followed forward and assigned to exposure sub-cohorts: Untreated (RA-U), 3 cohorts of RA-DMARD3 (azathioprine, cyclosporine, cyclophosphamide, gold salts or penicillamine) and assigned to exposure sub-cohorts: Untreated (RA-D), 3 cohorts of RA-DMARD3 (biologic DMARDs1, RA-DMARD5, RA-DMARD6); TNF-inhibitors (RA-TNF); and other biologic therapies (RA-OB). Patients could be in up to 1 sub-cohort. MG diagnosis was captured using diagnostic and procedure claims. Prevalent MG cases in the GP and RA cohorts were identified during the first 12 months of enrollment. Follow-up for GP began on day 366 following enrollment; for RA and RA-U it began on date they met the criterion for RA diagnosis, and for RA sub-cohorts it began on medication start date. Follow-up continued until MG diagnosis, disenrollment from the database, end of study, and for the sub-cohorts, 90 days after discontinuation or switch in treatment. Incidence rates and 95% confidence intervals per 100,000 person-years were estimated for MG, excluding prevalent cases. Incidence and prevalence estimates were age- and sex-standardized to the GP.

**Results:** The mean age and sex distribution were 37.1 years and 52% female for GP and 56.3 years and 74% female for RA. Gender and age distributions in the RA sub-cohorts were similar to RA. Prevalence of MG was 24.3 per 100,000 in the GP cohort and 86.8 per 100,000 in the RA cohort while the incidence was 10.4 per 100,000 and 35.9 per 100,000 in the GP and RA cohorts, respectively. MG incidence was highest in the RA DMARD3 (azathioprine, cyclosporine, cyclophosphamide, gold salts or penicillamine) sub-cohort. Due to the small number of MG cases, there was no discernable incidence pattern in the other sub-cohorts. Sensitivity analyses allowing for different follow-up times or using different algorithms to define MG showed little difference in the results.

**Conclusion:** As with other autoimmune diseases, subjects with RA appear to be at a higher risk from MG than the general population. We found both the prevalence and incidence of MG to be 3-4 times higher among RA patients compared to GP, however, with the exception of the RA DMARD3 cohort, treatment did not appear to influence the incidence of MG following RA diagnosis.

**Disclosure:** S. C. Kim, S. Schneeweiss, Pfizer Inc, 2; S. Schneeweiss, Pfizer Inc, 2, Amgen, Inc., 1, Amgen, Inc., 3.
Among Persons Assayed with Lower Serum Interleukin-1 Beta (IL-1β) Levels, Serum Androstenedione (ΔA4) and Testosterone (T) Were Significantly Lower in a Community-Based Cohort of Rheumatoid Arthritis Multi-Years before Clinical Onset (Pre-RA) Than in Non-RA Matched Control (CN) Subjects. Aifa T, T. Zilber, Green A. Rehman and Jean C. Aldag. University of Illinois College of Medicine at Peoria, Peoria, IL.

Background/Purpose: Dysregulations in androgenic-anabolic (A-A) steroids and cytokines are recognized in RA and pre-RA subjects (Rheum Dis Clin N Am 2005; 31: 131-60). However, deviations in correlations of these interacting systems have not been reported. This study analyzed baseline serum levels of the IL-1 profile (IL-1α, IL-1β, IL-1ra, A-a steroids) and cigarette smoking in a cohort of pre-RA and CN subjects.

Methods: The community-based cohort enrolled 21,061 adults (12,381 F, 8,680 M) in 1974. Over 3-20 (median 12) yrs, 54 (36 F, 18 M) cases developed RA by 1988 ACR criteria. Four CN who did not develop RA were matched to each case on age (±2 yrs), sex, and race. Baseline stored (-70°C) sera were assayed in pre-RA-CN sets at national referral laboratories without knowledge of status. IL-1β and IL-1ra were assayed using ELISA immunoassays (R&D Systems Inc., Minneapolis, MN) and A-a steroids by RIA. Multiple imputation and aggregate methods were used to enter values for a minority of randomly missing test results. Biomarkers were normalized using z-scores within sexes to adjust for any dimorphism. Logistic regression searched for independent predictors of dependent lower vs higher IL-1β z-score subgroups. Predictors of A-A levels were identified by linear regression. Frequency distributions were determined for the dichotomous IL-1β and baseline IL-1ra subgroups with CN-A-A subgroups. IL-1α, IL-1β, and baseline cigarette smoking (7-scale), and evaluated by Fisher’s exact test.

Results: In 257 total subjects (54 pre-RA, 203 CN), lower (n=165) vs higher (n=92) IL-1β z-score subgroups strongly (p<0.0001) associated with combined RA and CN lower vs higher IL-1ra frequencies (Table 1). Logistic regression confirmed that only IL-1αa levels predicted the IL-1β dichotomy, including 6 other variables in the model (Table 2). In 165 lower IL-1β subjects (36 pre-RA, 129 CN), CN-RA had significant defects of higher ΔA4 (p<0.0001) and T (p<0.001) vs CN (Table 1). Linear regression confirmed that the dependent A-A steroid levels were predicted by the pre-RA vs CN status at strengths equivalent to known negative correlations with age. In the 92 higher IL-1β subgroup, 9 (50%) of 18 pre-RA vs 8 (10.8%) of 74 CN had higher cigarette usage (p<0.001), consistent with an inflammatory association of smoking and RA risk.

Conclusion: A-nordrostenedione and testosterone levels were significantly lower in pre-RA than CN subjects who had lower IL-1β levels, whereas cigarette usage was relatively greater in the RA subjects who had higher IL-1β levels. The new findings support neuroendocrine immune interactions in the risk of developing RA.

Table 1. Frequency Distributions of Lower vs Higher and Total IL-1β Z-Scores

<table>
<thead>
<tr>
<th>Bivariate Subgrouped by Lower vs Higher Z-Scores</th>
<th>Lower IL-1β Z-Scores</th>
<th>Higher IL-1β Z-Scores</th>
<th>Total IL-1β Z-Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>IL-1ra Lower</td>
<td>61.3%</td>
<td>38.7%</td>
<td>31.1%</td>
</tr>
<tr>
<td>p-values (2×2 Frequencies)</td>
<td>0.158</td>
<td>0.434</td>
<td>0.642</td>
</tr>
<tr>
<td>Androstenedione: Lower</td>
<td>70.1%</td>
<td>29.9%</td>
<td>35.1%</td>
</tr>
<tr>
<td>p-values (2×2 Frequencies)</td>
<td>0.018</td>
<td>0.438</td>
<td>0.656</td>
</tr>
<tr>
<td>Testosterone: Lower</td>
<td>66.7%</td>
<td>33.3%</td>
<td>33.3%</td>
</tr>
<tr>
<td>p-values (2×2 Frequencies)</td>
<td>0.072</td>
<td>0.123</td>
<td>0.068</td>
</tr>
<tr>
<td>Cigarette Smoking: Lower</td>
<td>32.4%</td>
<td>67.6%</td>
<td>32.4%</td>
</tr>
<tr>
<td>p-values (2×2 Frequencies)</td>
<td>0.008</td>
<td>0.019</td>
<td>0.282</td>
</tr>
</tbody>
</table>

Table 2. Regression Analyses of Lower vs Higher IL-1β and Other Dependent Outcome Variables

<table>
<thead>
<tr>
<th>Study Element</th>
<th>N</th>
<th>Dependent Outcome Variable</th>
<th>Independent Predictors</th>
<th>p-values</th>
<th>Exponent B</th>
<th>Non-significant Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>257</td>
<td>Lower vs Higher IL-1β</td>
<td>IL-1ra</td>
<td>&lt;0.001</td>
<td>2.269</td>
<td>Baseline age, sex, CN-RA, IL-1ra, androstenedione, testosterone</td>
</tr>
<tr>
<td>Lower IL-1β</td>
<td>165</td>
<td>Androstenedione</td>
<td>CN-RA-1</td>
<td>0.001</td>
<td>0.388</td>
<td>Cigarettes, age, sex, IL-1ra, cigarette smoking</td>
</tr>
<tr>
<td>Lower IL-1β</td>
<td>165</td>
<td>Testosterone</td>
<td>CN-RA-1</td>
<td>0.008</td>
<td>0.207</td>
<td>Sex, cigarettes</td>
</tr>
<tr>
<td>Lower IL-1β</td>
<td>165</td>
<td>IL-1ra</td>
<td>Baseline age</td>
<td>&lt;0.001</td>
<td>0.421</td>
<td>Sex, cigarettes</td>
</tr>
<tr>
<td>Higher IL-1β</td>
<td>92</td>
<td>Androstenedione</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Baseline age, sex, cigarettes</td>
</tr>
<tr>
<td>Higher IL-1β</td>
<td>92</td>
<td>Testosterone</td>
<td>Baseline age</td>
<td>0.012</td>
<td>0.256</td>
<td>Sex, cigarettes, CN-RA-1</td>
</tr>
<tr>
<td>Higher IL-1β</td>
<td>92</td>
<td>Sex</td>
<td>(F/M)</td>
<td>0.008</td>
<td>0.285</td>
<td>Baseline age, cigarettes, CN-RA-1</td>
</tr>
</tbody>
</table>

Disclosure: A. T. Mais, None; A. A. Rehman, None; J. C. Aldag, None.

2040

Opportunistic Infections in Patients Treated with Biologic Drug Therapy

Laura Encinas, Maria Haye Salinas, Veronica Saulit, Alejandro J. Alvarielos, Francisco Caero, Cristina Battaglotti, Ida Elena Exeni, Carla Gobbi, Bernardo Pons-Esteb, Ingrid Struberg, Sergio Para, Eduardo Musso, Maria Aa Paz, Ana Quinteros, Ana Capuccio, Mercedes De La Sota, Maria Laroude, Amelia Granell, Oscar Rillo, Enrique Soriano, Gustavo Citera, Diana Dubinsky, Mario Degtado, Ana Alvarez, Graciela Gomez, Gustavo Casado, Santiago Aguero, Monica Sacum, Mercedes C. Ordoñez, Sidney Soares de Souza, Edison Javier Velez, Carlos Parulo, Monica Patricia Diaz, Emilila Cavilloni, Juan C. Barea, Gimena Gomez, and E. Schenes.

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Background/Purpose: Biological drug therapy is frequently used to treat autoimmune diseases.

These drugs have an increased risk of infections, among them opportunistic infections.

To evaluate the frequency and type of opportunistic infections in patients with autoimmune rheumatic diseases treated with biologic drugs compared to controls.

Establest whether disease and treatment features influence frequency and severity of opportunistic infections.

Methods: Biobadasar is database of rheumatic diseases patients treated with biologic drugs. Created in 2010, it includes patients with a diagnosis according to accepted criteria treated with biologic drug therapy and controls not treated with biologic drugs.

Opportunistic infections are caused by pathogens (bacteria, viruses, fungi, parasites or protozoa), that usually do not cause disease in a healthy person (WHO).

The purpose of this work is to study the characteristics of opportunistic infections in patients with rheumatic diseases on biologic drug therapy compared with controls using the BIOBADAR database.
Reactivation of latent tuberculosis infection (LTBI) is a serious concern in patients treated with TNF-α inhibitors (TNFi). Conversely, TB chemoprophylaxis (CP) is time consuming, delays the initiation of required treatment, adds to the overall cost of treatment, and carries a risk of adverse events itself. Since 2002 our national guidelines require following a two-step screening algorithm prior to the initiation of the first TNFi. The first step includes tuberculin skin test (TST), and a chest X-ray (CXR). If TST < 5 mm, and the radiologist finds no changes consistent with TB on CXR TNFi is prescribed. If any test is abnormal, the patient is evaluated by a pulmonologist who usually orders Quantiferon TB Gold. Based on these results, different patients may require additional diagnostic procedures, such as interferon-gamma release assay (IGRA). These procedures are costly, may generate false positive results, and may delay the start of TNFi treatment, adding to the overall cost of treatment, and may cause anxiety and public health concern about drug resistance TB. We performed the analysis considering both TST and IGRA results, without the latter being considered positive.

**Table 1:** Demographic Characteristics, Pathology and Treatment According to the Presence of Opportunistic Infections in Patients Treated with Biologicals N: 1275

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>p OR (IC95 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (82.5)</td>
<td>0.69 (0.33-1.76)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Age (SD)</td>
<td>54.8 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Yrs n=25</td>
<td>59.5 ± 14</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Pathology and Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (7.5)</td>
<td>0.73 (0.36-3.98)</td>
</tr>
<tr>
<td>No</td>
<td>47 (92.5)</td>
<td></td>
</tr>
<tr>
<td>Kidney failure</td>
<td>3 (7.5)</td>
<td>0.03 (0.22-3.05)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (2.5)</td>
<td>0.43 (0.22-3.13)</td>
</tr>
<tr>
<td>EPOC</td>
<td>0</td>
<td>0.96 (0.95-0.97)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (51.0)</td>
<td>0.22 (1.12-4.44)</td>
</tr>
<tr>
<td>No</td>
<td>22 (49.0)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>17 (42.5)</td>
<td>0.27 (0.14-0.51)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10 (25.0)</td>
<td>0.12 (0.01-0.41)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1 (2.5)</td>
<td>0.36 (0.04-2.21)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (5.0)</td>
<td>0.79 (1.06-2.43)</td>
</tr>
</tbody>
</table>

Conclusion: Opportunistic infections were more frequent in patients treated with biological drugs than in controls. The most common opportunistic infection was Herpes zoster. A history of cancer and renal failure, and concomitant treatment with corticosteroids were associated with opportunistic infections.

Methotrexate therapy was not associated with OI.

**Disclosure:** L. Encinas, None; M. Haye Salinas, None; V. Saurit, None; A. J. Alvaradillos, None; F. Caero, None; C. Battaglotti, None; I. E. Exeni, None; C. Gobbi, None; B. Pono Estel, None; I. Strusberg, None; S. Paiva, None; E. Mussano, None; M. Apar, None; A. Quinteros, None; A. Capuccio, None; M. De La Sota, None; M. Larroude, None; A. Granell, None; O. Rillo, None; E. Soriano, None; G. C. Citera, None; N. Envisca, D. D. Dubinsky, None; M. Delgado, None; A. Alvarez, None; G. Gómez, None; G. Casado, None; S. Apar, None; M. Sacnum, None; M. Garcia, None; S. Soares de Souza, None; E. J. Velozo, None; C. Paruolo, None; M. P. Diaz, None; E. Cavillon, None; J. C. Barreira, None; G. Gómez, None; E. Schelthes, None.

**2041 Performance of a Two-Step Latent Tuberculosis Screening Algorithm in Patients with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis Prior to Treatment with Tumor Necrosis Alpha Inhibitors: Prospective Observational Data from the BiOrk Si Registry, 2014 Update.** Ziga Rota1 and Matja Tomsic1. 1University Medical Centre Ljubljana, Ljubljana, Slovenia, 2BiOrk Si, University Medical Centre Ljubljana, Ljubljana, Slovenia.

**Background/Purpose:** Reactivation of tuberculosis infection (TB) is a serious concern in patients treated with TNF-α inhibitors (TNFi). Conversely, TB chemoprophylaxis (CP) is time consuming, delays the initiation of required treatment, adds to the overall cost of treatment, and carries a risk of adverse events itself. Since 2002 our national guidelines require following a two-step screening algorithm prior to the initiation of the first TNFi. The first step includes tuberculin skin test (TST), and a chest X-ray (CXR). If TST < 5 mm, and the radiologist finds no changes consistent with TB on CXR TNFi is prescribed. If any test is abnormal, the patient is evaluated by a pulmonologist who usually orders Quantiferon TB Gold. The most frequent OIs were cytomegalovirus, Pneumocystis jirovecii, hominis Blastocystis, Cryptosporidium, Echinococcus and Proteus.

**Conclusion:** At follow-up our two-step algorithm is still performing well. Further vigilance is warranted, especially in RA patients and those treated with CZP.

**Disclosure:** Z. Rota, None; M. Tomsic, None.

**2042 Tuberculosis Conversion in Patients with Autoimmune Arthropathies Receiving Biologic Therapy.** Osvaldo Luis Cerda1, María de los Ángeles Correa2, Amelia Granell3, Ana Inés Marcos3, Claudia L. Girald3, Oscar L. Rillo3 and Gustavo Citera3. 1Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, 2Instituto de Rehabilitación Psicofísica, Tucumán, Argentina, 3Instituto de Rehabilitación Psicofísica, Luján, Buenos Aires, Argentina.

Statistical analysis was done using Chi-square test and t test with a significant p ≤ 0.05.

**Results:** We included 2356 patients, 1275 54% on biologic drug therapy and 1081, 46% controls: 1862/2356, 79% were women, mean age 53.83 (SD6.02) years. Rheumatoid arthritis was the most common diagnosis 1829/2356, 77.6%.

Opportunistic infections were diagnosed in 40/1275 3.1% of patients treated with biologics, while 11/1081, 1% of controls (p = 0.0004, OR 3.1, 95% CI 1.6–6.1).

Hospital admission was needed for 6/51, 11.7% of patients. The median number of months from disease onset to the OI was 127 (IQR 46–223) months and from biological treatment onset to OI was 9 (IQR 4–18.5) months.

**Background/Purpose:** Reactivation of latent tuberculosis infection (LTBI) is a serious concern in patients treated with TNF-α inhibitors (TNFi). Conversely, TB chemoprophylaxis (CP) is time consuming, delays the initiation of required treatment, adds to the overall cost of treatment, and carries a risk of adverse events itself. Since 2002 our national guidelines require following a two-step screening algorithm prior to the initiation of the first TNFi. The first step includes tuberculin skin test (TST), and a chest X-ray (CXR). If TST < 5 mm, and the radiologist finds no changes consistent with TB on CXR TNFi is prescribed. If any test is abnormal, the patient is evaluated by a pulmonologist who usually orders Quantiferon TB Gold IT (QF) and decides whether TB CP (rifampicin/isoniazid 600/300 mg qd for 3 months) is required prior to TNFi treatment.

In February 2002 we showed that in a setting with low background annual TB incidence rate (IR) (i.e. 8.4 per 105) following of this algorithm resulted in TB IR of 0.11 (95% CI 0.01–0.38), and 0.16 (95% CI 0.02–0.58) per 100 person years (PY) overall, and in RA patients, respectively. The costly CF and CP were required in 13.9%, and 5.2% of patients, respectively. Our aim was to reevaluate the performance of this algorithm.

**Methods:** In March 2014 we cross-linked the data from the obligatory national registry of patients treated with biological DMARDs and the national TB registry to identify cases of TB in patients who were ever treated with TNFi.

**Results:** 1535 patients were treated with at least one TNFi for 3,846 PY (Table 1). Flow of patients through the screening algorithm and case patient characteristics are depicted in Figure 1. QF was performed in 2735/1535 (18.2%), 96/1535 (6.3%) patients received CP. Four cases of TB were identified, hence IR was 0.10 (95% CI 0.03–0.27), and 0.19 (95% CI 0.05–0.48) per 100 PY overall, and in RA patients, respectively. Only RA patients developed TB. The TB IR for certolizumab vs. other TNFi prescribed for RA was 1.3 (95% CI 0.16–0.47) vs. 0.1 (95% CI 0.03–0.37) per 100 PY (p = 0.027 Fisher’s exact test). The first two received appropriate CP (adherence was good, isolated M. tuberculosis strains were susceptible to CP) prior to TNFi, in the third patient the screening was stopped after 1st step and in the fourth one after the 2nd step. Interestingly, the 3rd case was screened for TB again before switching to rituximab. At repeated screening two months prior to TB diagnosis the TST was 10 mm, CXR neg. and QF–.
**Background/Purpose:** Patients receiving biologic DMARDs are at increased risk of developing tuberculosis (TB). Tuberculosis skin test (TST) is recommended to screen for TB infection prior to starting biologic DMARDs. However, TST during treatment with biologic DMARDs is not routinely assessed. Objective: To investigate the frequency of TST conversion in patients receiving biologic DMARDs who initially had a negative result.

**Methods:** Patients with Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) and Spondyloarthitis (SPA) under treatment with anti-TNFα, Tocilizumab and/or A Batacept and who had a previous negative TST were included. A second TST was performed in all patients within a period of 2 months to 2 years after the first TST. TST conversion was defined as a variation greater than 5 mm between the two tests. Sociodemographic and clinical data were recorded. Moreover, presence of comorbidities as alcoholism, diabetes (DM), malnutrition, poverty and overcrowding, previous infection, or contact with TB and concomitant treatment (steroids, DMARDs and biologic treatment) were also taken into account for the analysis. Chi² test, Mann Whitney U test and logistic regression analysis were performed.

**Results:** Eighty-five patients were included, 78.8% females, mean age 51.76±11.9, 74.1% had diagnosis of RA, 16.5% Psoriatic arthritis, 4.7% JIA, and 4.7% AS. 75.3% were receiving anti-TNF treatment, 15.3% tocolizumab, and 9.4% abatacept. 84.7% were receiving concomitant MTX, 21.2% leflunomide and 16.8% were on high doses of steroids. 12.9% lived in overcrowded conditions, 10.6% had controlled DM, 5.9% had TB (complete treatment), and 2.4% reported having had contact with TB patients. Other risk factors were infrequent. TST conversion was observed in 9.4% (8 patients) being more common in males 62.5% vs. females 37.5% (p=0.009) and among those with longer mean disease duration 226±109 month in TST conversion patients vs. 130±105 month in TST negative patients (p=0.017). These results persisted even after adjusting for confounders. No association was observed with treatments and comorbid conditions. All patients with TST conversion received prophylactic isoniazid treatment, and one patient developed active TB and received appropriated treatment.

**Conclusion:** In patients receiving biologic DMARDs, TST conversion rate was 9.4% and was more frequent in males and in those with longer disease duration. No association was observed between TST conversion and underlying rheumatic disease, presence of comorbidities or treatments used.

**Disclosure: O. L. Cerda, None; M. D. L. A. Correa, None; A. Grand, None; A. I. Marcos, None; C. L. Giraldo, None; O. L. Rillo, None; G. Citera, None.**

### 2043

**How Correct Are the Assumptions Made for Tuberculosis Screening Algorithms before TNF-Alpha Antagonists?**

**Aysa Hacioglu**, Yesim Ozguler, Sermin Boroğlu, Vedat Hamuryudan, Hanefi Deniz Kecibaş, Ethem Kockar, Tufan Kav, Ebru M. Akcan-Arikan, Sibel Uğur, Aziz Fresko, Huri Ozdogan, Sebahattin Yurdaçik, Gul Ongen and Gulen Hatemi

**Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, University of Istanbul, Cerrahpasa Medical Faculty, Department of Pulmonary Diseases, Istanbul, Turkey, Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.**

**Background/Purpose:** During the development of algorithms for screening latent tuberculosis before starting TNF-alpha antagonists, it is assumed that BCG vaccination causes false positive PPD and that concomitant medications such as corticosteroids cause false negative PPD results, favoring the use of Quantiferon or Elispot in these patients. Moreover it is assumed that INH is difficult to tolerate in this patient group. However we hypothesized that these assumptions may be wrong since there is a long time between BCG vaccination and TNF-alpha antagonist use in most of the rheumatology patients; there is no consistent data to show that disease modifying agents and corticosteroids in doses used for rheumatologic conditions are associated with negative PPD results; and INH is usually well tolerated by most of our patients.

**Methods:** We included patients who were prescribed a TNF-alpha antagonist for the first time between January 2011 and December 2012 in our clinic. Patients who had a previous tuberculosis infection were excluded since this could cause PPD positivity. We used logistic regression to analyse the determinants of a positive PPD (≥ 5mm). The variables were having a BCG scar, drugs (prednisolone, methotrexate, leflunomide, azathioprine, cyclosporine-A and cyclophosphamide), age, gender, diagnosis and disease duration. We also evaluated the frequency of being able to complete 9 months of INH treatment, the reasons for discontinuation and the frequency of developing tuberculosis among those who used and who did not use INH.

**Results:** A TNF-alpha antagonist was started in 961 patients (503 men, 458 women, mean age 41.28 ± 13.10 years, disease duration 6.54 ± 6.80 years). 7 patients had positive BCG and 33 patients had who had previous tuberculosis treatment. Among the remaining 853, an initial PPD test was available in 671 patients. At least one BCG scar was present in 592 patients. Logistic regression showed that BCG vaccination (OR = 3.45, 95%CI 2.51–4.75, p<0.0001) and a diagnosis of ankylosing spondylitis (OR = 1.79, 95%CI 1.21–2.65, p= 0.003) were associated with PPD positivity, while corticosteroid use was associated with a negative PPD (OR = 0.96, 95%CI 1.09–3.51, p= 0.033). INH was started in 525 patients and 391 had reliable data regarding INH use. 346 patients (87%) completed 9 months of treatment, 22 with interruptions. 45 had to stop INH after 3.85 ± 2.46 months. The reasons for discontinuation were hepatotoxicity in 26, allergic dermatical reactions in 2, nausea in 2, dizziness in 2, pregnancy in 1, shortness of breath in 1, pancreatitis in 1 patient and non-willingness in 10 patients. Among the 26 who had to stop INH for transaminase elevation 13 were using concomitant methotrexate. None of the patients developed tuberculosis during our follow-up of up to 3 years.

**Conclusion:** BCG vaccination may still be a cause of false positive PPD in candidates for treatment with TNF-alpha antagonists. Corticosteroids seem to be associated with negative PPD while DMARDs are not. INH prophylaxis is generally well tolerated despite concomitant methotrexate. Longitudinal follow-up is necessary to determine the long term efficacy of INH treatment for preventing tuberculosis in these patients.

**Disclosure: A. Hacioglu, None; Y. Ozguler, None; S. Boroğlu, None; V. Hamuryudan, None; H. D. Kecibaş, None; E. K. Tufan, None; E. M. Akcan-Arikan, None; S. Uğur, None; E. Deniz, None; E. Fresko, None; H. Ozdogan, None; S. Yurdaçik, None; G. Ongen, None; G. Hatemi, None.**

### 2044

**Systematic Review of the Effect of Anti-Rheumatic Therapies upon Vaccine Immunogenicity.** Megan Whittaker1, James Galloway1 and Sujith Subesinghe2

1King’s College London, School of Biomedical Sciences, King’s College London and 2King’s College Hospital NHS Foundation Trust, London, United Kingdom.

**Background/Purpose:** Patients with rheumatoid arthritis (RA) are at increased risk of infection compared to the general population. The increased risk is attributable to factors relating to the underlying disease as well as the use of immunosuppression as the mainstay of management. Minimizing infection is an important challenge facing rheumatologists. Vaccination represents a unique opportunity to achieve this.

Current UK and European guidelines recommend annual influenza and one-off pneumococcal vaccination, however uptake of these vaccinations is poor, particularly regard to pneumococcal immunization in the context of rheumatic disease, and the evidence base for proving whether vaccinations reduce infections and associated mortality in RA is limited.

We conducted a systematic review of vaccination immunogenicity in the setting of anti-rheumatic therapy.

**Methods:** Studies evaluating the immunogenicity of either pneumococcal or influenza vaccinations in the setting of rheumatoid arthritis were identified using PubMed, Ovid, EMBASE. Search terms included (inflammatory arthritis OR rheumatoid arthritis) AND (immunization OR vaccination OR vaccine OR pneumococ OR prevenar).

This identified 3670 results, and 1853 after limiting to humans. A bstracts were then manually reviewed by two authors (G and M W) to identify articles reporting immunogenicity data for the vaccines of interest in adult patients with RA. The final selection identified 24 articles.

**Results:** The immunogenicity of vaccinations is influenced by factors including age, vaccine type, vaccine strain, disease and drugs. Concomitant drug therapy has the greatest effect on vaccine immunogenicity. Two types of pneumococcal vaccines are currently licensed for use in the adult population, subunit polysaccharide (Pneumovax) and conjugate (Prevenar). Direct comparison between these vaccines demonstrated similar antibody responses.

Methotrexate, Rituximab and A Batacept are associated with decreased immunogenicity to both influenza and pneumococcal vaccination. Anti-TNF biologics, Tocilizumab and Sulphasalazine do not appear to have a negative effect on immunogenicity, although data is limited for the latter two.
Of the studies reporting the effect of vaccination on disease activity, none reported a significant change following vaccination.

Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control Vaccine</th>
<th>Polyarthritis pneumococcal</th>
<th>Conjugate pneumococcal</th>
<th>Scenool influenza</th>
<th>Pandemic influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphapyrazone</td>
<td>HV (N)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>RA (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
</tr>
<tr>
<td>TNF</td>
<td>RA (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
</tr>
<tr>
<td>RTX</td>
<td>RA (N)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>RA (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>RA (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
<td>1 (N)</td>
</tr>
</tbody>
</table>

Key:
- (N) no difference in response related to control
- (Y) decreased response related to control

Index: One study, n = 20; two studies, n = 25; three or more studies, n = 30.

Conclusion: Although the humoral response to vaccination may be reduced by immunosuppressive agents, protective post vaccination titres are frequently achieved and accordingly vaccination is not precluded in this 'at-risk' population. Pneumococcal and influenza vaccination is safe in rheumatic disease and should be encouraged as part of the holistic management of RA patients. Challenges lie in determining the real world effectiveness of vaccination in RA, as well as how to maximise vaccine uptake through collaborative initiatives between primary and secondary care.

Disclosure: M. Whitaker, None; J. Galloway, None; S. Subesinghe, None.

ACR/ARHP Poster Session C
Epidemiology and Public Health (ARHP)
Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2045

Interaction Effects Between Genes and Blood Lead Level on a Composite Score of Multiple Joint Symptoms: The Johnston County Osteoarthritis Project. Yufang Liu1, Amanda Nelson2, and Joanne M. Jordan2. 1University of North Carolina at Chapel Hill, Chapel Hill, NC; 2University of North Carolina Dept of Epidemiology, Chapel Hill, NC.

Background/Purpose: Previous studies suggested that blood lead level is associated with multiple joint symptoms. In this study, we conducted a Genome-Wide Gene-Environment Interaction analysis to search for genetic variations which may modify such associations.

Methods: Caucasians from the Johnston County Osteoarthritis Project (JoCo) with valid covariates and cleaned genotype data were included in this study. A composite score of multiple joint symptoms was calculated as the mean of summed 0–3 scores (none = 0, 1 = mild, 2 = moderate, 3 = severe) from seven joint sites including the hands, knees, hips and low back as previously reported. Whole blood lead level was measured by inductively coupled plasma dynamic reaction cell-mass spectrometer analysis at the Centers for Disease Control and Prevention (Atlanta, GA). Genotyping was done using Illumina Infinium 1M-Duo bead arrays at Expression Analysis (Durham, NC). Original SNP data were imputed by software Mach using HapMap II Caucasian as the reference data. Linear models were applied across the genome-wide genetic data with adjustment for age, body mass index (BMI), sex, current alcohol use, smoking, and blood lead level. The residuals of the regression followed the normal distribution.

Results: Participants included 805 individuals, 63% of whom were women, with mean age 67 years (SD = 10.5) and mean BMI of 30 (SD = 6.4) kg/m2. Log transformed blood lead level (median = 0.53) was associated with multiple joint symptoms score with a p-value of 0.02. Two interactions between SNPs (rs2885880 and rs1598457) and lead significantly modified lead association with the multiple joint symptoms score (interaction p-value ≠ 5x10^-8). Rs2885880 is located in gene GUCY1A2 (Guanelyl Cyclase, Soluble, Alpha 2). Guanylyl Cyclases (GC) are a group of enzymes whose function requires the presence of metal ions such as Mg2+ or Mn2+. An additional promising interaction between fifteen SNPs (Table) and lead were identified (interaction p-values < 1E^-06). For all the identified SNPs, the main effects of those SNPs were also significant with p-values < 0.05.

Conclusion: Two interactions between lead and SNPs were identified by the Genome-Wide Gene-Environment Interaction analysis. Those two SNPs are located in RNF121 and GUCY1A2, both related to handling of metals. These two genes may influence the impact of blood lead level upon symptoms in multiple joint symptoms. These results will require validation in independent datasets.

Disclosures: Y. Liu, None; Nelson, None; J. M. Jordan, Aligymomics, Samumed, Flexion, ClearView Healthcare Partners, Trinity Partners, S.

2046

Perceived Discrimination in Individuals with Radiographic Knee and Hip Osteoarthritis. Rebecca J. Cleveland1, Jordan B. Renner2, John M. Jordan2, Joanne M. Jordan2, and Leigh F. Callahan2. 1University of North Carolina at Chapel Hill, Chapel Hill, NC; 2University of North Carolina Department of Radiology, Chapel Hill, NC; 3University of North Carolina Dept of Epidemiology, Chapel Hill, NC; 4University of North Carolina, Chapel Hill, NC.

Background/Purpose: To describe the characteristics of participants who reported feelings of discrimination among a cohort of participants with radiographic osteoarthritis (rOA) of the knee and/or hip in the Johnston County Osteoarthritis Project (JoCo).

Methods: A cross-sectional analysis was carried out on 766 individuals with rOA who were assessed in the second follow-up evaluation (2006-2010) of JoCo. rOA was defined as Kellgren-Lawrence grade ≥ 2 in at least one knee or one hip. Any perceived discrimination was assessed using a validated measure asking "how often have you been treated with less courtesy or less respect than other people?" Responses were assessed on alikert scale ranging from 1 to 4 (1 = never, 2 = occasionally, 3 = frequently, 4 = always). If indicating any discrimination, follow-up questions asked for the more specific reasons for discrimination such as gender, age, race, disability, education, religion and body size (yes or no). Descriptive characteristics were assessed and Chi-square statistics were performed to examine whether a participant perceived any type of discrimination, and if so, the specific reason for the discrimination. Additionally, we assessed discrimination according to whether an individual had knee or hip rOA, and according to demographic characteristics.

Results: Participants were on average 68 years old, mostly women (67.7%), African American (30.5%), and had a mean BMI of 31.5. There were 520 participants with knee rOA and 473 with hip rOA. Thirty-nine percent of participants reported feeling discrimination at least occasionally (36.7% occasionally, 2.5% frequently, 0.3% always). The most commonly
reported reason for perceived discrimination was disability (20.5%) followed by age (10.9%) and race (10.6%). Those with hip rOA reported any discrimination more often than those with knee rOA (40.6% vs. 36.5%) (Table 1). Any perceived discrimination tended to be reported more often among those who lived in poverty areas (p < 0.01) while those who reported discrimination for religion in lower poverty areas (p < 0.01). African Americans reported discrimination for skin color more often than Whites (p < 0.01). Racial discrimination was reported more frequently among men (p < 0.01).

**Conclusion:** Perceived discrimination is frequently reported in people with knee and/or hip rOA in this racially diverse population in North Carolina, with disability being the most commonly reported reason. Discrimination is also associated with several demographic characteristics that could have an important impact on rOA outcomes.

**Disclosure:** R. J. Cleveland, None; J. B. Renner, None; J. M. Jordan, Algimetrics, S. Samumed, S. Flexion, S. ClearView Healthcare Partners, S. Trinity Partners, LLC, S; L. F. Callahan, None.

### 2047

**No Association of Serum Uric Acid with Hip Fracture Risk in Older Men and Women from the Framingham Original Cohort.** Shivani Sahni1, Kelsey M Mangandì2, Katherine Tucker2, Caroliné Fox1, Douglas P. Kiel1, Xiaochun Zhang2 and Mariant T. Hannan1

**Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 1University of Massachusetts, Lowell, MA, 2NHBLI’s Framingham Heart Study and Center for Population Studies, Framingham, MA, 3Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 4Institute for Aging Research, Hebrew SeniorLife, Roslinlade, MA.

**Background/Purpose:** Serum uric acid (UA) has been linked with fractures in older men. Three different studies in older men showed conflicting results. The objective of this study was to examine the association of UA with hip fracture risk over 19.9y follow-up in men and women from the Framingham Original Cohort.

**Methods:** 2,969 men & women had measured UA concentration (mg/dl) at baseline (1973-76) and were followed for hip fracture until 2009. We used Cox-proportional hazards regression to estimate Hazard Ratios (HR) adjusting for age, sex, and menopausal status (men, pre- and post-menopausal women), weight and height. An interaction between UA and sex was tested. Analysis was conducted on a combined sample of men and women, if the interaction term was not significant (P > 0.05).

**Results:** The mean age was 66y (SD: 7.7, range: 53–85). 368 hip fractures occurred over the follow-up (mean of 19.9 years). The mean ± SD (mg/dl) uric acid at baseline was: 5.3 ± 1.4. Interaction between UA and sex was not statistically significant (P = 0.72); therefore, men and women were analyzed together. A rise in one unit of UA was associated with a 7% decrease in hip fracture risk in the crude model (HR [95%CI]: 0.93 (0.86–1.0); P = 0.048). Similar associations were observed when UA was analyzed as tertile categories (P-trend: 0.08). Participants in the highest tertile of UA (HR [95%CI]:0.79 (0.61–1.03) tended to have lower risk of hip fracture than those in the lowest tertile (P=0.08). These associations became non-significant after adjustment for covariates.

**Conclusion:** These results suggest that serum UA is not a risk factor for hip fracture risk in older adults.

**Table 1. Association of uric acid with hip fracture risk in men and women.**

<table>
<thead>
<tr>
<th>N</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>2,969</td>
<td>0.93 (0.86,1.0)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>2,966</td>
<td>1.01 (0.93,1.1)</td>
</tr>
</tbody>
</table>

1 Adjusted for: age, sex, and menopausal status (men, pre-menopausal women, post-menopausal women), weight and height, P > 0.01 and p < 0.1

**Funding support:** The ASBMR Foundation, NIH/NIA Ms R03 AR 062089, NIH AR #053205; FHS N01-HC-21519 R01 AR/AG 41398

**Disclosure:** S. Sahni, None; K. Mangano, None; K. Tucker, None; C. Fox, None; D. P. Kiel, Springer for editorial work and author royalties from UpToDate; 7. Institutional grants from Merck Sharp and Dohme, Amgen, Eli Lilly, Z. Merck Sharp and Dohme, Amgen, Eli Lilly, Ammonet Pharma and Novartis, 9. X. Zhang, None; M. T. Hannan, None.

### 2048


**Background/Purpose:** Patient global assessments are components of RA disease activity calculations. Patient global assessments, however, do not consistently agree with physician assessments. This discrepancy leads to the question of how patients form global assessments, specifically the role of factors beyond generally recognized RA symptoms and health status. In this analysis, we evaluate the role of demographic factors, health status, functional limitations, psychological status, and disability in patient global assessments.

**Methods:** Data were from the Rheumatoid Arthritis Outcomes Study (n = 438), collected in structured telephone interviews conducted in English or Spanish. Patient global assessments were obtained with the item: “Considering all the ways that your arthritis affects you, how well are you doing?”, with responses on a 0 – 100 (very poor – very well) scale. Demographic (age, sex, language, race/ethnicity, and education), health status (comorbid conditions, ratings of pain and fatigue, and current use of a DMARD, biologic therapy, or prednisone), functional limitations (measured with the Health Assessment Questionnaire, HAQ), depression, disability in valued life activities (VLA’s), and self-efficacy were entered into sequential linear regression models to examine the contribution of each variable or group of variables to the overall disease assessment. The VLA scale was scored to provide mean difficulty in obligatory (i.e., necessary for independence and self-sufficiency), commuted (associated with major life roles), and discretionary (e.g., socializing and engaging in activities that provide relaxation and pleasure) activities.

**Results:** Respondents were 88% female, mean age 60 ± 13 years, 18% Spanish-speaking, and mean RA duration 23±12 years. Demographic factors alone yielded a model R² of 0.13 (Table 1). A addition of RA, health status and medications increased R² to 0.20; addition of functional limitations increased R² to 0.23. R² was further increased by adding depression, VLA disability, and self-efficacy. Yet, the final model (Table 2) accounted for only 30% of the variation in patient global assessments, leaving the majority of such variation unexplained.

**Conclusion:** Difficulty in participating in discretionary valued life activities and self-efficacy — perhaps representing impact of disease on patients’ daily lives and their evaluations of their ability to cope with RA — play significant roles in RA patients’ global assessments of disease. The importance of these factors may provide insight into discrepancies between patient and physician assessments of disease.
Fatigue Is a Risk Factor for Subsequent Functional Decline in SLE.

Background/Purpose: In geriatrics, fatigue has been shown to be a harbinger of future functional decline. Fatigue is associated with poor function in systemic lupus erythematosus (SLE), but previous studies have not examined the longitudinal relationship between fatigue and poor function. In this analysis, we examine whether fatigue is a risk factor for subsequent functional decline among individuals with SLE.

Methods: Analyses use data from the Lupus Outcomes Study (2003-2011) obtained through annual structured telephone interviews. All participants have physician-confirmed SLE. Fatigue was measured with the SF-36 Vitality subscale. Scores range from 0-100, and higher scores reflect greater fatigue. Function was measured with the Valued Life Activities (VLA) disability scale, which has been validated in SLE. The VLA presents 28 life activities ranging from self-care to social, recreational, and work activities; respondents rate the difficulty they have in performing each on a 0 (no difficulty) to 3 (unable to perform). Scale. Two VLA scores were calculated: mean difficulty and the percent of VLAs an individual was unable to perform. Analyses aimed to determine if fatigue at one time point (T1) was a risk factor for a decline in functioning between T1 and the subsequent year (T2).

Results: The primary analysis included 5105 observations of 1019 individuals, 90% female, with mean age 47.1±13 years, and mean disease duration 13.9 years. At initial interviews, mean fatigue score was 54.1±23.7. In 11.8% of paired observations, there was a functional decline by mean difficulty, and in 7.8%, a decline by percent of activities unable to perform. In bivariate analysis, T1 fatigue was a significant risk factor for subsequent functional decline between T1 and T2 (see Table). After adjustment for age, sex and other potential confounders, subjects with knee arthritis had increased failure rate of completing the test of balance (odds ratio = 1.8, 95% confidence interval (CI): 1.3-2.3) and the 5 chair rise test (odds ratio = 2.1, 95% confidence interval (CI): 1.5-2.9), as well as impaired gait speed (mean difference = 0.204, 95% confidence interval (CI): 0.03-0.406) (Table).

Conclusion: Physical examination outcomes from the CHARLS study indicated that knee arthritis was positively associated with impaired physical function among the residents in China.

Disclosure: Q. Liu, None; X. Tang Sr., None; X. Wu, None; Z. Cao, None; J. Lin, None.

2051
Modification of Effects of Household Income and Homeownership By Block Group Poverty on Health Outcomes in a Cohort of African Americans with Rheumatoid Arthritis.
Rebecca Cleveland, Jennifer Smith,3 Antoine A. Baldassari,3 Beth L. Jonas,2 Doyt L. Conn,2 Larry W. Moorend,6 S. Louis Bridges Jr.,9 and Leigh F. Callahan,† University of North Carolina at Chapel Hill, Chapel Hill, NC, 2Ohio University, Athens, OH, 3Emory Univ School of Medicine, Atlanta, GA, 4University of Pittsburgh, Pittsburgh, PA, 5University of Alabama at Birmingham, Birmingham, AL, 9University of North Carolina, Chapel Hill, NC.

Background/Purpose: We previously found that household income less than $30k/yr and not owning a home influenced rheumatoid arthritis (RA) disease severity measures. We sought to further expand our findings to explore whether block group poverty (BGP) modified the associations between income and homeownership with RA health outcomes (RAHO).

Methods: We carried out a cross-sectional analysis in 898 African American participants with RA in the CLEAR Registry. We assessed the main effects of BGP (>=20% vs. <20%) on RAHO, and explored whether BGP modified the associations between income and homeownership and RAHO. Multivariate regression models for continuous, binary and count outcomes were used to estimate beta coefficients (β), odds ratios (OR) and prevalence rate ratios (PRR), respectively, and their 95% confidence intervals (CI). Associations between income and homeownership on RAHO were stratified by BGP and interaction p-values calculated. All analyses were adjusted for age, sex, BMI, smoking and drinking history, history of injury and hip fracture, and comorbidities.

Results: Among 17708 participants (men: 47.9%, mean: age 59.1 years, mean BMI: 23.4 kg/m²), the prevalence of knee arthritis was 9.1%, 13521 (76.4%) and 13240 (74.8%) subjects, respectively, consented to take the test of balance and the 5 chair rise test. 5725 (72.7%) subjects participated the gait test speed. After adjustment for age, sex and other potential confounders, subjects with knee arthritis had increased failure rate of completing the test of balance (odds ratio = 1.7, 95% confidence interval (CI): 1.3-2.3) and the 5 chair rise test (odds ratio = 2.1, 95% confidence interval (CI): 1.5-2.9), as well as impaired gait speed (mean difference = 0.204, 95% confidence interval (CI): 0.03-0.406) (Table).

Conclusion: Physical examination outcomes from the CHARLS study indicated that knee arthritis was positively associated with impaired physical function among the residents in China.
adjusted for gender, age, body mass index, disease duration, pack-years of smoking, number of comorbidities, current Methotrexate/Lefunomide use, current biologics use and study site.

**Results:** The cohort had a mean age of nearly 55 years, was largely female, and had disease duration of nearly 8 years. In regression models comparing the effects of BGP $>20\%$ with BGP $<20\%$ on RAHO, we observed strong positive associations with DAS, JSN and joint erosions as well as with HAQ score (Table 1). Stratification of the effect of income on RAHO by BGP poverty revealed no statistically significant interaction. However, when stratifying the analyses of homeownership, we observed effect modification that narrowly missed statistical significance (Table 2). Notably, among those who lived in an area with BGP $>20\%$, non-homeowners had a 69% higher joint alignment and motion (JAM) score than homeowners (PRR $= 1.69; 95\%$ CI $= 1.09-2.62$), whereas there was no association with JAM score for homeownership among those living in an area with BGP $<20\%$ (interaction $p$-value $= 0.11$). Other associations which narrowly missed statistically significant interactions were observed for joint space narrowing, joint erosion, and DAS (interaction $p$-values $= 0.13$, 0.05, and 0.14, respectively).

**Conclusion:** Our results suggest that block group poverty modifies the association between homelessness and joint damage measures. These findings suggest that further research is warranted to identify the underlying factors for these associations; for example monetary reasons precluding medication purchase or access to adequate medical care.

### Table 1. Adjusted estimates of cross-sectional associations of block group poverty $>20\%$ with disease severity of rheumatoid arthritis in the total cohort of CLEAR A. Americans

<table>
<thead>
<tr>
<th>Block group poverty $&gt;20%$</th>
<th>Disease activity</th>
<th>Joint damage</th>
<th>Autoantibody status</th>
<th>Self-report health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cohort (CLEAR I &amp; II) (N = 989)</td>
<td>DAS (0-30)* (OR)</td>
<td>0.29 (0.08,0.50)*</td>
<td>0.12 (0.88,1.36)</td>
<td>0.26 (0.13,0.66)</td>
</tr>
<tr>
<td>CRP levels (log mg/L) (0-386) (PRR)</td>
<td>0.08 (0.14,0.31)</td>
<td>1.07 (0.90,1.28)</td>
<td>1.14 (0.99,1.33)</td>
<td></td>
</tr>
<tr>
<td>No. of joint swelling (0-42)*</td>
<td>1.29 (1.01,1.64)</td>
<td>1.22 (1.07,1.38)</td>
<td>1.08 (0.83,1.41)</td>
<td></td>
</tr>
<tr>
<td>No. of joint tenderness (0-42)</td>
<td>1.07 (0.90,1.28)</td>
<td>1.14 (0.99,1.33)</td>
<td>1.14 (0.99,1.33)</td>
<td></td>
</tr>
<tr>
<td><strong>Easy damage</strong></td>
<td>Erosion (0-180) (PRR)</td>
<td>1.39 (1.01,1.90)</td>
<td>1.28 (1.04,1.54)</td>
<td>1.12 (0.89,1.42)</td>
</tr>
<tr>
<td>JSN score (0-166) (PRR)</td>
<td>1.18 (0.97,1.42)</td>
<td>1.32 (1.06,1.63)</td>
<td>1.08 (0.83,1.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Autoantibody status</strong></td>
<td>ACPA, % Positive (OR)</td>
<td>1.20 (0.88,1.63)</td>
<td>1.05 (0.77,1.44)</td>
<td>0.67 (0.46,0.97)</td>
</tr>
<tr>
<td>IgA-RF, % Positive (OR)</td>
<td>0.97 (0.69,1.38)</td>
<td>0.97 (0.69,1.38)</td>
<td>0.97 (0.69,1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Self-report health status</strong></td>
<td>Fatigue VAS (0-100) (PRR)</td>
<td>0.34 (0.20,0.59)</td>
<td>0.15 (0.05,0.42)</td>
<td></td>
</tr>
<tr>
<td>Pain VAS (0-10) (PRR)</td>
<td>0.10 (0.31,0.51)</td>
<td>0.09 (0.04,0.22)</td>
<td>0.96 (0.85,1.07)</td>
<td></td>
</tr>
<tr>
<td>HAQ Score (0-3) (OR)</td>
<td>1.03 (0.89,1.19)</td>
<td>1.03 (0.89,1.19)</td>
<td>1.03 (0.89,1.19)</td>
<td></td>
</tr>
<tr>
<td>RAI Score (1-5) (OR)</td>
<td>0.95 (0.82,1.09)</td>
<td>0.95 (0.82,1.09)</td>
<td>0.95 (0.82,1.09)</td>
<td></td>
</tr>
<tr>
<td><strong>HRQOL</strong></td>
<td>Limited activity days (0-30) (PRR)</td>
<td>1.09 (0.84,1.41)</td>
<td>1.09 (0.84,1.41)</td>
<td>1.09 (0.84,1.41)</td>
</tr>
<tr>
<td>Mentally unhealthy days (0-30) (PRR)</td>
<td>0.94 (0.78,1.13)</td>
<td>0.94 (0.78,1.13)</td>
<td>0.94 (0.78,1.13)</td>
<td></td>
</tr>
<tr>
<td>Physically unhealthy days (0-30) (PRR)</td>
<td>1.09 (0.84,1.41)</td>
<td>1.09 (0.84,1.41)</td>
<td>1.09 (0.84,1.41)</td>
<td></td>
</tr>
</tbody>
</table>

| **Adjustments** | Disease activity score: DAS, CRP; C-reactive protein; JSN: Joint-Space Narrowing; JAM: Joint Alignment and Motion; JSN: Joint-Space Narrowing; HAQ: Health Assessment Questionnaire (disability); RAI: Rheumatology Attitudes Index (helplessness); HRQOL: Health-Related Quality of Life. |

### Table 2. Adjusted estimates for the association of household income $<30k$ and not owning your home $>20\%$ with disease severity measures in the CLEAR cohort, stratified by block group poverty

<table>
<thead>
<tr>
<th>Household Income &lt;30k</th>
<th>Poverty $&lt;20%$</th>
<th>Poverty $&gt;20%$</th>
<th>Non-Homeowner Poverty $&lt;20%$</th>
<th>Non-Homeowner Poverty $&gt;20%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS (0-30)* (OR)</td>
<td>0.31 (0.20,0.44)</td>
<td>0.45 (0.44,0.87)*</td>
<td>0.30 (0.17,0.51)*</td>
<td>0.31 (0.24,0.40)</td>
</tr>
<tr>
<td>JSN score (0-166) (PRR)</td>
<td>0.30 (0.17,0.51)*</td>
<td>0.31 (0.24,0.40)</td>
<td>0.30 (0.17,0.51)*</td>
<td>0.31 (0.24,0.40)</td>
</tr>
<tr>
<td>JSN score (0-166) (PRR)</td>
<td>0.31 (0.20,0.44)</td>
<td>0.45 (0.44,0.87)*</td>
<td>0.30 (0.17,0.51)*</td>
<td>0.31 (0.24,0.40)</td>
</tr>
<tr>
<td>No. of joint swelling (0-42)*</td>
<td>1.39 (1.06,1.82)</td>
<td>1.42 (1.01,1.98)*</td>
<td>0.59 (0.34,0.96)</td>
<td>1.19 (0.71,1.93)</td>
</tr>
<tr>
<td>No. of joint tenderness (0-42)</td>
<td>1.25 (0.99,1.57)</td>
<td>1.34 (1.02,1.76)</td>
<td>0.67 (0.45,1.00)</td>
<td>1.25 (0.96,1.63)</td>
</tr>
</tbody>
</table>

*Adjusted for study site, gender, age, body mass index, disease duration, pack-years of smoking, number of comorbidities, current Methotrexate/Lefunomide use and current biologics use.

**DAS:** disease activity score; **CRP:** C-reactive protein; **JSN:** Joint-Space Narrowing; **JAM:** Joint Alignment and Motion; **RAI:** Rheumatology Attitudes Index (helplessness); **HAQ:** Health Assessment Questionnaire (disability); **HRQOL:** Health-Related Quality of Life.
Table 1. Significant factors associated with falls in univariate analysis. Data are presented as mean (SD) unless specified.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Non-fallers n=82</th>
<th>Fallers n=119</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>13.6 (12.8)</td>
<td>17.4 (13.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>HAQII</td>
<td>0.76 (0.60)</td>
<td>0.98 (0.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of co-morbid conditions</td>
<td>1.0 (0.9)</td>
<td>1.3 (1.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>History CVA/TIA, no. (%)</td>
<td>0 (0)</td>
<td>9 (7.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fear of falling (short FES-I)</td>
<td>11 (5)</td>
<td>13 (5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Foot and ankle features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 metre walk time (s)</td>
<td>5.8 (2.1)</td>
<td>6.2 (2.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak Plantar Pressure mid-foot (Kpa)</td>
<td>100 (44)</td>
<td>122 (71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Foot impairment (LFES-I)</td>
<td>12 (9)</td>
<td>16 (8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HAQ, Health Assessment Questionnaire; FES-I, Falls Efficacy Scale-International; LFES-I, Leeds Foot Impact Scale Activities/Impairment subscale

Disclosure: A. Brenton-Rule, None; N. Dalbeth, None; P. Parmer, None; S. Bassett, None; H. B. Menz, None; K. Rome, None.

2053

Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher mortality risk than the general population, with similar patterns over the last decades. However, more recent studies show conflicting results. Given these conflicting results, there is an obvious need to evaluate the risk of mortality in patients with RA, over a long period, using more recent mortality data.

Objectives: To investigate a) the mortality in a clinical cohort of patients with established rheumatoid arthritis in comparison with the general Dutch population over 15 years, b) the trend in the mortality ratio during the study period, and c) the causes of death and compare these with the general population.

Methods: In 1997, a sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam. Their mortality and causes of death between 1997 and 2012 were obtained from Statistics Netherlands. The Standardized Mortality Ratio (SMR) for all-cause mortality and the number of life-years lost in the study period were calculated. Linear poisson regression analysis was performed to evaluate change in all-cause SMR over time. Finally, the SMRs for cause-specific mortality were calculated.

Results: The mean age of the population at baseline was 60.4 (14.8) years and 72.6% of the patients were women. The estimated SMR (95% CI) for all-cause mortality was 1.54 (1.41, 1.67) with about one life-year lost over the study period. The SMR decreased with 2% annually (p = 0.05). Mortality increased for diseases of the circulatory system, respiratory system, musculoskeletal system, and digestive system (p < 0.05).

Conclusion: The observed mortality among patients with RA was more than 50% higher than in the general population. More than one life-year was lost over 15 years and the mortality seemed to decrease over time. The most frequent causes of death were the same as those in the general population.

Table 2. Significant factors associated with falls in univariate analysis. Data are presented as mean (SD) unless specified.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Non-fallers n=82</th>
<th>Fallers n=119</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>13.6 (12.8)</td>
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<td>0.03</td>
</tr>
<tr>
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<td>0.01</td>
</tr>
<tr>
<td>Number of co-morbid conditions</td>
<td>1.0 (0.9)</td>
<td>1.3 (1.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>History CVA/TIA, no. (%)</td>
<td>0 (0)</td>
<td>9 (7.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fear of falling (short FES-I)</td>
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<td>0.002</td>
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<tr>
<td>Foot and ankle features</td>
<td></td>
<td></td>
<td></td>
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HAQ, Health Assessment Questionnaire; FES-I, Falls Efficacy Scale-International; LFES-I, Leeds Foot Impact Scale Activities/Impairment subscale

Disclosure: J. van den Hoek, None; L. D. Roorda, None; H. C. Boshuizen, None; G. J. Tijhuis, None; T. van den Bos, None; J. Dekker, None.

2054
Physical and Mental Functioning in Patients with Established Rheumatoid Arthritis over an 11-Year Follow-up Period: The Role of Specific Comorbidities. Joëlle van den Hoek1, Leo D. Roorda2, Hendrik C. Boshuizen3, Gerard J. Tijhuis4, Trudi van den Bos5 and Joost Dekker2.

Background/Purpose: Comorbidity in patients with Rheumatoid Arthritis (RA) is highly prevalent and plays an important role in determining RA related outcomes. Several studies have reported the negative association of comorbidity with functioning in general. The information about the association of specific comorbidities with functioning in patients with RA is limited. Evaluating specific comorbidities will provide valuable information for clinical practice and the management of patients with RA.

The aim of this study was to investigate the long term association of a wide range of specific comorbidities with physical and mental functioning in patients with RA.

Methods: Longitudinal data over a period of 11 years were collected from 892 patients with RA at study inclusion. Somatic comorbidity was measured at baseline, with a questionnaire including 20 chronic diseases, from which 9 categories of chronic somatic comorbidity were created. Comorbid depression was measured at baseline, with the Center for Epidemiologic Depression Scale. Physical functioning was measured with the Health Assessment Questionnaire (HAQ) and with the physical component summary of the Short Form 36 health survey (SF-36). Mental functioning was measured with the mental component summary of the SF-36.

Results: The mean age of the patients at entry was 59.3 (SD 14.8) years, 72% of the patients were women, their median disease duration was 5.0 (IQR 2.0–14.0) years, and 68% had ≥ 1 comorbid condition. The mean HAQ score for an average patient was 0.98 on average over the 11 years follow-up period. Circulatory conditions (mean HAQ score 0.28) and depression (0.38) were associated (p < 0.05) with low physical functioning according to the HAQ. An average patient with a circulatory condition had a mean HAQ score of 0.98 + 0.28 = 1.26. Circulatory (mean SF-36 score -3.23), respiratory (-2.74), musculoskeletal conditions (-2.85), cancer (-5.26) and depression (-3.36) were associated (p < 0.05) with low physical functioning according to the SF-36. While respiratory conditions (-2.28) and depression (-12.81) were associated (p < 0.05) with low mental functioning. The improvement in physical functioning according to the HAQ was 0.01 annually for an average patient. Genitourinary conditions were associated with a decline in physical functioning over time (p < 0.05). An average patient with a genitourinary condition declined in physical functioning with 0.01 - 0.04 – 0.03 annually. Digestive conditions were associated (p < 0.05) with a decline in mental functioning.

Conclusion: Patients with specific comorbid conditions have an increased risk of low or declining functioning on the long term. Targeted attention for these specific comorbid conditions by clinicians and general practitioners is important. Diagnostics during the course of the disease, adequate referral to and working together with other specialists might improve physical and mental functioning in patients with RA.

Disclosure: J. van den Hoek, None; L. D. Roorda, None; H. C. Boshuizen, None; G. J. Tijhuis, None; T. van den Bos, None; J. Dekker, None.

2055

Rush Medical College, Chicago, IL, "Rheumatology Associates, Chicago, IL."

Background/Purpose: Fibromyalgia is not thought to have an immunological pathogenesis; however, few studies have been done to evaluate immunological abnormalities. We analyzed lymphocyte subsets in fibrom-
alalgia syndrome (FMS) patients and compared the results to established normal values in healthy controls.

**Methods:** 25 Patients (22 female and 3 male) with fibromyalgia meeting 2010 ACR criteria and followed in a rheumatology office practice had their blood analyzed by flow cytometry. Normal values for healthy controls were established by the University of Miami Immunology Laboratory where the analyses were performed.

**Results:** The following immunologic tests were abnormal in fibromyalgia patients

<table>
<thead>
<tr>
<th>CD4+</th>
<th>CD8+</th>
<th>CD4/CD8</th>
<th>CD8+CD95</th>
<th>CD4+CD11a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.138</td>
<td>125.895</td>
<td>180.473</td>
<td>139.472</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** CD4+CD8+ helper T cells were elevated in the FMS patients. CD4+CD8+, CD4+CD95+ and CD4+CD11a were reduced in FMS compared to normal healthy levels. This suggests possible increased T helper cell function and reduced CD8 cytotoxic/suppressor T cells in this group of fibromyalgia patients.

The immune system could play a yet undetermined role in fibromyalgia.

**Disclosure:** R. S. Katz, None; H. Bond, None; D. Picken, None.

**2056**

Fibromyalgia Symptoms Beyond the Pain and Its Impact on the Patient. Abdelmonem Helal1, Dia M F Mohasseb1, Noha AH El-Sawy1 and Yousra Abdel-Fattah2.

**Background/Purpose:** Fibromyalgia (FM) has been promoted as the most common cause of chronic, widespread non-articular musculoskeletal pain, stiffness and fatigue. Although pain is the central feature of FM, there are other common clinical features associated with the disease including: sensations of muscle tension and morning stiffness, chronic headaches, nonrestorative sleep, fatigue and waking unrefreshed, post-exertional muscle pain, and cognitive dysfunction.

**Methods:** Twenty-five female patients with a mean age of 30 years (18 to 57) diagnosed with primary FM according to 1990 American College of Rheumatology (ACR) diagnostic criteria as well as the 2010 ACR preliminary diagnostic criteria for FM were included in this study. Demographic characteristics and clinical data were collected from all patients. Pain severity, impact of the disease, sleep disturbance, severity of depression and anxiety were assessed by McGill Pain Questionnaire (MPQ), Fibromyalgia Impact Questionnaire (FIQ), visual analogue scale (VAS) for sleep evaluation, Hamilton Depression Rating Scale (HRSD) and Hamilton Anxiety Rating Scale (HAMA) respectively.

**Results:** The median complaint duration was 24 months (3 to 180), and the median number of tender points was 14 (11 to 18). Fourteen patients (56%) complained of numbness with normal neurological examination. The median score of the MPQ, Presenting pain intensity - Visual Analogue Scale (PPI-VAS) was 80 (50 to 100) and for the overall intensity was 3 (2 to 5). The FIQ showed a median score of 59.41 (41 to 76). Twenty two patients (88%) had irregular sleep patterns and poor sleep quality. Nineteen patients (76%) showed mild depression with normal neurological examination. The median score of the HRSD, Hamilton Depression Rating Scale was 3 (2 to 5) for the overall intensity was 7 (5 to 10). The FIQ showed a median score of 59.41 (41 to 76). Twenty two patients (88%) had irregular sleep patterns and poor sleep quality. Nineteen patients (76%) showed mild depression with normal neurological examination. The median score of the HRSD, Hamilton Depression Rating Scale was 3 (2 to 5) for the overall intensity was 7 (5 to 10).

**Conclusion:** Fibromyalgia highly influences the quality of life of the patients, and the severity of pain and associated symptoms significantly correlate with the impact of FM on the patients’ life. There is a significant correlation between the severity of pain and the severity of associated symptoms of FM as depression and anxiety; in the same context depression as well as anxiety were found to be strongly associated with FM.

**Disclosure:** A. Helal, None; D. M. Mohasseb, None; N. A. El-Sawy, None; Y. H. Abdel-Fattah, None.

**2057**


**Background/Purpose:** This study was designed to investigate the autonomic nervous system (ANS) and spinal inhibitory circuits in FMS by electrophysiological studies and compare the results with healthy controls.

**Methods:** Thirty patients with FMS diagnosed according to ACR classification criteria and thirty 30 age matched healthy controls were recruited for the study. Patients were clinically examined and evaluated by Beck depression scale, SF-36 and fibromyalgia impact questionnaire scales. Upper and lower extremity nerve conduction studies were performed to both groups to detect a large diameter peripheral neuropathy such as carpal tunnel syndrome or polyneuropathy. For evaluating the ANS, sympathetic skin response (SSR), R-R interval variation (Heart rate variability-RRIV) were studied. Spinal inhibitory circuits were assessed with cutaneous silent period (CSP).

**Results:** There were no statistically significant differences in distal latencies, amplitudes and nerve conduction velocities of motor and sensory nerves (p>0.05). Latencies and amplitudes of SSR recorded from median and tibial nerve, CSP latency and duration recorded from abductor pollicis brevis muscle and tibialis anterior muscle in FMS and healthy controls were also similar (p>0.05). Heart rate variability (RRIV) recorded from FS patients were significantly lower in comparison to healthy controls (p<0.05).

**Conclusion:** Heart rate variability was the only significant abnormal electrophysiological parameter in patients with FMS which suggested that there was an ANS dysfunction in FMS. Despite SSR is one of the classical methods for the assessment of sympathetic fibers impairment to evaluate peripheral neuropathies, patients with FMS had no abnormality. We thought that this parameter is not sensitive enough to detect an abnormality in patients with FMS. We also evaluated cutaneous silent period (CSP) which refers to the brief interruption in voluntary contraction that follows strong electrical stimulation of a cutaneous nerve. The CSP is a protective reflex that is mediated by spinal inhibitory circuits and is reinforced in part by parallel modulation of the motor cortex. A corroboration to our study this reflex was not effected in patients with FMS.

**Disclosure:** I. Ustun, None; I. Yagi, None; G. Akyuz, None; F. Unlu-Ozkan, None.

**2058**

The Impact of Environmental Stress on Pain in Fibromyalgia Patients. Robert S. Katz1, Ben J Small1 and Susan Shott2.

**Background/Purpose:** Many fibromyalgia syndrome (FMS) report that their illness is significantly affected by environmental stress. We compared FMS and RA patients with respect to the impact of a variety of environmental conditions on their pain.

**Methods:** 211 office patients with either FMS (150; 130 women and 20 men; mean age 51±12) or RA (61; 45 women and 16 men; mean age 55±15) completed a questionnaire about the effect of various environmental conditions on their pain, rated as 0 = no effect, 2 = mildly worse, 3 = moderately worse, and 4 = severely worse. The two-sided Mann-Whitney test was done to compare FMS and RA patients with respect to these ratings, using 0.05 significance level.

**Results:** Compared to RA patients, FMS patients had significantly worse ratings for cold weather (2.7±1.1 vs. 2.2±1.0, p = 0.003), humidity (2.5±1.1 vs. 2.0±0.9, p = 0.004), rain (2.6±1.1 vs. 2.2±1.0, p = 0.027), weather change (2.8±1.0 vs. 2.3±0.9, p = 0.004), smells (1.4±0.8 vs. 1.1±0.4, p = 0.002), season change (2.2±1.0 vs. 1.8±0.9, p = 0.018),
Fibromyalgia patients are known to sleep poorly. In this study, the mean time to fall asleep was 17.7 minutes in fibromyalgia patients compared to 27.7 minutes in controls. The total hours in bed were 8.4 hours in fibromyalgia patients compared to 7.3 hours in controls. The light sleep average was 3.4 hours in fibromyalgia patients compared to 3.3 hours in controls. The sound sleep average was 4.0 hours in fibromyalgia patients compared to 3.2 hours in controls.

Conclusion: Muscle tension is increased in fibromyalgia. The use of a simple device called a Stryker Pressure Monitor may be useful in the diagnosis and treatment of fibromyalgia.
Background/Purpose: The Fibromyalgia Rapid Screening Tool (FiRST) is a brief, simple and straightforward self-administered questionnaire with excellent discriminative value, of potential value for the detection of fibromyalgia in patients with diffuse chronic pain. To evaluate the usefulness of a Spanish version of the FiRST questionnaire for the detection of fibromyalgia (FM) in primary health care centers.

Methods: The Spanish translation of the original FiRST French questionnaire was carried out by Rheumatologists and Professors of French and Spanish Language. Translation was performed in second person, to enable self or hetero application (see annex). This study is prospective and multicenter, including 404 consecutive patients diagnosed with FM according to the 1990 ACR modified criteria and 2010 ACR criteria. FM was diagnosed by specialists in Rheumatology. We also included a control group of similar age and sex, consisting of 147 Rheumatoid Arthritis (RA) patients and 219 Osteoarthritids (OA) patients. The modified 2010 ACR criteria was applied, the number of tender points was evaluated, and the FiRST questionnaire and Fibromyalgia Impact Questionnaire (FIQ) were completed. Sensitivity, specificity and predictive value were analysed for each of the 6 items of the FiRST questionnaire and for the global score (5 or 6 positive items), as well as the correlation between the global score and other parameters. The results obtained were expressed as median and interquartile range and were analyzed with the Mann - Whitney U test using SPSS 15. P values less than 0.05 were considered significant.

Results: The mean age of patients with FM was 51.67 years. The mean FIQ score was 73.29. The median disease evolution was 12 years (IC: 6–21). Median tender points was 16 (IC: 14–18). 356 of 404 FM patients who met the 1990 ACR criteria and the 2010 modified criteria had a positive FiRST (scores 5 or 6). In the control group (AR = OA), 16 subjects had a positive FiRST, and the FiRST questionnaire and Fibromyalgia Impact Questionnaire (FIQ) were completed. Sensitivity, specificity and predictive value were analysed for each of the 6 items of the FiRST questionnaire and for the global score (5 or 6 positive items) with 95% interquartile range was 92 (88.9–95.1), the specificity 87.4 (80.8–94), positive predictive value 95.7 (93.3–98.1), and negative predictive value 78.2 (70.6–85.9). There was a significant correlation between total FiRST (scores 5 or 6) and Fibromyalgia Impact Questionnaire (p < 0.0001), Symptom Severity Scale (p < 0.0001), time to disease progression (p < 0.0001) and FIQ (p < 0.0001).

Conclusion: The FiRST questionnaire and FIQ were validated in a multicenter study. This questionnaire is easy to use and useful for the detection of FM patients in primary health care centers.

Disclosure: B. Casanueva, None; F. García-Fructuoso, None; R. Belenguer, None; J. L. Hernandez, None; M. Gonza´lez-Gay, None.

2065

A Cross-Sectional Analysis of Psychological Symptoms, Sleep Quality, and Functional Balance in Fibromyalgia. Vicky Chen1, William F. Harvey2, Jeffrey B. Driban3, Mei Chung4, Lori Lyn Price5 and Chenchen Wang6. 1Tufts University School of Medicine, Boston, MA, 2Tufts Medical Center, Boston, MA.

Background/Purpose: Previous studies suggest that FM may be associated with worse balance and falls. Balance requires the coordination of motor, sensory (ex. visual and vestibular), and cognitive abilities. These may be affected by the psychological symptoms present in FM. Depression, anxiety, and stress, have both cognitive (reduced attention) and somatic features (poor sleep quality and psychomotor slowing); and may therefore be related to the balance problems in FM. We intend to evaluate these relationships in this study.

Methods: We analyzed baseline data from a randomized trial comparing Tai Chi to aerobic exercise in individuals with FM. Balance was measured using a One-Leg Balance Test (OLBT): time standing on preferred leg with eyes closed; max time = 30 seconds. Psychological symptoms of depression, anxiety, and stress were measured using validated scales: Beck Depression Inventory (BDI-II), State-Trait Anxiety Inventory (STAI), State-Trait Anxiety Inventory (STAI), Depression Anxiety and Stress Scale (DASS), and Perceived Stress Scale (PSS). Higher scores reflect greater symptom severity. The mental component of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36 M CS) measured mental health related quality of life. Higher scores indicate better health status. Sleep quality was assessed using the Pittsburg Sleep Quality Index (PSQI). Higher scores reflect poor sleep quality. Chronic Pain Self-Efficacy Scale (CPSS) measured confidence in ability to perform a particular behavior or task. Higher scores reflect improved status. We used a logistic regression model to detect associations between balance times ≤3.02 seconds (defined by first quartile) and measures of psychological symptoms, self-efficacy, mental health-related quality of life, and sleep quality. Independent variables were analyzed in tertiles. Analyses were adjusted for age, gender, and BMI.

Results: 234 screened participants were included in our analysis. 9% were female. Mean age was 51.3±11.8 years and mean BMI was 29.7±6 kg/m². The median performance on OLBT was 4.7 seconds. Table 1 shows the odds ratios for OLBT ≤3.02 seconds and BDI-II, PSS, SF-36 Mental Component, PROMIS anxiety, PSQI, and CPSS. Better sleep quality and fewer depressive symptoms were weakly associated with improved balance, but no significant associations were found between balance and measures of psychological symptoms and sleep quality.

Conclusion: We were unable to demonstrate any significant associations between balance and psychological symptoms or sleep quality. Small sample size may limit data interpretation and evaluation of the results. We recom-
mend that future studies assess factors more directly related to balance such as muscle strength, proprioception, and attention. Such research is critical to understanding the mechanisms underlying balance problems in FM and may identify novel therapeutic targets for future longitudinal studies.

Table 1. Descriptive Statistics and Odds Ratios: Adjusted for age, sex, and BMI.

<table>
<thead>
<tr>
<th>Measure (range)</th>
<th>Turtle (Minimum, Maximum)</th>
<th>Odds Ratio (95% CI) One Leg Balance Ted With Eyes Closed &gt;3.02 seconds</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD1 (0-43)</td>
<td>Lowest (0.0, 16.0)</td>
<td>1.22 (0.51, 2.99)</td>
<td>0.65</td>
</tr>
<tr>
<td>High (27.0, 43.0)</td>
<td>1.47 (0.59, 3.69)</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>PSS (0-40)</td>
<td>Lowest (0.0, 16.0)</td>
<td>1.01 (0.45, 2.36)</td>
<td>0.93</td>
</tr>
<tr>
<td>High (24.0, 40.0)</td>
<td>0.70 (0.27, 2.13)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>SF-36 MCS &lt; 50 (0-100)</td>
<td>Lowest 1.25 (0.32, 5.02)</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>High (43.5, 68.8)</td>
<td>0.86 (0.31, 2.61)</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>PROMIS Anxiety 6a (36.3-82.7)</td>
<td>Lowest 1.45 (0.59, 3.56)</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>High (62.6, 82.7)</td>
<td>0.76 (0.22, 1.81)</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>PSQI (0-21)</td>
<td>Lowest (1.0, 9.0)</td>
<td>1.40 (0.59, 3.69)</td>
<td>0.42</td>
</tr>
<tr>
<td>High (15.0, 21.0)</td>
<td>1.40 (0.56, 3.70)</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>CPS* (0-10)</td>
<td>Lowest (1.0, 4.0)</td>
<td>1.13 (0.47, 2.71)</td>
<td>0.78</td>
</tr>
<tr>
<td>High (4.3, 6.0)</td>
<td>0.73 (0.31, 0.71)</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>High (6.1, 10.0)</td>
<td>REFERENCE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Ultra-orthodox religiosity may be associated with reduced levels of symptoms, including pain, sleep disorders as well as anxiety and depression and may modulate the effect of stress and trauma on these symptoms. These results constitute a novel aspect in the analysis of the effects of locus-of-control and belief on these symptoms and on the association between religious faith and resilience. Further research may shed additional light on the role of spirituality/religious faith and on the mechanisms involved in these apparent protective effects.

Disclosure V. Aloush, None; J. N. Ablin, None.

2067
Understanding the Factors Influencing Time to Diagnosis in Fibromyalgia.
Howard Amital1, Yael Bar-On2, Varda Shalev3, Dahlia Weitzman4 and Gabriel Chodick5. 1Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel. 2Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, 3Maccabi Healthcare Services, Tel Aviv, Tel-Aviv, Israel, 4Healthcare Services, Tel Aviv, Tel-Aviv, Israel.

Background/Purpose: Fibromyalgia (FM) is a chronic debilitating disorder considered to be part of a spectrum of central sensitization syndromes. The diagnosis of FM is a complex one, affected by many different factors including stigmatization of the disease, confounders such as comorbidities and different characteristics of patient and doctor.

Aim: Investigating the time passing from initial complaints till final diagnosis by an expert rheumatologist, and delineating the patient and physician characteristics affecting that time, using the comprehensive database of a large HMO in Israel.

Methods: Using a retrospective database search we identified patients diagnosed with FM1 by a rheumatologist or at release from hospitalization during (‘confirmed FM patients’), and sex and age matched FM-free enrollees. Different complaint patterns were tested, to ascertain time of initial complaints. The pattern with the best combination of sensitivity and specificity was applied on an FM population of all patients diagnosed by a primary physician, rheumatologist, or at release from hospitalization, during the same period (‘primary physician population’). Patient and primary physician factors associated with time between initial complaints and FM diagnosis were assessed. A multilevel generalized mixed linear model with a log-linked gamma distribution was used to account for clustering of patients associated with the same primary physician.

Results: Our study included 4,603 ‘confirmed FM patients’, of whom 90.8% were women, with a mean age of 50.63 years (±11.37). The complaint pattern chosen, as time of initial complaints, comprised of >4 complaints within 6 months. This pattern was found in 73.2% (1,944/2,656) of the ‘confirmed FM patients’, 18.4% (1,685/9,173) of the FM-free patients. Applying this pattern on the primary physician population, revealed a mean time to diagnosis of 4.7 ± 3.8 years. Within this time, the mean (SD) time that FM patients were associated with the ‘physician at diagnosis’ was 2.9 ± 2.8. The patient factors most significantly associated with a longer time to diagnosis were older age, female gender and low socioeconomic status. The physician characteristics most significantly associated with a longer time to diagnosis were older age, internal or general specialty vs. family specialty, and physician’s medical studies in West vs. East Europe.

Conclusion: The time to diagnosis of FM is significantly influenced by patients a and physician characteristics. This knowledge can contribute to future research and to better planning of physician education, concerning this disease.

Disclosure: H. Amital, None; Y. Bar-On, None; V. Shalev, None; D. Weitzman, None; G. Chodick, None.

2068
Joint Hypermobility Syndrome and Postural Orthostatic Tachycardia Syndrome (HyPOTS).
Artan Kaso and Ali Askari. University Hospital Case Medical Center, Cleveland, OH.

Background/Purpose: Joint hypermobility syndrome (JHS) is a chronically disabling disorder manifested as a widespread musculoskeletal pain and/or fatigue, in the presence of generalized joint hypermobility. It is often misdiagnosed as Fibromyalgia or Chronic fatigue syndrome. It is a condition that is often overlooked by clinicians.

Methods: Currently in our clinic, we have observed 25 patients between 22 and 58 yr who were diagnosed with JHS using the Brighton Criteria (1). All of them presented with one or more of these symptoms: chronic fatigue,
generalized musculoskeletal pain (arthralgias and myalgias), pre-syncpe, palpitations, dizziness caring the diagnosis of fibromyalgia. They do not have any Marfanoid features or certain types of Ehlers-Danlos syndrome or skin involvement.

Out of 25 patients 16 (64%) had a positive diagnostic tilt table test consistent with the diagnosis of postural orthostatic tachycardia syndrome (POTS), 6 (24%) have not had a tilt table test done yet (financial, non compliance, etc) and 3 (12%) had a negative tilt table test.

**Conclusion:** Ted Hose stocking, they showed improvement in their clinical presentation. Treatment for POTS with fludrocrotison, increasing water and salt intake, using clinically and confirmed by tilt table test in 64%. By applying standard of care mean age of 35 with a presentation consistent with fibromyalgia or chronic fatigue Center.

**Patient**

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**Symptoms of Autonomic dysfunction**

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**2069**

**Investigation of the Effects of Physical Exercise on the Control Mechanisms of Cutaneous Circulation in Patients with Fibromyalgia Syndrome.** Emre Esen and Alp Cetin,M.D., Ankara, Turkey.

**Background/Purpose:** Sedentary lifestyle and disabling widespread pain in patients with fibromyalgia syndrome (FMS) may after cardiovascular functions and can induce endothelial dysfunction. We evaluated cutaneous microvascular functions and their correlations with severity of disease assessed by revised fibromyalgia impact questionnaire (FIQ) and pain visual analog scale (VAS) in FMS patients, before and after participation in a moderate intensity 4-wk aerobic physical exercise program.

**Methods:** Forty female FMS patients without any known cardiovascular diseases and 20 healthy age-matched female controls were included in the study. Cutaneous blood flow was measured by a laser Doppler flowmeter (LDF) at the volar skin site of the forearm. Spectral analysis of LDF signals was used to assess the relative contribution of control mechanisms. The local thermal hyperemia was used to test the microvascular functions.

**Results:** Exercise improved pain VAS (from 8.5±1.5 to 4.7±1.4; p<0.0001) and FIQ scores (from 69.7±7.5 to 43.7±6.4; p<0.0001) and, improvement in myogenic and neurogenic mechanisms showed negative correlations with increase in FIQ scores. In contrast, cardiac signal was positively correlated with the FIQ scores, after exercise. Endothelial function was under the influence of pain, and basal nitric oxit (NO) activity was positively correlated with pain VAS.

**Conclusion:** These results suggest that the microvascular functions are impaired in FMS patients and, improvement in FIQ/pain score and the enhancement in vascular functions are possible by moderate exercise training.

**Disclosure:** E. Esen, None; A. Cetin, None.

**2070**

**Elevated Serum Leptin Concentrations in a Subset of Fibromyalgia Patients with High Inflammatory Markers.** Anne Quismorio, John Solyman, Lisa Asafhan, Samy Metyas, Covina Arthritis, Covina, CA, Research Associate, Covina, CA; Assistant Clinical Professor Of Rheumatology, Covina, CA.

**Background/Purpose:** Previous studies suggest heterogeneity in the presentation of fibromyalgia (FM) with differences in biological variables including elevated sedimentation rate (ESR), cytokine profile, and hormone levels. Whether these variables identify subgroups within FM population remains to be established. We have previously reported primary FM patients with elevated inflammatory markers. Metyas SK, et al. Ann Rheum Dis, 2007;66(Suppl II):S25.

**Methods:** A multi-biomarker disease activity score, validated to measure disease activity in rheumatoid arthritis (RA). It is a commercially available test designed to measure serum concentrations of 12 biomarkers in RA.

**Results:** Mean age was 43.5 years, 94% were female and 6% were male. The Vectra®DA was elevated for all patients with a mean score of 46.5 (range 30 to 84, or moderate to high activity). Among the twelve biomarkers (including IL-6 and CRP) serum concentrations were within the range reported in RA except leptin. 45% of subjects had leptin concentrations exceeding the range reported in RA (1-45 ng/mL). The mean leptin was 42.3 ng/mL (range 30–81 ng/mL).

**Conclusion:** There was a positive correlation between leptin concentration and BMI in the entire cohort; however, this correlation was not observed in the patient subgroup with leptin levels above the range in RA (P = 0.6). CRP but not ESR was positively correlated with the Vectra®DA score.

**Disclosure:** A. Quismorio, None; J. Solyman, None; L. Asafhan, None; S. Metyas, Cressco Bioscience, 8.

**2071**


**Background/Purpose:** The ACR 1990 diagnostic criteria for fibromyalgia includes a definition for chronic widespread pain (CWP) that depends on a particular distribution of pain sites. The new proposed ACR 2010 criteria instead has a Widespread Pain Index which takes into account the number of sites only. The purpose of this analysis was to see, amongst persons reporting multi-site pain, if the distribution of pain sites has any association with a number of potential risk markers after adjustment for the number of sites.
Methods: The MUSICIAN survey was a general population survey aimed at identifying people with CWP for an intervention study. A questionnaire was sent by post to adults registered at family doctors in two areas of the United Kingdom. Questions included age, gender, employment status, smoking behaviour, height, weight, and questions on pain included a manikin in 35 sections to indicate the location of the pain. Respondents were included in the analysis who indicated that they had between 3 and 16 areas of pain, and that the pain had lasted 3 months or more. (People with less than 3 sites could not meet the ACR 1990 definition of widespread pain, while most of those with more than 16 sites did). Participants were classed as having pain that was widespread or not according to the ACR 1990 criterion. A number of potential associations with having widespread pain were tested using logistic regression to provide odds ratios (OR) with 95% confidence intervals (CI). These models were then adjusted for number of pain sites to see if any associations with the distribution pattern remained after accounting for having pain in multiple areas.

Results: 14680 people responded to the questionnaire, of which 7536 reported some chronic pain (prevalence 51.3%). In those with chronic pain, the median number of pain sites was 5 (interquartile range 3 to 9), and the prevalence of pain that met the ACR 1990 criterion for being widespread was 32.1%. Included in the analysis were 5715 respondents with chronic pain in 3 to 16 areas, of which 2037 (35.6%) met the criterion for widespread pain. Gender, age, smoking and employment status all had significant associations with ACR 1990 widespread pain (see table). A further adjustment for number of pain sites most of these associations either became non-significant or were attenuated.

Conclusion: We have shown that when number of pain sites was taken into account, the particular distribution of sites did not continue to have significant relationships with many associated factors. This might indicate that is not so much that the pattern of pain locations that is important as the multiplicity of areas. This may have implications in conditions such as fibromyalgia where pain across multiple areas is involved. Based on this data, the use of a measure that looks at the number of pain sites rather than a particular distribution is acceptable as a diagnostic criterion.
Background/Purpose: In dangerous environments, hypervigilance conveys a survival value. A cave dweller who sleeps lightly and startles easily might escape a prowling bear while he is safely slumbering neighbor becomes a midnight snack. In safer environments, hypervigilance may cause dysfunctional stress. Some fibromyalgia syndrome (FMS) patients report symptoms of hypervigilance. We compared FMS and RA patients with respect to hypervigilance symptoms, and FMS patients with and without each hypervigilance symptom with respect to environmental stress.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51 ± 12) or RA (61; 45 women and 16 men; mean age 55 ± 15) completed a questionnaire about hypervigilance symptoms (present or absent) and the effect of various environmental conditions on their pain (rated as 1 = no effect, 2 = mildly worse, 3 = moderately worse, and 4 = severely worse). The chi-square test of association was done to compare FMS and RA patients with respect to percentages.

Results: Compared to RA patients, significantly higher percentages of FMS patients woke up more than once during the night (84% vs. 71%, p = 0.003), had trouble getting to sleep (63% vs. 38%, p = 0.001), and startled easily (53% vs. 30%, p = 0.003). FMS patients were uncomfortable in crowds (median 2.3 vs. 1.8, p = 0.001), FMS patients were made uncomfortable by people standing behind them (median 2.4 vs. 1.9, p < 0.001), FMS patients had trouble sleeping (median 2.1 vs. 1.9, p = 0.004), FMS patients did not feel at ease with strangers (median 2.2 vs. 1.9, p = 0.029), and FMS patients did not find it easy to trust strangers (median 2.3 vs. 1.9, p = 0.009).

Conclusion: FMS patients were significantly more likely to report hypervigilance symptoms compared to RA patients. The hypervigilance trait may be present in many fibromyalgia patients and could explain their hyperalgesia symptoms compared to RA patients.

Disclosure: R. S. Katz, None.

2075
The Lumbar Spine in Fibromyalgia. Robert S. Katz¹, Alexandra Small² and Anthony Farkasch³. Rush Medical College, Chicago, IL, ¹University of Illinois College of Medicine, Chicago, IL, ³Rheumatology Associates, Chicago, IL.

Background/Purpose: Radiographs of the lumbar spine appear normal in fibromyalgia. However, a previous study (ArthRheum50:134, 2004) found a reduced lordotic curve in the cervical spine of patients with fibromyalgia. We measured the Cobb angle on radiographs of the lumbar spine in patients with fibromyalgia and other rheumatic disease patients.

Methods: Fibromyalgia patients meeting the 2010 ACR criteria with a complaint of back pain, and patients with other rheumatic disease disorders who had back pain (osteoarthritis, spinal stenosis, degenerative joint disease, herniated disc and other forms of lumbar radiculopathy, and ankylosing spondylitis) were evaluated for lumbar spine straightening using the Cobb angle of lateral lumbar spine radiographs.

The Cobb angle was measured by drawing a line parallel to the superior portion to L1 and another line parallel to the inferior portion to L5 and measuring the angle where the two lines intersect.

Results: The number of fibromyalgia patients studied was 148 and the number of non-fibromyalgia patients with back pain but not fibromyalgia was 59. The mean ages were 45.4 years for fibromyalgia patients and the mean age for the non-fibromyalgia patients 52.5 years. In the fibromyalgia group there were 136 females, and 12 males; and in the non-fibromyalgia group 136 females, and 12 males; and in the non-fibromyalgia group with back pain (osteoarthritis, spinal stenosis, degenerative joint disease, herniated disc and other forms of lumbar radiculopathy, and ankylosing spondylitis) were evaluated for lumbar spine straightening using the Cobb angle of lateral lumbar spine radiographs.

The mean Cobb angle in the fibromyalgia patients was 14.0 degrees, and the mean Cobb angle in the rheumatic disease controls with back pain was 20.9 degrees.

Conclusion: FM S patients have a straight lumbar spine. We propose that increased muscle tension may be the cause of the reduced Cobb angle in these patients. Fibromyalgia patients have widespread pain over large muscle groups, muscle tenderness, and also have straight cervical spines and straight lumbar spines, by measuring the Cobb angle. It is quite possible that much of the pain experienced by fibromyalgia patients relates to increased muscle tension.

Disclosure: R. S. Katz, None; A. Small; None; A. Farkasch, None.

2076
Predictive Modeling of a Fibromyalgia Diagnosis: Increasing the Accuracy Using Real World Data. Birol Emir¹, Jack Mardelkian¹, Elizabeth T. Masters², Andrew Clair³, Max Kuhn³ and Stuart L. Silverman¹. ¹Pfizer Inc., New York, NY, ²Pfizer Inc., Groton, CT, ³Cedars-Sinai Medical Center, UCLA Center of Excellence, Los Angeles, CA.

Background/Purpose: The number of symptoms and comorbidities associated with the chronic pain condition of fibromyalgia (FM) complicates its identification and diagnosis.

Methods: This retrospective analysis used structured de-identified electronic health records from the 2011–2012 Humedica database, including demographics, clinical characteristics, and healthcare resource use. An FM cohort was defined as subjects ≥18 years in 2011 with at least two ICD-9 codes for FM (729.1) ≥30 days apart during 2012; the no-FM cohort did not have the ICD-9 code. Univariate analyses characterized between-cohort differences and determined the demographic, clinical, and healthcare resource variables associated with an FM diagnosis. A Random Forest (RF) model was used to predict FM and non-FM subjects by entering all variables into the model (1500 bootstraps) with internal down-sampling (to account for imbalance between cohorts). Importance of the variables was computed using RF to determine the trade-off on accuracy when only the top 10 variables were fitted. For practical clinical application, a rule-based model was used to derive simple statements to help explain which patient sets have the largest effect on the likelihood of an FM diagnosis.

Results: Significant differences were observed between the FM (n=4,296) and no-FM (n=583,665) cohorts for demographics (P<.0001) except for age, for most evaluated comorbidities (P<.0001), and for health-care resource use (P<.0001), with more comorbidities and resource use in FM subjects. Resources included proportions of subjects with utilization, and units per subject per emergency room visits, outpatient visits, hospitalizations, and medications. The top 10 variables for predicting an FM diagnosis were identified from the RF models based on level of importance as reflected by the percent of model iterations in which the variable was predictive (Figure). A receiver operator characteristic curve confirmed the predictive accuracy of the model variables (area under the curve of 0.810). Rules were developed to identify patients with high predicted probability of an FM diagnosis; e.g., the average predicted probability of 0.54 for a subset of patients with outpatient visits excluding office visits 0 and prescriptions administered/ordered ≤3 and the number of musculoskeletal pain conditions >0 was more than double the 0.22 predicted probability for those not in the subset. Similarly, a rule to identify non-FM (opioid prescriptions administered/ordered/written ≤0; visits where diagnostic/laboratory tests were ordered =0; and number of musculoskeletal pain conditions =0) correctly classified 100% of the sample.

Conclusion: Random forest modeling can be applied to determine likelihood of an FM diagnosis. Rules can simplify this method with good accuracy. Further validation of RF may help facilitate earlier diagnosis and enhance management strategies.


Methods: The study included consecutive patients with JPFS (ACR’90) and healthy controls matched by age and gender. Informed consent was obtained for all study subjects. Pairs of the proposed point, those accepted by the ACR and control points (biceps, quadriceps and lateral foot area) were assessed with digital pressure of approximately 4 Kg/cm² by previously trained rheumatologist and pediatrician in both subject groups. Sensitivity and specificity of all tender and control points examined were compared by unpaired t-test, ROC curve and McNemar test.

Results: Out of a total of 22 JPFS patients, 19 were female (F) and 3 were male (M), ages between 13 and 17 (14±0.30). The healthy control group included 27 high school students of similar age (14±0.23) and gender (21 F and 6 M) than the patients. The new planter point was positive in 20/22 JPFS patients (90.9%), bilaterally in 20 and unilaterally in 2 patients. None of the control group subjects had pain on the new planter point. Sensitivity and specificity for the new tenderness point were 90.9% and 96.4% respectively (positive LR of 25.25, ROC Area = 0.937 with CI 95% = 0.856 – 1.00). Several ACR tender points presented lower sensitivity and specificity than the new planter point: occiput was positive in 19/22 (86.4%) JPFS patients and 6/27 (22%) of the control group, 86.4% sensitivity, 75% specificity (positive LR of 3.46 ROC Area = 0.897 with CI 95% = 0.68 – 0.934), supraspinatus was positive in 20/22 (90.9%) JPFS patients and in 5/27 (18%) of the control group, 90.9% sensitivity, 78.6% specificity (positive LR of 4.25 (ROC Area = 0.847 with CI 95% = 0.733 – 0.962), second rib was positive in 19/22 (86.4%) JPFS patients and in 1/27 (20%) of the control group, 86.4% sensitivity, 79.5% specificity (positive LR of 3.46 ROC Area = 0.897 with CI 95% = 0.795 – 0.997), lateral epicondyle was positive in 19/22 (86.4%) JPFS and in 1/27 (3.7%) of the control group, 86.4% sensitivity, 92.9% specificity (positive LR of 12.17 ROC Area = 0.896 with CI 95% = 0.795 – 0.997), and trapezius was positive in 19/22 (86.4%) JPFS patients and 1/27 (3.7%) of the control group, 86.4% sensitivity, 92.9% specificity (positive LR of 12.17 ROC Area = 0.896 with CI 95% = 0.795 – 0.997).

Conclusion: The planter arch tender point has high sensitivity and specificity in patients with JPFS. Additionally, it presented higher specificity than other recognized tender points. Further investigations on this novel site specificity in patients with JPFS. Additionally, it presented higher specificity than other recognized tender points.

Disclosure: W. J. Spindler, None; C. Santarelli, None; A. J. Spindler, None; A. Berman, None; H. Berman, None; M. Santana, None.

A Proposed Simple 3-Variable Index for Identification of Fibromyalgia, Analogous to Classification Criteria for RA and SLE. Sung-Hoon Park1, Jung-Yoon Choe2, Seong-Kyu Kim3, Hwajeong Lee4 and Theodore Pincus5. 1Arthritis and Atoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, 2Catholic University of Daegu School of Medicine, Daegu, South Korea, 3Catholic University of Daegu, Daegu, South Korea, 4Catholic University of Daegu School of medicine, Daegu, South Korea, 5Rush university medical center, Chicago, IL.

Methods: A cumulative index that includes various quantitative data has been useful in developing classification criteria for various rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Previous reports indicate that self-report patient scores on a multidimensional health assessment questionnaire (MDHAQ) provide clues to identify patients with fibromyalgia (FM). Since the diagnosis of FM is made primarily on the basis of patient report of pain and other symptoms, a cumulative scale of quantitative patient self-report scores as well as a physician estimate of a level of FM might be useful to identify patients with FM. To analyze a simple 3-variable cumulative scale to identify patients with FM, and distinguish them from patients with RA, SLE, and anklyosing spondylitis (AS) seen in a usual care setting in Korea.

Methods: All patients seen at a Korean rheumatology setting complete an MDHAQ/RAPID3 (routine assessment of patient index data), which includes scores for physical function, visual analog scales (VAS) for pain, global status and fatigue, and a list of 60 symptoms as a checklist review of symptoms. Physicians also complete a brief ACR form which includes a 0–10 VAS physician global estimate of patient status, and 0–10 VAS subscales for inflammation, damage, and level of symptoms not explained by inflammation and damage, such as FM. Preliminary cross tabulations were performed to compare scores for MDHAQ variables in patients with FM versus RA, SLE, and AS. Based on these preliminary analyses, a 3-variable cumulative scale was developed: 1) VAS pain score of < 5 out of 10, 2) symptom checklist of ≤15 out of 60 symptoms 3) physician estimate of FM level ≥ 3 out of 10. The numbers of patients with FM, RA, SLE and AS who scored 0, 1, 2, or 3 were computed; chi square tests and receiver operator curves (ROC) were used to analyze statistical significance.

Results: Data were available concerning 32 patients with FM, 18 with AS, 17 with SLE and 277 with RA. Overall, 53% of patients with FM had scores of 2 or 3 of these criteria, compared to 5.5% with AS, 20.2% with RA and 5.8% with SLE (p = 0.001). ROC area was 0.734, with standard error of 0.047 and 95% confidence interval of 0.642 – 0.826. A score of 2, which does not require any physician data, was associated with a positive likelihood ratio for FM of 2.9, sensitivity of 53.1 and specificity of 81%, with 79% correctly classified. A score of 3 was associated with a positive likelihood ratio for FM of 1.4, with 90% correctly classified.

Disclosure: S. H. Park, None; J. Y. Choe, None; S. K. Kim, None; H. Lee, None; T. Pincus, None.
fibromyalgia have less radiographic straight neck when compared to patients with other rheumatic diseases.

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<td>Straight neck &lt;14° (%)</td>
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<td>FM according 2010 ACR criteria (%)</td>
<td>14 (100%) 6 (100%) 0 (0%) 0 (0%) &lt;0.0001</td>
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Background/Purpose: Explore crossover effects and their influence on crossover and randomized withdrawal design (RWD) studies.

Methods: We examine pregabalin crossover and RWD studies in fibromyalgia (FM), painful diabetic peripheral neuropathy (pDPN), and post-herpetic neuralgia (PHN). Data visualization methods and meta-analytic summaries are used to explore the difference in crossover effects across studies and pain types. Weekly mean pain scores are compared for 4 crossover studies of similar design, 2 in FM (studies 1165 and 1275) and 2 in pDPN (1268, 1269), for patients randomized to the pregabalin to placebo treatment sequence (Pgb - Pla) or to the placebo to pregabalin (Pla - Pgb) treatment sequence (Figure 1).

Results: In fibromyalgia crossover studies, a greater return of pain occurred following pregabalin treatment than in the pDPN studies (Figure 1). There was a differential effect of period one treatment on period two outcomes. FM crossover studies returned to a common pain level regardless of period one treatment, whereas DPN crossover studies did not return similar results hold for the pregabalin to placebo arm in the FM vs DPN RWD studies.

Figure 1. Crossover Studies in Fibromyalgia and Painful Diabetic Peripheral Neuropathy
FM: Fibromyalgia; DPN: Painful Diabetic Peripheral Neuropathy; Pain NRS: Pain Numeric Rating Scale; Pgb: Pregabalin; Pla: Placebo; Bsl: Baseline; P1: Period 1; P2: Period 2; W/O: placebo washout period.

Conclusion: The type of pain under study may affect the ability of crossover or RWD studies to determine the magnitude of treatment effect; pain type should be carefully considered when choosing among study designs for pain.


2081
Ehlers-Danlos Hypermobile (EDS-HT) Patients and Postural Instability: Another Clue to Explain Pain and Fatigue? Roland Jaussaud1, Élodie Viarnyck1, Rami Haidar2, Dorotheé Lambert2, Violaine Laurent-Noël3, and Amlène Servetzz1. 1CHU de Reims, REIMS, France, 2Cabinet d'Orthopedie-Versailles, France, 3Cabinet d'Orthopedie-Lille, France. 1CHU Reims, Reims, France, 2Hôpital Robert Debré. CHU de Reims, Reims, France.

Background/Purpose: Postural instability was found in several functional disorders including dyslexia, chronic pain and fibromyalgia. Furthermore, the link between vertical heterophoria (VH) and postural control is now clearly established. EDS-HT patients shared symptoms usually encountered in patients presenting postural instability.

Methods: Aim: To assess the presence of postural instability and the role of vertical heterophoria among patients suffering from EDS-HT.

Design of study: 30 patients meeting the Villefranche criteria for diagnosis of EDS-HT (generalized joint hypermobility, skin involvement, recuring joint dislocations, chronic joint/limb pain and positive family history) were prospectively examined. Their postural performance was compared to that of 15 healthy subjects.

Methods: To measure postural instability, we used a force platform. The surface of the center of pressure (CoP) excursions, the standard deviations of lateral (SDx) and antero-posterior (SDy) body sways and the variance of speed were recorded. The surface area was measured with confidence ellipse including 90% of the CoP positions sampled, eliminating the extreme points. Vertical heterophoria (VH) was qualitatively detected with Maddox rod. Pain was evaluated using a subjective visual analogical scale (VAS) of 10 cm validated for chronic pain. Fatigue severity scale (FSS) was used.

Results: Among the EDS-HT patients the mean VAS score was 67 mm. 84% had a FFS > 6. All these patients presented with symptoms of muscle hypertonia, disturbance of spatial location and other perception disorders. With respect to EDS-HT patients, they used more energy to stabilize postural sway during quiet upright stance than healthy subjects. The presence of vertical heterophoria was associated with a greater antero-posterior postural sway. Most of them had abnormal footprints (asymmetrical or hollow feet).

Conclusion: These data suggested that a dysfunction implicating somesthetic signals or central neurological integration could affect the balance control performance following the example of patients suffering from chronic low back pain. VH and hypermobility both or alone could be the sign or the trigger of this dysfunction. Postural instability could explained part of the symptoms of pain and fatigue in EDS-HT.

Disclosure: R. Jaussaud, None; R. Viarnyck, None; R. Haidar, None; D. Lambert, None; V. Laurent-Noel, None; A. Servetzz, None.

2082
Presence of Acrocyanosis in Patients with Joint Hypermobility. Ayhan Dinc1 and Göksal Keskin2. 1Patio Clinic, Ankara, Turkey, 2Medical School of Ankara, Ankara, Turkey.

Background/Purpose: Joint hypermobility is a common but often poorly recognized connective tissue condition with joint laxity in the absence of any hereditary systemic disease. Acrocyanosis is symmetric, painless, blue discoloration in the distal parts of the body with aggravation by cold exposure, and frequent association with local hyperhidrosis of hands and feet. Primary acrocyanosis is mostly a disease of young adults, only few cases persist into middle age.

Methods: During 18 months, a group of 350 consecutive rheumatology patients (<45 yrs. old) investigated for joint laxity and acrocyanosis. For each patient a Beighton score measured and those with a score of >4 regarded as benign joint hypermobility. For patients suffering from acrocyanosis, we qualitatively detected it with Maddox rod. Acrocyanosis was diagnosed clinically by proper history and physical examination. Other relevant clinical findings were also recorded.

Results: A total of 43 patients (F: M, 26:17) were diagnosed as hypermobility. Nearly all patients had a mild-moderate hypermobility. The mean Beighton score was 4.9±0.7. Of those patients, 19 had also acrocyanosis (44.1%). In the group lacking hypermobility (303), only 6 cases of acrocyanosis detected (0.2%). In the acrocyanosis patients, whether or not accompanied with hypermobility, average hand and foot sizes per stature are larger than those without.

Conclusion: It has been known that, patients with hypermobility may have some vascular problems, including Raynaud’s phenomenon and vari-
2083

E evaporative Dry-eye Disease and Aqueous Deficient Dry-eye Disease Associated With Fibromyalgia. William Pachas,1,2 Jack Greiner3 and Paula Olivar3, 4,5 Center for Rheumatology, Osteoporosis and Fibromyalgia, Boston, MA, 6The Boston Ocular Surface Center, Boston, MA, 7The Boston Ocular Surface Center, Boston, MA.

Background/Purpose: Fibromyalgia (FM) patients with ocular discomfort often describe symptoms characteristic of dry eye diseases, but frequently do not fulfill criteria diagnostic of Sjögren’s syndrome. Thus, ophthalmologic subjective and objective testing were performed to (1) establish the association of FM with dry eye diseases and (2) attempt to identify the type(s) of dry eye diseases associated with FM.

Methods: Consecutive patients (n = 30) meeting American College of Rheumatology criteria for FM were evaluated as part of a comprehensive rheumatological examination. Subjective evaluation employed dry eye questionnaires, Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness (SPEED). Objective tests included determination of minimum tearfilm lipid layer thickness (LLT), tearfilm osmolarity (TOSM), tearfilm breakup time (TIBUT), Schirmer tear test (STT), corneal fluorescein-staining, and meibomian gland assessment (MGA) scores.

Results: Measurements were compared with widely accepted “Normal Values” (NV). OSDI 32.38 ± 20.7 (range, 2.27–79.16) 60% lower than NV (p < 0.001); SPEED 11.38 ± 7.1 (range, 0–25.3) 47% higher than NV (p < 0.001); LLT 49.72 ± 17.2 nm (range, 28–90) 38% lower than NV (p < 0.001); TOSM 312.2 ± 14.1 μm (range, 290–341) higher than NV (p < 0.001); TIBUT 5.01 ± 3.1 sec (range, 1–15.24) 50% lower than NV (p < 0.001); STT 6.02 ± 3.9 nm (range, 0–11.5) 40% lower than NV (p < 0.001); and MGA scores 11.70 ± 5.51 (range, 4–27) lower than NV (p < 0.001).

Conclusion: Fibromyalgia patients demonstrate evidence for both evaporative and aqueous-deficient dry eye diseases. FM patients should be routinely questioned for signs or symptoms of dry eye diseases and referred for a comprehensive evaluation to determine the type(s) of their dry eye disease(s) in order to recommend appropriate treatment(s).

Disclosure: W. Pachas, None; J. Greiner, None; P. Oliver, None.

ACR/ARHP Poster Session C
Genetics, Genomics and Proteomics
Tuesday, November 18, 2014, 6:30 AM–4:00 PM

2084

Are Genetic Markers Associated with Myocardial Infarction in Patients with Early Rheumatoid Arthritis? Lisbeth Årlestig1, Petros Zamout2, Lena Innala3, Eva Freyhurst4, Solveig Wällberg Jonsson5 and Solbritt Rantanpää-Dahlqvist6.

1Institute of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, Sweden, 2Institute of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, 3Institute of Public health and clinical medicine/Rheumatology, University of Umeå, Umeå, Sweden, 4Bioinformatics Infrastructure for Life Sciences, Uppsala, Sweden.

Background/Purpose: Cardiovascular disease (CVD) are increased in patients with rheumatoid arthritis (RA). Traditional as well as disease related risk factors seem to contribute to the development.

To evaluate the impact of genetic markers for development of myocardial infarction (MI) or angina pectoris (AP) leading to coronary intervention (PTCA or CGBP) in patients with early RA in relation to inflammation and traditional risk factors.

Methods: Patients with early RA (1987 American College of Rheumatology criteria) from northern Sweden and consecutively recruited since Dec 1995 into a national register were followed prospectively for disease progression, treatment and into a register for presence of CV risk factors. Of the patients 899 had donated DNA and were analysed for the genetic markers.

The follow-up started at inclusion and ended at the first MI/ AP, death or until Dec 31 2011 by co-analysing with the national registers of hospitalization and death in Sweden using classification of diseases (ICD-9 and 10). Genetic polymorphisms were analysed using Immunochip (SNP&SEQ Technology Platform Uppsala, Sweden). Univariate Cox regression and a likelihood ratio test was adopted to find SNPs most strongly associated with MI/ AP. The potentially important (likelihood ratio p < 0.05) clinical factors were also identified using univariate Cox regression. Selected clinical factors were combined with one SNP at the time in a multivariate Cox regression model and a likelihood ratio test was adopted to assess whether the SNP added significant information to a model based on only the selected clinical factors.

Results: Analysis using the Axiom chip yielded 131 523 SNPs, whereas 44 367 independent SNPs were identified after linkage analyses. In total 795 patients are included in the statistical analyses (some are excluded due to many missing values in the genetic data). The total follow-up time was 5607 person years until first MI/ AP after RA disease onset. 52 patients had experienced a MI or AP leading to intervention. The strongest SNPs related to MI/ AP were rs241425 (p = 3.02e-06), rs2239701 (p = 8.12e-06), rs9262155 (p = 8.62e-06), rs2269706 (p = 1.43e-05), and rs222418 (p = 3.08e-05). Besides sex and age, hypertension, previous CV event, HLA-shared epitope, and oral corticosteroids were indicated as important in univariate Cox models (p < 0.05). Likelihood ratio p-values after adjusting for the clinical factors were slightly lower than in the univariate models; rs241425 (p = 1.04e-04), rs2239701 (p = 4.75e-04), rs9262155 (p = 9.20e-05), and rs222418 (p = 1.87e-04).

Conclusion: SNPs analyzed by Immunochip could be associated with MI/ AP in patients with RA unrelated to more traditional risk factors.

Disclosure: L. Årlestig, None; P. Zamout, None; L. Innala, None; E. Freyhurst, None; S. Wällberg Jonsson, None; S. Rantanpää-Dahlqvist, None.

2085

Association of Circulating miRNAs with Spinal Involvement in Patients with Axial Spondyloarthritis. Klára Prážlerová1, Markéta Fojtíková2, Sárka Foregová1, Astrid Jünger1, Steffen Gy2, Karel Pavelka1, Jiri Venkovsky1, Ladislav Senol1 and Maria Filkova1.

1Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 2Zürich University Hospital, Zurich, Switzerland.

Background/Purpose: The altered expression of miRNAs and dysregulation of their target genes has been shown to contribute to the development and maintenance of autoimmune diseases. In addition, cell-free circulating miRNAs appear promising diagnostic and/or prognostic biomarkers. Our aim was to identify circulating miRNAs in patients with axial spondyloarthritis (AxSpA) and to investigate their relationship with spinal involvement.

Methods: The study included 20 patients with non-radiographic AxSpA (nr-AxSpA) according to the ASAS criteria with sacroiliitis confirmed by MRI, 48 patients with radiographic AxSpA (with and without spinal involvement, including 5 patients with a bamboo spine), and 29 healthy controls (HC). Total RNA from plasma was isolated using phenol-chloroform extraction and equal amount of RNA was used for reverse transcription. A comprehensive analysis of miRNAs was performed using TaqMan® Low Density Array (TLDA) in 5 samples from each group. dCt method was used for relative quantification as follows: dCt = Ct(array average) - Ct(miRNA) followed by x-fold change calculation. The expression of selected miRNAs was further validated by single assays in the remaining samples and the levels of miRNAs were normalized to an average of 3 spike-in controls of C. elegans. Data were analyzed using one-way ANOVA and unpaired t-test with Welch’s correction.

Results: Out of total 760 miRNAs analysed by TLDA, 162 miRNAs were detected in a group of HC, 156 miRNAs in patients with nr-AxSpA and 110 in patients with radiographic AxSpA. All patients with AxSpA had at least 2-fold lower levels of 56 miRNAs when compared with HC. In patients with radiographic AxSpA, 72 miRNAs showed at least 2-fold decrease in comparison with nr-AxSpA. Twenty-one miRNAs were selected according to the differential expression between groups of patients and possible relationship to the pathogenesis of AxSpA for further analysis. Out of 21 selected miRNAs, 14 miRNAs were significantly lower (p < 0.05) in all patients with AxSpA compared to HC. mir-625* (p = 0.0055) and mir-222 (p = 0.045) showed significantly lower levels in patients with nr-AxSpA compared with HC. In all patients with radiographic AxSpA, 20 miRNAs were significantly lower when compared with the group of nr-AxSpA and 17 miRNAs in patients with nr-AxSpA were significantly lower (p < 0.001). Levels of these miRNAs were significantly lower (p < 0.001 for miR-24, miR-27a, miR-106a, miR-222 or miR-223 (p < 0.0001). A total of 15 miRNAs were significantly lower (p < 0.001 for miR-24, miR-27a, miR-106a, miR-222 or miR-223 (p < 0.0001).

Conclusion: The expression of miRNAs is altered in patients with AxSpA and this alteration is associated with spinal involvement. The altered miRNA expression might be used as biomarkers for monitoring disease activity and may provide important clues to the pathogenesis of AxSpA.
Conclusion: Expression of circulating miRNAs is altered in patients with AxSpA. Reduced expression of several miRNAs was associated with the degree of spinal involvement, with the lowest expression observed in patients with the bamboo spine. Given the involvement of these dysregulated miRNAs in innate immunity and new bone formation, our data suggest their role in the pathogenesis of AxSpA and potential use of circulating miRNAs as biomarkers of disease progression.

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Disclosure: K. Pražijarová, None; M. Fojtíková, None; Foretová, None; A. Jüngel, None; S. Gay, None; Pavelka, None; J. Vencovsky, None; L. Senolt, None; M. Filková, M HCR project 023728, 2.

2086

Replication of PTPRC As Genetic Biomarker of Response to TNF Inhibitors in Patients with Rheumatoid Arthritis. Antonio Gonzalez1,2, Aída Ferreiro-Iglesias2, Juan Gomez-Reino1,2 and on Behalf of Their Collaborators3. 1Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, 2Instituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago de Compostela, Spain, and 3multiple, multiple, Spain.

Background/Purpose: The use of biomarkers to predict response to the different drugs available for treating rheumatoid arthritis (RA) is a very desirable goal. However, success of the many studies already performed has been limited. Genetic studies of response to the TNF inhibitors (TNFi) have reported multiple associations. At least 14 are from relative large candidate gene studies including hundreds of patients and other 16 are from GWAS also with hundreds of patients. A couple of them, in the PTPRC and PDE3A-SLC01C1 loci, have been replicated in a second study, but none has yet been confirmed with full confidence. We aimed to replicate here the 14 genetic associations proposed in large candidate gene studies.

Methods: We analyzed the response to TNFi treatment of 755 patients with RA naïve to biologic DMARDs and of European ancestry. They have been treated with the three most common TNFi (infliximab, adalimumab, and etanercept). Their response to these drugs was evaluated either as change in DAS28 (ΔDAS28) between baseline and 3, 6 and 12 months of treatment, or as classification according to the EULAR response criteria (good + moderate responders vs. non-responders) at the same time points. The genotypes of the 14 previously associated SNPs plus the putative causal SNP at one of them were obtained with a single-base extension multiplex methodology. We considered the SNPs according to an additive genetic model in linear and logistic regression analyses, for ΔDAS28 and EULAR criteria, respectively. Baseline DAS28, gender and treatment were considered as covariates. Statistica 7.0 (Statsoft, Tulsa OK) software was used to perform these analyses.

Results: All the SNPs were successfully genotyped (call rate = 99.1%; HWE P > 0.05). Only one of the 14 loci was associated with response to TNFi. This was the PTPRC SNP rs10919563 that is a confirmed RA susceptibility locus. The RA risk allele (G) of this SNP was associated with higher ΔDAS28 at 6 months (B = 0.33, [95% CI] 0.09 to 0.57, P = 0.006) and showed a trend to association with good response as defined with the EULAR criteria (odds ratio [OR] 1.49, [95% CI] 0.94 to 2.33, P = 0.08). A second PTPRC SNP, rs6683595, very correlated with rs10919563, which is a putative causal polymorphism of this RA locus because it maps in an active regulatory region in CD4+ Treg cells showed an even stronger association: its G allele was associated with higher ΔDAS28 at 6 months (B = 0.39, [95% CI] 0.18 to 0.61, P = 0.0003) and with good response (OR = 1.56, [95% CI] 1.04 to 2.37, P = 0.03).

Conclusion: We have obtained a new replication of the association of the PTPRC RA risk locus with response to TNFi. In this way, it has become the most replicated to date of the genetic biomarkers of response to these drugs with three studies including hundreds of patients each showing consistent results. In addition, we have found stronger association with a putative causal polymorphism in this locus that pave the way for functional studies exploring its involvement in RA and its treatment.

Disclosure: A. Gonzalez, None; A. Ferreiro-Iglesias, None; J. Gomez-Reino, None; O. B. of Their Collaborators, None.

2087

Defective Regulation of L1 Endogenous Retroelements in Primary Sjogren’s Syndrome and Systemic Lupus Erythematosus: Role of Methylyzing Enzymes. Clio Mavragani1, Adriano Nezos1, Irina Sagalovskiy2, Surya V. Seshan3, Kyriakos A. Kirou4, Haralampos M. Moutsopoulos1 and Mary K. Crow2. 1School of Medicine, University of Athens, Athens, Greece; 2Hospital for Special Surgery, New York, NY.

Background/Purpose: To investigate whether deranged methylating mechanisms are involved in the inappropriate expression of LINE-1 (L1) retroelements in primary Sjogren’s syndrome (SS) and systemic lupus erythematosus (SLE).

Methods: Minor salivary glands (MSG) were obtained from 35 patients with primary SS (23 without adverse predictors for lymphoma development (SS-low risk) and 12 complicated by B-cell lymphoma (SS-lymphoma)) and 17 sicca controls (SC). Additionally, kidney biopsy specimens and PBMCs were obtained from 23 and 73 lupus patients respectively. Relative mRNA expression was quantified for full-length L1 transcripts, along with mediators of methylation. In an independent set of 22 MSG samples (8 SS-low risk, 11 SS-lymphoma and 3 SC), methylation levels of the L1 promoter were determined by bisulphite pyrosequencing.

Results: A strong positive correlation was demonstrated between L1 transcripts and gene products that mediate de novo and constitutive DNA methylation, DNA methyltransferase (DNMT3B, DNMT1), and methyl CpG binding protein 2 (MeCP2), in both SS MSG and lupus renal tissues. A significant negative correlation was observed between expression of L1 and lymphoid-specific helicase (LSH, encoded by HELLIS) in both SS MSG and SLE kidney tissues, as well as between DNMT3A transcripts and L1 expression in SLE kidney tissues and PBMCs. Reduced levels of L1 promoter methylation along with increased DNMT3B, DNMT1, and MeCP2, but reduced LSH levels were detected in SS-low risk patients compared to both SS-lymphoma and SC. The SS-lymphoma group was also characterized by a profound decrease of MeCP2 and DNMT3B compared to SC.

Conclusion: Our data support a contributory role of altered methylation mechanisms in the pathogenesis of systemic autoimmune disorders and related lymphoproliferative processes and suggest that LSH and DNMT3A should be investigated as candidate upstream mediators of decreased L1 promoter methylation and increased L1 expression.

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2088

Association of TNFAIP3 Gene Polymorphisms with the Risk for RA and Prediction of Therapy Outcome of TNF-α-Blocker Treatment. Susanne Drynda, Marietta Gloetzner and Jöern Kekow. Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany.

Background/Purpose: The TNF-α inducible protein 3 (TNFAIP3-A20) is an important regulatory protein for the inhibition of NFκB activation in TNFα and TLR pathways. It belongs to a group of genes that have been described as regulated differentially in mononuclear blood cells from patients with rheumatoid arthritis treated with TNF-α-blockers early in the course of treatment in association to the clinical outcome. Recently published studies demonstrated that sequence variations in the TNFAIP3 gene are associated with the risk for several autoimmune diseases including RA, SLE and psoriasis. It was the aim of our study to analyze the frequency of two independent SNPs (rs583522 and rs2230926 in 5’ UTR, exon 3) in the TNFAIP3 gene in CCP-antibody positive and negative RA patients and to determine their potential role as a predictive biomarker for therapy outcome of anti-TNF-α treatment.

Methods: 423 RA patients with high disease activity and 93 healthy controls were included in the study. Genotyping was performed with pre-designed TaqMan assays for rs583522 and rs2230926 in 5’ UTR reaction mixtures containing 10 ng genomic DNA. HLA-Genotyping was performed using the HLA-DRB1 Shared epitope reverse Hybridization Kit (AID GmbH, Germany). CCP-antibody levels were determined with the CCP-2 assay (Menarini, Italy). Disease activity and therapy response were assessed according to the EULAR criteria. Disease activity and therapy response were assessed according to the EULAR criteria.

Results: For the intronic SNP rs583522 (T/C) a significant lower frequency of the minor allele was observed in patients with RA compared to controls (p=0.014), no significant differences were seen in the allele frequency between CCP-antibody positive and negative RA patients nor in association to the shared epitope encoding alleles. A higher frequency of the
minor allele (G) was found in RA patients compared to controls for rs2230926 (T/G), without reaching statistical significance (p = 0.160). CCP-antibody negative patients had a higher frequency of the T/G genotype compared to CCP-antibody positive patients. In contrast to the entire RA group, the subgroup of CCP-antibody negative RA patients had a significant higher allele frequency of the minor allele compared to healthy controls (p = 0.042). Disease activity was comparable for the three genotypes of the intronic SNP. For rs2230926 a significant higher disease activity was observed in T/T genotype in contrast to T/G genotype (DA528, 5.78 ± 0.08 vs 5.07 ± 0.31, mean ± SEM). No differences were found in the genotype distribution for both SNPs between TNF-blocker responders and non-responders.

Conclusion: Our data confirm earlier reports of an association of the non-synonymous polymorphism rs2230926 in exon 3 resulting in an amino acid substitution Phe/Cys with the risk for RA, particularly for CCP-negative disease. The association of the intronic SNP rs583522 with the risk for RA has not been described before. A predictive importance of the analyzed polymorphisms for therapy outcome of TNF-blocker therapies could not be observed. Due to the low frequency of the minor allele of rs2230926 data have to be considered preliminary and confirmed in larger cohorts.

Disclosure: S. Drynda, None; M. Gloeotner, None; J. K ekow, None.

2089

The APOL1 Gene Is Not Associated with Lupus Nephritis in Individuals with Enriched Amerindian Ancestry. Julio Molineros1, Hannah Ainsworth2, Robert Kimberly3, Michelle A. Petri4, Rosalind Ramsey-Goldman4, LUIS M. Villa4, John D. Revelle4, Elizabeth E. Brown5, Swapan Nath5, Carl D. Langefeld6, Bernardo Pons-Estel on behalf of GENLES5, Gracia S. Alarcon11 and Marta E. Alarcon Riquelme1. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2Wake Forest, Winston-Salem, NC, 3University of Alabama, Birmingham, AL, 4Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, 5Northwestern University and Feinberg School of Medicine, Chicago, IL, 6University of Puerto Rico Medical Sciences Campus, San Juan, PR, 7University of Texas Health Science Center at Houston, Houston, TX, 8University of Alabama at Birmingham, Birmingham, AL, 9Wake Forest University Health Sciences, Winston-Salem, NC, 10Sanatorio Parque, Rosario, Argentina, 11Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

The APOL1 Gene is not associated with Lupus Nephritis in Individuals with Enriched Amerindian Ancestry Background/Purpose: The APOL1 gene coding variants G1 and G2 have been described to be associated with chronic renal disease and end-stage Renal Disease (ESRD) in patients of African descent with different nephropathies. The association of these genes with ESRD but not lupus nephritis (LN) per se has also been recently reported in SLE patients of African descent. A1merindian ancestry has been found to be associated with the occurrence of LN among these SLE patients from the Americas exhibiting a large Amerindian ancestral background. Our results can be ascribed to the low proportion of African ancestry within the locus.


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2090

Contribution of MTHFR Gene Polymorphisms in Sjögren’s Syndrome Related Lymphomagenesis. Sofia Fragkioudaki1, A. Diarios Nezos2, A. Ristea Papageorgiou1, Michael Voulgarelis3, Mary K. Cory4, Haralampos M. Moutsopoulos5 and Clio M avraginis6. 1School of Medicine, University of Athens, Athens, Greece, 2Hospital for Special Surgery, New York, NY.

Background/Purpose: Sjögren’s syndrome (SS) exhibits the highest susceptibility, among systemic autoimmune diseases, to non-Hodgkin lymphoma (NHL) development. Genetic instability and DNA methylation have been previously implicated in the pathogenesis of lymphoproliferative disorders. Methylene tetrahydrofolate reductase (MTHFR) is an enzyme essential in DNA synthesis and methylation pathways. Two common polymorphisms of the MTHFR gene, C677T and A1298C, have been implicated in the development of NHL, as they reduce the MTHFR enzyme activity and may affect DNA methylation and stability. The aim of this study was to investigate the possible contribution of the MTHFR C677T and A1298C polymorphisms in SS-related lymphomagenesis.

Methods: 189 SS patients without NHL, 72 SS patients with NHL (57 with MALT and 15 with non-MALT lymphoma), 160 healthy controls (HC) and 124 rheumatoid arthritis (RA) patients were genotyped for the detection of the MTHFR gene polymorphisms (C677T and A1298C) using polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP). Methylation levels of Cpg islands of the promoter of the long interspersed nuclear element 1 (LINE-1) - a marker of global methylation status – were also evaluated in DNA sequencing in genomic DNA derived from 23 salivary gland tissues from SS (10 with NHL and 13 without) patients.

Results: Non NHL SS patients had significantly reduced rates of the A1298C AC heterozygous genotype compared to both RA patients and HC (OR = 0.57, 95% CI: 0.36–0.91, p = 0.02 and OR = 0.57, 95% CI: 0.37–0.88, p = 0.01 respectively). In contrast, the prevalence of both MTHFR C677T and A1298C polymorphisms did not significantly differ between SS patients complicated by NHL compared to uncomplicated SS, RA and HC groups. Further analysis according to the lymphoma subtype revealed 67/77 T as a risk allele and the 1298 C as a protective allele for non-MALT NHL development in patients with SS (OR = 2.1, 95% CI: 0.99–4.45, p = 0.05 and OR = 0.19, 95% CI: 0.04–0.80, p = 0.01). The concomitant presence of 1298 AA and 677 TT genotype conferred an increased risk for non-MALT NHL development among SS patients (OR: 3.4, 95% CI: 1.1–10.9, p = 0.04). Of interest, an association was observed between the presence of the MTHFR 677 T but not MTHFR 1298 C allele with lower methylation levels (TT vs CT vs CC: 67.9 ± 2.2 vs 69.7 ± 2.9 vs 72.3 ± 2.1, p = 0.027, by Kruskal Wallis-test), implying methylation defects as potential underlying mechanisms in the pathogenesis of SS-related non-MALT lymphoma.

Conclusion: In the current study, we identified novel associations of MTHFR polymorphisms with non NHL SS as well as with SS complicated by non-MALT lymphoma. Preliminary data suggest that alterations of global methylation related to the presence of MTHFR 677 T variants may contribute to the pathogenesis of non-MALT lymphoma among SS patients.
2091
Plasma Microparticle Protein Features Distinctively Classify Systemic Lupus Erythematosus and Systemic Sclerosis and Their Clinical Phenotype. Ole Østergaard¹, Christoffer T. Nielsen², Line V. Iversen³, Anders A. Bengtsson⁴, Søren Jacobsen⁵ and Niels H. H. Heegaard⁶. ¹Statens Serum Institute, Copenhagen S, Denmark; ²University Hospital Rigshospitalet, Copenhagen, Denmark; ³Statens Serum Institute, Copenhagen, Denmark; ⁴Lund University, Lund, Sweden ⁵Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; ⁶Odense University Hospital, Odense, Denmark.

Background/Purpose: Plasma microparticles (MPs) comprise a heterogeneous population of submicron membrane vesicles shed from the cell surface both constitutively and as a consequence of pathological processes. We isolate MPs from well-characterized patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and from healthy controls (HCs) for thorough comparative analysis at the proteome levels.

Methods: MPs were isolated from 1 mL platelet poor citrate plasma by repeated ultracentrifugation using a standard protocol (1) before in-solution digestion with trypsin followed by analysis by tandem mass spectrometry for protein identification and quantification (2). In total, MPs from 45 SLE patients and 37 SSc patients (all fulfilled the relevant American College of Rheumatology Disease Criteria) were analyzed and compared to MPs from 35 age- and sex-matched healthy controls.

Results: More than 1000 proteins were identified from each group. Univariate statistics, hierarchical clustering, and principal component analysis were applied to analyze the protein intensities to search for disease classifiers. Samples from SLE patients showed increased levels of complement factors, immunoglobulin, galectin-3-binding protein, CDS-like protein and decreased levels of organellar and membrane associated proteins. In addition, proteins intensities from C1q, G3BP and 14-3-3 showed correlation with disease levels of organellar and membrane associated proteins. In addition, proteins immunoglobulin, galectin-3-binding protein, CD5-like protein and decreased levels of tropomyosin-1 and various mitochondrial proteins. Principal component analysis on the centered dataset could differentiate the SLE samples from the NOR and SSc samples.

Conclusion: In-depth proteomic characterization of plasma MPs in SLE and SSc supports their putative role in disease pathology, immune regulation and as biomarkers.


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Background/Purpose: The use of objective biomarkers of clinical disease characteristics such as disease activity would be beneficial in informing patients, physicians and payers. Recently, a number of potential biomarkers for RA disease diagnosis, prognosis and activity have been described in the literature. However, the majority of these have not been validated in independent cohorts.

Methods: We assessed the performance of available biomarkers of RA disease as well as developed and validated novel tests using samples from multiple cohorts of severe to RA patients. Serum samples from subjects enrolled in two Phase III studies (GO-FURTHER and GO-SAVE; clinicaltrials.gov - NCT00973479 and NCT01004432) and a Phase II study (NCT00718718) were obtained at multiple timepoints. Using samples from the GO-FURTHER (NCT00973479) cohort we evaluated commercially available correlates of disease activity as well as developed novel molecular readouts of disease activity.

Results: We were able to develop two serum-based alternatives to DAS28-CRP score with similar performance using both informed and inclusive approaches to protein selection. The two tests were developed using a set of proteins profiled via ELISA; and a highly multiplexed (SomaLogic) proteomic platform. The tests had consistently good performance in samples from cross-validation runs and samples from same subjects left out of the modeling step. We have also observed similar or better performance in patients enrolled in independent cohorts coming from other two clinical trials and additional replication is underway.

Conclusion: Validation of objective biomarkers of clinical disease state is important for advancing the evaluation and comparison of novel therapeutics in RA.


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Improvement of Rituximab Response Prediction in Rheumatoid Arthritis Via Correction for Prednisone-Related Suppression of Type I Interferon Response Gene Expression. Tamarah D. de Jong¹, Saskia Vossalam², Marjo Helen Blits³, Gertjan Wolbink³, Michael T. Nurmohamed³, Connie van der Linden³, Gerit A. Ansar³, Alexander E. Voskuyl³ and Cornelis L. Verwei³. ¹VU University Medical Center, Amsterdam, Netherlands; ²Jan van Breemen Research Institute Reade, Amsterdam, Netherlands.

Background/Purpose: Elevated type I IFN response gene (IRG) expression has been described to be clinically relevant in predicting the non-response to rituximab in rheumatoid arthritis (RA) patients. Interference between glucocorticoids (GCs) and type I IFN signaling has been demonstrated in vitro. Since the use and dose of oral GCs is highly variable among patients prior to the start of treatment with rituximab, we aimed to determine what the effect of GC usage is on the IRG expression in relation to the clinical response to rituximab.

Methods: The study was performed in two independent cohorts of established RA patients (n=32 and n=182) and a third cohort of 40 established RA patients that were candidates for rituximab therapy, recruited from the VU University medical center and the Jan van Breemen Institute Reade in Amsterdam. All patients fulfilled the revised American College of Rheumatology (ACR) 1987 criteria for the diagnosis of RA. In all patients, peripheral blood gene expression of 8 IRGs was determined by microarray or multiplex quantitative (q)PCR and an IFN-score was calculated. GC use consisted of oral prednisone in doses varying from 2.5–10mg/day in 19%, 29% and 70% of the patients in the three cohorts, respectively. The clinical response to rituximab was determined after 6 months of therapy based on the change in 28 joints Disease Activity Score (ΔDAS28); patients with ΔDAS28>2.1 were considered responders. The IFN score was tested for its predictive value using Receiver Operating Characteristics (ROC) curve analysis in the patients who started with rituximab (n=40).

Results: In all three cohorts, we consistently observed suppression of the IFN-score in patients using prednisone (PREDN) compared to patients that were not using prednisone (PREDN'). No clinical differences were observed between PREDN' and PREDN patients. The suppression of IFN-score appeared to be dose-dependent as it was most pronounced in the highest dose range (10mg/day). In the rituximab cohort, separate ROC analysis on PREDN patients alone revealed improved prediction of non-response to rituximab by baseline IFN-score with an AUC of 0.969 compared to 0.848 when analyzed in all patients, whereas prednisone use itself had no predictive value in this cohort. Using a subgroup-specific cutoff of the IFN-score in the PREDN' and PREDN groups the sensitivity increased from 41% in all patients up to 88% in the PREDN group, combined with a specificity of 100%.

Conclusion: Prednisone use in RA patients causes suppression of IRG expression. Rituximab response prediction based on the IFN-score at baseline could be considerably improved when prednisone use is taken into account.

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Deep Sequencing Reveals Differential RNA Expression during Malignant Transformation in Major Salivary Glands in a Mouse Model of Sjögren's Syndrome. Kaiyu Jiang1, Long Shen2, Zihua Hu3, Julian Ambrus4 and James Jarvis5. 1The University at Buffalo, Buffalo, NY, 2SUNY at Buffalo, Buffalo, NY, 3University of Buffalo, Buffalo, NY, 4University Of Buffalo, Buffalo, NY, 5SUNY Buffalo School of Medicine, Buffalo, NY.

Background/Purpose: Sjögren’s syndrome (SS) is a chronic autoimmune disease of unknown etiology that targets salivary and lacrimal glands and may be accompanied by multiorgan systemic manifestations. To further the understanding of immunopathology associated with SS and identify potential biomarker loci, we examined the expression of salivary glands in a mouse models of Sjögren’s syndrome through disease progression.

Methods: We isolated RNA from salivary glands of interleukin-14 alpha-transgenic mouse, a model of SS, at 3 different disease stages: pre-autoimmune, autoimmune and malignant. RNA samples were prepared for sequencing using the Illumina TruSeq RNA prep kit. Sequencing was performed using the Illumina Hiseq 2500. The fast pass reads were mapped to the genome (NCBI/bUILD 37.) using TopHat (version 2.0.4). Probable transcripts were assembled using Cufflinks (version 2.0.2), and differential expressed transcripts were determined using DESeq. Fold change (FC) calculations were obtained using the log2(FPKM) ratio, where FPKM is the fragments per kilobase of exon model per million mapped fragments.

Results: Salivary glands RNA’s demonstrated disease-stage specificity. For example, when we compared autoimmune to pre-autoimmune stages, there were 26 DE genes (10 down-regulated, 16 up-regulated) that demonstrated a 2.46 fold change or greater when we compared malignant vs pre-autoimmune. Ingenuity pathway analysis demonstrated that the DE genes are associated with cancer, development disorders, hereditary disorder, ophthalmic disease, organ injury and abnormalities, and reproductive system disease (e.g. GSK3A, KRT12, KRT34, KRT36, KRTAP9-4, NEURD6, OAS2, PRDM5, RHPN2, TPC11). Sixteen DE genes, including type IFN responsive salivary OA52, were common to the autoimmune to pre-autoimmune and the malignant to pre-autoimmune comparisons. Further evidence that the 16 DE genes, which expression are up-regulated associated disease severity, i.e. gene expression level in malignant is higher than in autoimmune; and in autoimmune higher than in pre-autoimmune.

Conclusion: The sensitivity and dynamic range of RNASeq allow a detailed view of salivary glands transcriptome. Multiple RNA transcripts show disease-state specificity, suggesting that they may be directly involved in pathogenesis. These finding are expected to lead to new insights into SS pathogenesis and biologic processes leading to SS-associated malignancy.

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Two Novel Serum Urate Levels Associated Genetic Loci Identified By GWAS In European Were Confirmed in Chinese Han Population. Minhui Hua1, Wenfeng Tan2 and Miaojia Zhang3. 1the first affiliated hospital with Nanjing medical university, nanjing, China, 2THE FIRST AFFILIATED HOSPITAL OF NANJING MEDIC, NANJING, China, 3the first affiliated hospital with Nanjing medical university, nanjing, China.

Background/Purpose: Previous GWAS have identified four novel loci (SNP rs11264341, rs6770152, rs2941484 and rs7224610) significant with serum urate levels in European. Here, we further assess the association of these 4 loci in the phenotypic expression of hyperuricemia in Chinese Han population.

Methods: A total of 1341 unrelated participants (701 hyeruricemia cases and 640 healthy individuals) were enrolled into our study. All individuals of this study participated from Jiangsu and Anhui Province. DNA samples were genotyped using TaqMan probes that specifically target the alternate alleles. We used $chi^2$-test to determine whether the genotypes of cases and controls of all SNPs deviated from Hardy-Weinberg equilibrium. Differences in allele frequencies between dichotomous traits were calculated employing the same method. Differences in continuous variables between groups were calculated using a two-tailed unpaired t-test. Power analysis was carried out using QUANTO 1.2.

Results: SNP rs11264341 and rs7224610 were newly discovered susceptible loci in mainland Chinese Han hyperuricemia population. The distributions of SNP rs11264341 and rs7224610 were significantly different in hyperuricemia participants and healthy controls. The study also successfully confirmed the association of SNP rs11264341 and rs7224610 with hyperuricemia ($p<0.05$) in Chinese Han population. C-allele in SNP rs11264341 seemed to be a risk factor in the influence of serum uric acid level. C-allele in SNP rs7224610 played a role of protection in the mean serum urate concentration ($p<0.05$).

Conclusion: This study confirmed 2 newly SNP rs11264341 and SNP rs7224610 were significant associated hyperuricemia susceptibility in Chinese Han and the genetic variation of these two SNPs could affect the serum urate concentration in Chinese Han population.

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Background/Purpose: Metabolomics is an emergent research field within the omics sciences aimed at characterizing the metabolome in complex biological samples. It provides a powerful approach to identify physiopathological processes and metabolites that can be useful biomarkers in clinically relevant applications. The present study represents the first metabolomic analysis on a large cohort including multiple immune-mediated inflammatory diseases (IMIDs). Its objective is the identification of diagnostic and activity biomarkers through the analysis of the whole urine metabolome of 6 IMIDs.

Methods: Proton nuclear magnetic resonance (1H-NMR) data of urine samples was acquired among 6 IMID cohorts (n = 200 Spanish patients per cohort) including: rheumatoid arthritis (RA), psoriasis (PS), psoriatic arthritis (PA), Crohn's disease (CD), ulcerative colitis (UC) and systemic lupus erythematosus (SLE). Each IMID cohort was selected in order to include low and high activity patients according to the consensus activity index of each disease. Distributions of sex, age, extraction time and fasting time were matched between these cohorts to avoid false positive associations due to confounding epidemiological factors. The statistical analysis identified 45 metabolic peaks significantly associated (P-value < 1E-4) in at least one of the performed disease diagnostic or activity tests (Figure 1). When analyzing each IMID cohort separately, RA, CD and UC obtained the largest number of diagnostic biomarker candidates: n = 27, n = 18 and n = 21 respectively. Interestingly, CD and UC shared common metabolic disturbances although differential biomarkers between them were also identified. PS and PA showed a little impact on their common metabolic disturbances although differential biomarkers between diseases (IMIDs). Its objective is the identification of diagnostic and activity relevant applications. The present study represents the first metabolomic analysis within the omics sciences aimed at characterizing the metabolome in complex disease systems important for the production of pro-inflammatory cytokines such as interleukin-(IL)-1β and IL-18. Cardiovascular disease is over-represented in patients with rheumatoid arthritis (RA), and chronic inflammation is believed, at least partly, to underlie this circumstance. Recent studies have suggested that the NLRP3 inflammasome influences both the severity of RA and development of atherosclerosis. NLRP3-Q705K and CARD8-C10X are functional polymorphisms which have been shown to influence inflammasome function, and to associate with plasma IL-1β levels in healthy individuals. Also, a number of reports have described synergistic effects between these polymorphism. Therefore, we sought to determine whether NLRP3-Q705K and CARD8-C10X influence the risk of cardiovascular disease (CVD) in patients with RA.

Methods: The incidence of CVD was assessed in 522 patients with established RA fulfilling the 1987 ACR criteria by a retrospective survey of medical records in combination with a 6 year prospective follow-up. CV events were defined as myocardial infarction (MI), severe verified angina pectoris treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention, or stroke/transient ischaemic attack (TIA). NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

Results: From the onset of RA to the 6-year follow-up, 121 patients were recorded as undergoing a CV event(s): 74 had suffered an MI, 20 had angina pectoris with intervention and 50 experienced a stroke/TIA. Carriage of the minor allele of NLRP3-Q705K was associated with an increased risk of a CV event(s): 74 had suffered an MI, 20 had angiography pectoris with intervention and 50 experienced a stroke/TIA. Carriage of the minor allele of NLRP3-Q705K was associated with an increased risk of a CV event(s): 74 had suffered an MI, 20 had angiography pectoris with intervention and 50 experienced a stroke/TIA. NLRP3-Q705K and CARD8-C10X genotypes were evaluated in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

Conclusion: Genetic variants of the NLRP3 inflammasome are associated with the risk of stroke/TIA, but not of MI/angina pectoris treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention, or stroke/transient ischemic attack (TIA). NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

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Genetic Variants of the NLRP3 Inflammasome Are Associated with Stroke in Patients with Rheumatoid Arthritis. Alf Kastbom1, Lisbeth Årlestig2 and Solveit M. Rantapää-Dahlqvist3. 1Linköping University, Linköping, Sweden, 2Umeå University, Umeå, Sweden.

Background/Purpose: Inflammasomes are intra-cellular protein complexes important for the production of pro-inflammatory cytokines such as interleukin-(IL)-1β and IL-18. Cardiovascular disease is over-represented in patients with rheumatoid arthritis (RA), and chronic inflammation is believed, at least partly, to underlie this circumstance. Recent studies have suggested that the NLRP3 inflammasome influences both the severity of RA and development of atherosclerosis. NLRP3-Q705K and CARD8-C10X are functional polymorphisms which have been shown to influence inflammasome function, and to associate with plasma IL-1β levels in healthy individuals. Also, a number of reports have described synergistic effects between these polymorphism. Therefore, we sought to determine whether NLRP3-Q705K and CARD8-C10X influence the risk of cardiovascular disease (CVD) in patients with RA.

Methods: The incidence of CVD was assessed in 522 patients with established RA fulfilling the 1987 ACR criteria by a retrospective survey of medical records in combination with a 6 year prospective follow-up. CV events were defined as myocardial infarction (MI), severe verified angina pectoris treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention, or stroke/transient ischaemic attack (TIA). NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

Results: From the onset of RA to the 6-year follow-up, 121 patients were recorded as undergoing a CV event(s): 74 had suffered an MI, 20 had angina pectoris with intervention and 50 experienced a stroke/TIA. Carriage of the minor allele of NLRP3-Q705K was associated with an increased risk of a CV event(s): 74 had suffered an MI, 20 had angina pectoris with intervention and 50 experienced a stroke/TIA. Carriage of the minor allele of NLRP3-Q705K was associated with an increased risk of a CV event(s): 74 had suffered an MI, 20 had angina pectoris with intervention and 50 experienced a stroke/TIA. NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

Conclusion: Genetic variants of the NLRP3 inflammasome are associated with the risk of stroke/TIA, but not of MI/angina pectoris treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention, or stroke/transient ischemic attack (TIA). NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

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Methods: Psoriasis patients were followed prospectively beginning in 2006, and were assessed yearly by a rheumatologist for the presence of PsA. Psoriasis patients who developed PsA were termed ‘converters’, and serum samples were taken at baseline from all and again at PsA diagnosis from a subset of converters. A genetic and sex-matched patients who did not develop PsA over the same duration of psoriasis were termed ‘non-converters’. Serum CXCL10, IFNA2, IL-17A, IL-23, and TRAIL were measured using a multiplexed microsphere-based assay on the Luminex 200 platform. Protein levels were compared between samples taken before and after PsA diagnosis by paired t-test, and between converters and non-converters by logistic regression.

Results: Forty-six psoriasis patients developed PsA. At baseline, these converters were 54.3% males, with a mean age of 46.1 ± 13.0 years, mean psoriasis duration of 25.5 ± 14.9 years, mean age at psoriasis onset of 20.9 ± 16.5 years, and mean PSAS of 7.0 ± 7.2. Converters were compared to 46 non-converters who were 50% males, with a mean age of 45.5 ± 12.3 years, mean psoriasis duration of 27.5 ± 16.0 years, mean age at psoriasis onset of 18.9 ± 16.3 years, and mean PSAS of 6.3 ± 6.1. Candidate biomarkers were first tested in half of the converter and non-converter samples (discovery cohort), then were validated in the remaining samples. In the discovery cohort, CXCL10 was significantly elevated in baseline samples from converters compared to non-converters (OR = 1.6, 95% CI 1.2-2.2, p = 0.005). TRAIL was also elevated in converters at baseline (OR = 1.0-0.95 CI 1.0-1.1, p = 0.05) however it was not independent of CXCL10 in multivariate analyses. IFNA2, IL-15, IL-17A, and IL-23 were below the detectable range in several samples and were not significant. CXCL10 remained significantly elevated (OR = 1.3, 95% CI 1.1-1.5, p = 0.003) in a combined analysis of the discovery and validation cohorts. Twenty-three converters had samples taken at both baseline and at PsA diagnosis. Although mean CXCL10 level was high in baseline samples, it declined significantly following PsA onset from 932 ± 458 pg/ml to 543 ± 310 pg/ml (p < 0.001), which is not significantly different from the mean CXCL10 levels observed in non-converters (421 ± 216 pg/ml, p = 0.06).

Conclusion: We demonstrated that CXCL10 was elevated in the serum of psoriasis patients who later developed PsA, but following PsA onset returned to levels closer to those observed in psoriasis patients who did not develop PsA. Further studies are needed to elucidate the dynamics of the serum CXCL10 levels in the progression from psoriasis to PsA, and to determine how well CXCL10 levels indicate PsA risk in psoriasis patients.

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Activation of NFκB Pathways in Sjögren’s Syndrome Related Lymphomagenesis: Role of the His159Tyr Mutation of the BAFF-R Receptor.

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Background/Purpose: Sjögren’s Syndrome (SS) bears the highest risk for lymphoma development among all autoimmune diseases. A growing body of evidence suggests activation of NF-κB pathways as a critical step in the pathogenesis of both SS and B-cell non Hodgkin’s lymphomas (NHL), the major type of SS-related lymphomas. The mutation His159Tyr of the BAFF-R receptor has been found to confer increased risk in patients with NHL through activation of the NF-κB pathway. The aim of the current study was to evaluate the contribution of NF-κB pathways activation in SS related lymphomagenesis and explore the potential role of the His159Tyr BAFF-R mutation.

Methods: Quantitative gene expression of both NFκB1 and NFκB2 transcripts was measured by real-time PCR in peripheral blood (PB) derived from 31 SS, 13 SS-lymphoma and 30 healthy controls (HC), in isolated B cells from 2 SS, 6 SS-lymphoma and 5 HC as well as in minor salivary gland tissues (MSG) tissues from 31 SS, 10 SS-lymphoma and 17 sicca controls (SC). The BAFF-R His159Tyr mutation was evaluated in 247 SS patients (177 non lymphoma and 70 SS-lymphoma patients), 145 systemic lupus erythematosus (SLE) patients, 101 rheumatoid arthritis (RA) patients and 180 healthy controls (HC), by PCR-RFLP and PCR-sequencing.

Results: NFκB2 transcripts were significantly upregulated in the PB, MSG tissues and isolated B cells derived from SS patients complicated by lymphoma compared to HC in PB and B-cells, and to both SS-non lymphoma patients and SC in MSG tissues. At PB level, an opposite pattern was observed in regard to NFκB1 transcripts; they were found to be significantly reduced in SS patients complicated by lymphoma compared to the HC group. As a result, NFκB2/NFκB1 ratio was significantly increased in the peripheral blood from SS patients complicated by lymphoma compared to both SS and SC with an area under the receiver operating characteristic (ROC) curve of the NFκB2/NFκB1 being 0.804, p = 0.002, 95%CI (0.670–0.938). In regard to His159Tyr BAFF-R mutation, we observed an increased prevalence in SS patients compared to HC [17 out of 247 (6.9%) vs 3 out of 180 (1.7%), p = 0.011]. No such statistically significant difference was found among SS, SLE and RA groups (6.9% vs 3.5% and 3% respectively, p-values: 0.05 in all comparisons). Both SS subgroups exhibited significantly higher frequencies of the His159Tyr BAFF-R mutation compared to HC (SS-lymphoma: 8.6% and SS-non lymphoma: 6.2% vs 1.7% in HC). When we stratified the SS-lymphoma subgroup according to the lymphoma subtype and the age of SS onset, the His159Tyr BAFF-R mutation was detected in 71.4% of patients with mucosa associated lymphoid tissue (MALT) NHL and an age of SS onset between 31–40 years old, conferring an 147.5 fold increased risk compared to HC (95% CI: (20.0–1087.5, p = 0.0001)).

Conclusion: Taken together, our data suggest activation of alternative NFκB pathways as a central pathogenic event in the malignant transformation in the setting of SS, with mutation of the BAFF-R receptor being a main contributor particularly in MALT patients with an SS onset at the fourth decade of life, though other concomitantly operating mechanisms cannot be excluded.

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Epigenetic Study of Advanced Ankylosis in Patients with Ankylosing Spondylitis.

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Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory spinal disease characterized by ankylosis of the spine. A subset of patients develops significant ankylosis resulting in mobility issues. In this pilot study, we hypothesized that epigenetic modifications may account for differences in the degree of ankylosis of the axial spine.

Methods: AS patients satisfying the New York criteria with advanced ankylosing (characterized clinically with spinal flexion) and radiographically with at least 4 contiguous ankylosed vertebrae were categorized as advanced ankylosis. Control AS patients had normal posture on clinical evaluation and had absence of syndesmophytes on plain radiographs. All patients were Caucasians of Northern European Ancestry. Genome-wide DNA methylation profiling was performed on the blood DNA samples from 23 AS patients with advanced ankylosis and 25 patients with no syndesmophytes. The profiling was performed using Illumina HumanMethylation450K Beadchips, which measures ~480,000 different CpG sites per sample and covers 98% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: A advanced ankylosis patients were predominantly males (22/23), with mean of disease onset at age 21.9 years and age at time of assessment (ankylosis) was 43.72. Meanwhile, AS patients with no syndesmophytes were predominantly males (24/25), with mean of disease onset at age 24.6 years and age at time of assessment was 44.1 years. Methylation data were normalized using BM10 method and no batch effects were detected by PCA analysis. Methylation analysis was performed on 382,232 autosomal CpG sites after quality controls. One outlier was identified and excluded in the subsequent analysis. Analysis revealed 100 locations where there was a difference between patients with and without spinal ankylosis. The three locations that differentiated the most included CpG sites in KIAA0319 (hypomethylated) (p = 1.7x10^-3); JAKMIP3 (p = 6.4x10^-5) and LGY2 (p = 9.6x10^-5). Based on functional relevance to AS pathogenesis, particularly antigen presentation, cytokine signalling, and bone remodeling, 5 candidate genes (4 hypomethylated; 1 hypermethylated) emerged: GPC5 (beta diff = -0.222; p = 0.006), SMDA3 (beta diff = -0.16664; p = 0.047), AKAP11 (beta diff = -0.177; p = 0.007), MATN4 (beta diff = -0.119; p = 0.008), and NLRC5 (beta diff = -0.11542; p = 0.052).

Conclusion: These preliminary results demonstrate that the global DNA methylation pattern in advanced AS differs from AS patients with no spinal damage. High priority candidate genes identified in this study warrants further validation.
A Tissue-Specific lncRNA in the TRAF1-C5 Risk Locus As a Putative Cis-Regulator, Bridging Genetics and Disease.

Methods: We performed knockdown of the intergenic region using shRNA.

Results: Using expression quantitative trait loci (eQTL) datasets, we observed an association between the risk allele and expression of TRAF1 and C5 at the mRNA level in various blood-related cell types. As part of an underlying mechanism we identified a novel large non-coding RNA intergenic of TRAF1 and C5 (CST1-lincRNA). The lincRNA is transcribed in the same orientation as TRAF1 and C5 by RNA polymerase II, is highly transcribed in liver, and its expression is rapidly induced in different immune cells by specific immune stimuli. Expression of CST1-lincRNA correlated with either C5 or TRAF1 expression in a tissue specific manner. In addition, knockdown of the intergenic transcript in a hepatocyte cell line resulted in decreased C5 levels.

Conclusion: Together our data support the involvement of a novel lincRNA in regulating C5 and TRAF1 expression. We propose that this lincRNA, which is fully located within the associated region, is responsible for the RA associated altered RNA levels of TRAF1 and C5 and plays a role in RA susceptibility.

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A Tissue-Specific lncRNA in the TRAF1-C5 Risk Locus As a Putative Cis-Regulator, Bridging Genetics and Disease.


Background/Purpose: In the last decade genome wide association studies (GWAS) have identified genetic polymorphisms that associate with Rheumatoid Arthritis (RA). However, the way these genetic regions contribute to disease remains ill defined. We previously identified the TRAF1-C5 locus as a predisposing risk factor to the development of RA. In the present study we investigated functional consequences of this risk locus.

Methods: We fine-mapped likely causal variants by querying Eqt1 datasets and identified a strong signal between TRAF1 and C5. We measured by RT-PCR the intergenic region in different tissue panels. We performed knockdown of the intergenic region using shRNA.

Results: Using expression quantitative trait loci (eQTL) datasets, we observed an association between the risk allele and expression of TRAF1 and C5 at the mRNA level in various blood-related cell types. As part of an underlying mechanism we identified a novel large non-coding RNA intergenic of TRAF1 and C5 (CST1-lincRNA). The lincRNA is transcribed in the same orientation as TRAF1 and C5 by RNA polymerase II, is highly transcribed in liver, and its expression is rapidly induced in different immune cells by specific immune stimuli. Expression of CST1-lincRNA correlated with either C5 or TRAF1 expression in a tissue specific manner. In addition, knockdown of the intergenic transcript in a hepatocyte cell line resulted in decreased C5 levels.

Conclusion: Together our data support the involvement of a novel lincRNA in regulating C5 and TRAF1 expression. We propose that this lincRNA, which is fully located within the associated region, is responsible for the RA associated altered RNA levels of TRAF1 and C5 and plays a role in RA susceptibility.

Disclosure: T. Messemeker, None; R. Marques, None; T. Huizinga, None; A. Adriaans, None; A. Bakker, None; A. Berendsen, None; N. Daha, None; R. E. M. Toes, None; H. Mikkers, None; F. Kurreeman, None.

ACR/ARHP Poster Session C
Health Services Research

Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2103

Benefits of Early Onset of DAS28 (CRP) <2.6 Soon vs Late. To control for differences in baseline covariates, generalized linear models were used for continuous outcomes of HAQ, SF-12, EQ-SD and PHQ-9; logit models were used for categorical outcomes of resource use. Covariates in the multivariate analysis included baseline demographics, duration of RA disease, smoking status, baseline disease status, and treatment.

Results: 417 pts with RA were included in the current analysis: 151 (36.2%) were ‘DAS28 <2.6 Soon’ and 266 (63.8%) were ‘DAS28 <2.6 Late’. At baseline, pts in the two groups were similar, respectively, in sex (33 vs 64% females), mean age (SD) (54.2 (12.7) vs 58.3 (13.0) yrs) and never smoked status (53.0% vs 48.9%). Fewer pts in the ‘DAS28 <2.6 Soon’ group were on biologic DMARDs than in the ‘DAS28 <2.6 Late’ group (31.1% vs 38.7%, respectively). Pts in the ‘DAS28 <2.6 Soon’ group had significantly better MHAQ and QoL, as well as fewer hospitalizations, DME use and ER visits in univariate analysis than the ‘DAS28 <2.6 Late’ group. Similar findings for all outcomes, except hospitalization/ER visits, were observed in multivariate analysis (see table).

Table: Difference in Outcomes at 1 year and 2 years in Patients Attaining DAS28 <2.6 Soon vs Late

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1-year post evaluation Mean difference between DAS28 &lt;2.6 Soon vs Late</th>
<th>p-value</th>
<th>2-year post evaluation Mean difference between DAS28 &lt;2.6 Soon vs Late</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>0.127</td>
<td>0.003</td>
<td>0.097</td>
<td>0.0213</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>Not available</td>
<td>-</td>
<td>3.84</td>
<td>0.0034</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>Not available</td>
<td>-</td>
<td>1.16</td>
<td>0.035</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>0.057</td>
<td>0.001</td>
<td>0.036</td>
<td>0.0244</td>
</tr>
<tr>
<td>Odds ratio for DAS28 &lt;2.6 Soon vs Late</td>
<td>1.057</td>
<td>0.001</td>
<td>1.036</td>
<td>0.0244</td>
</tr>
<tr>
<td>DME use</td>
<td>0.55</td>
<td>0.32-0.92</td>
<td>0.49</td>
<td>0.26-0.92</td>
</tr>
<tr>
<td>ER</td>
<td>1.17</td>
<td>0.34-4.03</td>
<td>1.52</td>
<td>0.40-6.88</td>
</tr>
</tbody>
</table>

Conclusion: Pts achieving LDA within 1 year benefit more (i.e. more improvement in HAQ and QoL outcomes and lower DME use during follow-up) vs those attaining LDA later. Programs geared towards earlier achievement of guideline targets can improve overall clinical and economic outcomes in RA.

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; S. Joo, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; H. Kawabata, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; M. Banerjee, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; M. Frits, None, C. Iannacoane, None, N. Shadbick, AbbVie, Amgen, Genentech, 2, BMS, UCB, Crescendo Biosciences, 9; M. Weiblatt, BMS, Crescendo Bioscience, UCBB, AbbVie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2.

2104

Effectiveness of a Workplace Integrated Care Intervention on Work Productivity in Workers with Rheumatoid Arthritis.

M. ythe van Vlisteren 1, Cécile Boot 2, Dirkjan van Schaardenburg 2, Romy Steenberk 3, A.E. Voskuyl 4 and Johannes Anema 5. 1Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands, 2Rade, Amsterdam, Netherlands, 3body@Work, Research Center Physical Activity, Work and Health, TNO-VU University Medical Center, Amsterdam, Netherlands, 4VU University Medical Center, Amsterdam, Netherlands, 5Research Center for Insurance Medicine A M C-UUM CG-UW-VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease with a profound impact on a person’s working life. Besides permanent work disability and sick leave, at-work productivity is often impacted by RA. It was shown that reduced at-work productivity has the greatest impact on costs for RA patients, followed by wage loss from stopping or changing jobs, decreased hours, and finally missed work days (absenteeism). At-work productivity decreases when a person is present at work, but is limited in meeting work demands. The Care for Work intervention program is a multidisciplinary intervention with the aim to improve at-work productivity. The intervention program consists of integrated care, coordinated by a clinical occupational physician, and a participatory workplace intervention, coordinated by an occupational therapist. The intervention was evaluated in a randomized controlled trial (RCT) which includes 113 participants.

Objectives: To determine the effects of the intervention program on work productivity, work instability, and supervisor support after 6 months of follow up in workers with rheumatoid arthritis compared to usual care.

Methods: This study is an RCT. Participants were RA patients who are involved in paid work for at least 8 hours per week, recruited from outpatient clinics of rheumatology. Outcome measures were at-work productivity

Tuesday, November 18
2105

Nonsurgical Treatment Patterns in Patients with Chronic Spinal Cord Injury. Brian Le1, Monique Bethel1, Lauren Bailey2, Frances Weaver3, Stephen Burns3, Jelena Svircev2, Michael Heggeness4 and Laura Carbone5.

Background/Purpose: Sublesional loss of bone mineral density is a common complication in patients with chronic spinal cord injury (SCI) putting them at high risk for low-impact fractures. Fracture management in patients with SCI is predominantly nonsurgical. However, to our knowledge, there are no large scale studies which report which nonsurgical procedures are most commonly used. The purpose of this study is to evaluate the distribution of nonsurgical treatments at different fracture sites in patients with SCI.

Methods: Males with chronic, traumatic SCI were identified from the Veterans Administration Spinal Cord Dysfunction data from fiscal years 2002-2007. From this population, patients with incident fractures were identified, excluding fractures due to external (“E-coded”) and pathologic fractures. Current Procedural Terminology (CPT) codes for nonsurgical treatments of fractures were collected and subsequently categorized into four categories: splints, casts, closed reduction without internal fixation, or “other.” The “other” category included knee immobilizers, walking boots, and other orthotic devices. These CPT codes were identified within six weeks following an incident upper extremity, lower extremity or unspecified fracture site. Differences in medical treatment modality were determined among fracture locations.

Results: 1,453 males with chronic traumatic SCI with non-traumatic and non-pathologic incident fractures were identified from 33,452 male SCI patients. 388 CPT codes for nonsurgical treatments of fracture were identified within 6 weeks post-fracture for 262 unique fractures. Fracture sites were grouped by number and location: single upper extremity, single lower extremity, single unspecified or multiple. Among fracture sites, there were significant differences among the types of nonsurgical treatments for single upper extremity fractures (P = 0.017). Among single upper extremity fractures, forearm fractures were most frequently casted; carpal and metacarpal fractures, splinted; and phalangeal fractures, treated with closed reduction without internal fixation, or “other.” Among multiple fractures, “other” outnumbered all other treatment modalities.

Conclusion: There are a number of different nonsurgical treatments done for single upper extremity, single lower extremity, single unspecified, and multiple fractures in men with chronic SCI.

Acknowledgements: This material is based upon work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development and the Rheumatology Research Foundation, Ephraim P. Engleman Resident’s Preceptorship Award.

Disclaimer: This work does not reflect the views of the Veterans Health Administration or the United States government.

Disclosure: B. Le, None; M. Bethel, None; L. Bailey, None; F. Weaver, None; S. Burns, None; J. Svircev, None; M. Heggeness, None; L. Carbone, None.

2106

Surgical Compared with Nonsurgical Management of Fractures in Men with Chronic Spinal Cord Injury. Monique Bethel1, Lauren Bailey2, Frances Weaver3, Brian Le1, Stephen Burns3, Jelena Svircev2, Michael Heggeness3 and Laura Carbone5.

Background/Purpose: Patients with a chronic spinal cord injury (SCI) develop osteoporosis and are at high risk for fracture. However, there is limited information on how these fractures are currently treated. The purpose of this report was to examine treatment modalities (surgical compared with nonsurgical) of incident appendicular fractures in men with a chronic SCI of traumatic etiology.

Methods: Patients with a chronic spinal cord injury (SCI) develop osteoporosis and are at high risk for fracture. However, there is limited information on how these fractures are currently treated. The purpose of this report was to examine treatment modalities (surgical compared with nonsurgical) of incident appendicular fractures in men with a chronic SCI of traumatic etiology.

Results: 1,453 male Veterans with 2464 incident fractures met inclusion criteria for the study. These fractures included 345 upper extremity fractures (ICD-9 codes 810.x-819.x), 1,667 lower extremity fractures (ICD-9 codes 808.x, and 820.x-828.x) and 452 unspecified fractures (ICD-9 829.x). 875 patients (60%) sustained a single fracture, while the remainder had 2 or more fractures over the five year time period of the study. Only a minority of patients (9.6%) were treated with surgical intervention, most commonly for hip fractures. Amputations accounted for 20.6% (32/155) of total surgical procedures, or 1.3% of all fractures. There were 20 above the knee amputations (AKAs), 6 below the knee amputations (BKAs), 4 occurring at other sites (foot, toe and finger) amputations, and 2 hip disarticulations one of which was associated with a femur fracture and the other a trochanteric hip fracture. Of the 32 amputations, 72% were done as delayed procedures.

Conclusion: Current patterns of appendicular fracture treatment in SCI indicate that the majority of fractures are managed nonsurgically within the VA healthcare system. A substantial number of surgical procedures were amputations. Many amputations were delayed, suggesting that they may represent failures of initial nonsurgical fracture treatment. There is a critical need to prospectively address optimal treatment (nonsurgical vs. surgical) by fracture site in patients with SCI.

Acknowledgements: This material is based upon work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development and the Rheumatology Research Foundation, Ephraim P. Engleman Resident’s Preceptorship Award.

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Disclosure: M. Bethel, None; L. Bailey, None; F. Weaver, None; B. Le, None; S. Burns, None; J. Svircev, None; M. Heggeness, None; L. Carbone, None.

2107

Characterization of Social Stigma in Rheumatic Diseases and Correlation with Quality of Life and Medication Adherence. Gihyun Myung1, Nancy D. Harada2, Stephanie L. Fong3, Cleopatra Aquino-Benton4 and Melka A Fang4.

Background/Purpose: Patients with rheumatoid arthritis and other rheumatic conditions may have physical deformities and functional limitations which make them vulnerable to health-related stigma. The objectives of this study were 1) to examine the prevalence of self-reported social stigma, and 2) to assess the relationships between stigma, medication adherence, and quality of life.

Methods: We conducted a descriptive cross-sectional study by surveying patients from rheumatology clinics at a Veterans Affairs Healthcare System. Patients completed five sets of questionnaires including 1) sociodemographic characteristics, 2) 12-item Short Form Health Survey (SF-12), 3) the Illness Attitude Questionnaire, 4) Social Stigma Scale (CISS), score range from 1 [very unlikely] to 5 [very likely]) for anticipated stigma, 3) Neurology Quality-of-Life Stigma short form (Neuro-QoL, score range from 1 [never] to 5 [always]) for enacted and internalized stigma, 4) short form-36v2 (SF-36) for quality of life measurement, and 5) 8-item Miskoky
Background/Purpose: Prior research has shown that the technical quality of SLE care is associated with the degree of subsequent accumulated damage. However, it is not known whether the patient experience with providers and health systems is associated with the technical quality of care.

Methods: We analyzed data from the UCSF Lupus Outcomes Study (LOS), a national sample of persons with SLE interviewed annually using a structured telephone survey. The survey includes batteries from AHRQ’s Consumer Assessment of Health Plans (CAHPS) and the Interpersonal Processes of Care Scales (IPC) to rate care along six dimensions of patient care experiences with providers (patient-provider communication, shared decision-making, and trust) and health systems (promptness/timeliness of care, care coordination, and assessment of health plans) from 0–100. Because ratings were highly skewed, we dichotomized the measures at the lowest versus the highest three quartiles. The survey also includes the 13 technical quality indicators (QIs) for SLE that have been validated for patient report. The QIs were aggregated into a pass rate, defined as the number of QIs received as a proportion of those for which one is eligible. We used generalized estimating equation models to model the relationship of the QI pass rate with being in the lowest quartile of ratings of each individual dimension and with being in the lowest quartile on 0, 1–3, and 4–6 of the dimensions.

Results: 640 LOS participants with ≥1 visit to their principal SLE provider in the year prior to interview were eligible for analysis. Mean age was 52.8±12.6 years and mean disease duration was 20.1±8.8 years. 38% were non-whites and 14% were in poverty. Overall pass rate was 70 (95% CI: 68, 71). Being in the lowest quartile of ratings on any one individual dimension was not associated with a statistically significant difference in QI pass rates. Being in the lowest quartile of ratings on 4–6 dimensions was associated with significantly lower pass rates (.63 vs. .70 and .71 for those in the lowest quartile on 1–3 or 0 dimensions, respectively [Table 1]).

Conclusion: Consistently low ratings on multiple dimensions of health care experiences may be a sentinel for poor technical quality of care. Because ratings of providers and health plans are in the public domain, individuals with SLE may find this information useful when choosing where to receive clinical care.

Table 1. Technical Quality of Care Pass Rates, by Number of Dimensions with Ratings of Health Care Experiences with Providers and Health Systems in the Lowest Quartile

<table>
<thead>
<tr>
<th>Number of Dimensions</th>
<th>Q1 Pass Rate (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>.71 (.68, .74)</td>
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<tr>
<td>1–3</td>
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Disclosure: E. H. Yelin, None; I. Trupin, None; J. Yazdany, None; C. Tonner, None.

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Background/Purpose: Published data on adherence of biologics shows a wide range of calculation methods. To compare methods of calculating adherence and persistence for immunology biologics.

Methods: A retrospective database analysis of claims from 1/1/2000 through 12/31/2001 were sourced from a leading national health care provider. The first biologic claim between 5/1/2000-6/30/2010 was the pre-index period (Method I), to establish induction period status, followed by assignment of dosing intervals based on product labeling. Method II followed the pre-index period (Method II), to establish induction period status, followed by assignment of dosing intervals based on product labeling. Method IV used either days' supply from the pharmacy claim or estimated infusion interval criteria of ≤ 21 days (Method IV), or alternatively, activity in the pre-index period (Method IV), to establish induction period status, followed by assignment of dosing intervals based on product labeling. The other methods were adjusted for age, race/ethnicity, education, poverty status, presence and kind of health insurance, specialty of principal SLE physician, disease duration, disease activity (measured by SLAQ), and disease damage.

Results: 638 patients were included in this study. Mean age was 52.8±12.6 years and mean disease duration was 20.1±8.8 years. 38% were non-whites and 14% were in poverty. Overall pass rate was 70 (95% CI: 68, 71). Being in the lowest quartile of ratings on any one individual dimension was not associated with a statistically significant difference in QI pass rates. Being in the lowest quartile of ratings on 4–6 dimensions was associated with significantly lower pass rates (.63 vs. .70 and .71 for those in the lowest quartile on 1–3 or 0 dimensions, respectively [Table 1]).

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Disclosure: E. H. Yelin, None; I. Trupin, None; J. Yazdany, None; C. Tonner, None.

2109


Background/Purpose: Prior research has shown that the technical quality of SLE care is associated with the degree of subsequent accumulated damage. However, it is not known whether the patient experience with providers and health systems is associated with the technical quality of care.

Methods: We analyzed data from the UCSF Lupus Outcomes Study (LOS), a national sample of persons with SLE interviewed annually using a structured telephone survey. The survey includes batteries from AHRQ’s Consumer Assessment of Health Plans (CAHPS) and the Interpersonal Processes of Care Scales (IPC) to rate care along six dimensions of patient care experiences with providers (patient-provider communication, shared decision-making, and trust) and health systems (promptness/timeliness of care, care coordination, and assessment of health plans) from 0–100. Because ratings were highly skewed, we dichotomized the measures at the lowest versus the highest three quartiles. The survey also includes the 13 technical quality indicators (QIs) for SLE that have been validated for patient report. The QIs were aggregated into a pass rate, defined as the number of QIs received as a proportion of those for which one is eligible. We used generalized estimating equation models to model the relationship of the QI pass rate with being in the lowest quartile of ratings of each individual dimension and with being in the lowest quartile on 0, 1–3, and 4–6 of the dimensions.

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Disclosure: E. H. Yelin, None; I. Trupin, None; J. Yazdany, None; C. Tonner, None.

2108

Anxiety in Caregivers of Patients with Chronic Rheumatic Conditions. Anna K. Cristina Gutierrez-Rubio, Geraldine Racaza, Maria Lourdes Dianoncog and Ester Penserga.Philippine General Hospital, Manila, Philippines.

Background/Purpose: People caring for patients with chronic illnesses, such as systemic lupus erythematosus, rheumatoid arthritis, or osteoarthritis, may experience depression and anxiety due to the burdens of managing debilitating and disabling diseases. Our primary objective was to determine the prevalence of anxiety and depression in caregivers of patients with SLE, RA, OA.

Methods: Persons acting as the primary caregiver to patients with SLE, RA or OA were included in this study. Demographic data were collected. The hospital anxiety and depression scale (HADS), a 14-item rating scale with independent subscales for anxiety and depression, was administered to each participant. A score of 11 or higher indicated probable depression or anxiety.

Results: A total of 438 patients were included in this study. All patients included were acting as the caregiver of an individual with a rheumatic condition, with 182, 151, and 107 caring for patients with SLE, RA, OA, respectively. The prevalence of probable depression among caregivers of patients with SLE, RA, and OA were 2.2±10%, 0±0%, and 19±10%, respectively with a 95% CI. The prevalence of probable anxiety among caregivers of patients with SLE (17.58±10%) was significantly higher than, RA and OA (9.93±10% p = 0.05, and 8.57±10% p = 0.04 respectively). Other variables, such as low income, presence of comorbid illnesses, or the number of weeks per day spent caring for the patient were not found to be significant factors.

Conclusion: The prevalence of anxiety among caregivers of patients with SLE were found to be significantly higher than those of RA and OA, implying that the illness of the patient they are caring for impacts their risk for anxiety. More studies are needed to determine risk factors for anxiety among caregivers of patients with SLE, and the impact this may have on patient care.

Disclosure: A. K. Gutierrez-Rubio, None; G. Racaza, None; M. L. Dianoncog, None; E. Penserga, None.

2109

a qualitative a priori review of medical benefit transaction reporting frequencies. Adherence was measured using Proportion of Days Covered (PDC-“fixed period” 364 days post-index) and Medication Possession Ratio (MPR-“variable period” index to cessation of treatment or end of observation). Several new methods of reporting adherence were tested, including: Proportion of Patients with treatment gap ≥20% of expected (PPgap≥20), Sum of Gap Days ≥20% of expected (SoGD≥20), Sum of any Gap Days (SoGD), and Number of Gaps ≥10% of expected (NoG≥10). Persistence alternatives included Number of days from Index to a gap ≥90 days, and Number of days from Index to a gap ≥10% of expected interval. Results are reported descriptively using means, standard deviations (SD), and percentages.

Results: 636 patients had IFX claims; while in a separate sample, 523 chart review patients had only subcutaneous claims (SQ). Method III produced comparatively low adherence and persistence rates. PDC-type fixed period vs. MPR-type variable period consistently reported a 10–15% lower adherence rate, and a 30–50 day shorter time to event rate. For Method IV, variable period techniques - the IFX cohort had an MPR of 0.94 (SD 0.12) while the SQ cohort had MPR of 0.82 (SD 0.19). For alternative adherence measures, using M method IV, variable period techniques, comparing infusion (IFX cohort) vs. self-administered (SQ cohort) showed the Pgap≥20 was 39.8% vs. 74.2% respectively. The SoGD≥20 was more than twice as great for the SQ cohort (56.1 (SD 65.0) vs. 23.2 (SD 46.3)) respectively. The SQ cohort reported more than 2.5 times the NoG≥10 vs. IFX cohort (2.59 (SD 2.14) vs. 0.97 (SD 1.22)) respectively.

Conclusion: Substantial differences may result from assumptions made regarding missing days’ supply and calculation methods for persistence and adherence when using medical claims. Quality reporting should include all details for days’ supply assumptions and calculation methods. Alternative methods of reporting adherence may have greater clinical significance than MPR or PDC.


2111

Overcoming Barriers to Acute Patient Access: Is There a Need for Urgent Care Clinics in Rheumatology Practices? Ruchi Jain, Narender Annapureddy, Isabel Castejón, Theodore Pincus, Daniel Garcia and Joel A. Block. Rush University Medical Center, Chicago, IL.

Background/Purpose: Urgent access for patients with rheumatic disease is limited in the United States, and it is often difficult to accommodate patients’ requests to be seen for urgent issues such as flare. No reports of Rheumatologists with urgent care clinics (UCC) built into practices similar to primary care are available. Currently many Rheumatologists use reserved slots in a provider’s schedule for urgent patients. This may be inadequate as these slots may be filled, particularly in academic practices which comprise providers who see patients only a few days per week, and may produce daily unpredictability in schedules. The primary objective of our study was to analyze a validated patient survey to determine a possible need to institute a dedicated UCC in our academic practice.

Methods: 390 patients were given validated surveys measuring access: Did you call for a concern that required urgent attention in the past 12 months? If so how often did you get an appointment as soon as you felt you needed: Always Usually, Sometimes or Never. Patients in the Always group needed: Always Usually, Sometimes or Never. Patients in the Always group reporting: Always

Conclusion: We observed an unmet need to provide urgent care access for patients with rheumatic diseases in our academic practice. This need is heightened especially in patients of providers with limited clinics in a week. Furthermore, mean confidence scores appear to be driven more by access than by the frequency that the provider practices clinically. A dedicated UCC might improve patient access and confidence in Rheumatology practices.

Disclosure: R. Jain, None; N. Annapureddy, None; I. Castejón, None; T. Pincus, None; D. García, None; J. A. Block, None.
Tuesday, November 18

The Number of Morbidities Drives the Health Care Expenditures and Presence of a Musculoskeletal Condition Is Additionally Accountable for Higher Costs. Antje van der Zee-Neeuwen¹, Polina Putrik², Sofia Ramiro³, Andras Keszei⁴, Astrid M. Chorus⁵, Rob de Bie⁶ and Annemles Boonen⁷, ¹Maastricht University Medical Center, Maastricht, Netherlands, ²Maastricht University, Maastricht, Netherlands, ³Maastricht University Medical Center, Maastricht, Netherlands, ⁴Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, ⁵Netherlands Organization for Applied Scientific Research, Leiden, Netherlands.

Background/Purpose: In Europe, 70-80% of all healthcare expenditures are attributable to chronic diseases and a large part of these are musculoskeletal conditions (MSCk). Having >1 disease (multimorbidity) is likely to increase the costs of care but little is known about the association of multimorbidity and health care costs (HCC) and the specific role of MSCk as co-morbid disease in this association. We aimed to explore(1) whether the number of morbidities has an important association with costs of care and 2) whether MSCk have an additional impact when occurring as co-morbid disease.

Methods: Dutch cross-sectional study; 8904 subjects (>18 years) completed a questionnaire on sociodemographic and lifestyle factors, self-reported physician-diagnosed diseases (MSCk, diabetes, cardiovascular diseases, cancer, migraine, respiratory, skin, mental and bowel conditions) and health care use (general practitioner, rheumatologist, orthopedist, physiotherapist, other specialists, hospitalization in regular/academic hospital or nursing home, home care and domestic help). The total HCC were computed for a 3-months period using reference prices of the Dutch manual for pharmacoeconomic healthcare evaluations 2010, accounting for inflation by Consumer Price Index. Missing values were imputed by means of multiple imputation. To deal with skewness, zero-inflated negative binomial regression (ZINB) models were computed to assess 1) the association of number of diseases and HCC and 2) which disease or combination of diseases (in- or excluding MSCk) was associated with the largest increase of HCC using the healthy as referent. Models were adjusted for age, gender, BMI, education and smoking-status.

Conclusion: The number of morbidities increases with increasing number of morbidities. MSCk are accountable for higher costs of care compared to other diseases independent of the number of morbidities. These important findings deserve the attention of policy makers, especially by prioritizing MSCk in healthcare budgets.

Table 1. Association of type (or combination) and number of morbidities with costs of health care utilization during a 3 month period

<table>
<thead>
<tr>
<th>Morbidity or combination of morbidity</th>
<th>exp(β) [95% CI]</th>
<th>Raw costs (€), mean (SD) $/H11022</th>
<th>Predicted costs ($/H20038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal condition when occurring alone</td>
<td>2.2 [1.8–2.5]</td>
<td>575 (2169)/488 (1904)</td>
<td>328/483</td>
</tr>
<tr>
<td>Any other chronic morbidity when occurring alone</td>
<td>1.5 [1.4–1.7]</td>
<td>388 (1906)/401 (2801)</td>
<td>220/323</td>
</tr>
<tr>
<td>Any combination of 2 morbidities when MSC is one of them</td>
<td>3.0 [2.7–3.7]</td>
<td>664 (1863)/493 (4895)</td>
<td>483/711</td>
</tr>
<tr>
<td>Any combination of 2 morbidities when MSC is not one of them</td>
<td>2.2 [2.0–2.7]</td>
<td>595 (1385)/626 (1928)</td>
<td>355/522</td>
</tr>
</tbody>
</table>

Disclosure: M. De Vera, None; E. C. Sayre, None; C. Baldwin, None; J. Galo, None; J. A. Avina-Zubieta, None.
Winnipeg, MB, 3Siksika Health Services, Siksika, AB. Mosher1, Hani El-Gabalawy2, Tyler White 3, Marvin Fritzler1 and Cheryl Barnabe1. 1University of Calgary, Calgary, AB, 2University of Manitoba, 47 years, diagnosis of rheumatoid arthritis n was calculated. The frequency with which a treatment change was recommended, was used to describe changes in disease activity measures over a 24 month collection of disease activity measures and patient-reported outcomes, as well program held in a First Nations community between June 2011 and August Nations primary care setting, in achieving IA activity targets. influenced by health service models that mitigate logistical barriers to care and effects Canada’s First Nations population. Treatment outcomes may be ame-


Inflammatory Arthritis Treatment Outcomes at a First Nations Reserve Rheumatology Specialty Clinic. Erin Bell1, Sharon Lecercq2, Danine P. Mosher3, Hani El-Gabalawy4, Tyler White4, Marvin Fritzler2 and Cheryl Barnabe1. University of Calgary, Calgary, AB, University of Manitoba, Winnipeg, MB, Siksika Health Services, Siksika, AB.

Background/Purpose: Inflammatory arthritis (IA): rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthropathy) disproportionately affects Canada’s First Nations population. Treatment outcomes may be ameliorated by health service models that mitigate logistical barriers to care and provide specialty services embedded in the primary care context. This study assessed the effectiveness of a specialized care model, delivered in a First Nations primary care setting, in achieving IA activity targets.

Methods: Consenting participants were recruited to an arthritis screening program held in a First Nations community between June 2011 and August 2012. Those determined to have IA (n=47) received ongoing follow-up with collection of disease activity measures and patient-reported outcomes, as well as treatment recommendations, at each visit. Repeated measures ANOVA was used to describe changes in disease activity measures over a 24 month period. The frequency with which a treatment change was recommended, based on moderate or high disease activity state determined from the DAS28, was calculated.

Results: A total of 131 visits by 47 participants (79% female, mean age 47 years, diagnosis of rheumatoid arthritis n=34) occurred over the 24 month study period. At the baseline visit, 70.6% of participants had moderate or high disease activity (DAS28>3.2). Significant decreases in joint counts (/28) were achieved (mean swollen joint count decrease of 7.0, 95% CI 3.5-10.4, p=0.0063; mean tender joint decrease of 7.2, 95% CI 4.1-10.3, p=0.0116). Patient-reported outcomes for pain, global assessment and physical function were not significantly improved during treatment. A recommendation for treatment change was made at 67% of visits where patients were classified in moderate or high disease activity.

Conclusion: Although the program adequately addressed physician-derived disease activity targets, patient-reported outcomes were not signifi-
cantly improved during follow-up. This suggests that the program should be modified to include a multi-disciplinary team that can address holistic aspects of First Nations health and reduce loss to follow-up from specialty care. A quality improvement initiative will be introduced to document reasons for deviation from the treat-to-target protocol.

Disclosure E. Bell, None; S. Lecercq, None, D. P. Mosher, None; H. El-Gabalawy, None; T. White, None; M. Fritzler, None; C. Barnabe, None.

Hospitalization Rates and Utilization Among Rheumatoid Arthritis Patients: A Population-Based Study from 1987 to 2012. C. John M ichel III1, Katrina Strobova2, Sara J. Achenbach1, Cynthia S. Crowson3 and Eric L. Matteson1. 1Mayo Clinic College of Medicine, Rochester, MN, 2Charles University, Prague, Czech Republic, 3Mayo Clinic, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) experience chronic management issues and are at risk for complex comorbidities. It is unknown, however, to what extent the complications of the disease may lead to hospitalization. The goal of this study is to discern whether patients with RA are at greater risk for all-cause hospitalizations when compared to the general population.

Methods: This retrospective, population-based cohort study utilized patients who were 18 years or older and diagnosed with RA (as defined by the 1987 ACR criteria) between 1/1/1980 and 12/31/2007, and a reference cohort of patients without RA matched on age, sex, and calendar year. Each patient’s medical record was examined for hospitalizations from 1987 through 2012. For this analysis, follow-up began with the latter of index date or 1/1/1987 and ended at the earlier of death, last follow-up or 12/31/2012. Discharge diagnoses were grouped together using the Clinical Classifications Software for ICD-9-CM from Healthcare Cost and Utilization Project. Data were analyzed using person-year methods and rate ratios comparing RA to non-RA.

Results: The 799 RA and 797 non-RA cohorts each consist of patients with a mean age of 56 years (68% female) and a mean follow-up of 12 years and 13 years respectively. The patients with RA had 2968 hospitalizations and the non-RA patients had 2069 hospitalizations. RA patients proved to be at greater risk for all causes of hospitalization (Table 1). Increased risk for all-cause hospitalizations for patients with RA also held true for both sexes and all age groups.

Two discharge diagnoses are of interest. First, hospitalization for depres-
sion is a greater risk for male patients with RA (23 hospitalizations) than for the general male population (3 hospitalizations) (Rate Ratio [RR] 7.16, 95% Confidence Interval [CI] 2.78, 30.67). Second, patients with RA are at greater risk of hospitalization for diabetes (31 hospitalizations) than patients without RA (13 hospitalizations) (RR 2.45, CI 1.34, 4.68). Female patients with RA are at a significantly increased risk of hospitalization for diabetes (16 hospitalizations) when compared to the general female population (6 hospitalizations) (RR 2.65, CI 1.14, 7.45). An increased risk of hospitalization for diabetes is especially true for all RA patients age 45-64 (22 hospitalizations) when compared to the general population (0 hospitalizations) (RR 4.76, CI 8.32, 45072.3).

Conclusion: In this first ever analysis of all-cause hospitalizations in a population-based cohort, patients with RA appear to be at greater risk for hospitalization than patients without RA. This risk is true for both sexes and all age groups. RA patients are also markedly more likely to be hospitalized for depression if they are male. Furthermore, hospitalization for diabetes is prevalent among patients with RA, especially among females and patients in the 45-64 age group.

Disclosures C. J. Michel III, None; K. Strobova, None; S. J. Achenbach, None; C. S. Crowson, None; E. L. Matteson, None.

Association Between Depression and High Utilization of Emergency Department in Patients with Systemic Lupus Erythematosus from the Southeastern United States: The Goal Cohort. Alfredo Aguirre1, S. Sam Lim1, Gaobin Bao1, Charles T. Molta2, Hong Kan3 and Cristina Drenkard3. 1Emory University, Atlanta, GA, 2Emory University School of Medicine, Division of Rheumatology, Atlanta, GA; 3Gliax-Smithline, King of Prussia, PA, 4GSK, Durham, NC.

Background/Purpose: Frequent visitors of the emergency department (ED) among the general population share several demographic, health system and disease characteristics, including older age, poverty, government-financed insurance and poorer health. The burden of depression is also high among frequent ED visitors. Depression strikes up to 75% of SLE patients and is more severe among blacks compared to whites. Previous reports among predominantly white SLE samples suggest that there is an association between depression and ED usage. We sought to examine whether the severity of depressive symptoms increases the risk of being a frequent user of the ED in a predominantly black SLE cohort in the Southeastern US.

Methods: Georgians Organized A gainst Lupus (GOAL) is a longitudinal cohort largely drawn from a population-based registry of people with SLE, which has been established in Atlanta, GA. A monthly surveys furnish self-administered data on demographics, disease outcomes and healthcare utilization. Over 75% of participants are black, and 35% live under the poverty

*Rate of hospitalizations per 100 person-years

Disclosures C. J. Michel III, None; K. Strobova, None; S. J. Achenbach, None; C. S. Crowson, None; E. L. Matteson, None.
level. We used the 9-item Patient Health Questionnaire (PHQ-9) to assess severity of depressive symptoms. PHQ-9 can be assessed as a continuous (score range 0–27) or categorical (5 categories from minimal to severe depressive symptoms) variable. Individuals who visited the ED ≥ 3 times in the past year were considered frequent ED users. We conducted logistic regression analyses to test the effect of depression severity on being a frequent ED user, after controlling for potential confounders.

Results: Of 566 SLE participants, 96 (17%) visited the ED at least 3 times in the past year. Frequent use of the ED was found in 10%, 17%, 26%, 24%, and 28% of patients with minimal, mild, moderate, moderately severe, and severe symptoms of depression, respectively. Severity of depressive symptoms, demographic factors, type of insurance, disease activity, and organ damage were associated with frequent ED utilization (Table 1). The PHQ-9 score remained positively associated with the outcome after controlling for major confounders. PHQ-9 and self-reported disease activity (SLAQ) scores were highly correlated (rho = 0.65). The association between the PHQ-9 score and frequent ED usage was not longer significant when SLAQ was included in the model (OR = 0.98; p = 0.85).

Conclusion: Our data suggest that the severity of depressive symptoms may modulate healthcare-seeking behavior in SLE. However, other factors often disproportionately prevalent among socioeconomically disadvantaged subgroups with SLE, such as severe organ damage, greater disease activity and being on Medicaid showed stronger association with the outcome. Longitudinal studies are needed to tease out the complex pathways implicated in the usage of avoidable healthcare resources among minorities with SLE, particularly among those stricken by depressive symptoms.

Table 1. Association of Depressive Symptoms with Frequent Usage of the Emergency Department

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariable OR (95% CI)</th>
<th>p Value</th>
<th>Multivariable OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms (5-unit increase in PHQ-9 score)</td>
<td>1.43 (1.21–1.70)</td>
<td>&lt;0.0001</td>
<td>1.30 (1.07–1.59)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age at diagnosis (5 year increase)</td>
<td>0.91 (0.83–1.00)</td>
<td>0.051</td>
<td>0.85 (0.75–0.95)</td>
<td>0.006</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.35 (0.25–0.48)</td>
<td>0.0008</td>
<td>0.28 (0.19–0.38)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Race (non-white)</td>
<td>2.46 (1.43–4.22)</td>
<td>0.003</td>
<td>2.22 (0.95–5.19)</td>
<td>0.07</td>
</tr>
<tr>
<td>Disease duration (1 year increase)</td>
<td>0.62 (0.29–1.30)</td>
<td>0.23</td>
<td>0.70 (0.32–1.55)</td>
<td>0.35</td>
</tr>
<tr>
<td>Educational attainment (3 year increase)</td>
<td>0.80 (0.63–1.05)</td>
<td>0.10</td>
<td>0.90 (0.63–1.27)</td>
<td>0.56</td>
</tr>
<tr>
<td>Household income below poverty level</td>
<td>2.90 (1.81–4.63)</td>
<td>&lt;0.0001</td>
<td>2.10 (1.27–3.50)</td>
<td>0.003</td>
</tr>
<tr>
<td>Insurance type (ref: Private)</td>
<td>2.03 (1.17–3.54)</td>
<td>0.021</td>
<td>1.83 (0.71–4.75)</td>
<td>0.80</td>
</tr>
<tr>
<td>No Insurance</td>
<td>3.29 (1.65–6.55)</td>
<td>0.0007</td>
<td>2.30 (0.98–5.39)</td>
<td>0.05</td>
</tr>
<tr>
<td>Medicare</td>
<td>6.57 (2.83–15.3)</td>
<td>&lt;0.0001</td>
<td>3.63 (1.31–10.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>0.59 (0.37–0.94)</td>
<td>0.028</td>
<td>0.76 (0.45–1.31)</td>
<td>0.32</td>
</tr>
<tr>
<td>Disease activity (5-unit increase in SLAQ score)</td>
<td>1.65 (0.84–3.25)</td>
<td>0.0001</td>
<td>0.60 (0.28–1.27)</td>
<td>0.16</td>
</tr>
<tr>
<td>Organ damage (SA-BILD score)</td>
<td>2.07 (0.95–4.51)</td>
<td>0.067</td>
<td>1.89 (0.82–4.34)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mild damage (1–2) vs. no damage</td>
<td>1.49 (1.12–2.04)</td>
<td>0.0003</td>
<td>0.45 (0.24–0.84)</td>
<td>0.011</td>
</tr>
<tr>
<td>Severe damage (&gt;3) vs. no damage</td>
<td>4.91 (3.43–10.73)</td>
<td>&lt;0.0001</td>
<td>3.51 (1.38–8.37)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Abbreviations: LR: logistic regression; PHQ-9: 9-item Patient Health Questionnaire; SA-BILD: Self-Administered Brief Index Lupus Damage; SLAQ: Systemic Lupus Activity Questionnaire.

Disclosure: A. Aguirre, None; S. S. Lim, NIH, 2, GlaxoSmithKline, 2, Emory University, 3; G. Bao, GlaxoSmithKline, 2, Emory University, 3, C. T. Molta, GSK, 1, GSUK, 1, GSK, 1, H. Kan, 1, GSUK, 1, GSK, 3, C. Drenkard, NIH, 2, Emory, 3, GlaxoSmithKline, 2.

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1University of British Columbia/Arthritis Research Centre of Canada, Van- couver, BC, 2University of British Columbia, Vancouver, BC, 3Univ of British Columbia, Vancouver, BC, 4Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Low socioeconomic status (SES) negatively impacts health outcomes in the general population, as well as in systemic lupus erythematosus (SLE), but the impact on healthcare costs is unknown. In addition, there are little data on the long term costs of SLE cases beginning from diagnosis. To address these knowledge gaps, we examined the relationship between SES at diagnosis, and direct medical costs for 10 years following, in a general population-based context.

Methods: Data Source: Our administrative data captured all provincially-funded outpatient encounters and hospitalizations (1990–2010), and all dispensed medications (1996–2010) regardless of funding source, in British Columbia, Canada. Sample: We assembled a population-based cohort of all incident cases of SLE who received care from 1996–2010, based on the following validated algorithm: a) two ICD-9-CM codes for SLE at least 2 months apart but within a 2 year period by a non-rheumatologist physician; or b) one ICD code by a rheumatologist or hospitalization. Statistics Canada neighborhood income quintile data for the year of SLE diagnosis was used to define SES. Cost Calculation: Costs for outpatient services and prescriptions were summed directly from billing data. Case-mix methodology was used for hospitalizations. Statistical Analysis: We report the cumulative 10-year costs (adjusted for censoring) for each SES group. Parametric bootstrapping was used to obtain 95% confidence intervals (CI). Costs are reported in 2010 Canadian dollars.

Results: We identified 4,209 incident SLE cases (86% female, mean age 49 years) contributing 18,028 person-years. The 10-year costs from all cases totalled $312,762,777 with 30% from outpatient, 41% from hospitalizations and 30% from medications.

After adjusting for age, sex and baseline Charson's comorbidity index, predicted costs were significantly greater (21%, p < 0.01) for the lowest SES cases compared to the highest, and averaged $12,489 more per-patient over 10 years.

Hospitalization costs over 10 years were 64% greater for the lowest-SES cases versus the highest ($13,097 vs. $8,001, p < 0.05), with most hospitalizations (85%) occurring within 12 months of SLE diagnosis. Medications costs were 10% greater for the lowest SES than the highest, but unlike hospitalization costs, these costs continued to increase over time.

Conclusion: Lower SES at SLE diagnosis is associated with higher healthcare costs, with medication costs driving this disparity over the long term.

Disclosure: N. McCormick, None; M. Sadatashvili, None; W. Chen, None; C. A. Marras, None; J. A. Vina-Zubieta, None.

2119

Off Work Days Decreased RATE In Musculoskeletal Disease Patients: Usefulness of the EARLY Intervention Program. Francisco Miguel Ortiz Sanjuan, Isabel Martínez-Cordelá, José Ivorra, José Luis Válerio, Inmaculada Chalmeta, Elena Grau, Carlos Feced, Rosa Nequeregas, Luis González-Pulido, Cristobal Nuñez-Cornejo Piquer, Cristina Alcàfí, Ezetín Labrador and José Andrés Roman Ivorra. Department of Rheumatology, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

Background/Purpose: In March 2012, a new project was started at HUP La Fe following the pilot project carried out at San Carlos Clinical Hospital in M a drid, where patients who were off work for musculoskeletal causes were referred to us from Primary Care. The aim of the study is to analyze the variation in days off work in those individuals included in this program with respect to the normal average of days off.

Methods: Cohort, observational, cross-sectional study from April 2012 to December 2013, which included patients from the HUP La Fe area, referred for the first time to the Rheumatology Early Intervention consultation program because of temporary disability due to musculo- skeletal problems. These patients are referred to a medical appointment with a maximum waiting time of one week and were provided medical treatment, ultrasound, joint injections and directed exercises if necessary.
needed. The patient is reviewed continuously until discharge. We excluded patients whose disabilities were due to trauma or surgery or if their situation could cause permanent disability.

**Results:** We included a total of 250 patients with a mean age of 48 years and 53% were women. The most frequently reported diseases were: back pain (53%), neck pain (16%), shoulder pain syndrome (13%) and other tendinopathies (10%). 100% of patients received medical treatment, 39% underwent arthrotomy ultrasonic, 35% of them underwent injections and 62% were treated to perform physical therapy exercises at home. The pathology that had a higher average number of days from the first visit to the medical discharge was lumbar/sciatic pain (38 days), neck pain (30 days), and painful shoulder syndrome (34 days). Comparing our data with the control population in the San Carlos Hospital study, there was a decrease of the days off, being in the control group lumbosciatica (57.6 days), neck (37.4 days) and neck pain (37.4 days).

**Conclusion:** Results obtained in our study show that early intervention by rheumatologists in patients with temporary disability of musculoskeletal origin decreases the number of days off work compared to patients who receive routine treatment and they can be incorporated in work early. Consequently, it saves all costs resulting from such temporary disability.

**Disclosure:** F. M. Ortiz Sanjuan, None; I. Martinez-Coradal, None; J. Ivorra, None; J. L. Valero, None; I. Chalmeta, None; E. Grau, None; C. Fecon, None; R. Nguerolos, None; L. Gonzalez-Puig, None; C. Nuiiez-Conrno Piquer, None; C. Alcanniz, None; E. Labrador, None; J. A. Roman Ivorra, None.

### 2120

**Societal Preferences for Rheumatoid Arthritis Treatments. Evidence from a Discrete Choice Experiment.** M.ark Harrison, 1 C.arlo M. arr, 1 K. am Shojania 2 and N. ick Bansback 1. 1University of Manchester, Manchester, United Kingdom, 2University of British Columbia, Vancouver, BC.

**Background/Purpose:** The cost-effectiveness of new interventions is increasingly assessed using the cost per quality-adjusted life year (QALY). QALYs are calculated by multiplying the length of time spent in a health state by the value of that health state, usually representative of the general public and estimated using a generic preference-based measure such as the EQ-5D. A limitation of generic preference-based instruments is that they may fail to describe benefits of a treatment that patients experience and that society might value such as the method or convenience of treatment. The aim of this study was to determine the value society places on aspects of rheumatoid arthritis treatment, including mode of administration.

**Methods:** A discrete choice experiment (DCE) was administered using a web survey in a representative sample of the Canadian general population using an online panel. Focus groups led to the development of a DCE with 7 attributes (route and frequency of administration, chance of serious and minor side-effects, confidence in benefit and side-effect estimates based on GRADE definitions), and life expectancy. An experimental design led to 120 choice sets. Each respondent was randomized to complete 10 of these. A conditional logit regression model was used to estimate the significance and relative importance of attributes in influencing preferences. The life years attribute enables the DCE to estimate values on the linear scale for use in QALY calculations.

**Results:** Responses from 733 respondents who provided rational responses to the choices in the experiment were included in the analysis. They were recruited from all provinces and territories in Canada, and their mean age (44), gender (55% female) and education (45% had up to a high school education) were representative of the general population. Six attribute levels within four attributes significantly influenced preferences for treatments. Respondents were willing to give up to a year of life expectancy over a 10 year period to increase the probability of benefitting from treatment, or two thirds of a year to reduce minor or serious side-effects to the lowest level or improve the confidence in benefit/side-effect estimates. There was some evidence of a preference for oral drug delivery and sub-group analysis suggested this preference was restricted to injection naive respondents.

**Conclusion:** As expected, our study found societal values the benefits and side-effects of treatments. However, our study also found that people also value the degree of confidence in the estimates of risks and benefits of treatments, and to a lesser extent, the route of administration. Since economic evaluations typically focus only on the health outcomes of treatments, they may miss process aspects of treatment that are valued by society. This study provides important evidence to policy makers determining the cost-effectiveness of treatments in arthritis.

**Disclosure:** M. Harrison, None; C. Marra, Pfizer Inc.; K. Shojania, Abbvie, Janssen, BMS, UCB, Roche, Amgen.; N. Bansback, None.
understand this variability, comparing practice to an adapted standardized treatment pathway.

Methods: A standardized treatment pathway was developed based on the 2012 ACR guidelines for treatment of patients with early moderate to severe RA (Singh JA et al., 2012) and was endorsed by the rheumatologists in our practice (Figure 1). This pathway differed from the ACR guidelines primarily by liberalizing the duration required for each treatment step.

We reviewed charts of 224 patients with ≥ 3 ICD 9 codes for RA (714.0) seen at our single center academic practice who initiated a new bDMARD (first time use or a change from prior bDMARD) from January through December 2013. Data were abstracted using a standardized form, including demographics, RA characteristics, complete available medication history and reasons for medication choices. Each patient was included only once. We categorized patients as having treatment courses that did or did not follow the treatment pathway. Inter-rater reliability (kappa), assessed by re-review of charts of patients with treatment courses that varied from the pathway, was 0.82, p < 0.001. When reviewers disagreed, final adjudication occurred through a consensus process.

Results: 224 patients initiated a new bDMARD during the study period. Mean age was 53 (range 20−84) and 183 (82%) were female. 197 (88%) had disease duration of over 2 years. Erosive disease was seen in 99 (44%) and 116 (52%) were seropositive. Only 13 patients (6%) had treatment courses that did not follow the treatment pathway (Table 1). The reasons for these variations included co-morbidities (n = 8), disease severity (n = 1) and initial care at other institutions (n = 4). None of the included patients had failed oral triple therapy prior to initiation of a biologic.

Conclusion: We examined practice patterns for the prescription of bDMARDs at our institution and found little variability based on an adapted standardized treatment pathway. Variations from the pathway were justified by patient co-morbidities and disease characteristics, suggesting that existing variability may be appropriate.

Table 1: Reasons for patient treatment not following suggested pathway (N = 13 out of 224)

<table>
<thead>
<tr>
<th>Deviation</th>
<th>Number</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept as initial DMARD</td>
<td>8</td>
<td>Therapy started at another institution (4) Co-morbidity considerations (4) -Liver disease (1) -Lung disease, sulfa allergy (1) -Pregnancy/post-partum breastfeeding (2)</td>
</tr>
<tr>
<td>Infliximab + methotrexate as initial DMARDs</td>
<td>1</td>
<td>Severe symptoms with high disease activity (1)</td>
</tr>
<tr>
<td>Rituximab as initial biologic DMARD</td>
<td>4</td>
<td>Co-morbidity considerations (4) -Multiple sclerosis (1) -Active leiomysarcoma (1) -Intestinal lung disease (1) -Latent tuberculosis (1)</td>
</tr>
</tbody>
</table>

Disclosure: H. O. Tory, None; J. A. Awosoga, None; A. J. Dave, None; J. S. Coblyn, CVS Caremark; S. D. Solomon, None; P. P. Desai, None.

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Characteristics of Medicare Beneficiaries Travelling Long Distances to Visit a Rheumatologist. Gabriela Schmajuk1, Chris Tonner 2 and Jinoos Yazdany2. 1UCSF/San Francisco VA, San Francisco, CA, 2University of California, San Francisco, San Francisco, CA.

Background/Purpose: Studies of the distribution of rheumatologists across the United States suggest that a significant number of patients travel long distances to visit a rheumatologist. The geographic, health care market, and patient factors associated with travel distances have not been described. We examined individual and area-level predictors of travelling long distances to see a rheumatologist.

Methods: Data derive from nationwide Medicare fee-for-service claims files for 2009 for a 5% random sample of beneficiaries, including all medical and pharmacy claims. Included beneficiaries had RA (2 fact-to-face visits coded as 714.xx within the calendar year), were continuously enrolled in a pharmacy plan, and had at least one prescription for a disease-modifying drug. Source of biologic coverage (Part B or Part D) was tabulated for all biologic users according to LIS status and stratified by state. We calculated the proportion of LIS vs. non-LIS beneficiaries receiving Part B biologics in each state and examined the correlation between these variables within states. Individuals residing in states with fewer than 50 eligible beneficiaries were examined the correlation between these variables within states. Indiividuals residing in states with fewer than 50 eligible beneficiaries were censored from this analysis to increase the precision of our estimates.

Results: 1790 beneficiaries received a DMARD for RA; 2013 (26%) received biologic drugs. 25% of biologic users received a low-income subsidy (LIS). Among LIS recipients, 8% received their biologic through Part B and 20% through Part D. Conversely, among non-LIS patients, 18% received their biologic through Part B and 8% through Part D. Across states, Part B biologic use ranged from 5–26% for non-LIS patients (median 9, IQR 14–22) and 0–5% (median 2, IQR 1–3) for LIS patients (Figure). Proportions of non-LIS and LIS patients using Part B biologics within a state were modestly correlated (r² = 0.15).

Conclusion: We found substantial variations between states in the proportion of patients with RA receiving biologics, and whether patients received biologics through M edicare Part B or Part D. Variations were even observed for those receiving LIS, suggesting that factors other than cost-sharing influence biologic drug selection. Further studies should examine how both insurance coverage policies and physician practice variation impact the choices available to patients.

Disclosure. C. Tonner, None; G. Schmajuk, None; J. Yazdany, None.
between the center of the patient’s 5-digit ZIP code and the center of the rheumatologist’s office 5-digit ZIP code for the first rheumatologist seen during the calendar year. We compared the characteristics of patients travelling ≥ 50 miles to see a rheumatologist to all others based on sociodemographic (age, sex, race, dual Medicare/Medicaid eligibility, and state buy-in, a measure of personal income) and area-level variables (ZIP-code level socioeconomic status, state-level supply of rheumatologists per 100,000 residents, state-level price-adjusted total Medicare spending per person). Two percent of observations were censored due to missing data. Included variables were tested for noncollinearity. We used general estimating equations to adjust for individual and area-level characteristics in a single multivariate model.

**Results:** We studied 42,571 Medicare patients who had at least one visit to a rheumatologist during 2009. Median distance traveled was 9.3 miles (IQR 4-22); 9% of patients travelled ≥50 miles to see a rheumatologist. Patients who travelled ≥50 miles were more likely to be younger (age 70.7 vs. 73.3) male (25% vs 20%), White (92% vs. 88%), and live in a low-SES ZIP code (40% vs. 23%). They were also more likely to reside in regions with the lowest supply of rheumatologists (34% vs. 23%). In the adjusted model, the effects of age, sex, race, area-level SES, and rheumatologist supply remained significant although area-level SES had the strongest effect (Table).

**Conclusion:** Patients travelling very long distances to visit a rheumatologist are more likely to be male, White, and live in lower SES areas compared to patients travelling less far. Sociodemographic effects are at least as strong as the effect of low rheumatologist supply. These findings suggest that interventions beyond increasing the number of rheumatologists in low supply areas will be necessary to reduce travel distances and improve access to rheumatology care in the U.S.

| Table Individual and Area-level Predictors of Traveling ≥ 50 Miles to See a Rheumatologist. |
| **Variable** | **Adjusted odds ratio (95% Confidence Interval)** |
| **Individual Characteristics** |  |
| Age |  |
| Age ≤ 67 | 1.62 (1.48, 1.78) |
| Age 68-74 | 1.42 (1.29, 1.57) |
| Age 75-80 | 1.32 (1.19, 1.45) |
| Age ≥ 81 | Referent |
| Male (vs. female) | 1.20 (1.11, 1.29) |
| Race |  |
| African-American | 0.42 (0.37, 0.49) |
| Asian | 0.50 (0.32, 0.80) |
| Other | 1.16 (0.91, 1.47) |
| White | Referent |
| State buy-in (vs. none) | 0.73 (0.66, 0.81) |
| No Part D coverage (vs. yes) | 0.87 (0.81, 0.94) |
| **Area-level Characteristics** |  |
| ZIP-level SES index |  |
| Quintile 1 (low) | 5.15 (4.52, 5.82) |
| Quintile 2 | 2.92 (2.58, 3.31) |
| Quintile 3 | 1.95 (1.71, 2.23) |
| Quintile 4 | Referent |
| Quintile 5 (high) | 1.27 (1.10, 1.47) |
| Regional rheumatologist supply |  |
| Quarters 1 (low) | 1.90 (1.72, 2.11) |
| Quarters 2 | 1.84 (1.66, 2.03) |
| Quarters 3 | 1.05 (0.94, 1.17) |
| Quarters 4 (high) | Referent |
| Regional Medicare spending |  |
| (price-adjusted) |  |
| Quartile 1 (low) | 1.65 (1.51, 1.80) |
| Quartile 2 | 0.87 (0.79, 0.96) |
| Quartile 3 | 1.00 (0.91, 1.10) |
| Quartile 4 (high) | Referent |

*Adjusted for all variables shown
*Regional Medicare spending estimates from Dartmouth Atlas Data (2009); estimates adjust for age, sex and race of the underlying Medicare population and regional differences in prices.

**Disclosure:** G. Schmajuk, None; C. Tonner, None; J. Yazdany, None.

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**Burden of Illness in Refractory Gouty Arthritis: A One-Year Prospective Multinational, Observational Study.** Louis Bessette1, Frédéric Liote2, Carmen Moragues2, Rüdiger Moeick3, Zhang Zhiyi4, Alberto Ferreira4, Pascal Lecomte5, Sophia Kessabi6, Hajun Tian7 and Jasvinder Singh8.

CHUL, Quebec, QC, 1Hôpital Lariboisière & University Paris Diderot, Paris, France, 2Hospital Plant, Barcelona, Italy, 3Institut für Präventive Medizin & Klinische Forschung Gbr, Magdeburg, Germany, 4The First Affiliated Hospital of Haerbin Medical University, Haerbin, China, 5Novartis Pharma AG, Basel, Switzerland, 6Novartis Pharmaceuticals Corporation, East Hanover, NJ, 7Mayo Clinic, Rochester, MN.

**Background/Purpose:** Refractory gouty arthritis (RGA) is a condition characterized by appearance of recurrent flares and contraindication, intolerance, or lack of efficacy to first-line anti-inflammatory therapy (NSAIDs/colchicine/steroids) and conventional uric acid lowering therapies (ULT). The objective of the study was to assess the humanistic and economic burden of RGA over 1 year during presence or absence of a flare.

**Methods:** This 12-month, multinational (6 countries), prospective, observational study investigated the disease impact in patients suffering from RGA who had experienced 3 or more flares in past 12 months. Patients who were enrolled were also refractory to first-line anti-inflammatory therapy (NSAIDs, colchicine, or steroids) or to ULTs. Patients were divided in two groups as per the presence or absence of gout flares. Summary statistics pooled for all visits are presented as mean and SD for continuous variables, and proportions for categorical variables. The utility score derived from the combinations of responses to the multiple questions of the EuroQol Health Status Questionnaire SD (EQ-5D) was used as the primary outcome measure. Secondary outcomes included Gout Assessment Questionnaire-Gout Impact Scale (GAQ-GIS) and Healthcare resource utilization (ER visit, hospitalization, physician visit and home care).

**Results:** A total of 454 eligible patients were enrolled in the study (mean age: 56; males: 86.1%). Patients who were experiencing a flare experienced greater difficulty on all 3 dimensions of the EQ-5D descriptive system and mean EQ-5D utility scores pooled across all the visits were worse for patients having a flare [0.614; 95%CI 0.600, 0.628] as compared to patients without a flare [0.867; 95%CI 0.861, 0.872]. The results for mean EQ-5D VAS scores were lower in patients having a flare [60.7; 95%CI 59.3, 62.1] than patients without a flare [79.5; 95%CI 78.9, 80.1]. The mean GAQ-GIS scores for patients with a gout flare vs. those without a gout flare were higher for various parameters such as overall gout concern [81.27 vs 70.06], medication side effects [59.12 vs 51.26], unmet treatment needs [48.26 vs 37.19], wellbeing during attack [57.32 vs 45.23], and gout concern during attack [63.58 vs 54.09]. Furthermore, higher healthcare utilization was observed in patients experiencing a flare (table 1).

**Conclusion:** RGA imposes a considerable humanistic and economic burden. Gout flares were associated with increased healthcare resource utilization and diminished quality of life. These findings suggest unmet medical needs in refractory gouty patient population.

**Table 1. Healthcare resource utilization survey over 12 months’ observation period (All locations)**

<table>
<thead>
<tr>
<th>Patients having a gout flare</th>
<th>Patients not having a gout flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 334</td>
<td>N = 119</td>
</tr>
<tr>
<td>Percent of patients visited emergency unit for gout in the last year</td>
<td>21.3% 6.7%</td>
</tr>
<tr>
<td>Percent of patients admitted to the hospital for gout in the last year</td>
<td>15.0% 5.9%</td>
</tr>
<tr>
<td>Percent of patients who visited their doctor or another physician for gout in the last year</td>
<td>62.0% 49.6%</td>
</tr>
<tr>
<td>Percent of patients who needed help at home due to gout in the last year</td>
<td>43.7% 21.8%</td>
</tr>
</tbody>
</table>

**Disclosure:** L. Bessette, Novartis, 2; F. Liote, Novartis, Ipsen, Sanofi, 1; Novartis, SOBI, Astra-Zeneca, Savient, Ipsen, Menarini, M-Ayloly-Spindler, 2; Novartis, Ipsen, Menarini, Savient, Astra-Zeneca, M-Ayloly-Spindler, 3; C. Moragues, Novartis, 2; R. Moeick, Novartis, 2; Z. Zhiyi, Novartis, 2; A. Ferreira, Novartis Pharma AG, Basel, 3; P. Lecomte, Novartis Pharma AG, Basel, 3; S. Kessabi, Novartis Pharma AG, Basel, 3; H. Tian, Novartis Pharmaceuticals Corporation, East Hanover NJ, 3; J. Singh, Takeda, Savient, Novartis, 2; Savient, Takeda, Regeneron and Aligaran, 5.
Background/Purpose: The objective detection and quantification of disease activity in its earliest pathophysiological stage is critical for achieving optimal therapy results. Fluorescence optical imaging (FOI) is a novel imaging modality for the hands & wrists, and automated quantification of the ensuing images using DACT (Disease ACTivity)-FOI as a novel algorithm representing activity. This study was designed to determine the utility of FOI as a diagnostic tool, and whether it could be used in lieu of color/power Doppler ultrasound (US) to quantify and ascertain apparent & non-apparent active synovitis.

Methods: A total of 872 hand/wrist joints in 26 patients (18 female, 8 male, average age 51.5 years) with various rheumatic diseases (RA: 12, IIA, SLE, DM, FM, PA & polyarthritis 1-2 each) were examined by standard clinical assessment, US and DACT-FOI. Joints swollen & tender or swollen only were considered clinically inflamed. Active synovitis was defined as having synovial thickening & Doppler activity on US. Joints positive by FOI displayed abnormal focal optical intensities by visual inspection. Silent synovitis was defined as showing synovitis by US but not clinically. The DACT value was digitally quantified per patient by an automated computer-based algorithm of the composite image (240 frames). After clinical, US and FOI positive joints for each hand were calculated, the sensitivity, specificity & kappa stats calculated & compared with the mean DACT values for all patients.

Results: Out of 872 joints, 242 (16%) were inflamed clinically, 241 (28%) by US, and 229 (26%) by FOI. There was moderate agreement for synovitis detection between clinical examination & US (kappa 0.45 ± 0.033; 95% CI: 0.459 – 0.589), and between clinical examination & FOI (kappa 0.450 ± 0.035; 95% CI: 0.381 – 0.519). Of the 241 inflamed joints by US, 196 (81%) were also inflamed by FOI, while only 119 (49%) were inflamed clinically. Agreement between US and FOI in synovitis detection was good (kappa 0.773 ± 0.024; 95% CI: 0.725 – 0.821). Depending on the gold standard used to define inflammation, FOI was 73–83% sensitive and 86–95% specific for detecting synovitis.

Of 730 non-inflamed joints by clinical examination, 608 (83%) were non-inflamed by US and 605 (83%) were non-inflamed by FOI. Of these clinically non-inflamed joints, 122 (17%) were inflamed by US. For detecting silent synovitis, FOI was 80% (98/122) sensitive and 96% (581/608) specific. The number (mean ± SD) of active joints detected by clinical, US and FOI was 5.4 ± 7.6, 9.4 ± 9.6, and 9.3 ± 9.7 respectively, and the overall average disease activity DACT-FOI was 4.3 ± 2.1. There was a strong positive correlation (r = 0.556; p = 0.003) between the clinical detection of synovitis & DACT-FOI. The mean DACT values also correlated significantly with US (r = 0.479; p = 0.013) and semi-quantitative FOI (r = 0.515; p = 0.007).

Conclusion: FOI and the automated analysis DACT-FOI were technically feasible with high reproducibility and agreement with clinical scoring & US. For detecting synovitis semi-quantitatively, FOI had a lower sensitivity but similar specificity compared to US. FOI may be particularly useful in identifying patients with clinically non-apparent hand/wrist inflammation (silent synovitis).

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Background/Purpose: Recurrent flares in RA patients in complete remission (CR) are not an uncommon phenomenon. Studies with advanced imaging techniques have suggested that residual subclinical synovitis can still be present despite clinical remission and has been linked to ongoing radiological damage. Our group has shown that positron emission tomography with macrophage targeting (18F-C1-PK11195 PET) is a highly sensitive and specific technique to visualize (sub)clinical arthritis activity. In the current study we investigated if 18F-C1-PK11195 PET can depict residual disease activity in early RA patients in drug-induced CR and whether the inflammatory activity on the scans was associated with the development of a flare (as compared to MRI).

Methods: 18F-C1-PK11195 PET (HRRT, CT1/Siemens) of hands/wrists was performed in 25 RA patients that had no tender or swollen joints after treatment with combined DMARD therapy (DA S44<16). (R) - 18F-C1-PK11195 uptake (visual score: 0 (low)-3 (high)) in metacarpophalangeal, proximal interphalangeal and wrist joints (n=22/joint/patient) was scored and corrected for background uptake. Individual joint scores were summed to obtain a cumulative PET score (range 0-66). Follow-up duration was 1 year after PET. Flare of clinical disease activity was defined as ≥ 1 swollen joint.

Results: Of the included patients, 14 out of 25 (56%) developed a clinical flare of arthritis anywhere within 1 year of follow-up. (R)-18F-C1-PK11195 PET showed enhanced tracer uptake in at least one scanned joint in 11/25 (44%) patients. Cumulative PET scores of patients developing a flare tended to be higher than that of patients without a flare (median (IQR) 1 (0–4) vs 0 (0–1), p=0.04). Patients with a cumulative PET score of 4 and higher, all developed arthritides in hands/wrists within 6 months. As comparison, MRI scans of all included patients were positive regardless of flare, not distinguishing between subgroups of flare and no flare (Fig right).

Conclusion: Macrophage targeting by (R)-18F-C1-PK11195 PET can visualize subclinical synovitis in hands/wrists of drug-induced remission in early RA. Uptake of (R)-18F-C1-PK11195 was higher in patients with a flare compared to those without a flare. High cumulative PET scores seem to be associated with short-term development of flare. In comparison to MRI, PET may have superior diagnostic value with respect to specificity. Larger cohort studies are needed to confirm these data.
these criteria were 4.35 and 4.13, respectively, and no differences were observed between these two groups in clinical presentations. FDG-PET/CT revealed that all PMR cases showed a high FDG uptake in PMR-specific accumulation sites, including the shoulder joints, sternoclavicular joints, hip joints, spinous processes, ischial tuberosities, and greater trochanters. However, non-PMR cases showed various patterns of accumulation. Furthermore, no non-PMR case showed a high FDG uptake in the PMR-specific accumulation sites.

**Conclusion:** These results indicate the usefulness of FDG-PET/CT for the differential diagnosis of polymyalgia-like illness including paraneoplastic syndrome. Together with the current diagnostic criteria, accumulation of FDG in PMR-specific sites is useful to more accurately diagnose PMR. Various patterns of FDG uptake on FDG-PET/CT in patients with polymyalgia-like illness reveal the diversity of pathogenesis in similar clinical presentations.

Figure 1. Typical FDG-PET/CT findings in a patient with PMR. PMR case showed a high FDG uptake in PMR-specific accumulation sites, including cervical and lumbar spinous processes (A), shoulder joints and sternoclavicular joints (B), hip joints and greater trochanters (C) (ischial tuberosities, and knee joints (D)).

**Disclosure:** H. Horikoshi, None; T. Nakashiki, None; R. Takahashi, None; F. Kimura, None; K. Ishih, None.

2129

**Sensitivity and Specificity of the “Green Nail” Sign in Fluorescence Optical Imaging in Psoriatic Arthritis.**

**Oliver Wiemann**1, Stephanie G. Werner2, Hannah Röver3, Gudrun Lind-Albrecht1, Sabine Mettler1, Marina Backhaus2 and Hans-Eckhard Langer1. 1RHIO (Rheumatology, Immunology, Osteology), Duesseldorf, Germany, 2Charite University Hospital, Berlin, Germany, 3University of Erlangen-Nuremberg, Erlangen, Germany.

**Background/Purpose:** ICG-enhanced fluorescence optical imaging (FOI) is a novel technology for the assessment of inflammation in arthritis [1,2]. Recent work suggested that a “green nail” sign in a FOI sequence could possibly be diagnostic for psoriatic arthritis (PsA) [3]. The objective of this study was to determine the sensitivity and specificity of this finding.

**Methods:** 215 consecutive FOI sequences (n=54 PsA, n=29 RF + RA, n=67 RF - RA, n=19 uA, n=16 SpA, n=30 other) were read for PVM, P1, P2 and P3 [1] separately. “Green nail” was defined as a caldera-like configuration with a larger rounded green area in the center of the nail and a smaller surrounding of circular or semicircular red or white FOI signals (fig).

**Results:** The green nail sign was observed in 18/54 subjects with PsA (33%), 2/29 RF + RA (7%), 10/67 RF - RA (15%), 4/19 uA (21%) and 5/46 other diagnoses (11%) (sensitivity of 0.33, specificity of 0.87). In 9 subjects with green nails and diagnoses different from PsA, clinical findings (e.g. nail changes, enthesitis, dactylitis) were suspicious to PsA. After exclusion of those cases specificity increased to 0.93. In PsA green nails were observed predominantly in FOI phase 1 or in early phase 2. The finding was observed more frequently in advanced (≥ 24 months, 13/36, 36%) than in early arthritis (5/18, 28%). The green nail sign has to be distinguished from a green dot phenomenon that was observed in some cases with RA (small green dot at the borderline between nail and nail fold) and from signs of impaired perfusion in connective tissue diseases and vasculitis that are typically located in the distal, acral regions of the fingers.

**Conclusion:** While the prevalence of the green nail sign in FOI sequences is relatively low the high specificity for psoriatic arthritis suggests that this finding could provide important additional information for differential diagnosis.

**References**


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2130

**Bone Microstructure in Patients with Cutaneous Psoriasis and No History of Psoriatic Arthritis Shows Bone Anabolic Changes at a Greater Extent Than in Healthy Controls.**

**David Simon**1, Francesca Faustini1, Matthias Englbrecht2, Amd Kleyer2, Roland Koci2, Judith Haschka1, Stephanie Finzel1, Sebastian Kraus1, Axel J. Hueber1, Michael Sticherling1, Georg Schett1 and Jürgen Rech1, 1University of Erlangen-Nuremberg, Erlangen, Germany, 2St. Vincent Hospital, Vienna, Austria.

**Background/Purpose:** Psoriasis (PSO) is a frequent disease which affects about 1–2% of the population and can be associated to arthritides (PsA). Skin disease often predates the onset of PsA and the transition from skin to joint pathology has been not yet fully elucidated. PsA bone changes include erosions and new bone formation. A aim of the present study was to investigate whether patients with PSO, without clinical history of synovitis, dactylitis or enthesitis at any time and no fulfillment of CASPAR criteria show early changes of the periarticular bone that are typical of PsA.

**Methods:** PSO patients and healthy subjects (HS) underwent HR-pQCT (Xtremed, T. Scanco Medical, Switzerland) scans of the dominant hand which focused on the metacarpal head and phalangeal base of the MCP joints 2 and 3. Erosions, defined as cortical breaks within the joint and visible in two planes, were assessed by frequency and volume (mm³). Bony spurs, defined as bony projections emerging from the cortical shell and located in the periarticular region were assessed by frequency and maximal height (mm) i.e.
the distance between the highest surface of the lesion and the original cortical surface). Patients participated after signing informed consent. The study was conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BSF).

**Results:** Images were acquired from 55 PSO patients (mean age 49.5±11.5 y, 36.4% females) and 47 HS (mean age 45.8±13.0 y, 48.9% females). Mean age and sex distribution were comparable. PSO patients had mean disease duration of 15.2±15.4 y, a mean PSAI score of 6.2±8.0, while the most prevalent subtype was psoriasis vulgaris (73%). Nail psoriasis was present in 51% and scalp involvement in 29%. Erosions were identified in PSO and HS (27 vs 18). The most frequent location of the erosions was the radial aspect of the metacarpal head 2 in both groups. The volume of the erosion was not significantly different between the groups. An average number of 6 bony spurs was found in the PSO patients while this accounted for 3 in the HS (total number 306 vs 138). A similar trend of distribution of the number of 6 bony spurs was found in the PSO patients while this accounted for 1.2 respectively, 0.3 mm, 0.3 mm respectively,

In the phalangeal base 2 the PSO patients showed a mean size of 1.3±0.7 mm, and the HS of 0.7±0.3 mm, p=0.001. In the phalangeal base 3 mean values accounted for 1.2±0.7 mm and 0.8±0.2 respectively, p=0.005.

**Conclusion:** A multivariate logistic regression (forward and backward procedure) to explain the potential of flares to represent the persistence of disease activity and it was used to determine whether these flares can worsen radiographic joint damage. The aim of this study was to see whether transient flares increase the risk for radiographic progression.

**Methods:** From 287 patients included in the AMBRA trial, 276 RA patients with low disease activity (DA28-ESR < 3.2, and no swollen joints at baseline) with radiographs available at baseline and data about flares, were followed for two years. An annual clinical evaluation was performed by a senior rheumatologist and at the same occasion the patients were asked to recall the occurrence of flares during the past year, according to: No flares, transient flares or persistent joint complaints with tender and swollen joints. Radiographs of hands and feet were performed at baseline and after two years and scored according to the Sharp/van der Heijde method. The change in total Sharp Score (TSS) and its components (Joint Space Narrowing (JSN) and Erosions (E)) were calculated. The proportion of patients who progressed (ΔTSS, ΔJSN/ΔE > 0 units) across the three groups were compared using Chi-square test and interpreted based on Relative Risks (RR).

**Results:** 70% of patients were women, median age [IQR] was 63 years [55.70]; 73% were rheumatoid factor positive, 71% anti-CCP positive and all had established RA (median [IQR] 7 years [4;13]). In total 268 out of the 276 patients had two year radiographic scores: Radiographic progression depicted by either ΔTSS, ΔJSN, or ΔE, respectively, was seen in 33%, 7%, and 28% of no-flares group (n=82); 36%, 17%, and 31% of patients with transient flares (n=144) and in 46%, 24%, and 34% of patients with persistent joint complaints (n=50). Only differences in worsening of JSN (Figure 1) were statistically significant (P=0.026); RR was 2.37 for the transient flares group and 3.28 for the group with persistent joint complaints compared to the no flares group. Worsening of TSS and E showed some tendencies according to the flare phenotype, but they were not statistically significant.

**Conclusion:** RA patients with established low active disease, who report transient flares or persistent joint complaints with tender and swollen joints, have more radiographic damage on JSN (which has recently been reported as the main driver of physical disability) in comparison to no-flares patients.

**Disclosure:** D. Simon, None; F. Faustini, None; M. Engbrecht, None; A. Kleyer, None; R. Kocijan, None; J. Haschka, None; S. Finzel, None; S. Kraus, None; A. J. Hueber, None; M. Sticherling, None; G. Schett, None; J. Rech, None.

**2131**

The Impact of Patient-Reported Flares on Radiographic Progression in Rheumatoid Arthritis Patients with Low-Disease Activity: Secondary Analyses from a Randomized Trial

**Background/Purpose:** Flares, potentially disabling and disease worsening even when a patient is in low disease activity, are common features in patients with rheumatoid arthritis (RA) that may escape the routine clinical control. Consequently the current treat-to-target goal to achieve remission or low disease activity fails to take into account the potential of flares to represent the persistence of disease activity and it remains unknown whether these flares can worsen radiographic joint damage. The aim of this study was to see whether transient flares increase the risk for radiographic progression.

**Methods:** From 287 patients included in the AMBRA trial, 276 RA patients with low disease activity (DA28-ESR < 3.2, and no swollen joints at baseline) with radiographs available at baseline and data about flares, were followed for two years. An annual clinical evaluation was performed by a senior rheumatologist and at the same occasion the patients were asked to recall the occurrence of flares during the past year, according to: No flares, transient flares or persistent joint complaints with tender and swollen joints. X-rays of hands and feet were performed at baseline and after two years and scored according to the Sharp/van der Heijde method. The change in Total Sharp Score (TSS) and its components (Joint Space Narrowing (JSN) and Erosions (E)) were calculated. The proportion of patients who progressed (ΔTSS, ΔJSN/ΔE > 0 units) across the three groups were compared using Chi-square test and interpreted based on Relative Risks (RR).

**Results:** 70% of patients were women, median age [IQR] was 63 years [55.70]; 73% were rheumatoid factor positive, 71% anti-CCP positive and all had established RA (median [IQR] 7 years [4;13]). In total 268 out of the 276 patients had two year radiographic scores: Radiographic progression depicted by either ΔTSS, ΔJSN, or ΔE, respectively, was seen in 33%, 7%, and 28% of no-flares group (n=82); 36%, 17%, and 31% of patients with transient flares (n=144) and in 46%, 24%, and 34% of patients with persistent joint complaints (n=50). Only differences in worsening of JSN (Figure 1) were statistically significant (P=0.026); RR was 2.37 for the transient flares group and 3.28 for the group with persistent joint complaints compared to the no flares group. Worsening of TSS and E showed some tendencies according to the flare phenotype, but they were not statistically significant.

**Conclusion:** RA patients with established low active disease, who report transient flares or persistent joint complaints with tender and swollen joints, have more radiographic damage on JSN (which has recently been reported as the main driver of physical disability) in comparison to no-flares patients.

**Disclosure:** D. Simon, None; F. Faustini, None; M. Engbrecht, None; A. Kleyer, None; R. Kocijan, None; J. Haschka, None; S. Finzel, None; S. Kraus, None; A. J. Hueber, None; M. Sticherling, None; G. Schett, None; J. Rech, None.

**2132**


**Background/Purpose:** Persistent inflammation on Power Doppler (PD) by ultrasound (US) was associated with relapse and structural progression after one year of follow up in a cohort of RA patients in low disease activity (LDA).

**Methods:** Patients with RA (1987 ACR criteria) were included in 2007–2008 in one centre if their diagnosis of RA was recent (≤ 2.4). All patients underwent clinical and biological assessments every year. Hands and forefeet X-ray were performed at baseline and at 5 years and evaluated blindly by two investigators (van der Heijde Sharp score: mTSS). Progression was defined as a variation of the mTSS superior to the smallest detectable difference (SDD) of 6.6 points. The metacarpophalangeal (MCPs) joints 2-5 and wrist of the dominant hand were examined with a 0.2T dedicated MRI scanner. 

**Results:** The association between the structural progression at 5 years and MRI/US covariates was measured by Wilcoxon Mann-Whitney tests or Fisher’s exact test, then by a multivariate logistic regression (forward and backward procedure) to explain a progression > SDD.

**Conclusion:** 85 patients were included: mean age 50.7 (±13.5) y; mean disease duration 35 ±(±20.7) months, 63.5% patients were anti-CCP positive and mean DAS44 was 1.5 (± 0.54). At baseline the median score [interquartiles] of the grade of synovitis for US and MRI was respectively 3 [1,5] and 0.5 mm, 0.5 mm respectively, 0.3 mm, 0.3 mm respectively, 0.3 mm.
3 [4;7]. The median of the number and the grade of synovitis PD positive were 0 [0;1]. The median of the number and the grade of bone marrow edema (BME) were 0 [0;0]. 17 patients (20%) and 8 patients (9%) had respectively score of PD or BME above the median. At 5 years, 13 patients of 70 followed up, were considered in progression. In bivariate analysis X-ray progression at 5 years was associated with baseline number of synovitis PD >0 (p = 0.0001), grade of synovitis DP >0 (p = 0.0001), and total RAMRIS = 14 (p = 0.03). In multivariate analysis the number of synovitis PD >0 (adjusted OR 9.8 [95% CI 1.7–4.1]) was associated with X-ray progression.

**Conclusion:** Persistence of Doppler signal on US was the best predictor of structural progression on X-ray at short and long term, in a cohort of patients in LDA. Further studies should assess whether patient management guided by US may decrease relapses and X-ray progression.

Disclosure: V. Foltz None; L. Biale None; F. Gandja-bachik None; L. Gose None; P. Bourgeois None; B. Granger None; B. Fautrel None.

**2133**

**Efficacy of Tocilizumab Therapy in Patients with Rheumatoid Arthritis Based on FDG-PET/CT.** Koichi Okamura1, Yukio Yonemoto 1, Chisa Okura2, Kenji Takagishi1, Gunma University, Maebashi, Japan, 2Gunn University Graduate School of Medicine, Maebashi, Japan.

**Background/Purpose:** A humanized anti-interleukin-6 receptor (anti-IL-6R) antibody, tocilizumab (TCZ), is one of the biologics and the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) immediately following administration, 4–6 hours and 24 hours post injection. Immunosintigraphic findings were scored as either negative (no or faint uptake), inconclusive (clear uptake, but small and non-progressive inflammation) or positive (large uptake). The number of positive scintigraphic joints was counted at baseline and at 6 months and standard clinical assessments were performed. Statistical analysis for the joint based response (tender and swollen) was based on a logistic regression model including patient as random effect to accommodate for clustering of the joints in the patients and using the odds ratio (OR) as summary statistic.

**Results:** 20 patients were included (RA n = 5, SpA n = 15), scanned and treated according to the protocol. Images 4–6 hours post-injection yielded the best discriminatory results of radiolabeled uptake. Immunoscintigraphy was a good predictor for a joint being swollen at baseline as only 2.2% of the immunoscintigraphic joints remained swollen and 63.3% of the immunoscintigraphic joints remained positive.

**Conclusion:** Baseline immunoscintigraphic detection of TNFα with radiolabeled anti-TNFα antibodies may be helpful to optimize and monitor the effect of TNFα blockade. This technique may facilitate evidence-based biological therapy by in vivo measurement in inflamed joints of a cytokine, prior to therapeutic administration of a biologic.

Disclosure: P. Carron None; B. Lambert None; F. De Vos None; G. Verbruggen None; E. Elewaout None; F. Van Den Bosch None.

**2134**

**Baseline Scintigraphic Detection of TNFα As a Predictor of Therapy Response after Treatment with Certolizumab Pegol in Rheumatoid Arthritis and Spondyloarthritis Patients.** Philippe Carron1, Bieke Lambert2, Filip De Vos3, Gust Verbruggen1, Dirk Elewaout4 and Filip van Den Bosch3.

1Department of Rheumatology Ghent University Hospital, Ghent, Belgium, 2Department of Nuclear Medicine Ghent University Hospital, Ghent, Belgium, 3Department of Radiopharmacy Ghent University, Ghent, Belgium.

**Background/Purpose:** A major challenge in the biologic era is to predict clinical response. A large variability in the effect of TNF-α blockade has been recognized which may influence the outcome of TNF-α antagonism. Thus far, treatment decisions are solely based on clinical disease activity. In this way, only 40% of rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients achieve a clinically important response (ACR50 or ACR70). We hypothesized that in vivo assessment of TNFα by scintigraphy with 99mTc-radiolabeled anti-TNFα antibodies may be helpful to optimize and monitor the effect of TNFα blockade. This technique may facilitate evidence-based biological therapy by in vivo measurement in inflamed joints of a cytokine, prior to therapeutic administration of a biologic.

**Objective:** Predict response to therapy by baseline immunoscintigraphy before starting anti-TNF treatment in active RA and SpA patients.

**Methods:** Certolizumab pegol (CZP) was radiolabeled with Tc99m. Whole body images and static images of hands and feet were acquired immediately following administration, 4–6 hours and 24 hours post injection. Immunoscintigraphic findings were scored as either negative (no or faint uptake), inconclusive (clear uptake, but small and non-progressive inflammation) or positive (large uptake). The number of positive scintigraphic joints was counted at baseline and at 6 months and standard clinical assessments were performed. Statistical analysis for the joint based response (tender and swollen) was based on a logistic regression model including patient as random effect to accommodate for clustering of the joints in the patients and using the odds ratio (OR) as summary statistic.

**Results:** 20 patients were included (RA n = 5, SpA n = 15), scanned and treated according to the protocol. Images 4–6 hours post-injection yielded the best discriminatory results of radiolabeled uptake. Immunoscintigraphy was a good predictor for a joint being swollen at baseline as only 2.2% of the immunoscintigraphic joints remained swollen and 63.3% of the immunoscintigraphic joints remained positive.

**Conclusion:** Baseline immunoscintigraphic detection of TNFα with radiolabeled anti-TNFα has a significant predictive value at baseline and after 24 weeks treatment with CZP on the tender joint count. Tender joints not identified by immunoscintigraphy respond to a lesser degree to anti-TNF treatment, potentially indicating another biological reason for a painful joint. Therefore TNFα-immunosintigraphy could offer a new tool to identify good clinical responders to biological treatment.

Disclosure: P. Carron None; B. Lambert None; F. De Vos None; G. Verbruggen None; E. Elewaout None; F. Van Den Bosch None.
Rheumatoid Arthritis Erosion Detection and Measurement in Longitudinal Datasets Using High-Resolution Peripheral Quantitative Computed Tomography. Stephanie Finzel*, Cheryl Barnabe*, Kathryn Stok*, A. Scharmgä, Andrew J. Burghardt†, Ellen-Margrete Haugen‡, Hubert Marotte‡, Stephanie Boutroy*, Klaus Engelke*, Dominique Toepfer*, Sebastian Kraus*, Roland Kocijan*, Xiaojuan Li‡, and J. de Jong*. 1University of Erlangen-Nuremberg, Erlangen, Germany, 2University of Calgary, Calgary, AB, 3ETH Zurich Institute for Biomechanics, Zurich, Switzerland, 4Maas-tricht University Medical Center, Maastricht, Netherlands, 5Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, 6Aarhus University Hospitals, Aarhus, Denmark, 7University Hospital of Saint Etienne, Saint Etienne, France, 8INSERM U1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, 9Institute of Medical Physics Synarc, Hamburg, Germany, 10St. Vincent Hospital, Vienna, Austria.

Background/Purpose: An operational case definition for identification of erosions imaged by HR-pQCT was achieved and tested in a first reliability exercise (RELEX-I) using cross-sectional data. Aims of the study: to test the case definition and define landmarks for measurement of erosion size in 2D in a longitudinal dataset.

Methods: The Early Rheumatoid Arthritis Study (ERAS) is an inception cohort that recruited 1,465 recent onset, DMARD naïve, RA patients from 9 hospitals in England between 1986 and 1998, with follow up for up to 25 years. Data collected included demographics, disease activity (DAS), functional disability (HAQ) and radiographs of hands and feet (Larsen). A total of 1,409 (96%) patients had at least one DAS score over the first 5 years of follow-up. Patients mean DAS score over the first 5 years was calculated, and patients were split into three categories based on this score. Patients with a mean score of 5.2 as severe (n=304), in accordance with the EULAR definitions. A mixed effects negative binomial regression was conducted to analyse the rate of Larsen progression over the first 5 years of disease. Follow-up year, age at onset, sex, treatment at 5 years, baseline HAQ and baseline HB were controlled for in the model.

Results: Patients in the severe group were older, more likely to be female, Rheumatoid Factor positive, higher baseline HAQ, lower baseline HB and shorter follow-up. Patients in the moderate group had a significantly higher progression of Larsen over the 5 years compared to those patients in the mild group (P<0.001). There was no significant difference in 5 year Larsen progression between the moderate and severe groups.

Conclusion: Patients with moderate disease had similar radiographic progression to severe disease, whilst controlling for treatment. Similarly, patients with moderate disease had significantly higher Larsen progression compared to those with mild disease. Results highlight that targeting this group and aiming for remission, or at least better disease control, is as important as for those with high disease.

Disclosures: L. Carpenter, None; E. Nikiphorou, None; S. Norton, None; K. Jayakumar, None; J. Dixey, None; A. Young, None.

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Rheumatoid Arthritis Erosion Detection and Measurement in Longitu-dinal Datasets Using High-Resolution Peripheral Quantitative Computed Tomography. Stephanie Finzel*, Cheryl Barnabe*, Kathryn Stok*, A. Scharmgä, Andrew J. Burghardt†, Ellen-Margrete Haugen‡, Hubert Marotte‡, Stephanie Boutroy*, Klaus Engelke*, Dominique Toepfer*, Sebastian Kraus*, Roland Kocijan*, Xiaojuan Li‡, and J. de Jong*. 1University of Erlangen-Nuremberg, Erlangen, Germany, 2University of Calgary, Calgary, AB, 3ETH Zurich Institute for Biomechanics, Zurich, Switzerland, 4Maastricht University Medical Center, Maastricht, Netherlands, 5Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, 6Aarhus University Hospitals, Aarhus, Denmark, 7University Hospital of Saint Etienne, Saint Etienne, France, 8INSERM U1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, 9Institute of Medical Physics Synarc, Hamburg, Germany, 10St. Vincent Hospital, Vienna, Austria.

Background/Purpose: An operational case definition for identification of erosions imaged by HR-pQCT was achieved and tested in a first reliability exercise (RELEX-I) using cross-sectional data. Aims of the study: to test the case definition and define landmarks for measurement of erosion size in 2D in a longitudinal dataset.

Methods: Patients meeting the new ACR/EULAR classification criteria for RA at various stages of disease duration and severity received a HR-pQCT scan of the 2nd and 3rd MCP joints at 0 and 12 months. Standard image acquisition and segmentation was performed for a 2.7 cm scan area. Images were evaluated for erosions at 8 surfaces per joint (ulnar, radial, dorsal, palmar surfaces of the proximal phalanx and metacarpal head). The erosion case definition requires the presence of a definite interruption in the cortical bone extending over at least 2 consecutive slices, visualized in 2 orthogonal planes, with true erosion of existing bone and being non-linear in shape. The maximal width of the cortical break is identified and measured in the axial multiplanar resolution (MPR), with the maximal depth recorded perpendicular to this line. This same method is repeated in the corresponding MPR. Five readers blinded to patient identity and time sequence of the scan scored 36 baseline and follow-up images (18 joints from 9 patients). Percent agreement and a kappa score for erosion detection (minimum of 2 readers in agreement) was calculated. The variation in width and depth measurements of erosions in axial and perpendicu lar planes between readers was calculated using the root-mean-square coefficient of variance (RM SCV). M C N ema r’s test was used to test for a significant change in the number of erosions identified from 0 to 12 months. Paired t-tests were used to calculate the average width and depth changes from 0 to 12 months.

Results: A score for the presence or absence of an erosion was 92.9% (k=0.711, 95%CI 0.539–0.839). Mean (SD) dimensions of the erosions were: axial width 1.66 (SD 0.99) mm, perpendicular width 1.60 (SD 0.78) mm, axial depth 1.16 (SD 0.66) mm, and perpendicular depth 1.17 (SD 0.57) mm. The respective RM SCV were 36.4%, 30.3%, 15.7% and 27.3%. Seven erosions were detected at both 0 and 12 month timepoints (k=0.755, 95%CI 0.616–0.895) and all readers agreed on a single new erosion developing over 1 year but a trend to reduction in mean size was observed, with an axial width decrease of 0.171 mm (95%CI -0.168, 0.509, p=0.310), perpendicular width decrease of 0.014 mm (95%CI -0.202, 0.230, p<0.098), axial depth increase of 0.007 mm (95%CI -0.147, 0.133, p=0.917), perpendicular depth decrease of 0.133 mm (95%CI -0.075, 0.340, p=0.201).

Conclusion: The case definition for erosions imaged by HR-pQCT is valid in longitudinal datasets. Despite variability in measurements, a trend towards changes in erosion size is demonstrated.

Disclosures: S. Finzel, None; C. Barnabe, None; K. Stok, None; A. Schargmä, None; A. J. Burghardt, None; E. M. Hauge, None; H. Marotte, None; S. Boutroy, None; K. Engelke, None; D. Toepfer, None; S. Kraus, None; R. Kocijan, None; X. Li, None; J. de Jong, None.

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Linear Extrapolation of Missing Radiographic Progression Scores Does Not Spuriously overestimate overall Radiographic Progression in Rheuma-toid Arthritis. Iris Markusse, Robert Landéwé, Melliën Ho, Martin Jenkins and Desiree van der Heijde*. 1Leiden University Medical Center, Leiden, Netherlands, 2Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 3AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom.

Background/Purpose: Linear Extrapolation (LE) is a frequently applied method to impute missing radiographic data in trials. However, there is frequent critique that LE overestimates overall progression. Therefore, ‘Last Observation Carried Forward’ (LOCF) has been suggested by regulatory bodies as a more conservative method. In the OSKIRA-1 trial (NCT01197521), radiographs were taken at the 12 week (wk) time point, where early escape was possible, in all patients thus providing an excellent opportunity to compare extrapolations based upon LOCF and LE to the truly observed radiographic progression.

Methods: The phase 3 OSKIRA-1 trial enrolled rheumatoid arthritis patients (pts) with an inadequate response to methotrexate. Films of hands and feet were obtained at baseline, wk 12 and 24 in those pts still on study, and were assessed by two readers in random time order using the van der Heijde modified total Sharp score (mTSS). Ten datasets with an artificially, randomly selected sample of 20% missing wk 24 data were created, based upon pts with complete sets of films. First, these missing data were imputed using LE as $mTSS \text{ at wk 12 } + \text{ progression wk 12 - 24, corrected for the actual days between films}$. Second, the missing data were imputed using LOCF. This approach was iterated for 10 random samples with 50% missing data and 10 random samples with 80% missing data. The datasets obtained with LE and LOCF were compared to the dataset with truly observed data at week 24.

Disclosures: S. Finzel, None; C. Barnabe, None; K. Stok, None; A. Schargmä, None; A. J. Burghardt, None; E. M. Hauge, None; H. Marotte, None; S. Boutroy, None; K. Engelke, None; D. Toepfer, None; S. Kraus, None; R. Kocijan, None; X. Li, None; J. de Jong, None.

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Results: Complete sets of films were available for 579 pts. All our analyses were essentially similar in the 3 treatment arms, so here we present the analysis on pooled data. Mean (SD) observed progression from baseline to wk 24 was 0.33 (2.42). Table 1 shows the average (SD) and range of the mean radiographic progression in the 10 random samples. Using LE, the mean progression estimates were closer to the observed data, and not affected by the proportion of missing data. The SD however increased by increasing proportions of missing data. Using LOCF, the mean progression estimates were consistently lower than the observed progression. LOCF increasingly underestimated observed progression by increasing proportions of missing data. As expected, the SD of the LOCF estimates remained stable by increasing proportions of missing data.

Conclusion: In contrast to LOCF, linear extrapolation gives a more accurate impression of true mean radiographic progression at a group level and is less influenced by the proportion of missing data. Since LE inflates the standard deviation of progression scores, the statistical power to detect a significant difference between active treatment and placebo may decrease by increasing proportions of missingness. LE does therefore not overestimate mean treatment deviation of progression scores, the statistical power to detect a significant influence of treatment subgroups (T-only, E-only, T switch to E, and E switch to T).

Table 1: Change in the van der Heijde modified total Sharp score (mTSS) from baseline to week 24.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean (SD)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE</td>
<td>0.28 (2.43)</td>
<td>0.20</td>
<td>2.38</td>
<td>0.28 (2.48)</td>
<td>0.20</td>
<td>2.44</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.33 (2.43)</td>
<td>0.24</td>
<td>2.38</td>
<td>0.33 (2.48)</td>
<td>0.24</td>
<td>2.44</td>
</tr>
</tbody>
</table>

*of 10 random samples

LE, linear extrapolation; LOCF, last observation carried forward; mTSS, van der Heijde modified total Sharp score; SD, standard deviation.

Disclosure: I. Markevsic, None; R. Landewe, Rheumatology Consulting BV, 9; M. Ho, AstraZeneca, 3, AstraZeneca, 1; M. Jenkins, AstraZeneca, 3, AstraZeneca, 3; D. van der Heijde, AstraZeneca, 9, Imaging Rheumatology BV, 9.

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Background/Purpose: We investigated whether early, remission steered treatment can prevent disease progression in patients with early rheumatoid arthritis (RA) or undifferentiated arthritis (UA), and aimed to identify potential predictive factors for damage progression.

Methods: 610 patients with early RA (2010 criteria) or UA suspected to be early RA started treatment with methotrexate (MTX) and a tapered high dose of prednisone. Predictors for radiological progression were age and the combination of anti-CarP positivity and ACPA positivity.

Results: Progression scores were available for 488 patients with a median (IQR) of progression of 0 (0-0) point. There was no difference in median SHS progression score between RA and UA patients nor between treatment arms. In only 10% (50/488 patients) radiological progression (>0.5 SHS) was seen: 33/50 (66%) were in the early remission group, 9 (18%) in arm 1, 5 (10%) in arm 2 and 3 (6%) were treated outside the protocol. In 98 patients (7 in the early remission group and 1 in arm 2) the progression score was ≥5 points (minimally clinically important difference) after two years. Age (OR (95% CI) 1.03 (1.00-1.06)) and the combination of anti-CarbP (anti-carbamylated protein antibodies) positivity and ACPA (anti-citrullinated protein antibodies) positivity (2.54 (1.16-5.58)) were independent predictors for radiological progression.

Conclusion: After 2 years of remission steered treatment in early arthritis patients radiological progression in the majority of patients was practically zero. The lack of significant difference in RA and UA arms following initial combination therapy with methotrexate and a tapered high dose of prednisone. Predictors for radiological progression were age and the combination of anti-CarbP positivity and ACPA positivity.

Disclosure: G. Akdemir, None; L. Heimans, None; K. V. C. Wevers-de Boer, None; M. K. Verheul, None; A. A. Schouffoer, None; M. van Oosterhout, None; J. B. Harbers, None; C. Bijkerk, None; G. M. Steup-Beekman, None; L. R. Lard, None; T. W. J. Huizinga, None; L. A. Trouw, None; C. F. Allaart, None.

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Predictors of Radiologic Disease Progression during the Rheumatoid Arthritis Comparison of Active Therapies Trial. Alan Erickson, Denis Rybin, Mary Brophy, Robert Lew, T. Nikulis, Timothy More, Keri Hannagan, Edward Keystone and James O’Dell. 1OMaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE; 2VA Boston Healthcare System, Boston, MA; 3University of Nebraska Medical Center, Omaha, NE; 4University of Toronto and M cM ourt Sinai Hospital, Toronto, ON.

Background/Purpose: Halting joint damage is a central goal in the treatment of rheumatoid arthritis. Much research has been conducted to identify factors associated with progressive radiographic damage typically measured as the Sharp/van der Heijde score (SHS). Trials have also suggested that treatment choices impact disease course including the development of radiographic progression, defined as a threshold change in SHS ≥5 U/year. In the 48-week, double-blind, noninferiority RACAT trial, 353 patients with suboptimal methotrexate response were randomized to two treatment strategies, either first adding sulfasalazine and hydroxychloroquine (triple therapy or T) or first adding etanercept (E). A fter 24 weeks of treatment patients not achieving a DSAS improvement of 1.2 were switched in a blinded fashion to the other therapy. We explored the associations of strategy and baseline factors with SHS progression.

Methods: Two expert readers provided SHS for patients at baseline and 48 weeks. Using the mean value of the two readers, SHS change was categorized as an increase, no change or > 0.5 U. Possible baseline predictors of change evaluated included swollen and tender joint count, ESR, Global Health Assessment, DSAS 28, gender, smoking, RF status, disease duration and baseline SHS. From logistic regression models we obtained odds ratios (OR) for each predictor alone and in multivariable models with all factors. We analyzed patients in all two treatment subgroups (T and E) and the four treatment subgroups (T-only, E-only, T switch to E, and E switch to T).

Results: Of 304 participants with both-week 48 Sharp scores, only 4.3% (13 of 304) had increases in SHS ≥5 U evenly spread over the four treatment groups, while 23% demonstrated increases ≥0.5 units again evenly spread over treatments. Approximately 60% demonstrated changes of −0.5, 0, or 0.5 U, and 17% showed improvement (<−0.5 change). Baseline SHS values were significantly different for increases ≤0.5 U compared to increases >0.5 U (15.3 vs. 26.4, p=0.006). In multivariable analyses, only baseline SHS consistently predicted disease progression (see Table 1). Other measures, including treatment strategy, were not predictive of radiographic progression. No evidence suggested that any of the four treatments was associated with change defined either as ≥0.5 U or as ≥5 U. 4% had changes ≥5 U.

Table: Uniandor multivariable associations of patient factors with SHS progression (increase >0.5 U) over 48 weeks (same results obtained using stepwise up or down selection to detect intercorrelation); *model includes all variables shown

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Sharp Score at Baseline</td>
<td>1.02 (1.01,1.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.04 (0.63,1.78)</td>
<td>0.881</td>
</tr>
<tr>
<td>Ever Smoked</td>
<td>0.58 (0.34,1.01)</td>
<td>0.052</td>
</tr>
<tr>
<td>DSAS 28</td>
<td>1.22 (0.91,1.65)</td>
<td>0.185</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>1.02 (0.97,1.07)</td>
<td>0.487</td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>1.00 (0.96,1.04)</td>
<td>0.986</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate</td>
<td>1.01 (1.00,1.02)</td>
<td>0.042</td>
</tr>
<tr>
<td>Patient Global Health Assessment</td>
<td>1.00 (0.99,1.01)</td>
<td>0.779</td>
</tr>
</tbody>
</table>
Conclusion: Similar to other trials, we found that radiologic progression is most strongly associated with baseline SHS. A weak and non-significant association with positive RF status was observed. We found no significant radiographic advantage with either of the two treatment strategies or among the 4 treatment groups. Rapid radiographic progression, an increase in SHS with either of the two treatment strategies or among association with positive RF status was observed. We found no significant agreement among FDG-PET/CT, ultrasound and physical examination. Among the 10 patients, 300 joints were included in the analysis (340 separately). Agreement among the modalities was examined using Cohen’s kappa. Confidence intervals were generated using a bootstrapping method.

Methods: Ten patients with active inflammatory arthritis underwent physical examination, ultrasound, and FDG-PET/CT. Exclusion criteria included pregnancy, elevated fasting glucose (>150) or diabetes. The examination was performed by an attending rheumatologist. US was performed by an US-trained rheumatologist fellow or a trained ultrasonographer technician. US images were read by a US-trained rheumatologist and musculoskeletal radiologist blinded to the clinical examination. PET/CTs were read by a rheumatology fellow blinded to the examination and US results. Previously reported grading scales for US synovitis, Doppler and PET/CT were used but for analysis these variables were converted to binary measures (yes/no inflammation) for analysis. Agreement among the modalities was examined using Cohen’s kappa. Confidence intervals were generated using a bootstrapping method to account for clustering by individual.

Results: Four patients with rheumatoid arthritis and 6 with psoriatic arthritis were enrolled with mean age 52.7 years and 80% male. All patients were on therapy at the time of the assessments and had relatively mild disease activity. Among the 10 patients, 300 joints were included in the analysis (340 separately, 300 PET/CT, 180 US). Of these, 46 were swollen, 50 were tender, 56 had FDG uptake on PET/CT, 26 had signs of inflammation on US grayscale and 14 were Doppler positive. Agreement among the imaging modalities and examination was low (Table), with κ ranging from 0.01–0.22. Restricting the analysis to only large peripheral joints did not substantially change agreement.

Conclusion: This is the first study to examine agreement among PET/CT, US and physical examination in the assessment of joint inflammation. In this small pilot study, we found low agreement among PET/CT with US and both PET/CT and US with physical examination findings among patients on therapy with mild disease activity. It may be that each modality measures a distinct property of inflammation, all equally valuable in measuring the construct of inflammation.

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Table 1: JSW, SDD and progression in 195 patients with hand osteoarthritis

<table>
<thead>
<tr>
<th>JSW at baseline, mean (SD)</th>
<th>JSW at two years, mean (SD)</th>
<th>SDD, mm</th>
<th>Progression, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=4570)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIP joints (n=1524)</td>
<td>0.82 (0.11)</td>
<td>0.13 (0.09)</td>
<td>0.40 (2.5)</td>
</tr>
<tr>
<td>PIP joints (n=1522)</td>
<td>0.72 (0.10)</td>
<td>0.18 (0.09)</td>
<td>0.17 (1.9)</td>
</tr>
<tr>
<td>MCP joints (n=804)</td>
<td>1.34 (0.25)</td>
<td>1.32 (0.25)</td>
<td>0.20 (2.9)</td>
</tr>
</tbody>
</table>

Disclosure: W. Damman, None; E. de Bruin, None; B. C. Stoel, None; R. van’t Koolster, None; M. Kloppenburg. Dutch Arthritis Foundation, Z.

Background/Purpose: Osteophyte formation and evolution is a hallmark of knee OA, and their radiographic identification and progression is fundamental in clinical practice, observational research and randomized clinical trials. The most commonly used grading scales are ordinal, requiring subjective judgment and expert reading time potentially hampering precision and responsiveness. We have developed a semi-automated method for osteophyte volumetric analysis on MRI. Our objective was to evaluate the subjective judgment and expert reading time potentially hampering precision of clinical practice, observational research and randomized clinical trials of knee OA, and their radiographic identification and progression is fundamental.

Methods: Ninety subjects (51 KL 2 and 39 KL 3) were selected from the Osteoarthritis Initiative (OAI) Progression Cohort. Double echo steady state (DESS) sagittal images were obtained on a 3T Siemens Trio Mf system. Measurements were performed on coronal reformatted series. A reader (MH) used software to segment marginal femoral and tibial osteophytes of all 90 knees at baseline and 48 months, blinded to order of visit. The first and last slice of the central weight bearing region were identified and an edge detection algorithm demarcated the bone margins. The reader then ‘closed off’ each osteophyte by marking the expected normal bone contour. The software calculated the total volume (V) for each compartment, bone and knee. Reliability was assessed using an experienced MSK radiologist (M) on a random sub-sample of 20 subjects.

The primary outcome was change in osteophyte volume (ΔV). Statistics used were the average change (ΔV), the standard deviation of ΔV (SD), the standardized response mean of (SRM, defined as ΔV/SD), and the percentage of subjects with net increase in V. Intraclass correlation coefficient (ICC) and root mean square of the standard deviation (RMSSD) were used to assess reliability.

Results: The average change in osteophyte volume (ΔV) was 196 mm³(272), and the SRM was 0.72. A net increase in osteophyte volume from baseline to 48 months was observed for 84% (76/90, 40 KL 2 and 36 KL 3) of the subjects. The average reading time was approximately 10 minutes per knee.

Table 1 - Responsiveness to change over 48 months

<table>
<thead>
<tr>
<th>Baseline KL grade (n)</th>
<th>Net Increase</th>
<th>Mean ΔV</th>
<th>SD ΔV</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL 2 + KL 3 (90)</td>
<td>76 (84%)</td>
<td>196 mm³</td>
<td>272 mm³</td>
<td>0.72</td>
</tr>
<tr>
<td>KL 2 (51)</td>
<td>40 (78%)</td>
<td>155 mm³</td>
<td>233 mm³</td>
<td>0.67</td>
</tr>
<tr>
<td>KL 3 (39)</td>
<td>36 (92%)</td>
<td>250 mm³</td>
<td>309 mm³</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Table 2 -- Responsiveness to change by compartment

<table>
<thead>
<tr>
<th></th>
<th>Mean ΔV</th>
<th>SD ΔV</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial Compartment</td>
<td>53 mm³</td>
<td>88 mm³</td>
<td>0.60</td>
</tr>
<tr>
<td>Lateral Compartment</td>
<td>45 mm³</td>
<td>95 mm³</td>
<td>0.48</td>
</tr>
<tr>
<td>Medial Femur</td>
<td>72 mm³</td>
<td>99 mm³</td>
<td>0.72</td>
</tr>
<tr>
<td>Lateral Femur</td>
<td>60 mm³</td>
<td>115 mm³</td>
<td>0.52</td>
</tr>
<tr>
<td>Medial Tibia</td>
<td>34 mm³</td>
<td>72 mm³</td>
<td>0.47</td>
</tr>
<tr>
<td>Lateral Tibia</td>
<td>30 mm³</td>
<td>66 mm³</td>
<td>0.45</td>
</tr>
</tbody>
</table>

The intra-reader ICC was 0.98, and RMSSD 82 mm³, while inter-reader ICC was 0.97 and RMSSD 91 mm³.

Conclusion: A new computer-assisted method of osteophyte volume measurement is reliable and sensitive. It may provide a more responsive and rapid method for osteophyte change than traditional ordinal methods, making it feasible to assess a large number of knees in a short period of time.

This study was funded by NIH/NIAMS R01AR056664.

Disclosure: M. Hakky, None; C. Ratzlaff, None; M. Jarraya, None; A. Guermazi, None; J. Duryea, None.


1Maastricht University Medical Center, Maastricht, Netherlands; 2Eindhoven University of Technology, Eindhoven, Netherlands.

Background/Purpose: Conventional radiography (CR) is considered the gold standard for diagnosing bone erosions in rheumatic diseases. However, High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) and microCT (µCT) allow analysis of bone erosions in finger joints at micro level. This study aimed to quantify cortical breaks and erosions in hand joints assessed from CR, HR-pQCT and µCT images.

Methods: Eight metacarpal phalangeal and four proximal interphalangeal joints from eight female human cadaveric index fingers with unknown medical history were scanned by HR-pQCT (82 µm, Scanco XtremeCT) and µCT (18µm, Scanco µCT 80). Also radiographs were taken. A modified SPECTRA (Study group for xtrEme Computed Tomography in Rheumatoid Arthritis) algorithm was used by one reader to assess all cortical breaks and erosions. A cortical break was defined as an interruption of cortical bone on two consecutive slices on two orthogonal planes for HR-pQCT, and similarly, but on eight consecutive slices, on µCT. An erosion was defined as a definite cortical break, with irregular shape, and loss of underlying trabecular bone on two consecutive slices on two orthogonal planes on HR-pQCT, and eight consecutive slices on two orthogonal planes on µCT. CRs were independently scored for erosions by two rheumatologists. Descriptive, paired samples t-test, Wilcoxon signed-rank test, kappa and intraclass correlation coefficients (ICC) were calculated (p<.05 was considered significant).

Results: Figure 1 shows a picture obtained from the three imaging modalities used in this study. In total, twelve joints (mean± SD age 82±.91 years) were imaged by HR-pQCT and µCT. In total, 79 cortical breaks were detected on HR-pQCT (6.5±2.5 per joint) and 163 on µCT (13.5±4.9 per joint). A total of 11 erosions were detected on HR-pQCT (0.9±0.9 per joint) and 47 on µCT (3.9±3.0 per joint). The ICC for number of cortical breaks was .122 (p=.150), and for number of erosions -909 (p=.699). On CR, the total number of erosions scored was four by Reader 1, and two by Reader 2. Kappa was fair (κ=.250).

Conclusion: Three times more erosions were detected on HR-pQCT than CR and four times more erosions were detected on µCT than HR-pQCT. Furthermore, twice the number of cortical breaks was scored on µCT compared to HR-pQCT. These results indicate that further research, such as histological and longitudinal studies, will be necessary to reveal the prevalence, incidence and significance of cortical breaks and erosions as found by HR-pQCT and µCT of hand joints.

Figure 1. CR of MCP joint in posterior-anterior position (A), arrows indicating a cortical break on dorsal side on transversal slice of HR-pQCT (B) and corresponding µCT (C) image.

Disclosure: A. Scharma, None; A. van Tubergen, None; J. van den Bergh, None; J. de Jong, None; M. Peters, None; B. van Rietbergen, Scanco Medical AG, 9; P. Geusens, None.

2144 Quantification of Hand Bone Mineral Density By Radiogrammetry and Dual X-Ray Absorptiometry in Early Arthritis Patients. Irene Llorente Cubas1,2, Leticia M erino-M elendez1,2, Saturnino Gonzalez Ortega1, Ana M. Ortiz-Garcia1, Eugenio Escalano1, Esther Vicente-Rabadan1, Rosario Garcia-Vicuña1, Isidoro Gonzalez-Alvaro2 and Santos Castañeda-Sanz2.

Tuesday, November 18

S937
Background/Purpose: The evaluation of cortical bone mineral density (BMD) on metacarpal bones by digital radiography (DXR) has been proven to be a simple, reliable and predictive method to evaluate the severity of the disease in patients with early arthritis (EA). However, DXR is a tool that is not usually available in our environment. By contrast, dual X-ray absorptiometry (DXA) is a more familiar and accessible technique in our clinical practice.

Purpose: The aim of this study was to compare the association between BMD measurements of the hand by DXR and DXA with parameters of activity and severity at two years of follow-up in a cohort of patients with EA.

Methods: A prospective longitudinal study of patients with EA was done. DXR was performed in a total of 111 patients (87.4% women) and DXA was implemented in a total of 378 (82% women). Mean age at disease onset was 57 years [46 - 65 (p25 - p50)] in the DXR group and 54 years [44 - 66 (p25 - p50)] in the DXA group. Anthropometric and clinical data were collected per protocol during 2 years of follow-up. Forty-two percent of patients in the DXR group presented citrullinated peptide antibodies and 41.3% in the DXA group. In both, the 57% fulfilled RA 2010 criteria at the start of follow up (43% undifferentiated arthropathy). Each patient underwent a digital radiograph of both hands (GE © DX Definium 8000) at 0, 3, 12 and 24 months, determining BMD of each hand and the mean of both measured by DXR (Sectra, Linköping, Sweden). Also, DXA of global hand and metacarpophalangeal joints (MCPs) of the nondominant hand were performed and analyzed using a Hologic QDR -4500 Elite© densitometer at 0, 6, 12 and 24 months. In addition, a variable that measures the intensity of cumulative treatment received during the 2 year follow-up was specifically generated as a marker of severity. Statistical analysis was performed using the statistical package STATA 12.

Results: Our data show a good correlation between values of BMD obtained by DXR and DXA in the different locations studied (global hand and MCPs: r = 0.830 and 0.718, respectively, p = 0.0001), both at the baseline visit and along the two years of monitoring. In the bivariate analysis, a negative association is observed between baseline BMD values measured by DXA and disease activity by DAS28 at 2 yrs, which disappears when adjusting for other variables (age and sex). However, we found an inverse relationship between the intensity of cumulative treatment at two years and baseline BMD measured by DXA, both at global hand (r = −2.51, p = 0.041, n = 220) and MCPs (r = −3.45, p = 0.007, n = 221). The DXR association was not significant, probably due to the small sample size of the population (n = 32).

Conclusion: BMD of the global hand and MCPs of the nondominant hand assessed by DXA predicts disease severity and the intensity of cumulative treatment at two years of follow-up in a population of patients with EA. By contrast, the predictive value of the hand DXR was not significant. Further studies with a larger population are needed to obtain more consistent conclusions.

Optimal Hand Position for Reliable Volumetric Joint Space Width Measurements Using High-Resolution Peripheral Quantitative Computed Tomography

Background/Purpose: Joint space narrowing is an important outcome measure in rheumatoid arthritis, linked tightly to function and disability. HR-pQCT (high resolution peripheral quantitative computed tomography) allows detection of bone margins with high precision. Based on this capability, we have devised a software script to quantify volumetric joint space width based on the method of ‘fitting maximal spheres’. The reproducibility of this method may be affected by the angular positioning of the joint. Our study assesses variability of 3D volumetric joint space measurements with variations in joint flexion between 0 and 30 degrees.

Methods: The 2nd and 3rd MCP joints of six cadaver hands were imaged with HR-pQCT (n=12 joints). Using a positioning device, the MCPs were placed at 7 different angles of flexion (0, 5, 10, 15, 20, 25 and 30 degrees). Actual angles of acquisition were verified in the sagittal plane post-hoc. Descriptive statistics were used to calculate the mean, median, minimum, and maximum joint space widths and total volume measurements, by degree of angulation. The coefficient of variation (root-mean-square deviation), CV(RMSD), was calculated to determine the variability caused by angulation.

Results: There was little variation in positioned angle and post-hoc angle measurement up to 15 degrees of flexion (measured angle mean 2.1, 5.7, 10.7, 15.3 vs positioned angle 0, 5, 10 and 15 respectively). At greater degrees of flexion, positioning error was significant, with the post-hoc angle measurement ranging from 20.8 to 32.5 at 30 degrees. Mean, median, maximum and minimum joint space increased linearly between 5 and 30 degrees (Figure 1). The CV(RMSD) was optimized between 5 and 15 degrees of flexion (Table 1). Minimum joint space measurements were highly variable at all degrees of flexion.
Conclusion: Our 3D volumetric measurement method of joint space width for images acquired with HR-pQCT technology is reliable for MCP flexion angles of 0 to 20 degrees. Reproducibility metrics are optimized between 5 and 15 degrees. Care should be given to remaining in this parameter for longitudinal or repeated measures studies using this technology for joint space width assessment.

Disclosure: C. Barnabe, None; S. Manske, None; B. J. Jorgenson, None; S. K. Boyd, None.

2147
Automatically Extracted Quantitative Biomarkers for Assessing Connective Tissue Disease Using Nailfold Capillaroscopy. 
Michael Berks1, 2, Murray Dickson2, Andreea Murray2, Tonia Moore3, Chris Taylor4 and Arianne Herrick2. 1Centre for Imaging Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, 2Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, 3Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom.

Background/Purpose: Videomicroscopy can capture high-magnification images of nailfold capillaries, allowing non-invasive assessment of microvascular change indicative of connective tissue disease. Whilst images may be qualitatively graded visually, quantitative biomarkers are required for detailed analysis and tracking disease progression. To overcome the problems of manual measurement (time consuming, subjective), we have developed fully automated software to measure the spatial density, width and tortuosity of capillaries. Our objective was to assess how well these automated biomarkers differentiate between healthy controls (HC), subjects with primary Raynaud’s phenomenon (PRP), patients with systemic sclerosis (SSc), and patients with undifferentiated connective tissue disease (UCTD).

Methods: Our software was used to analyze 577 nailfold images (85 HC; 46 PRP; 402 SSc; 44 UCTD). Analysis is performed in four stages: the software 1) detects all vessels, measuring the orientation and width for each 2) locates the apex of each capillary and determines which belong to the distal capillary 4) combines these measurements to compute a single value of density, width and tortuosity for each image. For each biomarker one-way ANOVA, followed by Tukey’s range test, was used to check for differences between the means of each subject group.

Results: ANOVA tests showed significant group-wise differences for all biomarkers (all p <0.001). The group mean and 95% confidence interval of each biomarker are shown in Table 1, along with the pairs of groups that showed significantly different means under Tukey’s test.

Table 1: Group-wise means and confidence intervals for each automatically measured capillaroscopy biomarker. Pairs of groups with significantly different means are listed in the rightmost column.

<table>
<thead>
<tr>
<th>Biomarker type</th>
<th>Subject group means (95% confidence intervals)</th>
<th>Groups with significantly different means under Tukey’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary density</td>
<td>HC (n=85)</td>
<td>PRP (n=46)</td>
</tr>
<tr>
<td>Mean capillary width (per mm)</td>
<td>12.5 (12.3, 13.3)</td>
<td>13.4 (12.5, 14.2)</td>
</tr>
<tr>
<td>Mean capillary tortuosity (no units)</td>
<td>5.3 (5.2, 5.4)</td>
<td>5.9 (6.7, 7.6)</td>
</tr>
</tbody>
</table>

Conclusion: Images from patients with SSc had significantly lower capillary density and higher width and tortuosity than other subject groups (including UCTD), matching findings from earlier studies using manual or semi-automated analysis. No significant differences were observed between healthy controls and PRP, again, matching clinical expectations. Images from patients with UCTD generated biomarkers that lay in between healthy controls/PRP and SSc. These highly promising results suggest our software produces clinically useful biomarkers of connective tissue disease. Automated analysis is potentially a major step forward, enabling large datasets of images to be assessed quickly and efficiently, and obviating the inherent subjectivity of manual assessment.

maximum recorded serum urate (r²=0.502, p<0.022) but not with gout duration. Among the 10 patients with tophaceous gout, 9 had MSU deposits evident by DECT (sensitivity=90%). In an index case of tophaceous gout (Figure), we were surprised to see tophi evident by clinical examination (panel A), 3D volume rendering (Panel B), and bony erosion (panel C—lack of green deposits), that were negative by DECT (panel C—lack of green deposits). This prompted us to evaluate the sensitivity of DECT for individual gouty erosions (defined by the presence of an overhanging edge in a joint not affected by severe joint space loss). In 3 patients with extensive foot involvement, MSU deposits were detected by DECT within or immediately adjacent to 13/26 (50%) erosions.

**Conclusion:** DECT detected MSU deposits in non-tophaceous gout, with 65% sensitivity on scanning of both upper and lower extremity joints and only 18% on scanning of the crystal-proven joint. The sensitivity was 90% in tophaceous gout, but remained inadequate when evaluated on the basis of individual erosive lesions. The detection of MSU deposits by DECT may relate to their density and this could potentially be improved with an adjustment of algorithm input parameters.

**Disclosure:** T. Kurano, None; U. Thakur, None; G. Thawalt, None; E. Fishman, None; M. McAdams-DeMarco, None; J. W. Maynard, None; M. Fuld, Siemens Health, 3; J. A. Carrino, Siemens, 2; A. N. Baer, None.

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**Relationship Between the Magnitude of Bone Formation in the Anterior Vertebral Corners, As Assessed through 18F-Fluoride Uptake, and Lumbar Spine Bone Mineral Density in Patients with Ankylosing Spondylitis.** Seung-Geun Lee1, Eun-Kyoung Park2, Geun-Taek Kim2, Sang-Yeob Lee2 and Joung-Wook Lee4.

**Background/Purpose:** Available studies of craniocervical junction (CCJ) involvement in ankylosing spondylitis (AS) are based on conventional radiography, which has limited ability in the definition of many elements of the CCJ. The goal of the present study was to describe the spectrum of computed tomography (CT) findings in the CCJ in a cohort of patients with AS.

**Methods:** CT scans of the cervical spine of 11 patients with AS were reviewed and imaging findings related to the CCJ assessed. The standard anatomic intervals describing the CCJ were measured and compared to accepted normal standards. Findings, representing pathology were described, categorized by localization and relation to joints or ligaments of the CCJ.

**Results:** All patients were males with median age of 48 years and median disease duration of 20 years. The calculated median modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) for the cervical spine was 8.5, ranging from 0 to 27. Disease-related changes in one or more elements of the CCJ were detected in all patients. Patients with AS had a strong tendency to the narrowing of the atlanto-occipital joints and atlanto-dental interval, with some patients demonstrating complete fusion of these articulations. Atlanto-occipital joints were involved in 8 patients, while 3 patients had disease of the atlanto-dental articulation. Enthesopathy of the CCJ was observed in 7 patients. Significant changes of CCJ were observed also in patients with very low mSASS.

**Conclusion:** The CCJ is frequently involved in AS patients with advanced disease and may be independent on the mSASSS. Both articulations and ligaments of CCJ may be affected in AS patients.
I. Rosner, None; S. Croitoru, None; G.S. Saad, Julio C. B. Moraes, Eloisa Bonfá and Ana C.M. Ribeiro. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Ankylosing spondylitis of craniocervical junction.

Methods: Eighteen RA (ACR criteria) patients undergoing abatacept (ABA-RA) were selected and compared to 18 patients treated with anti-TNF (aTNF-RA) agents. Total and specific (IgG, IgM and IgA) gammaglobulin levels were assessed before and 6 months after biological treatment. Before entry, all patients were vaccinated for influenza/pneumococcus and they were evaluated for tuberculosis. A systematic clinical screening protocol for infection was performed before each dose and at least monthly and when indicated virus, bacteria and fungus etiologies were investigated. Central nervous system, upper/lower respiratory tract, cutaneous, gastrointestinal and genitourinary infections were classified in mild/moderate or severe (hospitalization). Demographic, clinical and laboratory data were also collected. Exclusion criteria were: low gammaglobulin level at baseline (<0.7) and previous abatacept or rituximab treatments.

Results: At baseline, median current age (55 vs. 53 years, p = 0.96), frequencies of female gender (78 vs. 78%, p = 1.0), DAS28 (5.73 vs. 5.67, p = 0.34), ESR (21.5 vs. 22mm/1sth, p = 0.84), CRP (15.5 vs. 12mg/dL, p = 0.37) and lymphocyte counts (2.200 vs. 1.800/mm³, p = 0.42) were comparable in ABA-RA and aTNF-RA groups. Medians of gammaglobulin (1.4 vs. 1.35 g/dL, p = 0.71), IgG (1167.5 vs. 1078.5 mg/dL, p = 0.84), IgM (107.2 vs. 112.6 mg/dL, p = 0.38) and IgA (333 vs. 322 mg/dL, p = 0.74) were also alike in both groups. At 6 months, median percentage variations of gammaglobulin levels from baseline were distinct with a significant reduction for ABA-RA compared to aTNF-RA: total (~20 vs. +4%, p < 0.001), IgG (~11 vs. +8%, p < 0.001), IgM (~15 vs +26%, p < 0.001), IgA (~13 vs. +2%, p = 0.002). Frequency of infections was similar in both groups (61 vs. 67%, p = 0.73) with only one severe infection in ABA-RA and no death. Respiratory tract was the most frequent site in both groups (33 vs. 50%, p = 0.34) followed by skin (29%) in aTNF-RA and urinary tract (28%) in ABA-RA. Of note, antibiotics or antifungal therapy were indicated less often for ABA than aTNF (44 vs. 85%, p = 0.028). ABA patients with and without infections had comparable levels at baseline and 6 months of IgG (p = 0.28 and p = 0.08) and IgM (p = 0.78 and p = 0.83).

Conclusion: The present work provides novel data demonstrating that in ABA-RA patients is not associated with the observed reduction in gammaglobulins induced by this co-stimulatory agent. Infections seem, however, to be less severe with this agent than with aTNF agents.

Disclosure: V. Dinis, None; V. S. T. Viana, None; E. P. Leon, None; C. A. Silva, FAPESP 2009/51897-5, CNPq 302724/2011-7 and Federico Foundation; 2; N. Boulman, None; D. Rimar, None; I. Rosner, None; M. Ozdah, None.

ACR/A RHP Poster Session C
Infections, Infection-related Biomarkers and Impact of Biologic Therapies
Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2515
Abatacept Related Infections: No Association with Gammaglobulin Reduction.

Background/Purpose: A recent study reported that abatacept (ABA) reduces rheumatoid arthritis (RA) related autoantibodies and gammaglobulins levels. However, the possible association of these findings with infections was not assessed. The aim of this study was, therefore, to evaluate immunoglobulins levels and infections in RA patients treated with ABA compared to anti-TNF agents, biological agents without any effect in immunoglobulin production.

Methods: Eighteen RA (ACR criteria) patients undergoing abatacept (ABA-RA) were selected and compared to 18 patients treated with anti-TNF (aTNF-RA) agents. Total and specific (IgG, IgM and IgA) gammaglobulin levels were assessed before and 6 months after biological treatment. Before entry, all patients were vaccinated for influenza/pneumococcus and they were evaluated for tuberculosis. A systematic clinical screening protocol for infection was performed before each dose and at least monthly and when indicated virus, bacteria and fungus etiologies were investigated. Central nervous system, upper/lower respiratory tract, cutaneous, gastrointestinal and genitourinary infections were classified in mild/moderate or severe (hospitalization). Demographic, clinical and laboratory data were also collected. Exclusion criteria were: low gammaglobulin level at baseline (<0.7) and previous abatacept or rituximab treatments.

Results: At baseline, median current age (55 vs. 53 years, p = 0.96), frequencies of female gender (78 vs. 78%, p = 1.0), DAS28 (5.73 vs. 5.67, p = 0.34), ESR (21.5 vs. 22mm/1sth, p = 0.84), CRP (15.5 vs. 12mg/dL, p = 0.37) and lymphocyte counts (2.200 vs. 1.800/mm³, p = 0.42) were comparable in ABA-RA and aTNF-RA groups. Medians of gammaglobulin (1.4 vs. 1.35 g/dL, p = 0.71), IgG (1167.5 vs. 1078.5 mg/dL, p = 0.84), IgM (107.2 vs. 112.6 mg/dL, p = 0.38) and IgA (333 vs. 322 mg/dL, p = 0.74) were also alike in both groups. At 6 months, median percentage variations of gammaglobulin levels from baseline were distinct with a significant reduction for ABA-RA compared to aTNF-RA: total (~20 vs. +4%, p < 0.001), IgG (~11 vs. +8%, p < 0.001), IgM (~15 vs +26%, p < 0.001), IgA (~13 vs. +2%, p = 0.002). Frequency of infections was similar in both groups (61 vs. 67%, p = 0.73) with only one severe infection in ABA-RA and no death. Respiratory tract was the most frequent site in both groups (33 vs. 50%, p = 0.34) followed by skin (29%) in aTNF-RA and urinary tract (28%) in ABA-RA. Of note, antibiotics or antifungal therapy were indicated less often for ABA than aTNF (44 vs. 85%, p = 0.028). ABA patients with and without infections had comparable levels at baseline and 6 months of IgG (p = 0.28 and p = 0.08) and IgM (p = 0.78 and p = 0.83).

Conclusion: The present work provides novel data demonstrating that in ABA-RA patients is not associated with the observed reduction in gammaglobulins induced by this co-stimulatory agent. Infections seem, however, to be less severe with this agent than with aTNF agents.

Disclosures: V. Dinis, None; V. S. T. Viana, None; E. P. Leon, None; C. A. Silva, FAPESP 2009/51897-5, CNPq 302724/2011-7 and Federico Foundation; 2; N. Boulman, None; D. Rimar, None; I. Rosner, None; M. Ozdah, None.

2152
Frequency of Postoperative Deep Infection in Patients with Rheumatoid Arthritis.
Masayuki Aukizawa and Hiromu Ito. Kyoto University, Kyoto, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is known to be associated with an increased risk of serious infection. It has been discussed about the risk of the surgical site infection in the RA patients. However there are few reports about the postoperative deep infection in those patients. The aims of the study were to investigate the postoperative deep infection in RA patients treated in our institution and to clarify the frequency of the postoperative deep infection.

Methods: We reviewed a total of 696 orthopaedic surgeries for RA patients underwent between January 2004 and December 2013. We investigated the cases of deep infection after surgery, the sites of infection, and surgical techniques. We researched the postoperative deep infection free rate for the RA patients.

Results: The mean follow-up period was 4.7 years. 27.3% of all RA patients used biological DMARDs. Twenty-five cases (3.6%) were suffered from the postoperative deep infection. Infection sites (surgical procedures) are 5 hips (bipolar hemiarthroplasty and total hip arthroplasty), 6 knees (total knee arthroplasty), 6 elbows (total elbow arthroplasty), one shoulder (total shoulder arthroplasty), 2 hands (metacarpophalangeal joint arthroplasty and proximal interphalangeal joint arthroplasty), one ankle (ankle arthrodesis) and 4 spines (Magerl technique, cervical posterior fixation, transforaminal lumbar interbody fusion). A according to the Kaplan-Meier survival analysis, the cumulative deep infection free rate of all patients in 3 months, in 2 years and in 5 years was 98.7%, 97.8%, and 97.0%, respectively. That of the patient treated with biologic DMARDs was significantly lower than that of without biologic DMARDs. (Log-rank Test: p = 0.0068)

Conclusion: These results suggest that the postoperative deep infection is likely to occur within the first 3 months after surgery in the RA patients, and that the use of biological DMARDs is a risk factor for postoperative deep infection. We should pay more attention to the postoperative deep infection within 3 months of a procedure.
Results: Of 208 patients with clinically suspected septic arthritis who underwent surgical intervention, 90 (43.3%) were synovial fluid culture-positive. The culture-positive and culture-negative groups were similar with respect to gender (approximately half were female), age (mean of 63 years), frequency of prosthesis joint involvement (about 60%), and frequency of knee involvement (about 60%). For the culture-positive group, mean LOHS and 60-day readmission rate were 11.4 days and 26.7%, respectively; in the culture-negative group, mean LOHS and 60-day readmission rate were 9.9 days and 36.4%, respectively (p = 0.09 for LOHS; p = 0.18 for 60-day readmission rate). An alternative diagnosis to explain the index admission was made in 3 (3.3%) cases in the culture-positive group and in 10 (9.3%) cases in the culture-negative group (p = 0.16). Among patients with native joints, mean LOHS, 60-day readmission rate, and frequency of alternative diagnosis did not differ significantly between the culture-negative groups.

Conclusion: In our medical center, the majority of patients with clinically suspected septic arthritis managed operatively had negative synovial fluid cultures at the time of diagnosis. While those with positive and negative synovial fluid cultures had similar baseline features, we observed a trend toward shorter length of hospital stay and more alternative diagnoses in the culture-negative group. The inclusion of additional presenting features (currently underway), including the presence of comorbidities, prior use of antibiotics, systemic signs of infection, and synovial fluid characteristics, may identify a subset of patients with suspected septic arthritis who may be managed safely without surgery.

Disclosure: S. B. Lieber, None; Z. Paz, None; R. H. Shmerling, None.

2154

Risk for Developing Adult T-Cell Leukemia in Patients with Human T Lymphotropic Virus Type-I Carrier Receiving Immunosuppressive Therapy. Kersuke Nakanishi1, Rita McGill2 and Mitsuyo Kinjo1. "Okinawa Chubu Hospital, Uruma City Okinawa, Japan, "AGH Nephrology Associates, Pittsburgh, PA.

Background/Purpose: Human T-lymphotropic virus type-I (HTLV-1) is a retrovirus associated with Adult T-cell leukemia (ATL) that is commonly seen in endemic areas. Several case reports suggest that immunosuppressants, including biologic agents, may be related to development of ATL in HTLV-I carriers. The purpose of this study was to evaluate the risk for developing ATL in HTLV-1 carriers who received immunosuppressive therapy for rheumatic or inflammatory bowel diseases, or cancer.

Methods: Medical records were reviewed at Okinawa Chubu Hospital to locate all HTLV-1+ patients from 2010 to 2013. After excluding 8 renal transplant patients, there were 727 HTLV-1+ patients. Incidence and progression of ATL were compared between subjects with and without immunosuppressive therapy. Data were collected on clinical features, medications and peripheral smears.

Results: We identified 83 HTLV-1+ subjects who received immunosuppressive therapy, including prednisolone, disease-modifying anti-rheumatic drugs (DMARDs) or biologic agents: 52/83 (64%) had rheumatic diseases. 90 subjects (12%) had non-ATL malignancy including solid cancer and hematological malignancy with or without chemotherapy (Table). Median observation period was 26 months (2–50) in patients receiving immunosuppressive therapy, and 26 months (2–50) in controls. Incidence of ATL did not differ between subjects on and off immunosuppressive therapy (P = 0.6). In 7 patients on biological agents (5 etanercept, 1 infliximab and 1 abatacept), no ATL occurred during the observation period (median 22 months, range 9–50).

Conclusion: No cases of ATL developed among HTLV-1+ patients on immunosuppressants over an observation period of 26 months. Immunosuppressive therapy may not promote development of ATL in HTLV-1+ patients with rheumatic diseases.

Disclosure: K. Nakanishi, None; R. McGill, None; M. Kinjo, None.
Chikungunya Fever in Patients Under Biologics. Lauren Brunier1, Katleen Polomat2, Christophe Deligny3, Veronique Dehlinger3, Patrick Numeric3, George Jean-Baptiste, Serge Artif4 and Michel De Bandt4. 1Unit of rheumatology, CHUM, Fort de France, France, 3Unit of Internal Medicine, CHUM, Fort de France, France, 4Unit of Rheumatology, CHUM, Fort de France, France.

Background/Purpose: Chik is an epidemic disease due to an arthropod-borne virus (Alphavirus) transmitted by Aedes mosquitoes. CHKV causes an acute illness with a febrile phase, followed by a period of severe polyarthritides that can last for months. There is no specific treatment, the best prevention is mosquito control and avoidance of bites. Martinique (French West Indies) is currently experiencing an outbreak of CHIK with 40,000 reported cases (June 1st). No data is available regarding the prognosis of Chikungunya in patients under biologics. We have observed 22 patients with Chik infection who followed-up on their biologics.

Methods: Physicians prescribing biologics were asked to declare patients under biologics experiencing Chik. For each patient we collected disease characteristics and cause, current treatment (steroids, immunosuppressants, biologics...), changes in the treatment during infection, and outcome. 22 patients were included, all with a diagnosis confirmed by PCR (20/22) or serology.

Results: Among these patients were 19 women and 3 men, 3 Caucasians and 19 Afro-Caribbean's. There were 5 spondyloarthritides (3 associated with Crotinh), 1 psoriatic rheumatism, 2 systemic lupus, 1 antithrombocyte syndrome and 1 with no associated disease (mean dose 21.6 mg). 3 Plaquengy, 2 Lasmid, 1 cellcept, 2 cyclophosphamide. 12/22 were under steroids (mean dose of 8.6 mg/d). 10/22 were under analgesic (alone 4/22), associated with NSAIDs (17/22) or anti-TNF (1/22). One patient had recurrent chronic arthritis. One patient had a traumatic fracture of the third right metatarsal on the third month of illness. Arthralgia was symptomatic and polyarticular in all cases, with the ankles being the most commonly affected joint area (71%).

Conclusion: Chikungunya can result in severe, debilitating arthralgia that affects daily activities, and may persist for as long as a year. Further studies are needed to determine the prevalence of persistent arthralgia, identify risk factors, and establish the real burden of disease.

Disclosure: A. K. Gutierrez-Rubio, None; E. Penserga, None.

Tuberculosis Reactivation Risk in Patients Treated with Tumor Necrosis Factor Alpha Inhibitors: A Turkish Experience with Higher Mortality and Different Bacterial Susceptibility Patterns.

Methods: TB data was collected during 2002-2007 at the University of Istanbul, Istanbul Faculty of Medicine. 73 patients were included, all with a diagnosis confirmed by PCR (20/22) or serology.

Results: Among 73 patients diagnosed with TB, 38 patients were under biologics. Patients under biologics are at increased risk for serious infections either viral or bacterial, but no data has been published regarding Chik. This study was not conducted to discover all cases of Chik among patients under biologics. Chik does not seem to aggravate pre-existing disease. It does not seem necessary to modify the basic treatment of rheumatism in the announcement forms. Chik does not seem to aggravate pre-existing disease. It does not seem necessary to modify the basic treatment of rheumatism in the announcement forms. Chik is an epidemic disease due to an arthropod-borne virus (Alphavirus) transmitted by Aedes mosquitoes. CHKV causes an acute illness with a febrile phase, followed by a period of severe polyarthritides that can last for months. There is no specific treatment, the best prevention is mosquito control and avoidance of bites. Martinique (French West Indies) is currently experiencing an outbreak of CHIK with 40,000 reported cases (June 1st). No data is available regarding the prognosis of Chikungunya in patients under biologics. We have observed 22 patients with Chik infection who followed-up on their biologics.

Background/Purpose: Chikungunya fever is a reemerging viral infection in the Philippines and neighboring countries. Persistent arthralgia following Chikungunya infection has been observed during previous epidemics, but few studies have discussed this aspect of the disease.

Methods: A adult patients who were diagnosed to have Chikungunya fever were included in this study. Patients were assessed at the time of acute infection and were followed-up at least 12 months after the acute disease occurred. Patients were asked questions regarding musculoskeletal symptoms and were examined on follow-up.

Results: Fourteen patients were included in this study. Ten (71%) were female. None of these patients reported a history of preexisting arthralgia. Eight (57%) had arthritis lasting at least 6 weeks following the acute infection, with a mean duration of 13.6 ± 5.72 weeks. Seven of the 14 patients (50%) had persistent arthralgia, with five (71%) having intermittent arthralgia, and 2 (29%) having continuous arthralgia. Two patients had recurrent chronic arthralgia. One patient had a traumatic fracture of the third right metatarsal on the third month of illness. Arthralgia was symptomatic and polyarticular in all cases, with the ankles being the most commonly affected joint area (71%).

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Disclosure: A. K. Gutierrez-Rubio, None; E. Penserga, None.
Severe Neutropenia in Patients with Rheumatic Diseases at a Tertiary Care Hospital in South Korea. Chang-Nam Son,1 J-Mi Kim2,3, Sang-Hyon Kim2,3, Sook-Yung Cho4, Yoon-Kyong Sung5, Tae-Hwan Kim5, Jae-Bum Jun6, Sang-Chel Bae1 and Dae-Hyun Yoo1. K Eimeung University School of Medicine, Daenyo, South Korea, 2Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, 3Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: Neutropenia is relatively common in patients with rheumatic diseases. Neutropenia is characterized by an absolute neutrophil count (ANC) of less than 1,500/μL. It is associated with diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) or it may be caused by the side effects of medications or accompanying infection. The risk of neutropenia-related infection increases with an ANC near 1,000/μL and rises dramatically as ANC falls below 500/μL (severe). Some patients with neutropenia require hospitalization in an isolation ward and are administered recombinant human granulocyte colony stimulating factor (rhG-CSF) or antibiotics to treat neutrophil fever. Our aim was to investigate the possible causes and clinical characteristics of severe neutropenia in Korean patients with rheumatic diseases.

Methods: The study participants (n=64) were enrolled from September 2003 to August 2013 from a population of patients with rheumatic diseases who were admitted to a tertiary care center. These subjects had severe neutropenia and received rhG-CSF at least once during hospitalization. We retrospectively examined data of the subjects including age, gender, initial diagnosis, concurrent medications, serial complete blood count, and bone marrow biopsy.

Results: The most frequent initial diagnoses were SLE (n=35; 55%), RA (n=13; 20%), and inflammatory myositis (n=6; 9%). The possible causes of severe neutropenia were therapeutic drugs (n=31; 48%), association with lupus (n=17; 27%), infection (n=12; 19%), and hematophagocytic syndrome (n=4; 6%). During hospitalization, nine deaths occurred (14%; 9/64). Mortality was higher in patients with sepsis than in patients with neutropenia associated with other causes (Table). Pneumonia was the most common cause of sepsis in patients with neutropenia (58.3%, 7/12). The frequency of sepsis and death was higher in the long-term recovery ward and are administered recombinant human granulocyte colony stimulating factor (rhG-CSF) or antibiotics to treat neutrophil fever. Our aim was to investigate the possible causes and clinical characteristics of severe neutropenia in Korean patients with rheumatic diseases.

Conclusion: In patients with rheumatic diseases, drug toxicity was the most common cause of severe neutropenia. Among the causes of neutropenia, sepsis is of greatest concern; therefore, physicians need to pay attention to the early detection of infection.

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Human T-Lymphotropic Virus Type 1 Biomarkers in Patients with Rheumatoid Arthritis. Akihiko Okayama1, Masako Iwanga2, Yasuko Sagará3, Toshikio Hidaka1, Kunihiko Umejita1, Kazuki Nakano1, Toshiki Watanabe4, Yoshitsuna Yamanaka5, Yohisato Harada6, Hideki Nakamura7 and Atsushi Kawakami8. 1The Jikei University of School of Medicine, Tokyo, Japan. 2Japanese Red Cross K Yushu Block Blood Center, Fukuoka, Japan. 3Zenjinkai Shimin-No-Mori Hospital, Miyazaki, Japan. 4Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. 5St. Marianna University School of Medicine, Kanagawa, Japan. 6Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. 7Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. 8Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Human T-lymphotropic virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia (ATL). It has been debated recently whether or not immunosuppressive agents for HTLV-1 carriers with a variety of inflammatory/immunological conditions can increase the risk of developing ATL, which is of important in terms of the pros and cons of anti-rheumatic treatment for HTLV-1 positive patients with RA. Through HTLV-1 biomarkers, whether the immunosuppressive medicines or biologics for HTLV-1 positive rheumatoid arthritis (RA) patients may affect adversely to the risk of ATL was speculated.

Methods: HTLV-1 antibody was screened for 808 patients with RA diagnosed in two regions in Japan, Nagasaki and Miyazaki prefectures, endemic areas of HTLV-1 infection. Among those, HTLV-1 positive RA patients treated with anti-rheumatic medicines including biologics (anti-TNFs, tocilizumab, and abatacept) were selected to be subjects for this study and evaluated about the levels in blood samples of HTLV-1 proviral load (PVL) by real-time PCR, antibody titer by particle agglutination assay, and soluble IL-2 receptor (sIL-2R) by enzyme immunoassay. The levels of the biomarkers were compared with those of age and sex matched asymptomatic HTLV-1 carriers (ACs) using Wilcoxon rank sum test.

Results: The HTLV-1 seroprevalence in patients with RA was 8.2% (66/808). Blood samples were available in 33 among the 66 HTLV-1 positive RA patients. The median HTLV-1 PVL of the 33 patients was 0.52 copies per 100 peripheral blood mononuclear cells (PBMCs), which was lower than that of age and sex matched 99 ACs (1.0 copy per 100 PBMCs) (p=0.08). The median antibody titer of the 33 patients was 22; which was lower than that of age and sex matched 99 ACs (22; p=0.03). The level of sIL-2R was not different between 2 groups (p=0.10).

Conclusion: The HTLV-1 seroprevalence in patients with RA in the endemic area in Japan was higher than we expected. Both HTLV-1 PVL and antibody titer in HTLV-1 positive RA patients treated with anti-rheumatic medicines showed lower values comparing with those in ACs. These findings, when viewed in light of a previous report that high HTLV-1 PVL is considered as the risk factor for developing ATL, suggest that treatment by anti-rheumatic medicines including biologics may not necessarily increase the risk for ATL development in HTLV-1 positive patients with RA. Further long-term follow-up study can determine the safety of anti-rheumatic treatment in HTLV-1 positive patients with RA.

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WITHDRAWN

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Interest of Systematic Lyme Serology in Context of Recent Onset Arthritis. Dewi Guellec,1 Valérie Nartonne2, Divi Comerc,1 Thierry Marharoud,3 M axime Dougados,1 Jean-Pierre Daures,1 Sandrine Jousse-Joulin,1 Valentine Devauchelle1 and Alain Saraux1. 1CHU Brest, Brest, France, 2Brest, Occitandre University, Brest, France, 3CHU de la Cavale Blanche, Brest, France, INSERM (U1153): Clinical Epidemiology and Biostatistics, Pres Saint-Pierre's, Cité, Paris, France, 4INSERM, Montpellier, France, 5Brest university medical school, EA 2216, Lab EX, INSERM, IGO,UBO and CHU de la Cavale Blanche, Brest, France, 6CHU Brest and EA 2216, UBO, Brest, France.

Background/Purpose: Lyme arthritis is a late manifestation of a tick-transmitted spirochetal infection, mainly caused by Borrelia burgdorferi. Lyme arthritis typically presents as a mono- or oligoarticular arthritis primarily affecting the large joints. However, various presentations including polyarthritis and polyarthalgias are possible (Puius et al.). It results that spirochetal infection is sometimes evoked by the rheumatologist in context of recent-onset arthritis, even in non-endemic regions.

The aim of this study was to determine the utility of systematic Lyme serology in a French cohort of patients with recent-onset arthritis, by determining the seroprevalence of Lyme antibodies according to the region of inclusion, the prevalence of Lyme arthritis and the diagnostic accuracy of serological testing.

Methods: The present study is an ancillary project from a French prospective and multicentric cohort study monitoring clinical, biological, and radiographic data for patients with inflammatory arthritis lasting less than 6 weeks to 6 months (Cormier et al.). Patients were included during the period of December 2002 to March 2005 in 14 regional centers. Antibodies against Borrelia at baseline were detected in 2006, using an IgG and IgM Immune Assay, from blood samples collected at baseline, without Western blot confirmation. This procedure was conducted independently of the physician’s strategy to detect
a possible spiritoetal infection. The final diagnosis was recorded after two years of follow-up. Global and regional seroprevalence of Lyme antibodies were determined. The proportion of patients with a final diagnosis of Lyme arthritis and the diagnostic accuracy of Lyme serology in context of recent-onset arthritis were recorded. The clinical and biological characteristics of patients according to the results of Lyme serology were analyzed in detail.

**Results:** Among the 814 patients included in the ESPOIR cohort, 810 were tested for the presence of Borrelia antibodies (99.5%). Of these patients, 7.6% had positive serology (62/810) and 2.6% had equivocal results (21/810). A positive result of Lyme serology varied significantly by region of inclusion (2.4% - 14.9%), the highest value being found in the endemic area. After two years of follow-up, no cases of definite Lyme arthritis were identified, although it was the main diagnostic hypothesis at baseline for 2 patients. Thus, diagnostic accuracy of Lyme serology in context of recent-onset arthritis seems very low despite a relatively high proportion of patients having an IgG positive serology. A statistical analysis revealed an association between the positivity of the immune assay and renal failure (p = 0.0005).

**Conclusion:** In France, where there is an heterogeneous risk of borrelia infection by region, the diagnosis of polyarthritis linked to borrelia was never validated in 19 patients and cryoglobulinemia was searched in 13 cases. Anticardiolipin antibodies (ACL) in 11 patients. Furthermore, C3 and C4 were decreased in 1 patient and anti-keratine or anti-CCP antibodies in 11 patients. Additionally, C3 and C4 were also decreased in one patient and anti-keratine or anti-CCP antibodies in 11 patients. A positive result of Lyme serology varied significantly by region of inclusion (2.4% - 14.9%), the highest value being found in the endemic area. After two years of follow-up, no cases of definite Lyme arthritis were identified, although it was the main diagnostic hypothesis at baseline for 2 patients. Thus, diagnostic accuracy of Lyme serology in context of recent-onset arthritis seems very low despite a relatively high proportion of patients having an IgG positive serology. A statistical analysis revealed an association between the positivity of the immune assay and renal failure (p = 0.0005).

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**Background/Purpose:** Self-lipids play an increasingly appreciated role in immunity and inflammation. Lipid antigens are presented by CD1d and CD1a-d molecules in mouse and human, respectively, to T cells. Glycolipids (GL) such as βGlucer and phospholipids (PL) such as phosphatidic acid (PA), phosphatidylycholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), and phosphatidylserine (PS), have been eluted and identified by mass spectrometry as natural human CD1d ligands, and PC and PE have been eluted from murine CD1d. Crystallography shows that complexes of CD1d bound to PL can exist. Diverse subsets of T cells recognize self lipids have been reported, including invariant natural killer T cells (INKT). Extensive work shows protective or pathogenic roles of GL αGalCer-reactive INKT cells in a wide range of diseases. However, the functions of T cells that recognize abundant self PL are not known. Here, we identified and characterized self PL-reactive T cells (PLT), investigated their in vivo functions, and elucidated the cellular and molecular participants in PL-mediated immune homeostasis.

**Methods:** CD1d tetramers were loaded with 8 PL or GL antigens, and cells analyzed by flow cytometry. Chemical binding of PL to CD1d was assessed by isoelectric focusing/gel shift analysis. CD1d-PA complex was crystallized by sitting drop vapour diffusion. A T oligoimmune hepatitis is mediated by INKT cells was induced by injecting conjugating A (ConA), and assessed by serum ALT, morphology, and histology.

**Results:** CD1d tetramers loaded with PL, namely PA, PE, PI, PS and BMP (bis(hydroxypropyl)cyclodextrin), identify 0.4-4% T cells in the lymphoid organs of wild-type and INKT-deficient Jα18 mice, but not in CD1d-/- mice. PLT cells don't recognize GL-loaded tetramers and don't respond to αGalCer, suggesting that PLT cells are distinct from INKT cells. PLT cells expand, express CD69, and produce cytokines upon in vivo priming. Chemical binding and crystal structure show that PA binds CD1d in the absence of lipid transfer proteins, and is centrally located in the CD1d binding groove opening for TCR recognition. Although PA binds slightly weaker to CD1d than a self GL, it competed with αGalCer to load onto CD1d. All PL tested profoundly inhibited the proliferation and cytokine production by INKT cells. Such PL-induced inhibition of INKT cells was abrogated upon depletion of granulocytes by gemicitabine that preferentially depleted the M DSC subset called monocyte-M DSC (mMDSC). Furthermore, PL induced IL-10 producing mMDSC that inhibited INKT cell proliferation in an IL-10-dependent manner. Finally, treatment with a PL ameliorated ConA-hepatitis, reduced pro-inflammatory cytokines, granulocyte accumulation and IFN-γ mMDSC, but promoted IL-10 mMDSC that upon adoptive transfer reduced the incidence/severity of ConA-hepatitis.

**Conclusion:** We identified a new role for self PL that activate a distinct subset of CD1d-restricted T cells that inhibit INKT cells by competitive inhibition and via induction of IFN-γ IL-10 mMDSC that ameliorate auto- immune hepatitis. These results have important implications for conditions with altered lipid metabolism and inflammation such as atherosclerosis and autoimmune disease.

Disclosure: R. R. Singh; None. C. Tran; None. P. Prasad; None. J. Wang; None. D. Zajonc; None. R. Halder; None.

**Background/Purpose:** Myeloid-derived suppressor cells (MDSCs) have been linked to T-cell tolerance, their role in rheumatoid arthritis (RA) remains exclusive. Here, we investigated the potential association of MDSCs with the disease pathogenesis using samples collected from RA patients and the experimental model of collagen-induced arthritis (CIA). Myeloid-derived suppressor cells (MDSCs) in peripheral blood and the synovial fluids of RA patients (n = 59), osteoarthritis patients (OA, n = 15), and healthy individuals (n = 20) was detected by flow cytometry. And their association with the disease severity and the levels of IL-17A was analyzed. Similarly, MDSCs in the peripheral blood, lymphoid tissues, inflamed paws, or synovial fluid and their association with disease severity, tissue inflammation, and the in vitro pathogenic T helper (Th) 17 cells was examined in CIA mice. The MDSCs in arthritic mice were characterized for their phenotype, inflammation status, T-cell suppressive activity, and their capacity of pro-Th17 cell differentiation. The contribution of MDSCs to Th17 response was examined by co-culturing MDSCs with naïve CD4 T cells under Th17-polarizing conditions both in RA patients and mice. Moreover, their pathogenic role in RA was further revealed by antibody depletion of MDSCs in CIA mice.

**Results:** MDSCs expanded significantly in RA patients and in CIA mice, which were correlated positively with disease severity and an inflammatory Th17 response. While displaying T-cell suppressive activity, MDSCs from arthritic mice produced high levels of inflammatory cytokines (e.g., IL-1β, TNF-α). Both human MDSCs (CD11b+CD33+) and mouse MDSCs (CD11b+Gr-1+) efficiently promoted Th17 cell polarization ex vivo. Elimination of MDSCs in CIA mice markedly ameliorated disease symptoms concomitant with reduced levels of Th17 cells.

**Conclusion:** Our studies revealed the unrecognized pathogenic role of MDSCs in RA with the capacity of driving Th17 cell differentiation. This cell population might be served as novel therapeutic target for RA.

Disclosure: F. Hu; None. C. Guo; None. X. Y. Wang; None. Z. Li; None.

**2166**

**Bim Suppresses the Development of Glomerulonephritis By Inhibiting M2 Polarization.** Fu-Nien Tsai Northwestern University, Chicago, IL.

**Background/Purpose:** Only recently have monocytes and macrophages been accepted as critical players in the pathogenesis of SLE. However, very little is known regarding the molecular rheostats that control the actions of monocytes and macrophages and their state of polarization. Previous studies have shown that loss of Bim, a pro-apoptotic protein, in all cells leads to SLE-like disease and early mortality. We have shown that reduction of Bim expression in B cells is sufficient to affect the macrophage functions independent of its role in apoptosis. Thus, we hypothesized that Bim is essential in monocytes and macrophages to limit the development of SLE-like disease.

**Methods:** We generated mice lacking Bim specifically in myeloid cells (Cre-yrBimfl/fl) and assessed mice at 8, 16, 24, 36 and 48 weeks of age for characteristic of SLE-like disease. Macrophage turnover, activation, and polarization were examined in vivo and in vitro using flow cytometric analyses and luminescent based assays.

**Results:** Cre-yrBimfl/fl mice displayed splenomegaly, lymphadenopathy, heightened amounts of serum pro-inflammatory cytokines, hypergammaglobulinemia, IC deposition in the kidney, proteinuria, GN, and early mortality as compared to Bim+/− and mice lacking Bim in either lymphocyte compartments. Bim functions independently of its role in apoptotic in macrophages and monocytes, since macrophages from Cre-yrBimfl/fl and Bim+/−mice had equal BrdU uptake. Moreover, MyD88 is not necessary as Cre-yrBimfl/flMyD88−/−mice also developed SLE-like disease. The protein kinase A Kt was increased in macrophages from Cre-yrBimfl/fl and Bim+/− mice and was co-immunoprecipitated with Bim in wild type cells. Additionally, the BH3 domain, which is essential for its apoptotic function is necessary for suppressing inflammatory response in macrophages. Mcl-1 bone marrow chimera were sufficient to reduce development of SLE-like disease in Cre-yrBimfl/fl mice, which suggests that Bim may affect macrophage development or polarization. To this end, we show that Bim is necessary to prevent the skewing of macrophages toward M2, pro-fibrotic phenotype.

**Conclusion:** The expression of Bim in monocytes and macrophages is sufficient to inhibit SLE-like pathogenesis. These data suggest that Bim acts through its BH3 domain to reduce the intensity of inflammation and polarization status in macrophages through suppression the activity of Akt. These studies are crucial for understanding the development and the persistence of SLE, as well as for translational studies leading to the development of new targets for SLE.

Disclosure: F. N. Tsai; None.

**2167**

**Snail is Critical for Cathespin D Activation and the Normal Lysosomal Function.** Bo Shi, Qi Quan Huang, Robert Birkett, Renee E. Koessler, Andrea Dorfleutner, Christian Stehlik and Richard M. Pope. Northwestern University Feinberg school of Medicine, Chicago, IL.

**Background/Purpose:** Our recent data indicates that Snail, a SNARE-associated protein, is critical for maintaining healthy autophagy and monocytes to macrophage (MFS) differentiation which requires functional autophagy. Snail and autophagosomes are increased in MFS from the joints of patients with rheumatoid arthritis. Reduction of Snail hindered the maturation of autophagosomes, resulting in autolysosome accumulation and delayed bacterial clearance in macrophages. Failure to digest the sequestered cargos in...
these vacuoles might have resulted from deficient capacity of lysosomal hydrolisis. Here, we examined cathepsin D activity, a major hydrolase in lysosomes, in macrophages following the forced reduction of Snapin.

**Methods:** The reduction of Snapin in primary human MФs was performed using siRNA, while in the J774A murine MФ cell line it was reduced by infection with a lentiviral vector expressing Snapin shRNA. Cell fractions enriched with lysosomes were isolated using a density gradient separation method. The protein levels of non-active pro-form and active cathepsin D were detected by Western blot analysis. The active cathepsin D in cells was also detected by staining with bodipy-pepstatin A which binds to catalytically portion of cathepsin D. A autophagosomes were identified by the accumulation of LC3 punctae. A clarification of autophagosomes was assessed by transection of tandem fluorescent LC3 plasmid expressing a tandem red (not pH dependent) and green (quenched at low pH) fluorescence-tagged LC3.

**Results:** Following the reduction of Snapin, bodipy-pepstatin A staining was greatly reduced in lysosomes in primary human MФs, suggesting a reduction of active cathepsin D. The forced reduction of Snapin in MФs resulted in 30% reduction in the active form of cathepsin D, identified by immunoblot analysis, in whole cell lysates, compared to control MФs, while the pro-form of cathepsin D was slightly increased. Cathepsin D extracted from lysosome enriched fractions from Snapin reduced J774A MФ cells showed a 40% reduction in the active form, but no reduction of the pro-form, indicating the cathepsin D activation was disturbed, rather than the delivery of hydroloases to lysosomes. Interestingly, cathepsin B activation was unchanged in both whole cell lysates and in lysosome enriched fractions. Cathepsin D is activated in a low pH environment. Disrupting the acidification process in lysosomes or in autophagosomes will reduce cathepsin D activation. The forced reduction of Snapin in HEK293 cells increased green LC3 punctae, indicative of an increase in pH in autophagosomes/autolysosomes.

**Conclusion:** Snapin in macrophages is necessary for cathepsin D activation in lysosomes and autophagosomes, preventing the maturation of autolysosomes, by limiting the degradation of cargo within the autophagosomes. Snapin may contribute to the pathogenesis of rheumatoid arthritis by maintaining healthy autophagy and monocyte to MФ differentiation.

**Disclosure:** B. Shi, None; O. Q. Huang, None; R. Birkett, None; R. E. Koessler, None; A. Dorfleutner, None; C. Stehlik, None; R. M. Pope, None.

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**Background/Purpose:** Many rheumatic diseases are driven by chronic, repeated activation of Toll-like receptors (TLR) causing the initiation and perpetuation of disease. However, TLR-activated innate immune cells undergo the well-known immunoregulatory phenomenon of TLR tolerance, whereby the initial activation of TLRs results in impaired proinflammatory responses to subsequent TLR stimuli. Therefore, it is unclear how TLR-driven inflammation persists in vivo. Our well-characterized model of repeated TLR-driven inflammation demonstrates that repeated activation of TLR9 results in a feed-forward, interleukin (IL)-12-mediated inflammatory response culminating in systemic immunopathology rather than tolerance. Using this model, we dissect the cellular mechanisms utilized to bypass TLR9 tolerance in vivo.

**Methods:** In vitro mixed TLR9 sufficient and deficient cell cultures were stimulated with CpG1826, a TLR9 agonist, to demonstrate that IL-12 is a readout of cell-intrinsic TLR9 activation. Y440 IL-12-reporter mice were treated with 4 doses of CpG1826 before tissue leukocytes were isolated and analyzed by flow cytometry to identify the IL-12-producing cells. Bone marrow, peripheral blood, and tissue leukocytes from CpG-treated mice were stained for myeloid progenitor cell markers to determine if myelopoiesis is altered during TLR9-mediated systemic inflammation.

**Results:** We demonstrate that inflammatory monocyte-derived dendritic cells increase in frequency and total numbers during TLR9-mediated systemic inflammation, and are the key IL-12-producing cell in this model. To determine the origin of these inflammatory tissue-invading cells, we tested peripheral blood and bone marrow of CpG-treated mice to enumerate the number of inflammatory monocytes and myeloid progenitor cells. To our surprise, the total number of peripheral blood inflammatory monocytes and bone marrow myeloid precursors was unchanged during TLR9-induced systemic inflammation. In contrast, extramedullary myeloid precursors were markedly increased in peripherally inflamed tissues of CpG-treated mice.

**Conclusion:** Our data highlight an important mechanism whereby persistent TLR9 activation bypasses TLR tolerance in vivo by increasing extramedullary myelopoiesis. Increased extramedullary myelopoiesis provides a continuous source of new TLR9-responsive cells that perpetuates TLR-driven inflammation. These new insights into the mechanisms driving persistent TLR-mediated inflammation may lead to novel therapeutic targets to ameliorate TLR9-mediated rheumatic diseases by intervening to suppress TLR-driven extramedullary myelopoiesis.

**Disclosure:** L. K. Weaver, None; E. M. Behrens, None.

**2169**

Targeting ITGAM+ Cells Successfully Treats a Model of Anti-RNP-Associated Pulmonary Hypertension. Vineet Gupta1, Yunjuan Zang2, Karen Young3, Jian Huang4, Inna Fernandez5 and Eric L. Greideringer6. 1Rush University Medical Center, Chicago, IL, 2University of Miami, Miami, FL.

**Background/Purpose:** Aggressive immunotherapy has shown modest effectiveness for pulmonary hypertension in anti-RNP Autoimmunity, but with high morbidity. We studied the ability of an ITGAM-targeted therapy that has been previously reported to have immunomodulatory properties to treat a model of this condition.

**Methods:** Following IACUC-approved protocols, study mice were adaptively transferred with splenic dendritic cells from anti-RNP-immunized syngeneic donor mice, and screened for elevations in serum Brain Natriuretic Peptide (BNP) levels. Mice developing increased BNP levels received a single IV dose of the ITGAM-specific small molecule agonist Leukatherin-1 (LA-1), a chemically similar compound without ITGAM specificity (LA-C), or sterile PBS. Mice were then followed for BNP levels and/or underwent right heart catheterization to directly assess pulmonary hypertension.

**Results:** The majority of splenic CD11c+ dendritic cells from anti-RNP donor mice express ITGAM by FACS. Treatment of these cells in vitro induces massive dendritic cell death, and prevents the development of adoptive transfer-induced lung disease. Mice receiving intact CD11c+/H11001 donor mice express ITGAM by FACS. Treatment of these cells in vitro induces massive dendritic cell death, and prevents the development of adoptive transfer-induced lung disease. Mice receiving intact CD11c+/H11001 donor mice develop substantial elevations in serum BNP levels, that correlate with increases in pulmonary pressures on right heart catheterization. Treatment of mice with established high serum BNP levels with LA-1 (but not controls) leads to rapid normalization of serum BNP levels and hemodynamic indices in 80% of study mice. No LA-1-induced toxicity was observed.

**Conclusion:** Adoptive transfer of ITGAM+ dendritic cells can induce pulmonary hypertension and ITGAM-targeted therapy can treat established pulmonary hypertension in a model of anti-RNP autoimmunity. These findings emphasize the potential importance of dendritic cells as mediators of tissue damage in anti-RNP autoimmunity, and raise the question whether the genetic associations of ITGAM with autoimmune disease risk could be mediated through effects on dendritic cells. LA-1 is a promising compound to develop for potential human trials.

**Disclosure:** V. Gupta, Adhaere Pharmaceuticals, 4; Y. Zang, None; K. Young, None; J. Huang, None; I. Fernandez, None; E. L. Greideringer, Adhaere Pharmaceuticals, 9.

**2170**

Human Tolerogenic Dendritic Cells Generated with Protein Kinase C Inhibitor Are Optimal for Regulatory T Cell Induction—a Comparative Study. Eddy Adnan, Hitoshi Hasegawa, Takuya Matsuomo, Jun Ishizaki, Sachiko Onishi, Koichiro Suzuki and Masaki Y asukawa. Ehime University Graduate School of Medicine, Toon, Japan.

**Background/Purpose:** Tolerogenic dendritic cells (tDCs) are a promising tool for autoimmune diseases, transplantation and allergy. Actually, tDCs have been tried for the therapy of rheumatoid arthritis and type 1 diabetes. To date, immunomodulatory DCs are prepared from monocytes for in vitro experiments by using various agents. Previously, we generated stable tDCs with protein kinase C inhibitor (PKC1) in human and mouse and PKC1-tDCs have been tried for the therapy of rheumatoid arthritis and type 1 diabetes. To determine the optimal agent for clinically applicable tDCs: efficient induction of functional regulatory T cells (Treg); CCR7-dependent migration; and stability under proinflammatory conditions. In this study, to select the optimal agent for clinically applicable tDCs, we compared the clinical-grade tDCs generated with various agents.

**Methods:** We compared tDCs generated with the following agents: vitamin D3 (Vit D3), dexamethasone (Dexa), bisindolylmaleimide I (PKCI), PPAR gamma plus retinoic acid (PPAR + RA), rapamycin (Rapa), IL-10, and TGF-beta. tDCs were prepared by adding these agents prior to the induction of maturation using TNF-alpha, IL-1beta and PGE2. We evaluated the effects of each agent on phenotype, CCR7-dependent migration, cytokine produc-
tion, phagocytosis, stability, T-cell suppression, and induction of IL-10-producing T cells and functional Foxp3+ Treg cells.

Results: All tDCs except Rapa-tDCs showed an immature or semi-mature phenotype, whereas the phenotype of Rapa-tDCs resembled that of mature DCs. PKC1-tDCs, TGF-DCs and Rapa-tDCs had moderate and high CCR7 expression, whereas tDCs generated with PPAR-RA, Vit D3, Deca or IL-10 had very low CCR7 expression. IL-10 production by IL-10-tDCs and PKC1-tDCs was high. Immature DCs (tDCs) and PKC1-tDCs showed high production of TGF-beta. Functionally, tDCs, PKC1-RA-tDCs, Vit D3-tDCs and IL-10-tDCs strongly suppressed T-cell activation, whereas Deca-tDCs, TGF-DCs and Rapa-tDCs weakly suppressed. All tDCs showed phagocytic ability and stable tolerogenic properties under proinflammatory conditions. From these findings, PKC1-tDCs showed moderate expression of CCR7, leading to migrating toward CCR7 ligands, maintained stability, and strongly suppressed T-cell activation by generating IL-10-producing T cells and functional Foxp3+ Treg cells.

Conclusion: PKC1-tDCs appear to be optimal for clinically applicable tDCs. We expect that PKC1-tDCs are useful for tolerance-inducing therapies.

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2171

Polymorphisms in the FCN1 Gene Coding for M-Ficolin Are Associated with Disease Activity, Radiographic Damage and Are the Strongest Predictors of DAS28 Remission in 180 DMDAR naive Early Rheumatoid Arthritis Patients. Christian G. Ammitzbøll1, Rudi Steffensen2, Steffen Thiel3, Jens Christian G. Lønstedt1, Kim Horsted-Petersen1, Torkel Ellingsen1, Marita Lund Heltø1, Peter Junker1, Mikkel Ostergaard1 and Kristian Stengard-Pedersen1. 1Arhus University Hospital, Aarhus, Denmark, 2Aalborg University Hospital, Aalborg, Denmark, 3department of Rheumatology, Copenhagen University Hospital, Glostrup, Copenhagen, Denmark. Disclosure: C. G. Ammitzbøll, None; R. Steffensen, None; S. Thiel, None; J. C. Jensenius, None; K. Horsted-Petersen, None; T. Ellingsen, None; M. L. Heltø, None; P. Junker, None; M. Ostergaard, Abbott/AbbVie, Centocor, Merck, Schering-Plough, 2, AbbVott/AbbVie, BMS, Boehringer-Ingelheim, Eli-Lilly, Centocor, GSK, Jansen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche UCB, and Wyeth, 5, None, 1, 3, K. Stengard-Pedersen, None.

Background/Purpose: M-ficolin is a pattern recognition molecule that collaborates with associated serine proteases as an activator of the complement system. High M-ficolin levels are strongly associated with high disease activity in early RA and low levels at baseline are strong predictors of both remission and low disease activity after one year. Single nucleotide polymorphisms (SNPs) in the M-ficolin gene FCN1 have been shown to influence the concentration and function of M-ficolin(2) and are associated with outcome in patients with systemic inflammation. We have now investigated associations of 7 FCN1 SNPs with DAS28, modified Total Sharp Score (mTSS), low disease activity (LDA), DAS28<3.2, and remission (DAS28<2.6) in a cohort of 180 early RA patients.

Methods: 180 DMDAR naive RA patients with disease duration <6 months were included in a randomized double blind placebo-controlled trial (OPERASudy,NCT00660647) of methotrexate, intra-articular glucucorticoids plus either adalimumab (OR between 2.49 to 2.66).

Results: Baseline characteristics were similar in the two groups, Table 1. The associations between SNPs and endpoints were evaluated using linear or logistic regression analysis adjusted for age, sex, anti-CCP and treatment with the common allele homozygous genotype selected as reference. Results: Baseline characteristics were similar in the two groups, Table 1. Table 2 states the four SNPs of which the minor allele was previously shown to be associated with higher plasma M-ficolin levels in healthy adults(2). Homozygosity of the minor allele in any of these 4 SNPs was associated with higher DAS28 at both baseline (p<0.005) and after one year of aggressive treatment (p<0.009), while no effect was observed in the heterozygote state. Homozygosity of the minor allele in the 4 SNPs was further associated with increased mTSS at both baseline (p<0.02) and at year one (p<0.04), except for rs7657015 (p=0.06). The four SNPs were, in multivariate logistic regression analyses, the only variables able to predict LDA at year one (OR between 0.16 to 0.18) and the strongest predictors of remission (OR between 0.24 to 0.26) followed by treatment with adalimumab (OR between 2.49 to 2.66).

Conclusion: Homozygosity of the minor allele of 4 FCN1 SNPs is associated with higher DAS28 levels and modified Total Sharp Score in early RA. The four SNPs were the only variables capable of predicting LDA and the strongest predictors of DAS28 remission. These data consolidate our previous findings that M-ficolin, a molecule of the innate immune system, is a strong prognostic marker at both the protein and gene level.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>OPERA Placebo treated group (n=31)</th>
<th>OPERA Adalimumab treated group (p=38)</th>
<th>P value</th>
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<tr>
<td>Baseline characteristics</td>
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<td></td>
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<tr>
<td>Female sex</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>Age, years</td>
<td>54 (28-77)</td>
<td>56 (26-78)</td>
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<tr>
<td>Disease duration, days</td>
<td>83 (42-150)</td>
<td>88 (42-162)</td>
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<tr>
<td>Anti-CCP positive</td>
<td>70%</td>
<td>67%</td>
</tr>
<tr>
<td>RF positive</td>
<td>74%</td>
<td>70%</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.6 (3.8-7.3)</td>
<td>5.5 (3.8-7.8)</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>15 (7-109)</td>
<td>15 (7-133)</td>
</tr>
<tr>
<td>Tender joint count(28)</td>
<td>8 (2-22)</td>
<td>8 (2-25)</td>
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<tr>
<td>Swollen joint count(28)</td>
<td>8 (2-22)</td>
<td>8 (2-25)</td>
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<tr>
<td>VAS-patient global, mm</td>
<td>65 (17-79)</td>
<td>70 (12-100)</td>
</tr>
<tr>
<td>X-ray erosions (Eiosity)</td>
<td>52%</td>
<td>54%</td>
</tr>
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</table>

Disclosures: C. G. Ammitzbøll, None; R. Steffensen, None; S. Thiel, None; J. C. Jensenius, None; K. Horsted-Petersen, None; T. Ellingsen, None; M. L. Heltø, None; P. Junker, None; M. Ostergaard, Abbott/AbbVie, Centocor, Merck, Schering-Plough, 2, AbbVott/AbbVie, BMS, Boehringer-Ingelheim, Eli-Lilly, Centocor, GSK, Jansen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche UCB, and Wyeth, 5, None, 1, 3, K. Stengard-Pedersen, None.

2172

PTPN22 Promotes TLR-Induced Amelioration of Arthritis. David Ewart, Erik J. Peterson and Y. Ya Wang, University of Minnesota, Minneapolis, MN.

Background/Purpose: Rheumatoid arthritis (RA) synovial fluid exhibits high levels of type 1 interferons (IFN). Type 1 IFN may exert potent anti-inflammatory effects, since a TLR3 agonist suppresses inflammatory arthritis in the type 1 IFN-dependent manner. PTPN22, encoding Lymphoid Tyrosine Phosphatase (Lyp), is a “risk” gene for RA. A PTPN22 disease-associated variant encodes an R620W substitution-bearing protein “LypW”. We showed previously that PTPN22 promotes Toll-like receptor (TLR) signaling and type 1 IFN production. Further, we found that LypW exhibits reduced function in poly(I:C)-mediated suppression of inflammatory arthritis in the K/BxN “serum-transfer” arthritis model. TLR9 agonists can also suppress arthritis through an unknown mechanism. We tested the hypothesis that PTPN22 is required for TLR9 agonist-driven amelioration of arthritis.

Methods: Serum-transfer arthritis was induced in control or Ptnp22−/− mice by intraperitoneal injection of K/BxN mouse serum. Mice were then injected with ODN 1668 (10 nmol), a CpG oligonucleotide agonist of TLR9.

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Arthritis scores were monitored. Synovial RNA was assayed for type 1 interferon and interferon-dependent gene expression via RT-qPCR.

Results: Confirming previous reports, ODN 1668 treatment ameliorated serum-transfer arthritis in control mice. However, Ptpn22−/− mice exhibited diminished suppressive response to ODN 1668. Reduced arthritis amelioration in Ptpn22−/− mice correlated with impaired TLR9 induction of Ifna4 and Cxcl10 (type 1 IFN-dependent chemokines) in synovium (Figure 1).

Figure 1: Mice (n = 3 per group) were injected with K/BxN serum together with ODN 1668 or vehicle alone. Arthritis severity scores (mean± SEM) are shown. WT, wild-type; KO, Ptpn22−/−.

Conclusion: Ptpn22 is required for CpG-induced amelioration of inflammatory arthritis, and for upregulation of type 1 IFN-dependent genes in synovium. These data support a model wherein Ptpn22 exerts anti-inflammatory arthritis, and for upregulation of type 1 IFN-dependent genes in synovium (type 1 IFN-dependent chemokines) in synovium (Figure 1).
to aberrantly expressed miR-146a, could contribute to the abnormal activation of T cells in the affected tissues of SS. This is supported by the observed reduction in regulatory cytokine IL-10 in SS T cells despite elevated expression of regulatory cytokine IL-10, PD-1, and the number of Foxp3+ Tregs.

Disclosure: A. Gauna, None; J. O. Jin, None; Q. Yu, None; C. Stewart, None; S. Cha, None.

2175

Macrophages from the Synovium of Active Rheumatoid Arthritis Exhibit an Activin a-Dependent Pro-Inflammatory Profile. Elena Izquierdo1, Blanca Soler Palacios2, Litzbeth Estrada-Capetillo2, Gabriel Criado3, Concha Nieto4, Cristina Municio5, Isidoro González-Alvaro6, Paloma Sánchez-Mateos7, Jose L. Pablos2, Angel L. Corbi7 and A. Mayra PuigKröger8. 1Centro de Investigaciones Biológicas (CSIC), Madrid, Spain, 2Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain, 3Instituto de Investigación Sanitaria Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Hospital Universitario La Princesa, Madrid, Spain, 4Instituto de Investigación Hospital 12 de Octubre (i12), Madrid, Spain, 5Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Hospital Universitario La Princesa, Madrid, Spain, 6Instituto de Investigación Hospital 12 de Octubre (i12), Madrid, Spain.

Background/Purpose: Synovial macrophages are key effector cells in rheumatoid arthritis (RA), where they are a major source of pro-inflammatory cytokines and contribute to the cartilage and bone destruction. Macrophages are phagocytic cells present in all tissues and show a remarkable plasticity in response to environmental signals. However, the polarization state of macrophages in RA has not been fully uncovered. To dissect the molecular basis for the tissue-damaging effects of macrophages in RA joints, we have characterized the phenotype and transcriptome of RA synovial macrophages. Moreover, we have studied the macrophage polarization ability of the synovial fluid of RA (RA-SF) patients.

Methods: Human monocytes (obtained from buffy coats from normal donors) and macrophages from RA-SF (RA-SF M0) were isolated by Ficoll gradient and subsequent magnetic cell sorting using anti-CD14 microbeads. Monocytes were cultured for 7 days in RPMI containing GM-CSF or M-CSF to generate GM-CSF-polarized macrophages (GM-M0) or M-CSF-polarized macrophages (M-M0). The phenotypic and transcriptomic characterization of ex-vivo isolated CD14+ RA-SF macrophages was accomplished by flow cytometry and quantitative real time PCR. In normal and synovial tissues, the expression of macrophage-polarization markers was analyzed by immunofluorescence labeling. To assess the RA-SF polarization ability, RA-SF was added onto monocytes or M-M0 (ratio 1:1 in culture medium) in the presence or absence of a blocking anti-activin a antibody for 72 hours and the expression of macrophage-polarization markers was analyzed by qRT-PCR and Western Blot.

Results: Flow cytometry and gene profiling indicated that RA-SF macrophages express pro-inflammatory polarization markers (MMP12, EGLN3, CCR2), lack expression of markers associated to homeostatic and anti-inflammatory polarization (IGF1, HTR2B), and express a transcriptomic profile that resembles the activin A-dependent gene signature of pro-inflammatory macrophages in vitro generated macrophages. In vitro experiments on monocytes and macrophages indicated that RA-SF promote the acquisition of pro-inflammatory macrophages (INHBA, MMP12, EGLN3, CCR2), but led to a significant reduction in the expression genes associated to homeostasis and inflammation resolution (FOLR2, SERPINB2, IGF1, CD36), thus confirming pro-inflammatory polarization ability of RA-SF. Importantly, the macrophage polarization ability of RA-SF was inhibited by an anti-activin a neutralizing antibody, thus demonstrating that activin a mediates the pro-inflammatory macrophage polarization ability of RA-SF. Moreover, and in line with these findings, multicolor immunofluorescence evidenced that macrophages within RA synovial membranes (RA-SM), expressed pro-inflammatory polarization markers whose expression is activin a-dependent.

Conclusion: Altogether, our results demonstrate that macrophages from RA synovial fluid and membrane exhibit an MMP12+ EGLN3+ CCR2+ pro-inflammatory polarization state whose acquisition is partly dependent on activin a from the synovial fluid.

Disclosure: E. Izquierdo, None; B. Soler Palacios, None; L. Estrada-Capetillo, None; G. Criado, None; C. Nieto, None; C. Municio, None; I. González-Alvaro, None; P. Sánchez-Mateos, None; J. L. Pablos, None; L. Corbi, None; A. PuigKröger, None.

2176

Macrophages-Mediated Response to Uric Acid Crystals Is Modulated by Their Functional Polarization. Emma García-Melchor1, Monica Guma2, Jordi Yagüe1, Maria del J. Juan3 and Jaqueline Harper4. 1Hospital Clinic Barcelona, Barcelona, Spain, 2University of California, San Diego, La Jolla, CA, 3Malignan et al. 4Medical Research, Wellington, New Zealand.

Background/Purpose: Macrophages have been involved in both initiation and resolution of gout flares. Accordingly, these cells are characterized by their plasticity as the environment modulates their phenotype exerting inflammatory or anti-inflammatory functions depending on their activation or polarization state. Macrophages in the presence of interferon-γ and lipopolysaccharide (LPS), what is known as classical activation, acquire an inflammatory phenotype and are also termed M1 macrophages. On the other hand, M2 or alternatively activated macrophages with IL-4 have anti-inflammatory and homeostatic functions. Equivalently, in the presence of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) macrophages become M1 or M2 respectively. As M-CSF is present in the blood stream at steady state some authors propose that both macrophages polarized with M-CSF could represent the population of resident macrophages. In this work we investigated M2 macrophages response to monosodium urate (MSU) crystals in vitro.

Methods: Macrophages were derived from peripheral blood monocytes of healthy donors after informed consent. Peripheral blood mononuclear cells were separated from whole blood by centrifugation with a density gradient. Monocytes were then isolated by negative selection with magnetic beads and cultured for 1 week with GM-CSF (1000 IU/ml) or M-CSF (20 ng/ml) to obtain M1 or M2 macrophages, respectively. M1 macrophages were then stimulated with MSU (200 µg/ml), LPS (100 ng/ml) or both for 18 hours and quantification of IL-1β and IL-10 in supernatants was performed by ELISA. Activation of caspase-1 in M1 and M2 macrophages was analyzed by flow cytometry with the Caspase-1 FLICA™ Detection Kit (Immunochrometry Technologies). Cytoplasmic pro-caspase-1 and pro-IL-1β were analyzed by western blot. Flow cytometry and statistics analysis were performed with the FACSDiva and GraphPad Prism 5 respectively.

Results: As expected, M1 macrophages produced inflammatory cytokines in response to LPS, whereas M2 macrophages were unable. Both M1 and M2 failed to produce IL-1β after MSU stimulation. However, when challenged with MSU and LPS, M2 macrophages produced IL-1β (mean+/-SEM, LPS 2.59 +/- 1.37 pg/ml, MSU + LPS 111.4 +/- 30.44 pg/ml, p= 0.0078) and reduced IL-10 production (mean +/-SEM, LPS 373.8 +/- 230 pg/ml, MSU + LPS 1587 +/- 386.4 pg/ml, p= 0.0039). Resting M2 macrophages exhibited lower levels of active caspase-1 and pro-caspase-1. M1 macrophage stimulation increased active caspase-1 levels in both M1 and M2 macrophages and the presence of MSU and LPS had a synergic effect in pro-IL-1β.

Conclusion: M1 and M2 macrophages failed to produce inflammatory cytokines after MSU challenging, according with the fact that MSU crystals can be found in asymptomatic joints. However, after MSU phagocytosis, M2 macrophages were able to produce IL-1β after LPS stimulation, explaining the requirement of a trigger, such as a copious meal or alcohol intake, for the initiation of an acute flare in gout. M2 macrophages also had lower levels of caspase-1 and pro-caspase-1, than M1 macrophages.

Disclosure: E. García-Melchor, None; M. Guma, None; J. Yagüe, None; M. J. Juan, None; J. Harper, None.

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Class A Scavenger Receptor (SR-a) Exacerbated Synovial Fibroblasts-Mediated Inflammation in Rheumatoid Arthritis. Yingni Li1, Fanlei Hu1, Li Zheng1, Linchong Su1, Lianjie Shi1, Pei Song2 and Zhanguo Li3. 1Peking University People’s Hospital, Beijing, China, 2Hubei Minzu University, Enshi, China.

Background/Purpose: Class A scavenger receptor (SR-A/CD204), mainly expressed on macrophages, plays an important role in the pathogenesis of atherosclerosis and in the pattern recognition of pathogen infection. However, its role in rheumatoid arthritis (RA) has not been defined. The aim of this study was to reveal the expression of SR-A in synovial fibroblasts (RASF) and its impact on synovial inflammation.

Methods: Immunohistochemistry (IHC) was performed to detect the expression of SR-A in the synovial tissues from RA and osteoarthritis (OA) patients. The expression of SR-A in RASF was demonstrated by both qPCR and western blot. To reveal the effects of SR-A on synovial inflammation, RASF were treated with either recombiant SR-A protein or SR-A specific antibodies.

Disclosure: E. Izquierdo, None; B. Soler Palacios, None; L. Estrada-Capetillo, None; G. Criado, None; C. Nieto, None; C. Municio, None; I. González-Alvaro, None; P. Sánchez-Mateos, None; J. L. Pablos, None; L. Corbi, None; A. PuigKröger, None.
siRNA. Then, the expression of pro-inflammatory cytokines (TNF-$\alpha$, IL-6, and IL-8) and M MPs (M MP-1, M MP-3, and M MP-9) were determined by real-time PCR and ELISA. Accordingly, the activation of the M AKPs and NF-$\kappa$B signaling pathways was evaluated by western blot when SR-A was silenced.

**Results:** The level of SR-A was higher in the synovial tissues from RA patients than those from OA patients. Moreover, we found that knocking down SR-A by specific siRNA suppressed the expression of these factors, with dampened activation of the ERK, JNK, p38 and NF-$\kappa$B signaling pathways.

**Conclusion:** SR-A exacerbated synovial inflammation and cartilage erosion in RA. Targeting SR-A might provide novel therapeutic strategies for overcoming this stubborn disease.

**Disclosure:** L. Li, None; F. Hu, None; L. Zheng, None; L. Su, None; L. Shi, None; P. Song, None; Z. Li, None.

2178

**Extensive Natural Killer Cell Receptor Phenotyping on NK and T Cells**

Discloses Differences in RA and PsA, Potentially Mirroring Diverse Immunoregulatory Functions.

Marta Cossu, Sandra TA van Bijnen, Mieke Roeven, Tim Jansen, Frank Preijers, Harry Dolstra, and Timothy Radstake. University Medical Center Utrecht, Utrecht, Netherlands. Radboud University Medical Center, Nijmegen, Netherlands.

**Background/Purpose:** Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are immune-mediated diseases, which share clinical features, but differ in the mechanisms, leading to aberrant immune responses. Natural killer (NK) cells tune the innate immune response depending on the integration of signals coming from a complex network of activating and inhibitory surface receptors. Here, we aim to elucidate the potential role of NK and T cells in inflammation and autoimmunity in RA and PsA and we focused on extensive characterization of the NK cell receptor (NKR) (co-)expression patterns on their surface.

**Methods:** The frequency of T and NK cells expressing KIR-like immunoglobulin receptors (KIR), NKG2 and Natural Cytotoxicity receptors was assessed by 10-color flow cytometry (FCM) in peripheral blood of 23 RA patients (ACR 1987 revised criteria), 12 PsA patients (Taylor et Al, 2006 classification of Psoriatic Arthritis Study Group criteria for PsA) and 18 healthy controls (HC). Cytotoxicity of NK cells against K562 cells before and after stimulation with IL-12 and IL-18 as broad activating signals was assessed in parallel.

**Results:** RA patients, but not PsA patients, had an increased frequency of NK cells expressing the inhibitory receptor NKG2A compared to HC, particularly in patients with rheumatoid factor positivity. The NKG2A+ NK population was predominantly CD56dim and lacked expression of KIRs and particularly in patients with rheumatoid factor positivity. The NKG2A+ CD56dim NK population was predominantly CD56dim and lacked expression of KIRs and especially in patients with rheumatoid factor positivity. CD4+ T cells expressing the Fcγ receptor CD16 were more frequent in RA than in HC. Compared to HC, we found higher frequencies of T cells expressing the KIRs CD158ab in both RA and PsA, and CD158c in RA. CD4+ T cells expressing the KIRs CD158ab, CD158c and CD158e1e2, although present at low frequency, were also significantly elevated compared to HC.

**Conclusion:** The differences in NKR expression on NK and T cells in RA and PsA could mirror the diverse pathogenic mechanisms implicated in these diseases; in particular, the immature phenotype (NKG2A+/-KIR-) of circulating NK cells in RA and the reversible impairment in their cytotoxic ability could reflect the activation status of the NK population described in RA. Synovial fluid and provide growing evidence for the potential of the exploitation of NKG2A blockade in this disease.

**Disclosure:** M. Cossu, None; S. T. van Bijnen, None; M. Roeven, None; T. Jansen, Abbievi, None; S. A. Preijers, None; H. Dolstra, None; T. Radstake, None.

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**The Monocyte-Phagocyte System in Gout: Enhanced Inflammamome Activity and Expansion of CD14++CD16+ M monocytes in Patients with Gout.**


**Background/Purpose:** The central role of the monocyte-macrophage system in gout has been highlighted during the last years. Macrophages initiate the inflammatory response to monosodium urate (MSU) crystals and secrete mediators that prime other inflammatory cytokines and chemokines that induce migration of blood monocytes to further amplify the inflammatory response. Different subpopulations of blood monocytes have been recognised: classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical (CD14+CD16+); characteristically intermediate monocytes are expanded in infectious and inflammatory diseases. One of the questions that remain unanswered is why some patients with hyperuricemia, and even with MSU deposits, remain clinically asymptomatic. We investigated the possibility that it could be due to a greater inflammamome reactivity to MSU crystals in patients who develop gout. Moreover, we analyzed the distribution of monocyte subpopulations in patients with gout.

**Methods:** Seventeen patients with gout were selected, 13 asymptomatic and in 4 patients samples were obtained during an acute flare. Nineteen healthy donors were selected for comparison. Inflammamome activity was assessed by the increase of active caspase-1 after stimulation with MSU in peripheral blood mononuclear cells (PBMCs). Flow cytometry using a Caspase-1 FLICA TM Detection Kit (Immunochemistry Technologies). Phagocytosis of MSU crystals was quantified by flow cytometry, as cells that phagocytosed crystals increased their side scatter (SSC) values. PBMCs were cultured for 24 hours in the presence of MSU (200 µg/ml). LPS (100 ng/ml) or both and IL-1ß was quantified by ELISA. Samples of peripheral blood were stained with CD45, HLA-DR, CD16, and CD14 antibodies and analyzed by flow cytometry. Uric acid, creatinine and C-reactive protein (CRP) were quantified in sera. Flow cytometry and statistics analysis were performed with the FACSDiva and GraphPad Prism 5 respectively.

**Results:** No differences were observed in active caspase-1 at baseline between patients and controls. However, when stimulated with MSU, monocytes from gout patients exhibited a higher increase of active caspase-1 (mean ÷ SEM, gout 2.20+-0.15, controls 1.66+-0.38, p=0.0419). Differences in phagocytosis of MSU crystals were excluded, as in both groups monocytes exhibited equivalent phagocytic capability. PBMCs of patients with gout exhibited diminished IL-1ß production when challenged with LPS and MSU (p=0.0473). Regarding monocyte subpopulations, the intermediate phenotype was expanded in patients with gout during an acute flare and a weak correlation between intermediate monocytes and CRP was observed.

**Conclusion:** Monocytes of patients with gout exhibited an enhanced inflammasome activation with MSU crystals, suggesting that the reduced threshold in the inflammatory response could be involved in the development of clinical gout. The expansion of intermediate monocytes was observed during gout flares and, although it cannot be excluded that intermediate monocytes could be “innocent bystanders” in the context of inflammation, it could suggest that these monocytes participate in the inflammatory response to MSU crystals.

**Disclosure:** E. Garcia-Melchor, None; C. Diaz-Torne, None; M. Guma, None; E. A. Gonzalez-Navarro, None; F. X. Alemany, None; J. Yague, None; M. Juan, None.

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**Macrophage Depletion Ameliorates Nephritis Induced by Pathogenic Antibodies.** Samantha Chalmers, Lea Herlitz, Violeta Chitu, Richard Stanley, and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY. Columbia-Presbyterian Medical Center, New York, NY. Albert Einstein College of Medicine, Bronx, NJ.

**Background/Purpose:** Kidney involvement affects up to 60% of lupus patients, and is responsible for significant morbidity and mortality. Previous studies using a variety of methods to reduce the number of macrophages have reached conflicting conclusions regarding the role of macrophages in the pathogenesis of lupus nephritis (LN). Moreover, “off target” effects occur in mice congenitally deficient in macrophages. In this study we investigated the role of macrophages in an inducible model of LN, using a novel depletion method that minimized the confounding factors seen in previous studies.

**Disclosure:** None.
Methods: To determine the role of macrophages in the antibody-mediated nephritis associated with lupus, we utilized the nephrotoxic serum nephritis model. This is an inducible model of nephritis which closely mimics LN and which is often used to model immune complex mediated renal disease. Mice received nephrotoxic serum (NTS) containing rabbit anti-mouse glomerular antibodies which deposited within the kidney to initiate nephritis. GW2580, an oral kinase inhibitor monospecific for the CSF-1 receptor, was used as a novel and highly selective method for macrophage depletion. GW2580 was delivered as a control gavage over a 10 day period (n = 18). A second group of mice received a control gavage of PBS in addition to the NTS transfer (n = 18). A third group was neither gavaged nor given NTS, and served as a healthy control population (n = 9).

Results: We found that NTS challenged mice, when treated with GW2580 from day 0, did not develop the significant increases in proteinuria, serum creatinine or BUN seen in control treated mice. Furthermore, GW2580 treated mice were protected from the robust kidney expression of inflammatory cytokines associated with LN seen in control treated mice, including RANTES, IP-10, VCAM-1, MCP-1 and IL-6. Flow cytometry analysis of kidney single cell suspensions revealed a significant decrease in inflammatory macrophages (CD11b⁺F4/80⁺) in GW2580 treated mice. Furthermore, IBA-1 staining confirmed profound depletion of macrophages within glomeruli of treated mice. There was no significant change in circulating monocyte numbers with GW2580 treatment. Spleen macrophages were significantly increased in the number of macrophages in the spleen. Importantly, GW2580 did not interfere with the induction of the disease model. Finally, treatment with GW2580 at a later time point in the disease model (beginning day 5) was also effective at attenuating nephritis.

Conclusion: Our results support an important role of macrophages in LN pathogenesis, and suggest targeting this cell type as a promising approach to the treatment of LN.

Disclosure S. Chalmers, None; L. Herlitz, None; V. Chitu, None; R. Stanley, None; C. Putterman, None.

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Background/Purpose: Dendritic cells (DC) are a heterogeneous population of professional antigen presenting cells which link both the innate and adaptive arms of the immune system. Myeloid and plasmacytoid DC represent the two major DC subsets and can be distinguished based on their morphological properties and the expression of surface markers and gene expression profiles. In this study we compared the percentage and activation status of myeloid versus plasmacytoid DC at the site of inflammation in RA compared to systemic circulation.

Methods: DC whole blood phenotyping was assessed using multicolour flow cytometry on the Beckman Coulter Cyan system using FlowJo software for suitable analytes. DC were defined as HLA-DR⁺, CD11c⁺, CD3⁻, and further subdivided as either myeloid (CD11c⁻, CD14⁻), or plasmacytoid DC (CD123⁺). Cell surface expression of CD80, CD83 and CD40 was used to assess the activation and maturation status of each subtype. For characterisation of synovial tissue DC, biopsies were digested using the GentleMACS mechanical and enzymatic digestion system. Viable CD45 cells were gated and subsequently assessed for DC pan markers in addition to maturation and activation markers. In parallel, synovial fluid and peripheral blood were comparatively assessed to profile DC from blood, fluid and tissue. To assess the effect of the synovial environment on DC maturation, immature DC were derived from CD14⁻ monocytes in the presence of GM-CSF (70ng/ml) and IL-4 (50ng/ml). Synovial tissue explants were cultured for 24hr allowing the spontaneous release of cytokines and soluble mediators into the culture medium. Monocyte derived dendritic cells (MoDC) were cultured in the presence of this explant conditioned media for 24hr after which the expression of maturation markers was analysed on CD11c⁺ CD14⁻ DC.

Results: RA patients have a decreased percentage of CD11c⁺ mDC circulating in peripheral blood compared to that of healthy controls. The percentage of CD123⁺ pDC between RA and healthy controls is not significantly different however the expression of CD40 on pDC in RA patients is significantly increased compared to healthy control (p = 0.001). A comparative analysis of mDC and pDC in peripheral blood, synovial fluid and synovial tissue highlighted an increase in DC maturation as DC migrate from blood, to fluid and finally tissue. CD40 and CD83 expression on mDC is increased in tissue compared to that of fluid or blood. Similarly an increase in CD40 and CD83 on pDC was found in synovial tissue compared to that of fluid or peripheral blood. Finally immature monocyte derived DC cultured in the presence of explant conditioned media have increased expression of CD80 and CD83 compared to basal DC medium.

Conclusion: DC have a more mature and activated phenotype in the synovial tissue compared to that in synovial fluid or peripheral blood. Given that there are also lower circulating levels of DC in RA patients compared to controls our data suggest that peripheral blood DC are recruited to the joint where they undergo a programme of maturation. Ongoing studies aim to elucidate the mechanisms in which these subsets are activated and matured.

Disclosure M. Canavan, None; M. A. O’Rourke, None; D. J. Veale, Abbvie, 2; MSD, 2; Pfizer Inc, 2; Roche, 2; Pfizer, 5; Roche, 8; U. Fearon, None.

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Investigating the Roles of Factor H-Related Proteins in Systemic Lupus Erythematosus (SLE) and Other Autoimmune Diseases. Alexandra Antonioli, Brandon Renner, Joshua Thurman, V. Michael Holers and Jonathan Hannan. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Complement plays a central role in the pathogenesis of systemic lupus erythematosus (SLE) wherein inappropriate activation of complement leads to substantial tissue damage, especially in the kidney. Factor H is a complement regulatory protein that controls activation of the alternative pathway in the fluid phase and on cell surfaces. Recent human linkage data implicate a role for a group of genes, encoding a family of factor H-related (FHR) proteins, in the pathogenesis of SLE. Specifically, a FHR3-1Δ deletion is associated with a higher risk for the development of SLE, while also demonstrating a protective association in age-related macular degeneration. To date, few functional studies have been carried out on the mouse FHR proteins, and these molecules have not been studied in any in vivo models of inflammatory or autoimmune disease. Our central hypothesis is that FHR proteins act as antagonists of FH function and increase complement deposition which exacerbates inflammation and injury.

Methods: To test our hypothesis that FHR proteins compete with FH-mediated complement regulation we: 1) Generated recombinant forms of the murine FHR proteins (mFHR-A and mFHR-B) using transiently transfected 293-F cells grown in serum free media. 2) Evaluated the capacity of each of these molecules to inhibit FH function using a hemolysis protection assay. 3) Performed ELISA assays to detect cross-species reactivity between murine FHRs and human complement components. 4) Used flow cytometry to evaluate C3b deposition on the surface of nucleated cells (Retinal Pigment Epithelial (ARPE-19) and/or murine tubular epithelial cells (TEC)) upon addition of mFHRs under both oxidatively stressed and non-stressed conditions. We are also producing antibodies directed to the murine FHRs in order to better understand how the FHRs may be involved in SLE and other autoimmune diseases and whether FHR levels are altered during different disease activity states (i.e. during SLE disease flares).

Results: Addition of 1μM of mFHR-A or mFHR-B results in 100% and 50% hemolysis, respectively, of sheep red blood cells which are normally associated complement regulators. We also observe a significant increase in C3b deposition under both stressed and non-stressed conditions on the surface of at least one type of nucleated cell (ARPE-19) upon addition of mFHR-A (mean fluorescence intensity is two-fold greater than serum only control). These results suggest that the murine FHRs are excellent surrogates by which to interrogate the underlying mechanisms linking variations within the human C3H gene family to complement deregulation in tissues such as the kidney or eye.

Conclusion: Our preliminary work supports recent studies which have shown that the FHR proteins modulate complement by competing with FH for binding to its major ligand, complement component C3b, likely disrupting FH-driven complement regulation on specific biological surfaces. The long-term objective of this work is to determine whether the FHR proteins are suitable therapeutic targets for the treatment of complement-driven inflammatory diseases such as SLE.

Disclosure A. Antonioli, None; B. Renner, None; J. Thurman, None; V. M. Holers, Alexion Pharmaceuticals, Inc., 7; J. Hannan, None.
Release of Enzymatically Active Peptidyl Arginine Deiminases (PADs) By Neutrophils Allows Generation of Citrullinated Extracellular Autoantigens in the Synovial Fluid of Patients with Rheumatoid Arthritis. Julia Spengler1, Bozo Lugojna1,2, Andrew Creese3, Jimmy Y Tertberg4, Karin Lundberg1,2, Mark Lundberg1,4, Christopher Buus2, Andrew Filer1, Karim Raza1, Paul Cooper1, Iain Chapelle1 and Dagmar Scheel-Toeller4. 1University of Birmingham, Birmingham, United Kingdom, 2Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, 3Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, 4University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Citrullinated proteins are important autoantigens in the inflamed joints of patients with rheumatoid arthritis (RA). Several of these proteins are derived from proteins generally found in the extracellular space, such as fibrinogen and type II collagen. It is therefore important to understand the source of extracellular peptide deiminases, (PAD) the enzymes responsible for citrullination. After entering the joints of RA patients, neutrophils are activated and release DNA in an active process termed NETosis. As this process involves histone citrullination by PAD4 we hypothesized that neutrophils undergoing NETosis in the rheumatoid joint release enzymatically active peptidyl arginine deiminases.

Methods: Extracellular DNA was quantified in the synovial fluid (SF) of patients with RA (n=27) and osteoarthritis (OA) (n=15). Presence of decondensed DNA in association with neutrophil elastase was studied on smear preparations of RA SF and synovial tissue. Release of PAD2 and PAD4 was measured in vitro using SF neutrophils stimulated with Western Blotting and verified by mass spectrometry and immunofluorescence. NETs isolated from in vivo and in vitro activated neutrophils were isolated and probed on western blots. PAD activity in the supernatant of in vitro stimulated neutrophils and in the SF of patients with RA (n=7) and OA (n=9) was determined by a conversion assay involving citrullination of target peptides.

Results: Extracellular DNA was detected in the SF from RA patients at significantly higher levels than OA SF (p<0.001) and correlated with SF neutrophil counts (r=0.58, p=0.002) and with PAD activity (r=0.4, p=0.03) in the SF. Immunofluorescence revealed the co-localization of neutrophil elastase with decondensed DNA in RA SF and within neutrophil precipitates on the surface of the synovial lining layer. Furthermore, PAD activity was detected at significantly higher levels in the SF of RA patients when compared to SF from OA patients (p<0.001) and the isoenzymes PAD2 and PAD4 were both found to be present in the SF of RA patients. Significantly higher PAD activity could also be detected in the supernatant of in vitro stimulated neutrophils when compared to unstimulated cells (p<0.05). Western blotting revealed the release of free PAD2 and PAD4 into the supernatant and also the association of both isoenzymes with isolated NETs. The loss of nuclear PAD4 enzymatic activity with decondensed DNA in RA SF and within neutrophil cytoplasm was confirmed by immunofluorescence staining.

Conclusion: These results demonstrate the enzymatic activity of PADs in the synovial fluid of RA patients. Combined with our findings from in vitro stimulated neutrophils the data suggest that neutrophils undergoing NETosis are a source of this extracellular activity. The correlation of the measured PAD activity with DNA levels and neutrophil cell counts in the synovial fluid of RA patients are in line with this hypothesis. This study highlights the possibility that activated neutrophils recruited into the joints could continuously release enzymatically active PADs which contribute to the continuous generation of citrullinated autoantigens and thus drive an inflammatory response in the joint.

Disclosure: J. Spengler None; B. Lugojna None; A. Creese None; J. Tertberg None; K. Lundberg None; M. Lundberg None; C. Buus None; A. Filer None; K. Raza None; P. Cooper None; I. Chapelle None; D. Scheel-Toeller None.

Selective Consumption of C2 Component in HCV Patients. Atila Granados Afonso de Faria1, Luis Eduardo C. Andrade1, Maria Lucia Gomes Ferraz2. 1Univesidade Federal de Sao Paulo, Sao Paulo, Brazil, 2Escola Paulista de Medicina - Universidade Federal de Sao Paulo, Sao Paulo, Brazil, 3Univesidade Federal de Sao Paulo, Sao Paulo, Brazil.

Background/Purpose: Hepatitis C virus (HCV) causes immunologic disorders (vasculitis, myositis, arthritis) and high frequency of autoantibodies and mixed cryoglobulinemia (CRYO). Recently, we observed that some HCV patients present absent serum C2 hemolytic activity without consumption of other components of the Complement System (CS). Liver enzyme (AST/ALT) serum levels were registered as the times the upper limit of normal (ULN). This study characterizes this phenomenon in a large series of consecutive HCV patients.

Methods: 1021 samples from 716 consecutive HCV patients were analyzed for CS parameters: functional assessment of C2 (radial immune-hemolysis); C2, C3 and C4 protein concentration (immune-precipitation). Clinical and laboratory data were obtained from a structured medical form.

Results: Samples were classified into three groups according to C2 hemolytic activity: 1) Absent activity (n=194, 15.1%); 2) Decreased activity (n=154, 15.1%); 3) Normal activity (n=473, 69.8%). All patients with decreased absent C2 activity had decreased serum C2 protein concentration. Serum C3 and C4 was normal in 89 (82%) and 82 (72%), respectively, of samples with absent C2 activity. Analysis of multiple sequential samples from 192 patients showed that the selective decrease in C2 activity is a transient phenomenon associated with variable duration in time. Patients with absent C2 activity had higher serum liver enzymes (AST/ALT (2.46±1.25 ULN and 2.29±1.5 ULN) and lower levels of C2 and C4 than those with normal C2 activity (AST 1.46±1.25 ULN p<0.001; ALT 1.62±1.47 ULN; p<0.03; albumin 43±0.5 p<0.01). Samples with absent C2 activity had higher frequency of CRYO (13%) than those with normal C2 activity (0.8%) (p<0.01). In vitro exposure of normal to CRYO induced selective decrease in C2 activity in a dose-dependent manner. C2 activity status was not associated with other clinical and laboratory parameters.

Conclusion: Selective decreased C2 activity is transiently observed in 30% of HCV patients. This phenomenon was associated with liver biochemical abnormalities and CRYO. Further studies are warranted to define the role of these and other yet unknown factors on selective C2 deficiency in HCV patients.

Disclosure: A. Granados Afonso de Faria None; L. E. C. Andrade None; M. L. Gomes Ferraz None.

Alterations in B Cell Complement Processing Related to a Lupus-Associated Variant in Complement Receptor 2. Brendan M. Giles and Susan A. Boackle. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: We have recently identified a variant in intron 1 of complement receptor 2 (CR2/CD21) that is associated with decreased risk of lupus (rs1876453; OR=2.8, p=0.005). Its effect was strongest in subjects with anti-dsDNA antibodies (OR=7.6, p=0.001). We hypothesized that increased CR1:CR2 ratio on the cell surface. CR1 binds the C3b and iC3b fragments of C3 and is a required cofactor for the degradation of C3b to the C3b-specific ligand C3dg. While crosslinking of CR2 and the B cell antigen receptor is known to lower the activation threshold, the role of CR1 during complement-processing and modify B cell activation.

Methods: A novel CR1 ligand (biot-C3b) was developed by biotinylating C3b in the thioester domain, the site of antigen attachment. The biotin ligand C3dg. While crosslinking of CR2 and the B cell antigen receptor is known to lower the activation threshold, the role of CR1 during complement-processing related to a lupus-associated variant in CR2.

Conclusion: By using a novel biot-C3b and varying the CR1:CR2 ratio on the cell surface, we showed that increased CR1 levels associated with the protective allele facilitate complement processing and modify B cell activation.

Disclosures: A. Granados Afonso de Faria None; L. E. C. Andrade None; M. L. Gomes Ferraz None.
Clinical and Immunologic Correlates in Cocaine Users with Serum Anti-Neutrophil Cytoplasmic Antibodies. Christian Lood and Grant C. Hughes. University of Washington, Seattle, WA.

Background/Purpose: Illicit cocaine use is associated with the development of serum anti-neutrophil cytoplasmic autoantibodies (ANCA) and a variety of clinical manifestations. However, the mechanisms linking cocaine use and autoimmunity remain obscure. A causal link between cocaine use and ANCA is suggested by known immunostimulatory properties of cocaine, and its frequent contamination with levamisole, an immunomodulatory chemical. Here, we describe the immunologic and clinical characteristics of a series of cocaine users found to have extremely high-titer serum ANCA. The purpose of this report is to generate testable hypotheses regarding possible links between cocaine use and autoimmunity.

Methods: Chart review of 12 consecutive patients referred for rheumatologic evaluation at 2 tertiary referral centers from 2008 to 2013 for active cocaine use and high-titer serum ANCA. Clinical and immunologic parameters with complete or near-complete data sets were chosen.

Results: Results are summarized in the table below. The majority of subjects were female users of crack cocaine. Half presented with hematologic abnormalities, but only a minority (2) presented with purpura, a frequently reported manifestation. Interestingly, 2 patients presented with diffuse alveolar hemorrhage (DAH) not readily explained by vasculitis or cryoglobulinemia. 3 patients presented glomerular disease. One presented with supraglottic inflammation, and another with ischemic bowel. Arthralgia/arthritis was common.

Conclusion: We observed a wide variety of clinical manifestations in cocaine users with high-titer serum ANCA reactivity. Immunologically, patients were more homogeneous, showing near-exclusive P-ANCA reactivity, frequent IgM (but not IgG) cardiolipin and/or b2-glycoprotein reactivity, and a complete absence of significant titer ANA - suggesting loss of immune tolerance to a limited set of self-Ags. That MPO reactivity was variably present further suggests P-ANCA reactivity was directed against other perinuclear neutrophil cytoplasmic Ags. The nature of these Ags in cocaine users, as well as the effects of cocaine use and levamisole on neutrophils, are the subjects of ongoing investigation.

Table: Clinical and Immunologic Parameters in Cocaine Users with Serum ANCA

<table>
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<th>ANCA (C+)</th>
<th>ANCA (N+)</th>
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<td>28</td>
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<td>F</td>
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<td>Pan</td>
<td>B</td>
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</table>

Disclosure: C. Lood, None; G. C. Hughes, None.
Results: There were 117 participants with RP ever recorded. In the validation study, 47/58 (81%) of cases were confirmed by a physician and unconfirmed cases were excluded. The analysis included 106 participants (42 men, 64 women) diagnosed with RP. The mean age (range) at diagnosis in men was 55 (17 to 81) years and in women 51 (11 to 79) years. There was a median interval of 1.9 years from first symptom consultation to diagnosis. The incidence of RP between 1990 and 2012 was 0.71 (0.55 to 0.91) per million population per year. There were 19 deaths from any cause. There were 16 observed deaths eligible for survival analysis and 7.4 deaths expected for the UK population of the same age, sex and period. The standardised mortality ratio was 2.16 (1.24 to 3.51), p = 0.01. Respiratory disease, cardiac conditions and cancer were the most frequent causes of death.

Conclusion: The incidence of RP may be lower than previously estimated and diagnostic misclassification and delay may be frequent. Mortality in RP is more than twice that of the general population.

Disclosure: N. Hazra, None; A. Dregan, None; J. Charlton, None; M. C. Gulliford, None; D. P. D’Cruz, None.

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Multicentric Reticulohistiocytosis: Case Series from a Tertiary Care Center. 
Namrata Singh1, Karolyn A Wanat2, Mary Stone2, Zuhair K. Ballas3 and Jacob W. Ijdo4. 1University of Iowa, Iowa City, IA, 2Iowa City VA and the University of Iowa, Iowa City, IA.

Background/Purpose: Multicentric Reticulohistiocytosis (MRH) is a rare systemic inflammatory disease with skin nodules and arthritis. On skin or joint biopsy the hallmark is the presence of multinucleated giant cells and histiocytes with a ground glass appearance of the cytoplasm secondary to lipid inclusions. In the past solitary or multiple cutaneous reticulohistiocytoma without joint involvement were thought to be a separate entity because it only affects the skin, albeit the histopathology is identical. Due to the rarity of the disease little is known about pathophysiology or treatment. A necrotic bone lesion was described in MRH and reports suggest that the use of TNF inhibitors and bisphosphonates may be beneficial. We wished to review the combined experience of this rare condition at a tertiary care institution.

Methods: After obtaining IRB approval, we searched the electronic medical records at the University of Iowa Hospital and Clinics (UIHCh) to identify all patients with MRH or cutaneous reticulohistiocytoma seen between January 2000 and December 2013. The aims of this retrospective study are to describe the different treatments and outcomes and concomitant diagnoses in patients with MRH/cutaneous reticulohistiocytoma with or without joint involvement.

Results: We have identified 16 patients of which 4 had both skin and joint involvement and 12 cases with cutaneous involvement only that were diagnosed and treated at UIHCh. All cases had a skin biopsy consistent with MRH/cutaneous reticulohistiocytoma. None of the patients were diagnosed with a malignancy.

Conclusion: Multicentric reticulohistiocytosis and cutaneous reticulohistiocytoma share identical histopathology but have different distribution and organ involvement. The pathogenesis and mechanism for different organ distribution of this systemic inflammatory disease is unknown. We report here the largest case series to date (16 cases) from a single academic institution in the last 13 years. It seems that MRH includes a wide spectrum ranging from no joint involvement to severe destructive arthritis. Follow up of patients with solitary and multiple cutaneous reticulohistiocytoma is warranted as joint involvement may develop with time.

Disclosure: N. Singh, None; K. A. Wanat, None; M. Stone, None; Z. K. Ballas, None; J. W. Ijdo, None.

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Features of Interstitial Lung Disease Associated with Connective Tissue Disease in a Spanish Southwest Cohort. 
Adela Gallego Flores1, Carmen Carrasco Cubero2, Raul Veroz Gonzalez1, Luz Maria Mellado Narciso1, Tamara Libertad Rodriguez Araya3, Juan Jose Aznar Sanchez1 and Eugenio Chamizo Carmona1. 1Hospital de Arco Iris, Mérida, Spain, 2Hospital de Mérida, Mérida, Spain.

Background/Purpose: Diffuse interstitial lung disease (ILD) can be associated with connective tissue diseases (CTD), and can increase morbidity and mortality significantly. Pulmonary involvement associated with CTD are often nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). UIP is more common in rheumatoid arthritis (RA). Pulmonary involvement in rheumatic diseases can be the first manifestation of these pathologies, preceding the onset of extrapulmonary symptoms. The presentation, clinical features and evolution of ILD associated with CTD can be variable, and therefore, it’s important to improve the prognosis by early diagnosis and treatment. The aim of this study is to describe the clinical features, treatments and outcome of patients with ILD associated with CTD found in the General Hospital of Mérida.

Methods: We systematically collected all cases of ILD associated with CTD reported in the Rheumatology Department from January 2008 to January 2014. We included patients over 18 years old, who had a CTD and radiological diagnosis of ILD.

Results: We found 23 patients with ILD associated with CTD: 17 rheumatoid arthritis (RA), 10 scleroderma (ES), 6 antisynthetase syndromes (SAS) and 3 SJogren’s syndrome (SS). The mean age was 66.08 years, with a female predominance (2:1). The diagnoses of RA preceded the diagnosis of ILD in 58.3 % (21). The ILD patterns were: 17 NSIP (47.2 %), more frequent in ES (9) and SAS (5 patients), 19 UIP (52.8 %), predominantly in RA.

Thirty patients were treated with IV cyclophosphamide (CF) and 14 with rituximab (RTX). We observed a sustained response in 13 patients (10 NSIP and 3 UIP): 2 patients had received CF, 6 RTX, 4 CF+RTX, and 1 antiTNF. All RA patients were rheumatoid factor (RF) positive, 33.3 % with a title over 100. The predominant pattern was UIP (73.2 %). M etoxotenate was used in 64.2 % of patients and it was suspended at the diagnosis of ILD, although no cases of pneumonitis were found by this drug. Patients with ES, SAS and SS were younger at diagnosis (63.7, 62 and 64.3 years respectively) than RA patients (69.23 years) and a predominance of NSIP pattern (66.7, 80 and 66.6 % respectively). All these patients had negative RF. A NAs were positive in 100 % of SAS, with a predominance of anti Ro 52 and anti J o1 (3 and 4 patients) and 77.8 % of ES and 66.6 % of SS. Two patients presented with poor responses to CF, one with UIP (ES) and 1 with NSIP (SAS), who died from infectious complications.

Conclusion: Usually the first manifestation of an ETC is due to the ILD, so it is advisable to maintain close cooperation with pneumologist. According to the literature, all patients with RA and ILD in our sample had RF+, as it usually occurs in rheumatoid extraarticular involvement. Otherwise, ILD was the predominant pulmonary pattern. Rest of ETC associated ILD had a predominance of NSIP pattern and positive A NAs, especially anti Ro, and anti J o1 in SAS. The RF was negative in all cases. Nine patients treated with RTX or sequentially with CF showed a better response. However, more studies need to be undertaken to reach better conclusions on the ways forward in treatment.

Disclosure: A. Gallego Flores, None; C. Carrasco Cubero, None; R. Veroz Gonzalez, None; L. M. Mellado Narciso, None; T. L. Rodriguez Araya, None; J. J. Aznar Sanchez, None; E. Chamizo Carmona, None.

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Intravenous Sodium Thiosulfate for Treatment of Refractory Calcinosis in Rheumatic Disease. 
Ross Thibaux, Bahnsen Miller and Stephen Lindsey. Louisiana State University Health Science Center, Baton Rouge, LA.

Background/Purpose: Calcinosis, or dystrophic calcification, is a poorly understood, debilitating condition commonly manifested in connective tissue diseases such as scleroderma and polymyositis. Despite treatment of the rheumatologic disease, patients typically endure pain, infections, and decreased joint mobility. Therapeutic options for calcinosis, including coumadin, corticosteroids, diltiazem, clonidine, and colchicine, have shown little success, and treatment failure is common. Intravenous sodium thiosulfate (IV STS) is commonly used to treat calciphylaxis, and several mechanisms are proposed for its effects. Intriguingly, the chelating properties of IV STS form water soluble calcium-thiosulfate, which aids in dissolving deposited calcium.
Successful Therapy with Intravenous Sodium Thiosulfate for Adult Dermatomyositis/Associated Calcinosis

Background/Purpose: Calcinosis cutis is the deposition of insoluble calcium salts in skin or subcutaneous tissue. In cases related to CTD, presents with normal calcium/phosphorus metabolism, and is frequently associated with SSC and DM. Despite therapies available, treatment response is often poor.

Methods: The subject is a 38-year-old male that presented with classic DM in 2007. Secondary causes were ruled out. He was treated with corticosteroids and methotrexate, with recovery of muscle strength and normalization of creatinine. In May 2008 without DM activity, he presented progressive painful subcutaneous calcifications in the axillary, gluteal and popliteal region, hands and back, confirmed by x-ray. Metabolic studies were normal.

Infliximab was initiated (200mg tid every 8 weeks totaling 5 doses), with poor response and progression of calcinosis. In August 2009 therapy with sodium thiosulfate was initiated: 50ml at 25% (12.5gr) in prolonged infusion over 60 minutes qid, with 10 doses per session. He received 17 monthly sessions, with a slow but significant regression of pain and calcinosis. A diverse effects were nausea, headache and infusion site pain, all mild. The patient has remained asymptomatic, without new calcinosis.

Conclusion: Sodium thiosulfate is a calcium chelating agent, with unknown mechanisms of action, such as the formation of soluble complexes, antioxidant, protector of the endothelium, vasodilator, anti-thrombotic, antimetalloproteases and increases endothelial function, vasodilatate blood vessels, and decrease tissue ischemia. Physiologically, it is feasible to hypothesize that IV STS may treat refractory calcinosis, but data is not available regarding its use. The following patient chart reviews illustrate this hypothesis:

Methods: Patients #1, a 63 yo Caucasian female with limited scleroderma, and #2, a 46 yo Black female with polymyositis, suffer with recurrent calcinosis deposits of the skin and soft tissue causing pain and functional loss. Patient #1 reported severe pain and decreased mobility of her hands, and patient #2 reported deposits in her posterior thigh causing severe pain on sitting down and standing up. A aggressive therapy, including corticosteroids, colchicine, calcium channel blockers, and surgical interventions, yielded little improvement in pain and function. Each patient regularly reported pain scores of 8–9/10. After discussing IV STS therapy and obtaining consents, infusions were started at 12.5 grams over one hour weekly and advanced as tolerated. The maximum doses achieved in patients #1 and #2 were 15 gm/week and 25 gm/week, respectively. Infusions were continued weekly for approximately seven months. The infusions were tolerated well, and the most common patient reported side effects were nausea and blurry vision. The most common laboratory abnormality was a non-gap metabolic acidosis.

Results: As early as two weeks after starting the infusions, improvements in pain scores and softening of calcinosis deposits were observed. Both patients reported improved pain scores of 3–4/10 at two weeks and 0–1/10 at four weeks, and this persisted throughout therapy. At four weeks, functional status improved; specifically, patient #1 was able to grip a drinking glass without difficulty, and patient #2 was able to sit and stand with ease.

Conclusion: The clinical improvements observed may be attributed to the inherent properties of IV STS. Intravenous STS therapy is approved for calciphylaxis as well as cyanide and chemo-related toxicities. Although calcinosis is pathologically different from calciphylaxis, the physiologic properties of IV STS may contribute to the clinical improvements outlined above. These findings illustrate the potential of IV STS to treat painful calcinosis and the need for further studies of its use in rheumatic disease.

Disclosure: R. Thibaux, None; B. Miller, None; S. Lindsey, None.

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Prevalence of Raynaud’s Phenomenon and Nailfold Capillaroscopic Abnormalities in Fabry’s Disease: A Cross-Sectional Study

Background/Purpose: Fabry’s disease (FD) is a lysosomal disorder leading to progressive systemic involvement, including neurologic and vascular. We hypothesize that the microangiopathy observed in FD could be documented, including at an early stage, by using nailfold capillaroscopy and assessing the prevalence of Raynaud’s phenomenon (RP). The objective of this study was to measure the prevalence of RP and nailfold capillaroscopic abnormalities in FD.

Methods: This cross-sectional study included a standardized questionnaire and a nailfold capillaroscopy assessing previous reported patterns in FD (dystrophic and giant capillaries, avascular field, irregular architecture, dilatation and density of capillaries, hemorrhage), and was conducted on 32 Fabry patients and 39 controls. Two independent blinded reviewers carried out the analysis of capillaroscopic photographs.

Results:

Table 1: Demographic and clinical characteristics of Fabry patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Fabry patients</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>45.5 ± 13.8</td>
<td>48.2 ± 11.5</td>
</tr>
<tr>
<td>Sex-ratio (males/females)</td>
<td>0.46 (20/22)</td>
<td>1.6 (24/15)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>1 (3)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Cannabis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (25)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>4 (13)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (3)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Pain in the extremities, n (%)</td>
<td>28 (88)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Enzyme replacement therapy, n (%)</td>
<td>25 (70)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Disclosure: M. C. Florestano, None; M. Álamo, None.
Patients with FD and RP all suffered from pain in the extremities, whereas none in the control group did (p = 0.011). RP was concomitant or prior to the occurrence of pain in the extremities in 42% of Fabry patients. Significantly more ramified capillaries were observed in Fabry patients (12/32, 38%) than in controls (5/39, 15%, p = 0.016). No other statistically significant difference was observed by nailfold capillaroscopy.

Conclusion: This study is, to the best of our knowledge, the largest one assessing nailfold capillaroscopy and the presence of RP in FD. RP was highly prevalent in our series of Fabry patients (38%) and involved 50% of males. FD should thus be considered as a cause of secondary RP. RP was concomitant or prior to the occurrence of pain in the extremities in almost 50% of Fabry patients. It could be, at least in part, a causal factor of these pains. Secondary RP should lead to a screening for FD, especially in men. By extension, in high-risk populations (i.e. hypertrophic cardiomyopathy, dialysis patients, stroke in young people), the presence of ramified capillaries and RP should also be assessed.

Disclosure S. Deshayes, Genzyme Corporation, 9; R. J. aussaud, SHIRE, 6, Genzyme Corporation, 6; B. Imbert, None; O. Lidove, SHIRE, 6, Genzyme Corporation, 6; J. J. Parienti, None; N. Triclin, None; L. Aubodie, None; B. Bienvenu, Genzyme Corporation, 6, Shire, 6.

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Blue Digit Syndrome: The Rheumatologist’s Perspective. Helena Borrell1, Javier Narvaez2, Eulalia Armero3, Miguel Risco, Gloria Aichert2, Sergio Heredia2, Andrea Zacarias1, Carmen Gomez Vaquero1 and Joan Miquel Nolla2. 1Hospital Universitario de Bellvitge, Barcelona, Spain, 2Hospital Universitario de Bellvitge, Barcelona, Spain, 3Hospital Universitario de Bellvitge, Barcelona, Spain.

Background/Purpose: Blue or purple digit syndrome (or sign) is a cutaneous manifestation of multiple diseases that produce acute or subacute ischemic compromise in one or more fingers or toes. The most frequent cause of this feature is a reduction in arterial blood flow due to embolism or occlusion of small peripheral vessels, with preservation of the distal pulses.

The finger or toe affected by ischemia turns blue or violet and may develop necrosis. Whatever the cause, blue digit syndrome is a medical emergency requiring rapid diagnosis and specific treatment, given the risk of progression to irreversible necrosis. Only a very small percentage of cases need surgical intervention; the great majority of patients can be safely managed by medical therapy. Given their nature, medical cases should be managed by rheumatology services. Our aim was to evaluate the frequency, etiology and outcome in a series of patients admitted with blue digit syndrome in the Department of Rheumatology of the University Hospital of Bellvitge, a tertiary care teaching institution in Barcelona, Spain.

Methods: A retrospective cohort study of all patients admitted to our department with blue digit syndrome between 1990 and the first quarter of 2014.

Results: 41 patients (12 women and 19 men) were identified, with a mean age at diagnosis of 55 ± 18.8 years (range: 23–86 years). In 75% (31/41) of patients showed ischemic compromise of one or more fingers (being the second and third fingers most commonly affected), in 15% (6/41) were affected one or several fingers feet, and in 10% (4/41) remaining fingers and toes are affected simultaneously. The main etiologies are summarized in Table 1.

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune diseases</td>
<td>11</td>
</tr>
<tr>
<td>Buerger’s disease</td>
<td>3</td>
</tr>
<tr>
<td>Crioglobulinemia related to Sjogren’s syndrome or HCV infection</td>
<td>7</td>
</tr>
<tr>
<td>Other primary systemic vasculitis or Vasculitis Associated with Systemic Disease (RA, SLE)</td>
<td>10</td>
</tr>
<tr>
<td>Systemic sclerosis (scleroderma)</td>
<td>1</td>
</tr>
<tr>
<td>Mixed connective tissue disease (MCTD)</td>
<td></td>
</tr>
<tr>
<td>Pseudovasculitis</td>
<td>2</td>
</tr>
<tr>
<td>Cholesterol crystal embolism</td>
<td>2</td>
</tr>
</tbody>
</table>

Sixty per cent of patients (24/41) also had cardiovascular risk factors, the most common being active smoking and high blood pressure. Three of the patients with Buerger’s disease were cannabis smokers.

Ninety per cent of patients (37/41) progressed well with conservative medical treatment and only 10% (4/41) required amputation (one case with arteriosclerosis and three patients with scleroderma).

Conclusion: In our experience, the most common causes of blue digit syndrome are systemic sclerosis and vasculitis. Differential diagnosis should also include pseudovasculitis, observed in a considerable percentage (17%) of these patients. Despite its severity, the ischemia usually responds to conservative medical treatment and amputation is unnecessary in most cases.

Disclosure H. Borrell, None; J. Narvaez, None; E. Armengol, None; M. Risco, None; G. Albert, None; S. Heredia, None; A. Zacarias, None; C. Gomez Vaquero, None; J. M. Nolla, None.

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Background/Purpose: Malignant atrophic papulosus (MAP) is an obliterative vasculopathy which presents with distinctive cutaneous lesions but can progress over months to years to systemic disease with a rapidly fatal course. Pathologic findings of involved tissues reveal dense deposition of membrane attack complex (MAC). Eculizumab is a monoclonal antibody which prevents activation of C5 to C5b and C5a. Within the past five years, based on immunopathology of the disease, eculizumab has been used in MAP. The relative importance of inhibition of formation of C5a and of inhibition of formation of MAC has not been determined.

Methods: A literature review and personal communication with physicians treating MAP patients throughout the world identified survivors and treatment failures (deaths). We attempted to identify those characteristics which distinguished the survivors from those who died.

Results: We identified eight patients who were treated with eculizumab at different stages of disease and in different circumstances. Among those eight patients, only three are alive, two for nearly five years since initiation of eculizumab. Two out of the three survivors presented with GI perforations and cardiovascular deterioration and were placed on eculizumab with an immediate and dramatic response. They did not receive systemic steroids. The third live patient presented with CNS involvement affecting the right eye requiring enucleation. Treprostinil was started after that event, temporarily suppressing cutaneous lesions, but because of gastrointestinal disease progression, eculizumab was later added. All other patients had received high doses of systemic steroids and may have had bacteremia at the time of treatment with eculizumab. In addition, one patient had very aggressive dermatomyositis overlap.

Conclusion: Our results suggest that eculizumab is a vital treatment option for patients with rapidly progressive systemic MAP. These individuals have a life expectancy of less than one year if left untreated. Treatment benefits likely arise both from the inhibition of C5a formation and from inhibition of formation of membrane attack complex. Treatment experience to date has been associated with high mortality, which we feel most likely is the consequence of increased risk of bowel perforation and septicemia in those who had already received systemic steroids. The avoidance of systemic steroid therapy is essential for a good outcome. Also, earlier identification of those at high risk for bowel perforation should improve outcome by reducing risk of bacteremia developing during treatment. We report long term survival of several individuals, but in none was eculizumab effective long-term as monotherapy.

Disclosure A. Toledo-Garcia, None; L. S. Shapiro, None; J. F. Farrell, None.

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Treprostinil Use in Malignant Atrophic Papulosis (Klippel-Meier-Degos Disease): Review of Worldwide Experience to Date. Lee S. Shapiro, Aixa Toledo-Garcia and Jessica F. Farrell. 1Steffens Schleroderma Center, Saratoga Springs, NY, 2The Center for Rheumatology, Albany, NY.
Background/Purpose: Malignant atrophic papulosis (MAP) is a rare thrombo-occlusive vasculopathy that presents with cutaneous only lesions but can progress after months or years to rapidly fatal systemic involvement. Until the very recent past, there were no reports of effective treatment of the systemic disease. A recent publication described successful use of treprostinil, a prostacyclin analog, in treatment of systemic MAP and in MAP- scleroderma-SLE overlap.

Methods: We performed a retrospective analysis of six patients using data collected from treating physicians worldwide through personal communications and our own experience. We also employed PubMed for a literature search, which yielded 200 articles, using the keywords malignant atrophic papulosis and Degos disease. We evaluated outcomes of six MAP patients who were treated with treprostinil to identify discriminating factors between survivors and non-survivors.

Results: Among the six treprostinil treated patients we know four are alive. Our first treprostinil treated patient was a female with scleroderma-SLE overlap who developed MAP lesions without systemic MAP involvement. As a result of pulmonary hypertension she was started on treprostinil. Cutaneous lesions subsequently resolved. We then treated a primary MAP male who had progressive CNS disease despite ongoing therapy with eculizumab. Within months after treprostinil was started MRI showed resolution of the lesions. A nother male on eculizumab with disease progression was started on treprostinil with resolution of symptoms. The fourth patient was a female with biopsy proven MAP who already had CNS involvement with loss of vision in the right eye that led to enucleation. Treprostinil was started with temporary stabilization of symptoms. In the fifth patient, treprostinil was started after severe systemic involvement had taken place. She had GI perforations and CNS involvement which led to death. Eculizumab was not the first line therapy in patients four and five. Lastly, through a literature search we found a sixth patient who was a female on treprostinil for pulmonary hypertension related to systemic sclerosis. She then developed a restricted form of MAP while on treprostinil and is possibly alive, making a total of five patients alive today.

Conclusion: MAP is a rapidly fatal systemic disorder with a life expectancy of less than one year after development of visceral involvement. After comprehensive review of treprostinil use for MAP, we found the majority of patients treated (4/5) are still alive up to 42 months after initiation of therapy. All survivors with systemic disease are on dual therapy with eculizumab. The first patient with cutaneous MAP and scleroderma/SLE overlap had resolution of skin lesions on treprostinil alone. Patient six developed a restricted form of MAP while on treprostinil leading the authors to believe treprostinil limited the MAP vasculopathic process. The efficacy of treprostinil in MAP may be related not only to antithrombotic and vasodilatory effects but also to its reported ability to increase the number of endothelial progenitor cells.

Disclosure: L. S. Shapiro, None; A. Toledo-Garcia, None; J. F. Farrell, None.


Background/Purpose: Malignant Atrophic Papulosis (MAP) is a rare vasculopathy of unknown etiology commonly presenting with cutaneous lesions, but can progress to multisystem disease with a fatal outcome. MAP has been reported in the setting of other CTDs. Currently, there is a limited understanding of the association between CTDs and overlapping MAP. We theorize that MAP can present independent or complicating a vasculopathic CTD.

Methods: We performed a retrospective review on approximately 200 MAP cases obtained through a PubMed literature search, personal experience and communications with treating physicians worldwide. Cases were then analyzed for overlapping CTDs and further stratified for factors associated with disease outcomes.

Results: Of the 200 MAP cases, we identified 33 with an overlapping CTD diagnosis. These included: 11 SLE, 1 chronic cutaneous lupus erythematosus (CCLE), 3 SSC, 8 DM, 1 amyopathic DM, 6 APL syndrome (including patients positive for antibodies) 1 undifferentiated CTD, 1 granulomatous polyangiitis, and 1 RA. Patients with systemic MAP had fatal outcomes. Patients positive for APL antibodies with cutaneous MAP have survived but patients with APL syndrome and MAP have died. DM patients given steroids have died. In the setting of SSC there are two females who are alive and one male who died of fulminating SSC. Both females were on treprostinil for pulmonary hypertension.

Conclusion: MAP complicating CTD represents a challenging picture diagnostically and therapeutically. The presence of MAP may be a marker of more severe microvascular disease in those with SSC and DM and may be associated with worse prognosis because of concurrent steroid use. Steroids have been associated with increase risk of GI perforations and death. We believe MAP can present in the setting of a CTD in both cutaneous only and systemic forms. Histologically lupus and MAP can have similar findings but are not the same disease. MAP is not a systemic vasculitis but in its initial stage can present with an inflammatory infiltrate that later changes to the characteristic dermal necrosis and atrophic dermis with non-inflammator endarterial thrombotic occlusion, leading to wedge-shaped skin necrosis, sclerosis and mucinosis. When MAP affects the CNS, the CNS pathology could have a perivascular lymphocytic infiltrate as a vasculitis, but MAP is not a vasculitis and seems to respond very poorly to steroids. Early intervention of systemic MAP can be lifesaving.

Disclosure: A. Toledo-Garcia, None; L. S. Shapiro, None; J. F. Farrell, None.

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The Aromatase Inhibitor Induced Musculoskeletal Syndrome: Is There a Potential Role of Osteoporosis Therapy and Menopause Timing? Zsolt Kulcsár, Clinton Morgan, Peter Kaufman, Jonathan Jones and William Rigby. 1Dartmouth-Hitchcock Medical Center, Lebanon, NH, 2Dartmouth-Hitchcock Medical Center, Lebanon, NH, 3Dartmouth-Hitchcock Medical Center, Lebanon, NH, 4Dartmouth-Hitchcock Medical Center and Dartmouth Medical School, Lebanon, NH.

Background/Purpose: Aromatase inhibitor (AI) therapy is the most effective hormonal treatment in post-menopausal estrogen receptor (ER) positive breast cancer. These patients may be seen by rheumatologists due to the side effects of arthralgias, termed aromatase inhibitor induced musculoskeletal syndrome (AIMSS), which limit their use in some patients. We evaluated factors associated with AIMSS and explored possible therapeutic options in a large cohort of patients.

Methods: We performed an IRB-approved retrospective review of breast cancer patients seen in the Norris Cotton Cancer Center clinics from April 2011 to January 2013. 378 patients were included in our chart review on the basis of taking an AI for breast cancer with follow up documented in the electronic health record. Statistical analysis was performed by chi squared test for dichotomous variables and students t-test for continuous variables.

Results: In our cohort 91% of patients were taking an AI as adjuvant therapy (9% for metastatic disease) with 41% (n=153) reporting new or worsening arthralgias after initiation of an AI. AIMSS was 42.5% (95%CI: 0.375 to 0.478) in the adjuvant and 22.7%(95%CI: 0.101 to 0.434) in the metastatic groups. The median time to symptom onset was 120 days. 2.1% (n=8) discontinued AI therapy due to AIMSS. There was no association with prior chemotherapy, baseline arthralgia, BMI, or statin use. We found an apparent increased risk of developing AIMSS with more recent menopause (p=0.055), and therapy in the adjuvant setting (p=0.067). We also note a potential association with baseline osteoporosis and osteoporosis therapies (p=0.005; Table 2). M anagement options included temporary discontinuation of AI, switching between AIs, and non-steroidal anti-inflammatory therapy (NSAIDs). Nearly all had improvement with temporary discontinuation, 24.5% improved after AI switch, and 84% had symptomatic benefit on NSAIDs.

Conclusion: The incidence of AIMSS in our review was 41%. Patients treated for metastatic disease may have a lower rate of AIMSS. Our cohort revealed that more recent menopause did seem to be a risk factor. Baseline osteoporosis and osteoporosis treatments have a potential association to be explored. Management options included switching between AIs, temporary discontinuation, and NSAID treatment. Updated analysis will be presented.

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on AI therapy</td>
<td>375</td>
</tr>
<tr>
<td>Type of Aromatase Inhibitor Used</td>
<td></td>
</tr>
<tr>
<td>Anastrozole</td>
<td>206 (54.9)</td>
</tr>
<tr>
<td>Letrozole</td>
<td>132 (35.2)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>37 (9.9)</td>
</tr>
<tr>
<td>Baseline T-score by Dexa Scan</td>
<td></td>
</tr>
<tr>
<td>Normal (T-score 0 to –1.499)</td>
<td>101 (26.9)</td>
</tr>
<tr>
<td>Osteopenia (T-score &lt; –1.499 to –2.5)</td>
<td>173 (46.1)</td>
</tr>
<tr>
<td>Osteoporosis (T-score &lt; –2.5)</td>
<td>41 (10.9)</td>
</tr>
<tr>
<td>Total patients experiencing AIMSS</td>
<td>153 (40.8)</td>
</tr>
</tbody>
</table>
Medically at from start of AI to AIMSS in days 120
Average age at IA initiation [SD] 61.8 ± 10
Attempted an AI switch 38 (24.8)
Reported improved symptoms after switch 27 (24.5)
Needed to stop drug temporarily due to AIMSS 52 (17.0)
Needed to stop drug permanently due to AIMSS 8 (2.1)
AIMSS = Aromatase Inhibitor Induced Musculoskeletal Syndrome, DEXA = Dual-energy x-ray absorptiometry

Table 2. Potential risk factors for the development of AIMSS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>N (%)</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of AI Used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole</td>
<td>204</td>
<td>112 (55.9)</td>
<td>92 (45.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Letrozole</td>
<td>130</td>
<td>83 (63.4)</td>
<td>48 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>36</td>
<td>23 (64.9)</td>
<td>13 (36.1)</td>
<td></td>
</tr>
<tr>
<td>Menopause timing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMP &lt; 5 years prior to AI start</td>
<td>151</td>
<td>79 (52.3)</td>
<td>72 (47.7)</td>
<td>0.055</td>
</tr>
<tr>
<td>LMP 5–10 years prior to AI start</td>
<td>40</td>
<td>23 (57.5)</td>
<td>17 (42.5)</td>
<td></td>
</tr>
<tr>
<td>LMP &gt;10 years prior to AI start</td>
<td>155</td>
<td>102 (65.8)</td>
<td>53 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Type of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediatric</td>
<td>348</td>
<td>200 (57.5)</td>
<td>148 (42.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>Baseline T-score by DEXA Scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (T-score 0 to –1.499)</td>
<td>112</td>
<td>55 (49.1)</td>
<td>57 (50.9)</td>
<td>0.049</td>
</tr>
<tr>
<td>Osteopenia (T-score –1.499 to –2.5)</td>
<td>171</td>
<td>96 (56.1)</td>
<td>75 (43.9)</td>
<td></td>
</tr>
<tr>
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<td>127</td>
<td>81 (63.8)</td>
<td>46 (36.2)</td>
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</tbody>
</table>

† Bisphosphonate/denosumab, LMP = Last menstrual period, AI = Aromatase Inhibitor, DEXA = Dual-energy x-ray absorptiometry

Disclosure: Z. Kucser, None; C. Morgan, None; P. Kaufman, Pfizer Inc, 5; J. J. Jones, None; W. Rigby, None.

2199

Intravenous Immunoglobulin Therapy for Secondary Hemophagocytic Lymphohistiocytosis: A Retrospective Study of 46 Patients. Bertrand W. Rigby 1, Magdalena Gerin 2, Claire Larroche 3, Catherine Montagnier-Petrisans 4, Loïc Guillevin 5 and Luc Mouthon 4. 1National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; 4Hopital Jean Verdier, Bondy, Petrisans 4, Loïc Guillevin 3 and Luc Mouthon 4. 2Hoˆpital Jean Verdier, Bondy, Petrisans 4, Loïc Guillevin 1 and Luc Mouthon 1. 3National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; 7Hôpital Jean Verdier, Bondy, Petrisans 4, Loïc Guillevin 1 and Luc Mouthon 1. 4National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; 7Hôpital Jean Verdier, Bondy, Petrisans 4, Loïc Guillevin 1 and Luc Mouthon 1. 5National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; 7Hôpital Jean Verdier, Bondy, Petrisans 4, Loïc Guillevin 1 and Luc Mouthon 1.

Background/Purpose: Intravenous Immunoglobulins (IVIg) have been reported as giving good results in infectious, but also auto-immune related syndromes. Of the 162 IVIg-treated patients for declared secondary HLH, 46 met the HLH-2004 criteria (29 male (63%), median age 47.5 yr (min 15; max 87)). Thirty-three (72%) had a history of immunodepression (AIDS (15/46), hemopathy (12/46), systemic disease (5/46)). Causes of HLH were: infection (18/46, 39.1%), malignant hemopathy (20/46, 43.5%), systemic disease (3/46, 6.5%); or undetermined (5/46, 10.8%). IVIg were administered mostly at 2 g/kg (25/46, 52%), with a median delay of 2 days (–12; 253) after diagnosis. One adverse event to IVIg administration occurred (shock). Other therapies included: corticosteroids (32/46, 70%), etoposide (10/46, 21.7%), chemotherapy (9/20 of the hemopathy group), anti-infectious agents (41/46, 89%), red blood cell (38/46, 82.6%) and platelet (30/46, 65%) transfusions. Twenty-nine patients (63%) required intensive care (respectively 10 (55.5%), 14 (70%), and 4 (80%) in the infection, hemopathy, and undetermined groups). Twenty-five patients (54.3%) died of HLH (respectively 6 (33.3%), 13 (65%), 2 (66.6%), and 4 (80%) in the infection, hemopathy, systemic disease, and undetermined groups), with a median time to death of 12 days (1; 142). While long-term survival was better in the infection group, short-term survival (at 20 and 60 days) and evolution of cytopenias did not vary significantly among the different etiological groups.

Conclusion: Short-term evolution of IVIg-treated HLH patients seems to be equally severe in all etiological groups, despite IVIg treatment. The impact of IVIg treatment on lower long-term mortality in the infectious-related group is hard to establish, owing to a higher long-term mortality related to the underlying cause in the hemopathy group.

Disclosure: B. Dunogue, None; M. Gerin, None; C. Larroche, None; C. Montagnier-Petrisans, None; L. Guillevin, None; L. Mouthon, None.

2200

Elevated Serum Ferritin Levels in Adult Inpatients As a Predictor of in-Hospital Mortality and Association with Macrophage Activation Syndrome. Matthew Mulliken, Marcin Trojanowski, W. W. Chatham and Bita Shakoor. University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Macrophage Activation Syndrome (MAS) is a syndrome similar to Familial Hemophagocytic Lymphohistiocytosis (HLH) characterized by increased proliferation and activity of T-cells and macrophages leading to massive systemic inflammation, multi-organ system failure, and often significant morbidity/mortality. Elevated serum ferritin is part of the diagnostic criteria for MAS/HLH and studies have shown that extremely elevated levels of serum ferritin have a high specificity for MAS. We sought to determine the correlation between significantly elevated ferritin levels (>2000) and in-hospital mortality as well as associated presence of MAS among adult inpatients.

Methods: Using Cerner EHR, patients were selected for study inclusion based on serum ferritin levels >2000 obtained during hospital admissions. Patients with hemoglobinopathy associated ferritin elevation were excluded. Patient charts during hospitalizations corresponding to the elevated serum ferritin were reviewed for mortality, diagnostic criteria for MAS, and treatment interventions. Patients were determined to have likely MAS based on either 1) whether current case definition criteria for HLH were met with at least 5 of the following: fever >100.4 degrees F, splenomegaly, two or more cytopenias (Hgb <90, ANC <1.0×109/L), hypertriglyceridemia (fasting >265 mg/dl), hypofibrinogenemia (measured checked, if they met 4 out of the 5 clinical/laboratory criteria: fever, splenomegaly, two or more cytopenias, hypertriglyceridemia, and hypofibrinogenemia or new coagulopathy defined as INR >1.5 if no fibrinogen level available.

Results: Patients were stratified into groups by peak serum ferritin levels: 2–5,000, 5–10,000, 10–20,000, and >20,000. Mortality rates were 70/370 (19%) in the 2–5,000 group, 82/2378 (36%) in the 5–10,000 group, 114/28 (40.7%) in the 10–20,000 group, 153/39 (39%) in the >20,000 group. A total of 48 patients met the designated criteria for MAS, comprising 2% of patients in the 2–5,000 group; 6% of the 5–10,000 group; 30% of the 10–20,000 group and 61% of the >20,000 group. In addition to treatment with corticosteroids, 29 of these 48 patients received treatment with the IL-6 inhibitor anakinra, 10 of whom died during the hospitalization (in-hospital mortality of 34.5%); among the 19 patients with identified MAS who did not receive anakinra as part of their treatment there were 15 in-hospital deaths (in-hospital mortality of 79%).

Conclusion: Our results demonstrate a correlation between elevations in serum ferritin levels and increased in-hospital mortality in adult patients. Furthermore, our results suggest that at least part of the increased mortality observed in patients with extremely elevated serum ferritin is attributable to unrecognized or undetected MAS.

Disclosure: M. Mulliken, None; M. Trojanowski, None; W. W. Chatham, None; B. Shakoor, None.

2201

Haematological Complications in Rheumatic Diseases: Not Only Lymphomas. Elena Elefantie, Chiara Baldini, Alice Parma, Elisa Cioffi, Francesco Fero, Roberta Vagelli, Martina Rousseau, Rosaria Talarcico, Sara Gaburletti and Stefano Bombardieri. 1Rheumatology Unit, Pisa, Italy; 2Hematology Unit, Pisa, Italy.

Background/Pressure: Several immunological abnormalities have been reported among patients affected by myelodysplastic syndrome (MDS). On
significant improvement of all the clinical manifestations and laboratory findings (follow up at 12 months). Repeated whole-body CT scans, FDG-PET imaging and 99mTc-MDP bone scans confirmed the clinical and biochemical improvement in all patients. Cardiac MRI of the patient who had cardiovascular involvement showed an improvement of the diastolic function. However, the single patient who had CNS involvement had neurological progression, albeit showing improvement of other disease sites. During follow-up, we demonstrated a progressive reduction of circulating pro-inflammatory cytokines levels found to be increased before treatment. Plasma levels of IL-6 increased in all patients after the first infusion, as already shown in patients with other diseases treated with TCZ.

Conclusion: Although data must be completed with the final analysis and possibly by larger studies, the interim analysis of the trial support the efficacy and safety of IL-6 targeting with TCZ in ECD patients, in particular when CNS is not involved. Of interest, TCZ showed beneficial effects on ECD cardiovascular involvement, which has been shown to be poorly responsive to most currently available treatments.


Disclosure: G. Cavalli, None; A. Bertu, None; B. Gulgielmi, None; M. Gedi, None; R. Biavasco, None; C. Campochiaro, None; A. Tomelleri, None; M. Ferrarini, None; M. G. Sabadini, None; L. Dagna, None.

2203

Adalimumab Therapy Improves Insulin Sensitivity in Non-Diabetic Psoriatic Patients: A 6-Month Prospective Study. Trinitario Pina Murcia1, Raquel Lopez-Mejias2, Fernanda Generala, Begona Ubilla3, Susana Arastemla, Marcos A. Gonzalez-Lopez4, Maria del Carmen Gonzalez-Vela4, Javier Llorca5, Ricardo Blanco5 and MA Gonzalez-Gay5. 1Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, 2Department of Epidemiology, Hospital Universitario Marques de Valdecilla, Santander, Spain, 3Service of Dermatology, Hospital Universitario Marques de Valdecilla, Santander, Spain, 4Dept. of Pathology, Hospital Universitario Marques de Valdecilla, Universidad de Cantabria, Santander, Spain, 5Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiologia y Salud Publica (CIBERESP), IDIVAL, Santander, Spain, 6Hospital Marques de Valdecilla, Santander, Spain.

Background/Purpose: Psoriasis is a systemic inflammatory condition that shares similarities with other inflammatory immune disorders. In this context, patients with psoriasis are at an increased risk of cardiovascular death, as it has also been reported in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. A accelerated atherosclerosis plays an important role in this regard. Several studies have reported a beneficial effect of anti-TNF-α therapy on the mechanisms associated with accelerated atherosclerosis in inflammatory arthritis, including a beneficial effect on insulin resistance. We aimed to prospectively evaluate for the first time whether the anti-TNF-α monoclonal antibody adalimumab may improve insulin sensitivity in patients with moderate-to-severe psoriasis.

Methods: A 6-month prospective study of adult patients (>18 years old) diagnosed with moderate-to-severe psoriasis who were put on treatment with adalimumab 40 mg every other week as a subcutaneous injection based on clinical indication (Spanish guidelines). Patients with history of cardiovascular or cerebrovascular disease, hypertension, diabetes, high body mass index (>35) or treatment during the previous 6 months before recruitment with corticosteroids or biologic therapies were excluded. At the time of enrollment and after six months of treatment, all patients were assessed for insulin sensitivity using the Quantitative Insulin Sensitivity Check Index (QUICKI). Laboratory tests including glucose, insulin, serum creatinine, ultra sensitive C-reactive protein [usCRP] and erythrocyte sedimentation rate [ESR], and data regarding disease activity (percent of body surface area affected [BSA], Psoriasis Area and Severity Index [PASI]), Psoriatic Arthritis Screening and Evaluation questionnaire [PASE], Nail Psoriasis Severity Index [NAPSI] and physician’s global assessment of disease severity [PGA]) were also collected at the onset of the treatment (time 0) and at month 6.

Results: Thirty-three consecutive patients (52% women), with moderate-to-severe psoriasis (mean BSA 37.2 ± 16.4%, mean PASI 18.8 ± 7.9) were recruited from the Dermatology outpatient clinics of the Hospital Universitario Marques de Valdecilla (Santander, Northern Spain). The mean age was 38.6 ± 10.7 years. A statistically significant improvement (p-value 0.008) of insulin sensitivity (QUICKI) was observed after six months of treatment with adalimumab (QUICKI at time 0: 0.35 ± 0.04 versus 0.37 ± 0.04 at month 6).

References:

Disclosure: E. Elefanté, None; C. Baldini, None; A. Parma, None; E. Collin, None; F. Ferro, None; R. Vagelli, None; M. Rousseau, None; R. Talarico, None; S. Galimberti, None; S. Bombardieri, None.
Also a significant improvement (p<0.05) of ESR, usCRP, BSA, PASI, NAPSI, PGA and PASe was found at month 6.

**Conclusion:** In keeping with previous results on patients with chronic inflammatory rheumatic diseases, our findings show an improvement of insulin sensitivity following treatment with adalimumab. Therefore, adalimumab could have a beneficial effect on the mechanisms associated with accelerated atherosclerosis in patients with psoriasis.

AbbVie Inc. funded this study.

### Disclosure

T. Pina Murcia, None; R. López-Mejías, None; F. Genre, None; B. Ubillía, None; S. Armesto, None; M. A. González-López, None; M. D. C. González-Vela, None; J. Llorca, None; R. Blanco, None; M. González-Gay, None.

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### 2204

**New Onset Vitiligo Under Biological Agents: A Case Series.**

Laure Mery-Bossard, Emmanuelle Mahé, Guillaume Charby, François Maccari, Nathalie Quilles, Ziad Reguiai, Abdallah Khemis, Anne Grasland, Morgane Guerin, Denis Jullien, Kelly Bagny, Jean Eliaibell, Eric Toussirot, and Resposo Le CRI.

**Centre hospitalier, Mantes la Jolie, France, 2Centre hospitalier, Argenteuil, France, 3University hospital, Aix en Provence, France, 4Centre hospitalier, Saint Mandé, France, 5University hospital, Marseille, France, 6University hospital, Reims, France, 7University hospital, Nice, France, 8University hospital, Colombes, France, 9University hospital, Lyon, France, 10Hopital Edouard Herriot, Lyon, France, 11University hospital, La Réunion, France, 12University Hospital of Strasbourg, Strasbourg, France, 13Rheumatology Department, University Hospital, Besançon, France, 14University Hospital, Paris, France.

**Background/Purpose:** Biological agents are now widely used in clinical practice for the treatment of chronic cutaneous, rheumatic and gastrointestinal inflammatory diseases. Various cutaneous lesions have been described in the patients receiving biologicals (including infections, paradoxical psoriasis or tumoral lesion). The development of depigmenting disorders is an unusual event under these treatments.

**Objectives:** To describe the characteristics of patients developing a depigmenting skin disorder while receiving a biological agent for the treatment of psoriasis, inflammatory bowel disease (Crohn’s disease or ulcerative disease), UC - or inflammatory rheumatic disease (rheumatoid arthritis - RA, ankylosing spondylitis - AS, or psoriatic arthritis).

**Methods:** A collection of case reports of new cases of vitiligo following biological (anti-TNFα, rituximab, tocilizumab, abatacept, anakinra, ustekinumab) treatment and our experience. Treatment was sent to the members of the French specialist networks “Resposo” (dermatologist), “Club Rhumatismes & Inflammation” (CRI) (rheumatologist and internal medicine). The skin lesion has to be confirmed by a dermatologist. The current and previous biological agents were recorded.

**Results:** 12 cases were reported over a one year period: 9 M, 3 F, mean age 42 ± 13.5 years. The underlying condition requiring a biological agent was plaque psoriasis in 5 cases, AS in 3 cases, RA in 3 cases and an UC in 1 case. They all had new onset non segmental vitiligo (achromic patches involving the face, hands, chest or back), excepting leucotrichia (lashes and eyebrows) in one case. 7 patients received adalimumab, 1 infliximab, 2 ustekinumab, 1 abatacept and 1 secukinumab. The mean delay between biologic treatment and the appearance of new vitiligo is 15.9 ± 15.8 months (range 1-72). This was the first line of biologicals in 10 cases. Laboratory testing ruled out thyroid disease. The biological agent was maintained in 7 cases, without worsening of hypopigmented lesions while it was stopped or switched for the other cases. Excepting dromocorticosteroids, no specific treatment was given for the hypopigmentation.

**Conclusion:** Experimental evidences have shown that TNF-α may play a role in the pathogenesis of non segmental vitiligo, and successful cases of vitiligo treated with TNFα inhibitors have been reported. However, a vitiligo may occur during a biological treatment. In this series, anti-TNFα was the main (67%) biological class associated with this event. Only non segmental vitiligo was observed allowing the maintenance of the treatment. Concomitant occurrence of vitiligo and inflammatory disease such as RA, AS or UC, although rare, has been described. On the other hand, the depigmentation may be related to the biological agent and could represent a new paradoxical side effect.

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### 2205

**Management of Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease.**

Dominick Sudano, Varun Bhalia, Neil M. Ampu, and Jeffrey R. Lisse.

**University hospital, Arizona, Tucson, AZ, 2Southern Arizona Veteran’s Affairs Medical Center, Tucson, AZ.

**Background/Purpose:** In the Southwestern United States, coccidioidomycosis (valley fever) is an endemic fungal infection which typically causes a self-limited pulmonary illness. Immunosuppressed patients, including those with rheumatic disease on disease-modifying antirheumatic drugs (DMARD) or biologic response modifiers (BRM), are at higher risk of more severe infection. The routine practice at our institution is to screen patients for coccidioidomycosis before initiating BRM therapy, and then annually thereafter. Through this process, patients have been identified with asymptomatic positive serologies. This is concerning as it indicates recent active infection in these patients. There are currently no guidelines regarding the management of these patients; however, a recent retrospective study proposed continuing antirheumatic therapy rather than stopping it.

**Methods:** A prospective chart review at two centers in Tucson, Arizona identified patients who developed coccidioidomycosis while on DMARD or BRM therapy. Several of those patients had asymptomatic illness as defined as a positive serology found on surveillance labs, not ordered in response to symptoms, and no concurrent signs or symptoms of active disease. Patients were seen at least once between 2007 and 2014. Review emphasized management of BRM/DMARD therapy, as well as antifungal therapy and duration.

**Results:** Seventy one patients with rheumatic disease were diagnosed with coccidioidomycosis, and 18 of them had positive serologies and no symptoms. Most of these patients had rheumatoid arthritis, 1 had psoriatic arthritis, and 1 had dermatomyositis. Fifteen patients were identified during routine annual surveillance, and three were identified during pre-BRM therapy screening. Six patients were on BRM alone, 10 on BRM with a DMARD, and 2 on a DMARD alone. Three patients were also on prednisone. All 6 patients continued their antirheumatic therapy. BRM therapy was restarted in 5 of these patients, most resuming therapy within 1 month of infection (range 0.5 – 12 mos). One did not resume therapy due to osteonecrosis of the jaw. Six patients received fluconazole, duration ranging from 6 to 73 months (median 30.5 mos). One of these patients remains on fluconazole for persistently positive serologies (42 mos.). Eight patients neither reduced antirheumatic therapy, nor started antifungal treatment. The median follow up is 31.5 months, and no patients have developed symptomatic illness. Three patients have been lost to follow up.

**Conclusion:** Positive coccidioidomycosis serologies are concerning in asymptomatic patient as they indicate a recent active infection. At present, the optimal screening interval and management in patients with rheumatic disease remains unclear. This series supports the management strategy of continuing BRM therapy in patients with asymptomatic disease. It also suggests that antifungal therapy may be reserved for those with persistently positive serologies. Future studies are needed to determine the significance of positive serologies in immunosuppressed patients with rheumatic disease, and the safest management strategy.

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### 2206

**The Incidence of Zoster in Patients with Cutaneous Lupus Erythematosus and Dermatomyositis Is Increased Compared to the Average U.S. Population.**

Elizabeth S. Robinson, Joyce Okawa, Rui Feng, Amie S. Payne, and Victoria P. Werth.

**1Veteran Affairs Affairs Medical Center, Philadelphia, PA, 2University of Pennsylvania, Philadelphia, PA.

**Background/Purpose:** Herpes zoster is a common condition that causes significant pain and, often, post-herpetic neuralgia. In the United States the incidence of zoster per 1,000 person-years is 6 for people 60 years old and increases with age to nearly 11 for people above 80 years old. The incidence of zoster may be increased in autoimmune diseases, but few studies have looked specifically at cutaneous autoimmune diseases. Prior studies have found that the incidence of zoster in systemic lupus erythematosus is up to 32.5 per 1,000 person-years (n=303).

**Methods:** This retrospective chart review examined the incidence of zoster in patients with cutaneous lupus erythematosus (CLE) (n=105), dermatomyositis (DM) (n=66) and pemphigus vulgaris (PV) (n=55) seen in the practices of two dermatologists between April 1, 2013 and September 31, 2013. An incidence of zoster was determined according to a matched text search for “zoster” or “shingles” in all available electronic medical records.
The date of the zoster episode, if known, and the medications that the patient was taking at the time of the episode were recorded. The date of each patient’s earliest visit with his dermatologist recorded in the electronic medical record until the most recent visit through September 31, 2013 or an episode of zoster, whichever was earlier, was used to estimate the time that the person had been at risk. The total number of incidences of zoster divided by the total number of person-years at risk was used to determine the incidence rate. Patients with a known history of zoster prior to the start of their electronic medical records and patients whose date of zoster was unknown were excluded from the incidence rate calculations.

**Results:** The incidence rate of zoster per 1,000 person-years was 23 for CLE, 34.5 for DM, and 7 for PV. The incidence rates were based on 6 episodes of zoster per 257.9 person-years for CLE, 8 episodes of zoster per 149.5 person-years for DM and 1 episode of zoster per 145.4 person-years for PV. Six CLE, 7 DM and 3 PV subjects had an unknown date of zoster. One CLE, 5 DM, and 2 PV patients had zoster prior to the start of their electronic medical records. The mean (SD) duration of follow-up was 2.7 (1.7) years for CLE, 2.8 (1.7) years for DM and 3.0 (1.8) years for PV. The mean age (standard deviation) of each group was: 46.2 (14.1) for CLE, 55.9 (14.2) for DM, and 56.1 (13.8) for PV. Fourteen of the 16 patients who had zoster were on immunosuppressive medications at the time of the zoster episode. Some patients were on more than one immunosuppressive therapy at the time of their zoster episode. The immunosuppressive medications were: mycophenolate mofetil (n=1), prednisone (n=6), methotrexate (n=1) and azathioprine (n=1). The majority of patients in each disease group were Caucasian women.

**Conclusion:** The incidence rate of zoster in CLE and DM is higher than in the average U.S. population at or above 80 years old. The incidence of zoster in PV is close to that of the average U.S. population of a similar age. The use of immunosuppressive therapies may play a role in the increased incidence of zoster in CLE and DM.

**Disclosure:** E. S. Robinson, None; J. Okawa, None; R. Feng, None; A. S. Payne, None; V. P. Werth, None.

**2207**

**Decreased Bone Mineral Density in Patients with Ehler-Danlos Syndrome.** Narender Annapureddy, Joel A. Block and Sonali Khandelwal. Rush University Medical Center, Chicago, IL.

**Background/Purpose:** Ehler-Danlos Syndrome (EDS) constitutes a heterogeneous group of inherited connective tissue disorders characterized by abnormalities of collagen I, III, V, or fibronection, and primarily affects the joints, skin and blood vessel walls. Other “true connective tissue diseases”, such as osteogenesis imperfecta, a disease of collagen I, are characterized by severe osteoporosis and fractures; however these are not commonly described in EDS.

Two case-series have examined bone mineral density in EDS: seven EDS patients with early onset osteoporosis were described by Deodhar et al., and Coelho et al. described 4 young Portuguese EDS patients who had osteopenia/osteoporosis primarily of the lumbar spine. Here, we have examined bone mineral density in a cohort of EDS patients followed at the Rush Connective Tissue diseases clinic.

**Methods:** Patients with a diagnosis of EDS where identified from the Rush inherited connective tissue disease repository from 2010- June 2014. The study was approved by the Institution’s IRB and informed consent was obtained from each participant prior to inclusion in the study. Demographics were recorded and areal bone mineral density (BMD) was assessed by dual photon X-ray absorptiometry (DEXA).

**Results:** 14 subjects with a diagnosis of EDS underwent bone mineral densitometry. Baseline demographics are described in the table. Of the 14 patients, two were male. None had prior exposure to glucocorticoids, though two patients whose date of diagnosis had undergone DEXA (one for mast cell degranulation syndrome and one for possible undifferentiated inflammatory arthritis). Of the 14 participants, 6 had osteopenia and 1 had osteoporosis. Those with low bone mineral density were older than those with normal density (43.0 ± 10.9 vs. 28.7 ± 10.8; p = 0.03, mean ± S.D.). Mean T-score at the femoral neck in the patients with decreased BMD was -1.44 (2.8 to -1.1) and the mean T-score at the lumbar spine was -0.97 (2.7 to -1.2). 5 out of the 7 patients had both their femoral neck and Lumbar spine T-scores < -1.0 and the remaining 2 patients had femoral neck T-score < -1.0.

**Table**

<table>
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<td>Age, years (mean, S.D.)</td>
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</tr>
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<td>12 (85 %)</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>3 (21 %)</td>
</tr>
</tbody>
</table>

**Conclusion:** Our data suggest that EDS may be associated with decreased BMD. Patients with EDS with decreased BMD were more likely to be older than EDS patients with normal BMD. Nevertheless, the mean age of those patients is still lower than when traditional screening for osteoporosis is recommended. If these findings are replicated in other cohorts, then it would suggest that EDS should be considered an indication for early BMD screening. Nonetheless, the clinical significance of these findings remains unclear, as does the role of potential therapy to prevent or treat such low BMD.

**Disclosure:** N. Annapureddy, None; J. A. Block, None; S. Khandelwal, None.

**2208**

**Ovarian Reserve Alterations in Premenopausal Women with Rheumatoid Arthritis, Behcet’s Disease and Spondyloarthritis - Impact on Anti-Mullerian Hormone Levels.** Joerg C. Henes1, Julia Froeschlin2, Andre Tan1, Theodoros Xenididis1 and Melanie Henes2. University Hospital Tuebingen, Tuebingen, Germany, 1University Tuebingen, Tuebingen, Germany, 2University Hospital for Women Tuebingen, Tuebingen, Germany, 3University Hospital for Women, Tuebingen, Germany.

**Background/Purpose:** Recent publications showed a negative influence of systemic lupus erythematosus and antiphospholipid antibody syndrome on female ovarian reserve (OR). Other authors did not find a significant impact of Crohn’s disease or early rheumatoid arthritis (RA) on anti-Mullerian hormone (AMH) levels. This study aimed to investigate the potential effect of Behcet’s disease (BD), RA and spondyloarthritis (SpA) on OR, as reflected by serum AMH levels.

**Methods:** Serum samples of 33 RA, 32 SpA and 30 BD patients without previous cytotoxic – especially cyclophosphamide – treatment were analyzed and compared to age matched, healthy controls. AMH was quantified using a standard ELISA with standard value 1-8 pg/ml; values < 1 µg/l defined as reduced, < 0.4 µg/l as severely reduced fertility. All patients gave written informed consent and filled out a questionnaire on menstrual irregularities, lifestyle, pregnancy outcomes and contraception. For statistical analysis SPSS 19.0 was used and p<0.05 considered statistically significant.

**Results:** The median age was 26, 28.5 and 33 years and the disease duration was 6, 5.9 and 7 years for RA, SpA and BD patients, respectively. Compared to healthy controls the patients had significant reduced AMH levels with a median value for RA of 1.83 (control. 2.44; p=0.009), SpA 1.46 (control; 2.3; p=0.013) and for BD of 1.08 (control; 1.93; p=0.007). The number of children was 0.4 for RA, 0.5 for SpA and 1.0 for BD patients. The HLAB51 status and origin in BD patients were not associated with significant reduced AMH levels.

**Conclusion:** This is the first study to show the reduced OR in patients with RA, SpA and BD. Together with the findings in SLE we conclude a negative influence of chronic rheumatic diseases on OR.

**Disclosure:** N. Hennes, None; J. Froeschlin, None; A. Tan, None; T. Xenididis, None; M. Henes, None.

**2209**

**Novel Biomarkers of Extracellular Matrix Remodeling in Inflammatory Bowel Disease: Different Patterns of Gut Injury in UC and CD.** Joachim Hög Mortensen1, Line Elberg Godskesen2, Michael Dam Jensen1, Lone Gabriels Klinge1, Jens Kjeldsen1, Aleksander Krag1, Morten Karsdal3 and Anne C. Bay-Jensen4. 1Cartilage Biomarkers and Research, Nordic Bioscience, Købehavn, Denmark, 2Odense University Hospital, Odense, Denmark, 3Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, 4Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark.

**Background/Purpose:** About 10 % of patients with IBD have symptoms that match both Crohn’s disease (CD) and ulcerative colitis (UC), termed...

**Table**

<table>
<thead>
<tr>
<th>Patients with decreased bone mineral density</th>
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<tbody>
<tr>
<td>Osteopenia</td>
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<td>3</td>
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<tr>
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**Mean T-score at the femoral neck in patients with decreased BMD**

| Mean T-score | -1.44 (Range: -2.8 to -1.1) |

| Mean T-score at the Lumbar spine in patients with decreased BMD |

| Mean T-score | -0.97 (Range: -2.7 to -1.2) |

**Conclusion:** Our data suggest that EDS may be associated with decreased BMD. Patients with EDS with decreased BMD were more likely to be older than EDS patients with normal BMD. Nevertheless, the mean age of those patients is still lower than when traditional screening for osteoporosis is recommended. If these findings are replicated in other cohorts, then it would suggest that EDS should be considered an indication for early BMD screening. Nonetheless, the clinical significance of these findings remains unclear, as does the role of potential therapy to prevent or treat such low BMD.

**Disclosure:** N. Annapureddy, None; J. A. Block, None; S. Khandelwal, None.
inflammatory bowel disease unclassified (IBDU). The hallmark of both diseases is inflammation, which leads to excessive extracellular matrix (ECM) remodeling and release of specific protein fragments, called neoepitopes. However, the pathophysiology, clinical manifestations and treatment is still different among the two diseases. Consequently, to ensure the best possible patient care, accurate diagnosis is essential. Therefore, we speculate that the biomarker profile panel of UC and CD represents a heterogeneous expression pattern, and thus these biomarkers will be a valuable non-invasive diagnostic tool to aid the diagnosis of UC and CD.

**Methods:** 37 patients with active CD (>150 CDAI) of which 24 had inflammation in colon or colon/ileum, and 56 patients with active UC (St. Marks score >2) were included in this study. All patients had standardized work-up at inclusion, including medical history, physical examination, endoscopy, C-reactive protein. Biomarkers of degraded collagens I, III-IV (C1M, C3M, and C4M), collagen type 1 formation (PINP) and citrullinated and MMP-degraded vimentin (VICM) secreted by activated macrophages were evaluated by a competitive ELISA assay system. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the discriminative power of the biomarkers. The combination of biomarkers was investigated by a backward logistic regression model.

**Results:** The serum level of the biomarkers, C3M and VICM, was significantly different between patients with either active UC or CD. C3M was significantly elevated in patients with UC compared to CD (P < 0.039). In contrast, VICM was highly elevated in patients with CD compared to UC (P < 0.0001). The biomarkers C3M and VICM showed the highest discriminative value were seen (ROC analysis). The biomarkers were adjusted for demographic variations (age, gender, BMI, and smoking). VICM showed an AUC of 0.76 (P < 0.0001) (CD vs. UC), while C3M showed a more modest AUC of 0.62 (P < 0.039) (CD vs. UC) (Table 1). Furthermore a logistic regression model was developed to find the best combination of the biomarkers. The best combination of biomarkers was VICM, C3M, and C4M with an AUC of 0.85 (P < 0.0001) (Table 1). When including only the patients with colon and ileocolonic inflammation the AUC was improved to 0.92 (P < 0.0001) (Table 1).

**Conclusion:** These data provide new insights into differences in mechanisms of gut injury in CD and UC. We observed a clinical relevant potential to aid the diagnosis of UC and CD.

**Table 1:** The AUC, sensitivity, specificity, and percentage of cases correctly classified of each ROC-analysis

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>CD vs. UC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Percent of cases correctly classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3M</td>
<td>0.63 (0.52-0.73)</td>
<td>23.6%</td>
<td>80.0 %</td>
<td>66.3%</td>
</tr>
<tr>
<td>C3M Adjusted</td>
<td>0.69 (0.57-0.78)</td>
<td>48.9%</td>
<td>80.0 %</td>
<td>63.0%</td>
</tr>
<tr>
<td>VICM</td>
<td>0.76 (0.66-0.85)</td>
<td>64.9%</td>
<td>83.6 %</td>
<td>69.6%</td>
</tr>
<tr>
<td>VICM Adjusted</td>
<td>0.77 (0.66-0.86)</td>
<td>64.9%</td>
<td>86.6%</td>
<td>76.8%</td>
</tr>
<tr>
<td>[C3M, VICM, C4M]</td>
<td>0.85 (0.75-0.93)</td>
<td>78.4%</td>
<td>87.3%</td>
<td>83.3%</td>
</tr>
<tr>
<td>[C3M, VICM, C4M] Adjusted</td>
<td>0.85 (0.75-0.92)</td>
<td>73.0%</td>
<td>91.1%</td>
<td>80.5%</td>
</tr>
<tr>
<td>[C3M, VICM, C4M] (colonic and ileocolonic inflammation)</td>
<td>0.92 (0.83-0.97)</td>
<td>79.2</td>
<td>93.3</td>
<td>88.4%</td>
</tr>
</tbody>
</table>

**Research Programming, Inc, Bethesda, MD,3Social and Scientific Systems,**

**Disclosure:** M. P. Payette, None; Y. Trosyanov, None; I. N. Targoff, None; J. P. Raynauld, None; S. Chartier, None; J. R. Goulet, None; E. Rich, None; T. Grodzicky, None; J. L. Senechal, None; M. Koenig, None; J. L. Senechal, None.

**Background/ Purpose:** Dermatomyositis (DM) is a major form of autoimmune myositis (AIM). The characteristic DM rash (Gottron’s papules, heliotrope rash) and perifasciolar atrophy (PFA) at muscle biopsy are regarded as diagnostic. However, new concepts are challenging the definition of DM. A modified Bohan and Peter clinical classification (mcBP) of AIM was proposed. In the mcBP, overlap features in presence of myositis allow a diagnosis of overlap myositis (OM), irrespective of the presence or absence of the DM rash or PFA. Therefore, our objective was to further differentiate DM from OM.

**Methods:** Using the mcBP, we performed a longitudinal study of 100 AIM patients, including 44 patients with a DM phenotype, defined as DM rash, and/or DM-type calcinosis and/or PFA at biopsy. Overlap features, DM rash course, adermatomyotic DM (aDM), cancer and survival were evaluated, as well as DM-specific and overlap autoantibodies by protein A immunoprecipitation.

**Results:** Two subsets were identified in patients with a DM phenotype: pure DM (n = 24) and OM with DM features, or OMDM (n = 20). In pure DM, the rash of DM was the first disease manifestation, was always present at the time of myositis diagnosis, and was chronic and associated with a high cutaneous score. Concurrent bilateral heliotrope rash and Gottron papules (PPV 91%), as well as the V-sign and/or shawl sign (PPV 100%), were diagnostic of pure DM. Anti-Mi-2, anti-M and anti-p155 autoantibodies were restricted to pure DM (PPV 100%) and present in 50% of patients. 21% of patients had cancer. Fifteen-year survival was high (92%).

In contrast, in OM DM the first manifestation was proximal muscle weakness or other skeletal muscle-related complaints. The DM rash appeared at diagnosis or followup and was associated with a low cutaneous score. aDM, absent in pure DM, predicted OMDM (PPV 100%). Autoantibodies, found in 70% of patients, included anti-Jo-1, anti-PL-7, anti-PM-Scl, anti-U1RNP and anti-U5RNP. OMDM was not associated with cancer but 15-year survival was only 65%.

PFA occurred as commonly in OMDM (n = 6/20 patients, 30%) as in pure DM (n = 4/24, 17%). These 6 OMDM patients had aDM at the time of myositis diagnosis. Only one of them developed a DM rash at follow-up, emphasizing the lack of specificity of PFA for pure DM.

**Conclusion:** Using the mcBP allowed identification of OMDM, a new clinical subset of OM. Furthermore, identification of OMDM allowed in turn recognition of pure DM as a new entity, distinct from OM or from OM without DM features. However, the absolute specificity of a DM rash and PFA for the diagnosis of pure DM was lost.

**Disclosure:** M. P. Payette, None; Y. Trosyanov, None; I. N. Targoff, None; J. P. Raynauld, None; S. Chartier, None; J. R. Goulet, None; E. Rich, None; T. Grodzicky, None; M. L. Fritzier, INOVA Diagnostics Inc, S. F. Joyal, None; M. Koenig, None; J. L. Senechal, None.

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**2211**

**Epidemiologic and Clinical Features of Patients with Adult and Juvenile Dermatomyositis, Polymyositis and Inclusion Body Myositis from Myositis registry.**

Abdulrah Faqi1, Payam Noroozi Farhad1, Nastaran Bayat4, Miakela Chase1, Anna Jansen1, Karen Malley1, Jesse Wilkerson2, Kathryn Rose3, Cole Caro2, Lukasz Iteg3, Anne Johnson4, Richard Morins5, Christine Parks1, Edward H. Giannini6, Hermine I. Bruener3, Frederick W. Miller4, Bob Goldberg2 and Lisa G. Rider1.

*Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, 3Social and Scientific Systems, Inc, Research Triangle Park, NC, 2Social and Scientific Systems, Inc., Durham, NC, 4Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 1NIEHS, NIH, Research Triangle Park, NC,* The Myositis Association, Alexandria, VA.

**Background/ Purpose:** The myositis syndromes are rare systemic autoimmune diseases, little is known about their epidemiology. We describe the demographics and comorbidities of patients in a large myositis patient registry.
Methods: Between December 2010 and July 2012, nine thousand two hundred eleven questionnaires were mailed to patients with adult and juvenile dermatomyositis (DM, JDM), polymyositis (PM, JPM), inclusion body myositis (IBM), and other forms of myositis in the US and Canada that had registered with The Myositis Association or learned of the survey from other sources. The questionnaire queried demographics, clinical features, environmental exposures, and quality of life. The response rate was 24.2% (N=2,209). One thousand two hundred sixty six participants were re- contacted to resolve missing and discrepant responses.

Results: One thousand eight hundred ten patients (708 DM, 463 PM, 466 IBM, 139 JDM, 10 PM) met probable or definite Bohan and Peter criteria or possible Griggs criteria and were included in the analyses. The median date of diagnosis was March 2002 with a median disease duration of 9.2 years. IBM patients were older at diagnosis (median 62.3 years) than PM and DM (47.8 and 46.4 years, p<0.009). Most patients were female (84% DM, 75% PM, 78% JDM), except for IBM (49%, p<0.0001). Most patients were non-Hispanic Caucasian (86% DM, 82% PM, 94% IBM, and 88% JDM); blacks were more frequent among PM patients (12%) than DM (5%), IBM (3%), or JDM (0.7%, p<0.003 for all). Twenty percent of patients reported having a graduate degree and 28% had a college degree. The majority of DM and PM patients were diagnosed by an adult rheumatologist (59% and 52%), whereas IBM patients were more often diagnosed by a neurologist (76%, p<0.005) and JDM patients by a pediatric rheumatologist (48%, p<0.016). DM and JDM frequently had skin rashes as a major clinical manifestation (85% vs. 14% PM, 6% IBM, p<0.0001 for all); DM most often had arthritis (49% vs. 34% PM, 21% IBM, p<0.0001); DM and PM were more likely to have lung disease (31% vs. 15% IBM, p<0.0001); and DM most often had fever (23% vs. 17% PM, 5% IBM, p<0.008 for all). The overall age, gender- and race-adjusted prevalence rate of self-reported diagnosis with another autoimmune disease was 23%, with an increased odds of RA (OR 2.1) and type 1 diabetes mellitus (OR 2.5) in DM and PM vs. IBM. The odds of SLE were higher in DM vs. IBM (OR 4.4). Multivariable modeling showed female gender (OR 2.5), arthritis (OR 1.7) and rashes (OR 1.5) to be risk factors for an associated autoimmune disease in DM. The age-, gender- and race-adjusted self-reported prevalence of malignancy, excluding skin cancers, within 2 years of myositis diagnosis was 3.8% of DM, 2.1% of PM and 2.5% of IBM patients. Age was a risk factor for malignancy in DM (OR 1.1) and dysphagia was protective in IBM (OR 0.39).

Conclusion: A nationwide registry of myositis patients has been established with similar demographic and clinical features to other myositis cohorts. Our results suggest that there is considerable variation in the demographic and comorbidity profiles of patients by myositis subtype. MYOVISION registry data will be useful in further clinical and epidemiological studies.

Disclosure: A. Faiq, None; P. Noroozi Farhadi, None; N. Bayat, None; M. Chase, None; A. J.ansen, None; K. Malley, None; J. Wilkerson, None; K. Rose, None; C. Co, None; N. Bayat, None; P. Morris and K. Rose, None; E. H. Giannini, None; H. I. Brunner, TMA and NIEHS; 9; F. W. Miller, None; B. Goldberg, CDC grant; 2; L. G. Rider, None.

2212

Serum Adipokines in Dermatomyositis: Correlation with Risk Factors Associated to Cardiovascular Diseases and Metabolic Syndrome. Marilda Guimarães Silva, Suzana Beatriz Verissimo de Mello and Samuel Katsuyuki Shinjo. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Adipokines are a group of cytokines produced by adipose tissue, which include adiponectin, resistin and leptin. The adiponectin has anti-diabetic, anti-inflammatory and anti-atherogenic effects, whereas leptin and resistin are considered atherogenic and pro-inflammatory associated with peripheral insulin resistance. Adipokines have been evaluated in many systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. However, there is no description of these cytokines in patients with dermatomyositis (DM), who have a high prevalence of risk factors to cardiovascular diseases and metabolic syndrome.

Methods: This one-center and cross-sectional study included 78 adult patients with DM (Bohan and Peter criteria, 1975), in the period of 2011 to 2013. As a control group, 120 healthy individuals were included in the same period. Systemic sclerosis was defined according to the criteria of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP/ATP III), B blood samples were collected in fasting and processed immediately for further adipokines analysis, basing on the multiplex assay according to the manufacturer’s protocol M lmplore.

Results: Age, gender and ethnicity were comparable between patients with DM and control (P=0.05). The mean duration of DM was 4.9±5.6 years. DM patients compared to the control group, showed a high prevalence of risk factors for cardiovascular disease: hypertension, diabetes mellitus, family history of cardiovascular disease, increased body mass index, waist circumference, serum triglycerides, insulin and glucose levels, lower serum levels of HDL cholesterol, and higher frequency of metabolic syndrome (P<0.05). Moreover, we noted higher serum adiponectin concentration (73.3 ± 56.1 vs. 60.4 ± 81.0 pg/mL, P=0.04). DM patients showed lower leptin (0.2 to 25.5) pg/mL vs. 15.4 (6.9 to 29.0) pg/mL, P<0.001 in patients with DM compared to control group. Serum resistin was similar in both groups. Further analysis showed that adiponectin was significantly correlated with serum levels of HDL cholesterol (rho=0.307, P=0.006) and negatively correlated with serum creatinine kinase (rho=0.223, P=0.050), aldolase (rho=-0.271, P=0.016), triglycerides (rho=-0.313, P<0.005) and metabolic syndrome (rho=-0.240, P<0.001) and lower leptin (rho=-0.009) correlated positively with serum insulin level (rho=0.305, P=0.010), interleukin-6 (rho=0.24, P=0.040) and C-reactive protein (rho=0.282, P=0.010).

Conclusion: The results of this study showed high serum adiponectin and low serum leptin in patients with DM which may mitigate the inflammatory response. Further studies are necessary to assess the possible role of these adipokines in patients with DM.

Disclosure: M. G. Silva, None; S. B. V. D. Melo, None; S. K. Shinjo, None.

2213

Gene Expression Profiling of T Helper Subsets in Blood and Affected Muscle Tissues Reveals Differential Activation Pathways in Patients with Juvenile and Adult Dermatomyositis. Consuelo Lopez de Padilla1, Molly S. Hein2, Cynthia S. Crowson5, Richard S. Pendeger6, Erik J. Peterson4, Emily Baechler4, and Ann M. Reed4, Mayo Clinic, Rochester, MN, 2Biomedical Statistics and Informatics, Rochester, MN, 3University of Minnesota, Minneapolis, MN.

Background/Purpose: The molecular and cellular basis for juvenile and adult dermatomyositis (JDM and ADM) presumably is similar. However, important differences in the clinical features, outcome and associated disorders suggest that different mechanisms, at least partially, may be involved. The aim of this study was to identify shared and differential molecular pathways in peripheral blood and affected muscle between JDM and ADM, and examine their association with disease activity.

Methods: Cytokine mRNA expression profiles were analyzed in paired PBMCs and muscle specimens in 7 JDM and 5 ADM. In addition, cytokine mRNA expression in blood in 21 ADM and 26 JDM subjects over 2 study visits (baseline and 6 months visit). Disease activity was also measured by IMACS core set measures and other validated tools. Expressions of type 1 helper (Th1)-related genes (IL-2, IL-12β, IFN-γ, TGBX21, STAT4, TNFα, TNSF51), Th2 (IL-4, IL-5, IL-9, IL-10, IL-13, IL-12p70, STAD, GATA3, IRF4, TH17 (IL-1β, IL-6, IL-21, IL-23a, IL-17A, IL-17D, IL-17F, IL-27, IL-23), STAT3, RORC), Tregs (FoxP3+, STAT5b), Th22 (AH2, IL-22) and Th17 (TH17), and of innate-related genes (MIP-1α, MIP-1β, IFN ν2, IFN-γ-8 and IL-8) were examined using a custom RT2 Profiler PCR Array. Wilcoxon tests, Spearman correlations and paired t-tests were used for analysis. Reported p-values were adjusted for multiple comparisons using the Bonferoni method.

Results: Expressions of cytokine mRNA in IL-23a (rho=0.001), IL-6 (rho=0.001), IL-17f (rho=0.022), IRF4 (rho=0.001), and BCL6 (rho=0.014) were significantly up-regulated in blood of JDM compared to ADM. In the muscle, however, there were no significant differences between JDM and ADM, probably due to the small sample sizes. We also compared the gene expression profiles in paired blood samples and muscle biopsies among 12 patients (7 JDM and 5 ADM). Expressions of AHR (rho<0.007), IFN-γ (rho<0.054), IL-23a (rho<0.050), STAT5b (rho<0.022), TBX21 (rho=0.047), TGF-β1 (rho=0.036), TNSF51 (rho=0.011), CCL3 (rho=0.022) were found at higher levels in muscle compared to blood of JDM/ADM patients. The majority of these genes were Th1 and Th17 pathway-associated genes. Finally, among 16 patients with samples tested at baseline and 6 months visits, there were no significant correlations between changes in gene expression profiles in blood and disease activity measures over time.

Conclusion: We observed differences in gene expression profiling in blood between new onset JDM and ADM, many of the overexpressed genes in JDM were Th17-cytokine genes. The upregulation of Th1 and Th17-related genes was apparent in muscle compared to blood in JDM/ADM patients and may reflect activation of different Th pathways between muscle and blood.

Background/Purpose: We have previously demonstrated that fasciitis is a common lesion of dermatomyositis (DM) detectable early after disease onset by en bloc biopsy combined with magnetic resonance imaging (MRI). Furthermore, we have shown by en bloc biopsy that the fascial microvasculature, rather than intramuscular microvasculature, is one of the primary sites for inflammatory cell infiltration. Serial MRI findings showed that inflammation progresses from the fascia into the muscle. These facts indicate that fasciitis may cause muscle symptoms such as myalgia even when the muscle biopsy reveals a lack of evidence of myositis. Therefore, the detection of fasciitis plays an important role in the diagnosis of DM especially in its early stage. Power Doppler ultrasonography (PDUS) is useful for detection of inflammation and vascularity in rheumatic diseases. We examined whether fasciitis is also detectable by PDUS in patients with DM.

Methods: Five patients newly diagnosed with DM and 5 patients newly diagnosed with polymyositis (PM), who fulfilled the Bohan and Peter criteria, were recruited from the Division of Rheumatology of Jikei University Hospital in Tokyo, Japan. In this study, all patients underwent MRI, PDUS, and en bloc biopsy before treatment with prednisolone and immunosuppressive agents. The muscles were resected en bloc with the skin, subcutaneous tissue, and fascia on the site at which patients were conscious of muscle pain, weakness, or stretched a feeling and/or in which STIR and gadolinium-enhanced fat-suppressed T1-weighted MR images showed an abnormal hyperintense area as described previously (Arthritis Rheum. 2010;62:3751-9). Hema-toxylin and eosin staining and immunohistochemical staining for CD31 were performed on paraffin-embedded sections.

Results: MRI showed significant fasciitis findings in 3 patients with DM, while in no patients with PM. PDUS showed abnormal stippled blood flow signals along the fascia in all patients with DM, but in no patients with PM. Fasciitis was histologically detected in 4 patients with DM, while in no patients with PM. Although fasciitis was not detected histologically in only the fifth patient with DM, there were mild perivascular inflammatory infiltrates and neovascularization along the fascia. Immunohistochemical staining for CD31 showed abnormal growth of capillaries and venules along the fascia in all patients with DM, not in any patients with PM. This suggests that PDUS did show the blood flow of neovascularization along the fascia in patients with DM.

Conclusion: Fasciitis, demonstrated histologically by en bloc biopsy, was detected by PDUS in patients with DM. Mild fasciitis undetectable by MRI can also be detected by PDUS. Our data suggests that PDUS allows early diagnosis of fasciitis associated with DM.

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Clinical Characteristics and Prognosis of Malignancies Associated with Active Myositis. Sang Jinn Lee1, Eun Ha Kang, Jun Jong Lee, Eun Young Lee2, and Yong Wook Song1.

Background/Purpose: To examine the clinical features and prognosis of cancers associated with active myositis and to compare them with cancers found in patients with myositis but unrelated to myositis activity.

Methods: Medical records of 289 patients who had been diagnosed as having polymyositis or dermatomyositis according to Bohan and Peter criteria were reviewed to identify fifty two cancer cases. Patients were screened for malignancies at the diagnosis of myositis but active cancer screening was not done during follow-up unless suspicious symptoms developed or their myositis worsened. Cancers were defined to be associated with active myositis if they were present during active phase of myositis (group A). If cancers were not detectable during active phase of myositis, they were defined to be unrelated to myositis activity (group B). Results: Thirty patients were included in group A consisting of those who developed myositis and cancer together (n = 25), whose myositis recurred with cancer development (n = 2), or who developed myositis when their cancers progressed/recurred (n = 3). Twenty two patients in group B were comprised of those who developed myositis during remission state of cancers with no further relapse of cancer (n = 6) or whose cancers were detected during remission state of myositis with no further relapse of myositis (n = 16). Group A tended to be male (14/30 vs 5/22, p = 0.077) and had an older age at myositis diagnosis compared with group B (60.5 ± 11.1 vs 49.3 ± 16.6 years, p = 0.022). Group A patients had shorter intervals between the diagnoses of myopathy and cancer (5.4 ± 9.0 vs 71.6 ± 46.6 months, p < 0.001). 90% of cancers in group A developed within 1 year of myositis diagnosis whereas 90% in group B beyond 1 year. Muscle power grades and enzyme levels were not significantly different between the two groups at baseline. Dysphagia was more frequent (p = 0.002) and interstitial lung disease less frequent (p = 0.001) in group A. Notably, stages at cancer diagnosis were far advanced in group A (stage 3 and 4, 24/29 vs 7/22, p < 0.001). Fewer patients in group A achieved normal muscle power during their course of myositis than in group B (p = 0.036). The recovery to normal muscle power was associated with initiation of cancer remission (p = 0.036). Group A patients showed poor survival compared to group B patients (hazard ratio for mortality [95% confidence interval], 7.4 [2.6–21.2], p = 0.001), which was still significant when adjusted for age and gender (4.3 [1.5–12.7], p = 0.008 by Cox regression model).

Conclusion: In patients with myositis, clinical features of cancers associated with active myositis were distinctive from those of cancers unrelated to myositis activity. The former were found to develop within 1 year of myositis in contrast to the latter, and to be more advanced at diagnosis. The outcome of associated myositis in the former cases was worse in terms of muscle power recovery. Successful cancer treatment was associated with better outcome of myositis. Patients who had cancers associated with active myositis showed poor survival compared to those who had cancers unrelated to myositis activity.

Disclosure: S. J. Lee, None; E. H. Kang, None; Y. J. Lee, None; E. Y. Lee, None; Y. W. Song, None.
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Ultrasoundography Analysis of Carotid Parameters in Patients with Idiopathic Inflammatory Myopathies: Correlation with Demographic Profile and Disease Activity.

Simone Barsotti, Maira Aurora Moraes, Rosaria Talarico, Claudia Ferrari, Nicola Di Lascio, Anna d’Ascanio, Elisabetta Bianchini, Stefano Bombardieri and Rosella Neri.

Background/Purpose: Subclinical cardiovascular (CV) involvement is frequent in patients with idiopathic inflammatory myositis (IIM). Growing interest exists on the role of markers of subclinical CV involvement including vascular parameters assessed at carotid artery. The primary aim of our study was to explore Intima-Media-Thickness (IMT), mean arterial diameter (mAD) and distensibility parameters assessed at carotid artery. The primary aim of our study was to explore Intima-Media-Thickness (IMT), mean arterial diameter (mAD) and distensibility.

Results: Twenty-one IIM patients (F/M: 15/6; mean age 55±9.8; mean disease duration 8.7±7.5 years) fulfilling the Bohan and Peter criteria were prospectively enrolled. We collected demographic data and disease activity parameters according to IMACS criteria. CV risk factors were collected: smoking habits, diabetes mellitus, hypertension, family history of CV disease, body mass index (BMI).

Each patient underwent a B-mode ultrasonography sampling of right common carotid artery, 1 cm beneath the bifurcation; the images were automatically analyzed (Carotid Studio, Quipu) for the measurement of IMT and mAD. Cross-sectional DC was computed as DC = ΔA/ΔPP where A is the diastolic lumen area, ΔA the stroke change in lumen area and ΔPP the local pulse pressure estimated by tonometry (Pulsepen, Diatessco). The results were compared with 17 healthy subjects, comparable for sex, age and CV risk factors.

Results: The patients presented mean CK and aldolase levels respectively of 175±159 UI/L (NV <175) and 8.6±3.2 UI/L (NV <7). MMT8 mean values were 72.5±7.8, HAQ 0.6±0.58, patient and physician VAS respectively 4.2±2.7 cm and 2.2±2.1 cm. Three patients were smokers, 4 ex-smoker, 9 hypertensive, 4 affected by diabetes mellitus, 15 had familiar history of CV disease. BMI mean values were 25.5±3.99.

Mean IMT, mAD and DC data in patients and healthy subject were reported in table 1; mAD was significantly higher in IIM patients. In IIM group the association between mAD and hypertension (p<0.02) and BMI (p<0.02) was found. Elevation of IMT positively correlate with age and BMI (p<0.02) and BMI

Conclusion: Our data have shown that IIM patients presented higher mAD than healthy subjects; ultrasonographic data seem to be influenced by hypertension, BMI and age but not with activity and duration of the disease. Further data are necessary to confirm our observation.

Table 1: Carotid parameters in IIM patients and healthy subjects

<table>
<thead>
<tr>
<th>IIM patients</th>
<th>Healthy subjects</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima media thickness - IMT (mean±SD):</td>
<td>0.62 ± 0.1</td>
<td>0.63 ± 0.16</td>
</tr>
</tbody>
</table>

| Mean arterial diameters - mAD (mean±SD): | 7.5 ± 1 | 6.9 ± 0.7 | 0.04 |
| Distasibility coefficient - DC (mean±SD): | 25 ± 8.2 | 30 ± 12 | ns |

Disclosure: K. Nagaraju, None; S. Gheimbovschi, None; S. Rayavarapu, None; A. Phadke, None; L. G. Rider, NIA/NIH, 2; NIEHS/NIH, 2; E. Hoffman, None; F. W. Miller, NIEHS/NIH, 2; NIA/NIH, 2; S. Ghimbovschi, None; A. Phadke, None; L. G. Rider, NIA/NIH, 2; NIEHS/NIH, 2; E. Hoffman, None; F. W. Miller, NIEHS/NIH, 2; NIA/NIH, 2.

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Endoplasmic Reticulum (ER) Stress-Induced Mitochondrial Dysfunction and Atrophy Can Be Prevented By Pharmacological Up-regulation of Heat Shock Protein 70 (Hsp70) in Cultured Murine Myotubes.

A dam P. Lightfoot, Malcolm J. Jackson, Anne Mcarlde and Robert G. Cooper.

The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: The symmetrical proximal muscle weakness typical of myositis often fails to improve completely with any treatment, due to irreversible muscle fibre degeneration. Although inflammatory cell infiltration is a primary feature of myositis, increasing evidence suggests that muscle weakness correlates poorly with the degree of infiltration (Englund et al. 2001; Li et al. 2004), and in fact may precede inflammatory cell infiltrates (Nagaraju et al. 2001). Research suggests that non-immune cell-mediated mechanisms contribute to muscle weakness, including activation of the ER stress response which is associated with muscle fibre dysfunction and damage (Nagaraju et al. 2005; Yoshida 2007). The mechanisms that mediate ER stress-induced muscle dysfunction in myositis remain unelucidated. However, studies suggest that interplay between the ER stress response, mitochondrial dysfunction and oxidative damage may be involved (Y uzelovych et al. 2013; Ca et al. 2014). Targeted transgenic up-regulation of molecular chaperones, termed Heat Shock Proteins (HSPs), specifically Hsp70, attenuates muscle dysfunction and oxidative damage in muscle of old rodents (Mcarlde et al. 2004; Broome et al. 2006). Similarly, pharmacological increases in Hsp70 content of muscle using 17-N-allylamino-17-demethoxygalanadamin (17AAG), provided an enhanced functional recovery of muscle following exercise-induced damage (Kayani et al. 2008). We hypothesised that, in myositis, ER stress induces mitochondrial dysfunction and oxidative damage, which is a major non-immune cell mediated factor contributing to muscle weakness. We further hypothesised that targeted pharmacological up-regulation of Hsp70 could provide a therapeutic strategy to protect muscle fibres in myositis.

Methods: C2C12 myoblasts were grown in standard cell culture conditions (5% CO2, 37°C) and differentiated to myotubes in growth media (DMEM) supplemented with 2% horse serum. Myotubes were treated with 1μg/ml Tunicamycin to induce ER stress, in the presence and absence of 17AAG (0.1mg/ml) for a period of 24 hours. Cells were harvested and oxygen consumption assessed using a Clark electrode (Hansatech Instruments), in the presence of electron transport chain (ETC) substrates and inhibitors: Succinate/Rotenone and Glutamate/Malate to determine the respiratory control ratio (RCR) and Phosphate/Oxygen (P/O) ratio. ATP generation was quantified using bioluminescence assay (Roche). Specific ER stress markers were measured using SDS-PAGE/western blotting and qPCR. M yotube morphology changes were assessed using light microscopy.

Results: Activation of the ER stress response in C2C12 myotubes resulted in mitochondrial dysfunction, evidenced by declines in RCR, P/O ratio and in ATP generation. Cells treated with Tunicamycin in the presence of 17AAG showed full preservation of mitochondrial function and ATP generation. ER stress-induced atrophy of C2C12 myotubes was prevented by the presence of 17AAG.

Conclusion: Data demonstrate that pharmacological up-regulation of Hsp70 provides protection against ER stress-induced mitochondrial dysfunction and atrophy in C2C12 myotubes.

Disclosure: A. P. Lightfoot, None; M. J. Jackson, None; A. McaRlde, None; R. G. Cooper, None.

2219

Contribution of Tripartite Motif Proteins Modulating Membrane Repair to the Pathogenesis of Autoimmune-Medi ated Myositis.

Jenna Alloush1, Nicholas A. Yong2, Kevin M. ElHannah3, Wael N. Jarjour4 and Noah Weisleder5.

1. The Ohio State University College of Medicine, Columbus, OH, 2. The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: The idiopathic inflammatory myopathies are a heterogeneous group of diseases that result in autoimmunity toward muscles and lead to tissue destruction, but the pathogenesis remains largely unknown. Synaptotagmin VII-knockout (Syt VII-/-) mice display mild myositis and we have previously demonstrated that combining this genetic defect with...
regulatory T-cell deficiency (Foxp3−/−) results in a robust inflammatory myositis when adoptively transferred into immunodeficient (RAG1−/−) recipients. Interestingly, Syt VII−/− mice have impaired sarcolemmal membrane resealing capacity, which allows exposure of intracellular antigens. Tripartite motif (TRIM) proteins have also been linked to membrane repair capacity and are associated with myopathy in human patients. Here, we examined protein expression levels and subcellular localization of several novel TRIM proteins linked to membrane repair capacity in muscle tissue from mice using the Syt VII−/−/Foxp3−/− model of myositis.

Methods: Membrane repair was monitored in vitro in cells using an established assay where the membrane of cultured cells is physically disrupted by glass microbeads. Mouse skeletal muscle was collected from wild type mice exercised on a treadmill or RAG1−/− mice adoptively transferred with lymph node preparations from Syt VII−/−/Foxp3−/− mice. Tissue was analyzed by standard Western immunoblotting and by immunohistochemistry.

Results: We identified multiple TRIM family proteins that can modulate membrane repair capacity in cultured cells. Our results show that TRIM27 translocates to the membrane of injured muscle cells in vivo, as shown by immunohistochemistry. Similarly, when mice were exposed to membrane disruption due to eccentric contractions during treadmill running, there was translocation of TRIM27 from a diffuse pattern to the damaged membrane. In skeletal muscle of RAG1−/− mice, expression of several TRIM proteins, including TRIM27, was altered and displayed differential subcellular localization.

Conclusion: We have identified altered expression and localization of TRIM proteins in muscle in this mouse model of myositis. These results highlight an association of decreased sarcolemmal membrane integrity in the development of myositis and suggest a mechanism that could be targeted for diagnostics and therapeutics in these diseases.

Disclosure: J. Alloush, None; N. A. Young, None; K. McElhanon, None; W. N. Jarjour, None; N. Weisleder, None.

2220
Overexpression of Ankyrin Repeat Domain Containing Protein 1 Gene (ANKRD1) in Polymyositis Muscle Biopsies Is Correlated to Hypoxia. Samuel Katsuyuki Shinjo1, Sueli Mieko Oba-Shinjo, M Iiyuki Uno and Suely Kazue Nagahashi Marie. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: ANKRD1 codes for ankyrin repeat domain containing protein 1, which belongs to the muscle ankyrin repeat protein family involved in a mecha-signaling pathway that links myofibrillar stress response to muscle gene expression. In addition, ANKRD1 has an important role in transcriptional regulation, myofibrillar assembly, cardiogenesis and myogenesis. Recently, at first time, our group had demonstrated that ANKRD1 was overexpressed in dermatomyositis muscle specimens. Herein, we analyzed ANKRD1 expression in muscle biopsies of patients with polymyositis (PM).

Methods: RNA was extracted from frozen muscle biopsy samples of 33 untreated adult patients with PM (Bohan and Peter’s criteria, 1975). As a control group, we analyzed 20 muscle biopsies with no histological change from untreated adult patients with non-inflammatory myopathy diseases. Additional to ANKRD1, the gene coding for hypoxia-inducible factor 1, alpha subunit (HIF1A) was also analyzed to estimate hypoxia degree. The ANKRD1 and HIF1A transcript expression levels were determined by quantitative real time PCR using Sybr Green method. Muscle biopsies were analyzed histologically by semi-quantitative method of HE stained biopsies. Expression and localization of ANKRD1 and HIF1A in muscle biopsies was assessed by immunohistochemistry.

Results: Higher ANKRD1 and HIF1A expressions levels were observed in PM samples relative to control group (p<0.001 and p<0.001). In addition, the expression levels of both genes were correlated (r=0.380, P=0.029). We also observed a positive correlation of both genes to degree of muscle impairment and inflammatory infiltration. However, ANKRD1 and HIF1A expression levels did not correlate to demographic, clinical and laboratory features (p<0.05). Immunohistochemistry showed that ANKRD1 and HIF1A were expressed mainly by affected muscle fibers.

Conclusion: Our results demonstrated ANKRD1 is overexpressed and correlated to HIF1A and to infiltrate inflammation found in PM muscle specimens. ANKRD1 involvement in myogenesis and angiogenesis mechanism will be further investigated.

Disclosure: S. K. Shinjo None; S. M. Oba-Shinjo, None; M. Uno, None; S. K. N. Marie, None.

2221
Reduction of Ovarian Reserve in Adult Patients with Dermatomyositis. Fernando Henrique Carlos de Souza1, Samuel Katsuyuki Shinjo1, Lucas Yugo Shiguehara Yamakami2, Vilma dos Santos Trinidad Viana3, Edmund Chada Barata4, Eloisa Bonfa2 and Clovis Artur Almeida Silva4. 1Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, 2Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil.

Background/Purpose: Dermatomyositis (DM) affects female gender during reproductive age, in which ovarian reserve and future fertility are major topics of interest. However, there is no systematic study assessing these abnormalities in patients with DM. Therefore, the aim of the present study was to evaluate ovarian reserve markers and anti-corpus luteum (anti-CoL) antibodies in patients with DM.

Methods: All 40 female patients with DM (Bohan e Peter criteria, 1975), aged between 18 and 42 years, followed at our tertiary center, from March 2011 to December 2012, were invited to participate. Exclusion criteria were hormonal contraceptive use in the last six months (n=3), neoplasia (n=3), overlap systemic autoimmune diseases (n=3), pregnancy (n=2), gynecological surgery (n=1) and did not agree to participate (n=2). The remaining sixteen DM patients and 23 healthy controls were evaluated at early follicular phase of menstrual cycle Igg anti-CoL (immunoblotting), follicle stimulating hormone (FSH), estradiol, inhibin B, anti-Müllerian hormone (AMH) serum levels (ELISA) and sonographic antral follicle count (AFC) were determined.

Results: DM patients and controls had comparable mean age (33.4±6.8 vs. 31.4±6.8 years, p=0.337), ethnicity and socioeconomic class (P<0.005). DM mean age of onset was 29±4.7 years and disease duration of 5.6±3.2 years. Comorbidities and life style were similar in both groups (P<0.05). Menstrual cycles were alike in both groups with a similar frequency of age at menarche, gynecological age, duration and length of menstrual cycle (P<0.005). DM may have a shortened reproductive lifespan. Further studies are necessary to assess the possible role of disease and treatment related factors underlying ovarian impairment in these patients.

Disclosure: F. H. C. de Souza, None; S. K. Shinjo, None; L. Y. S. Yamakami, None; V. D. S. T. Viana, None; E. C. Barata, None; E. Bonfa, None; C. A. A. Silva, None.

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Tuesday, November 18
Background/Purpose: Little is known about medications received for myositis and patients' responses to therapies. We present information on self-reported myositis therapy use and responses from a national patient registry.

Methods: MYOSITION consists of 1796 patients who met probable or definite Bohan and Peter criteria for DM/PM (708 DM, 483 PM, 139 JDM) or possible Griggs criteria for IBM (466 IBM) with a median diagnosis date of March 2002. Enrolled patients were queried about myositis treatments received and treatment effectiveness. Logistic regression modeling, using a backwards elimination approach, was used to determine demographic and clinical covariates; a significance level of <0.1 was required to retain variables in the model.

Results: Most DM, PM and JDM patients reported receiving prednisone (96–98%) and methotrexate (MTX) (70–84%); these treatments were reported less commonly in IBM patients (54% and 28%, p<0.0001 respectively). Use of azathioprine (43%, 47% and rituximab (14%, 16%) were reported more frequently in DM and PM, in contrast to IBM and JDM (11%, 15%, p<0.012 and 9%, 10% p<0.007, respectively). DM patients reported receiving hydroxychloroquine (60%), IV methylprednisolone (54%), IVIG (48%), and cyclosporine (19%) more frequently than other subgroups (2-10% <p<0.021 for all). Overall, ritux was the most common biologic therapy (13%), and anti-TNFs were received by 10% of patients. Factors associated with MTX treatment among DM, PM and IBM patients included higher age, SES, being treated by a neurologist and presence of dysphagia, fever, and lung disease were additional factors for DM.

Conclusion: Prednisone and MTX are the most frequently prescribed medications in DM, PM and JDM. Patients vary substantially in their assessment of the effectiveness of these and other treatment approaches. Demographics, clinical features and the specialty of the treating physician appear to influence whether patients respond or perceive their treatment as effective. In the absence of controlled clinical trials, prospective registries of inception cohorts may aid in identifying effective treatment therapies in rare disorders.

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2223

High Prevalence of Hepatitis C Virus Infection in a Japanese Inclusion Body Myositis Cohort. Akinori Uruha1, Saburo Noguchi, Yukihiro K. Hayashi2, Ikuya Nonaka1 and Ichiro Nishino1. 1National Center of Neurology and Psychiatry, Tokyo, Japan, 2Tokyo Medical and Dental University, Tokyo, Japan.

Background/Purpose: There have been several case reports of inclusion body myositis (IBM) that appeared after chronic hepatitis C virus (HCV) infection. However, the relationship between HCV infection and IBM remains unclear. In this study, we assessed the prevalence of HCV infection in IBM patients and re-evaluated the clinicopathological aspects of HCV-positive IBM by using our cohort.

Methods: We analyzed the presence/absence of anti-HCV antibodies of 118 patients (mean age 69.0±8.1y) who were pathologically diagnosed as IBM in 2002 to 2012. As a control, we analyzed likewise 44 age-matched patients (69.0±7.5y) who were pathologically diagnosed as polymyositis in the same period. Then we compared HCV-positive IBM group with HCV-negative group in terms of clinicopathological features including intervals in years from first symptom onset to each onset of symptoms characteristic for IBM and frequencies of fibers with rimmed vacuoles and ragged-red fibers.

Results: In IBM group, anti-HCV antibodies were detected in 34 patients (28.8%). This rate was higher than that of the polymyositis group and of the Japanese general population in the sixties (4.5% and 3.4%, respectively) (p<0.001). No significant difference was seen between HCV-positive and -negative IBM groups, in terms of age at onset (66.6±8.0 vs. 64.1±8.6 years of age), sex ratio (1.4:1 vs 1.4:1), periods after onset showing inability to walk (4.6±3.6 vs. 3.9±2.7 years), duration between disease onset and first treatment (4.2±2.3 vs. 4.1±2.3 years), dysphagia (4.9±4.8 vs. 4.5±2.3 years), non-ambulatory (6.1±4.0 vs. 7.1±3.2 years), and pathological findings including the frequency of fibers with rimmed vacuoles [1.7 (0.17–8.1) vs. 2.2 (0.2–23.6%)] and that of ragged-red fibers [0.5 (0.1–5.7) vs. 0.4 (0–4.8%)].

Conclusion: Our results confirm the association between HCV infection and IBM, and suggest a possible causal role of HCV infection in the pathogenesis of IBM.

Disclosure: A. Uruha, None; S. Noguchi, None; Y. K. Hayashi, None; I. Nonaka, None; I. Nishino, None.

2224

Increased Immune Complex Levels in Children with Juvenile Dermatomyositis Are Not Associated with Levels of Von Willebrand Factor Antigen, C4, Duration of Illness, Disease Activity Score, or the Absolute NK Count. Lauren M. Pachman1, Akadina Kachaoucha2, Gabrielle A. Pachman3, X. Wang X1, Ching-Ching Huang2 and Anil K. Chauhan. 1Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, 2Stanley Manne Children’s Research Institute, affiliated with Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, 3Stanley Manne Children’s Research Institute, affiliated with Ann & Robert H. Lurie Children’s Hospital of Chicago, Cure JM Myositis Center, Chicago, IL, Zilber School of Public Health, University of Wisconsin at Milwaukee, Milwaukee, WI, 4Saint Louis University, St. Louis, MO.

Background/Purpose: A potential mechanism for the vasculopathy of Juvenile Dermatomyositis (JDM), the most common pediatric inflammatory myopathy, has been attributed to complement mediated immune complex damage to endothelial cells with subsequent release of von Willebrand Factor Antigen (vWF:Ag). Although we previously reported that JDM C4 levels were decreased in 30% patients, associated with decreased gene copy number [A rhritis Rheum, 2012; 64(S10):S826], the role of C4 in this process has not been documented. The purpose of this cross-sectional study was to determine the concentration of immune complexes in JDM sera compared with healthy controls and their association with levels of C4, duration of illness, disease activity scores, vWF:Ag, and absolute number of natural killer cells (NKs)–previously found to be decreased in active disease in 55.7% of JDM.

Methods: 62 children with definite JDM and 20 healthy controls were enrolled and their sera were obtained for immune complex measurement. Among the JDM patients, 29 had normal levels of C4 (21 girls and 8 boys; mean age 14.7±6.8 years) and 32 had low C4 (22 girls and 10 boys, mean age 11.8±5.8 years). The healthy control sera was comprised of 11 girls and 9 boys, mean age 12.5±3.5 years. Immune complex level, measured as an aggregated human γ-globulin equivalent, was determined by ELISA. The association of immune complex levels with clinical variables was determined: disease activity scores (DAS, skin, muscle, total score), duration of untreated disease (DUD), and vWF:Ag. ANOVA was used to test the difference of immune complex levels among low, normal, and control groups. The Tukey post-hoc test was used to test the pair-wise mean difference.

Results: The immune complex level in pediatric healthy controls was 317±332 μg/mL (n=20) (A GH equivalent), 506±347 μg/mL in JDM with low C4 (n=32) and 534±350 μg/mL in JDM with normal C4 (n=29). The immune complex levels in JDM with low or normal C4 was significantly higher than that in healthy controls (p<0.01). However, there was no difference in the immune complex levels between children with JDM with low C4 and JDM with normal C4 levels (p=0.99). Furthermore, no significant correlation was observed between immune complex levels and a range of clinical features, including duration between disease onset and first treatment (p=0.99), DAS skin (p=0.14), DAS muscle (p=0.15), DAS total (p=0.25), level of vWF:Ag (p=0.86), or between immune complex level and the absolute NK count NK (p=0.29) among the patients with JDM.

Conclusion: We conclude that that immune complex levels are increased in children with JDM irrespective of C4 levels and are not associated with disease duration, activity or evidence of vascular damage. It is not known if these immune complexes are antigenic, or if they play a role in the initiation or perpetuation of disease.
Does Previous Corticosteroid Treatment Affect the Inflammatory Infiltrate Found in Polymyositis Muscle Biopsies?  

Mayara Mendes Pinhata, Juliana Jesus do Nascimento, Suely Kazue Wagahashi Marie and Samuel Katsuyuki Shinjo. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

**Background/Purpose:** We conducted this study because there have been no studies evaluating the effect of the use of corticosteroids (CE) on the presence of inflammatory infiltrates in muscle biopsies of patients with polymyositis (PM).

**Methods:** This single-center retrospective study, conducted from 2002 to 2013, evaluated 60 patients with defined-PM (Bohan & Peter criteria, 1975) with clinical and laboratory disease activity. Two researchers systematically and independently evaluated muscle biopsy samples that had been obtained at the time of the investigation and diagnosis of PM. The patients were divided into three groups according to the degree of the inflammatory infiltrate (semi-quantitative) present in the muscle biopsies: (a) minimal inflammatory infiltrate present only in an interstitial area of the muscle biopsy (endomysium, perimysium) or in a perivascular area; (b) moderate inflammatory infiltrate in one or two areas of the interstitium of the muscle biopsy or of the perivascular area; and (c) severe inflammatory infiltrate throughout the interstitium or intense inflammation in at least one area of the interstitium of the muscle biopsy, perimysium or of the perivascular area.

**Results:** The three groups (A −10, B =23 and C =27 patients) were comparable regarding the age at the time of the muscle biopsy, gender, ethnicity distributions, interval time between the muscle biopsy and the symptom onset, clinical manifestations, degree of muscle weakness and serum muscle enzyme measurements (P=0.05). Aproximately half of the patients in each group were using CE at the time of the muscle biopsy. The median (interquartile duration of CE use (4 (0–38), 4 (0–60) and 5 (0–60) days: groups A, B and C, respectively) and the median cumulative CE dose used (70 (0–1200), 300 (0–1470) and 300 (0–1800) mg) were similar between the groups (P>0.05).

**Conclusion:** Previous CE use did not influence the presence or the degree of inflammatory infiltrates found in muscle biopsies in PM with clinical and laboratory disease activity. Our study showed that muscle biopsies should be performed this population, even in individuals who have already been taking CE.

**Disclosure:** J. Lin None; A. Feima None; M. Patel None; J. Merola Biogen Idec; 2. Biogen Idec, Amgen, Eli Lilly, Novartis, Pfizer, 5. Abbvie; B. R. A. Vleugels None.

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Physical Impairment in Patients with Idiopathic Inflammatory Myopathies Is Predicted By the American College of Rheumatology Functional Status Classification Criteria

Laura Cleary1, Leslie J. Crofford2, Archana Srinivas1, Heather Bush1, Catherine Starnes1, Qian Fan3, Jidan Duan4, Kirk Jenkins4, Natasha Frase5, Matthew Rutledge2 and Beatriz Hanaka2. 1University of Kentucky, Lexington, KY; 2Vanderbilt University, Nashville, TN.

**Background/Purpose:** The American College of Rheumatology classification criteria of functional status (ACR-FS) in Rheumatoid Arthritis is used as a measure of the consequences of impairment in patients with IIMs. However, studies on the utility of applying the ACR-FS on data derived from chart review of patients with IIMs, as well as the relationships among ACR-FS, patient-reported outcome measures of health and physical activity, and objective measures of muscle strength, endurance and fatigability in IIMs are unknown. The goals of this study were to evaluate the predictive value of ACR-FS with known and suspected risk factors of disability, and to relate it with measures of muscle function in IIMs.

**Methods:** Demographic and clinical data on 118 patients with IIMs were obtained through retrospective chart review. Current ACR-FS was obtained by chart abstraction and direct patient report. Clinical and functional status evaluation, IPAQ, SF-36v2, muscle strength [manual muscle testing (MMT–8) and knee extensor maximal voluntary isometric contraction (MVIC)], muscle fatigability (percent loss of MVIC immediately following a 30-second MVC and after 2 minutes of recovery), muscle endurance (functional index–2) and body composition (Dual x-ray absorptiometry) measures were performed on a subset of 21 patients. Spearman’s correlations were used to examine the relationships between ACR-FS derived from chart abstraction and direct patient report; as well as between physical function, body composition measurements and ACR-FS assessments.

**Results:** Older age at diagnosis was associated with lower functional status (r=0.045). There was strong correlation between ACR-FS derived from chart abstraction and direct patient report (r=0.782, p=0.0001). There were strong to moderate correlations between ACR-FS assessments and measures of general health, physical function, physical activity, muscle strength and endurance (p<0.05). ACR-FS correlated best with lower extremity portions of the FI-2. Previous research has shown that performance tests of lower extremity function alone can accurately predict disability across diverse populations. Figure 1 shows pre, post and recovery MVIC normalized to total lean mass by ACR-FS by patient report. Pre, post and recovery MVICs clearly distinguished patients with no disability, mild to moderate disability, and severe disability. Pre, post and recovery MVICs were largely reduced in patients with severe functional status impairment, although this was not statistically significant.

**Conclusion:** A ge related frailty is likely an important contributor of functional impairment in older IIM patients. The ACR-FS is a simple measure of disability that can be used in chart abstraction studies involving IIM patients. We have demonstrated that ACR-FS correlates well with muscle performance tests of strength, endurance...
and fatigue, in general.

Figure 1: Fingering protocol: pre, post and recovery MMTs by current of intact patient reported ACR P.S.

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2228

Has MRI an Added Value over Serum Creatine Kinase Measurement in Myositis? Nicola Pipitone*, Antonella Notarnicola, Giulio Zuccoli, Lucia Spaggiari, Gabriele Levirini, Arnaldo Scardapane, Florenzo Iannone, Giovanni Lapadula and Carlo Salvarani. *Arcispedale S Maria Nuova, Reggio Emilia, Italy, ‡D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy, †Children’s Hospital of Pittsburgh, Pittsburgh, PA, ‡University of Bari, Bari, Italy.

Background/Purpose: MRI is a useful tool to assess disease activity in myositis. Muscle strength on short tau inversion recovery (STIR) sequences is thought to reflect active inflammation. However, it is unclear whether MRI has an added value over the cheaper, easier-to-obtain measurement of serum creatine kinase (sCK) levels. Our aim was to assess the concordance between sCK and MRI edema in a cohort of patients with myositis at their first presentation to our centers.

Methods: We enrolled in 2 Rheumatology centers 73 patients, 34 with dermatomyositis (DM) and 39 with polymyositis (PM) diagnosed according to Bohan and Peter criteria. In all patients, sCK were measured and MRI sequences were acquired at the same time. MRI edema (1 = present, 0 = absent) was assessed bilaterally in 17 thigh and pelvic floor muscles. A MRI composite edema score (0–17) was calculated by adding the separate scores bilaterally and dividing them by two as described elsewhere (1). sCK was calculated by adding the separate scores (0–17) was calculated by adding the separate scores bilaterally and dividing them by two as described elsewhere (1). sCK was measured and MRI compared with the Bohan and Peter criteria.

Results: Sixty-six patients were evaluated for DM and met study criteria. All patients had abnormal MRI edema (11), with normal sCK. Further studies of larger cohorts are warranted to confirm our findings.

Conclusion: MRI is a useful tool to assess disease activity in myositis, especially in DM, where it can be identified as a sizeable number of patients who have normal sCK. Further studies of larger cohorts are warranted to confirm our findings.

References:
(1) Clin Exp Rheumatol 2012; 30:570–3

Disclosure: N. Pipitone, None; A. Notarnicola, None; G. Zuccoli, None; L. Spaggiari, None; G. Levirini, None; A. Scardapane, None; F. Iannone, None; G. Lapadula, None; C. Salvarani, Novartis Pharma AG, 2.

2229

How Often Are Clinically Amyopathic Dermatomyositis Patients Truly Amyopathic? Edward J. Oberle, Michelle Bayer, Dominic Q. Co and Yvonne Chiu. *Medical College of Wisconsin, Milwaukee, WI, †Children’s Hospital of Wisconsin, Milwaukee, WI.

Background/Purpose: Juvenile dermatomyositis (JDM) is a chronic inflammatory disorder primarily involving the skin and striated muscle. Classic JDM presents with rash, proximal muscle weakness, and objective evidence of muscle inflammation. A subset of patients presenting with cutaneous manifestations in the absence of muscle weakness have been variably termed dermatomyositis sine myositis or amyopathic dermatomyositis. The prevalence in adult populations has been reported up to 20% while the prevalence in children is unclear. The extent of the evaluation for myositis in pediatric patients varies between individual practitioners. Given the variability in evaluation, we hypothesized that truly amyopathic JDM is rare when a comprehensive evaluation for myopathy is performed.

Methods: A chart review of the initial evaluation was performed on all patients with the diagnosis code for dermatomyositis (ICD-9 code 710.3) seen at the Children’s Hospital of Wisconsin between January 2000 and April 2013. Patients with disease onset after age 18 years or those previously treated with systemic anti-inflammatory therapy were excluded. Data collected included patient demographics, presenting symptoms and exam findings, muscle enzyme panel (AST, ALT, LDH, CK, and aldolase), muscle biopsy, electromyography (EMG), and magnetic resonance imaging (MRI).

Results: Forty-six patients were evaluated for JDM and met study criteria. All patients had at least one abnormal muscle enzyme. Of the four amyopathic patients with normal enzymes, two had an abnormal MRI consistent with myositis while the other two were normal. The two with normal MRIs and enzymes did not have any additional testing and were labeled as amyopathic based on these studies alone. One muscle biopsy was done in a patient with abnormal MRI and elevated enzymes; however it did not demonstrate pathologic features consistent with JDM. The EMG was performed on a patient with elevated enzymes and normal MRI; the EMG was normal.

Conclusion: In children, true clinically amyopathic dermatomyositis is rare when a full panel of muscle enzymes and other ancillary studies are performed. In our series, EMG and muscle biopsy were not consistently done, and it is not clear how much these studies contribute to the diagnosis. In patients with negative evaluation (enzymes and MRI), a muscle biopsy should be considered to confirm that the disease is truly amyopathic. Further research is necessary to define the natural history of true clinically amyopathic patients to determine if such a comprehensive evaluation is necessary and to help identify the appropriate therapy to initiate at time of diagnosis.

Disclosure: E. J. Oberle, None; M. Bayer, None; D. O. Co, None; Y. Chiu, None.

ACR/ARHP Poster Session C
Osteoarthritis - Clinical Aspects: Therapeutics
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Treatment of Symptomatic Knee Osteoarthritis with Oral Salmon Calcitonin: Results from Two Phase 3 Randomized Clinical Trials. Morten Asker Karsdal, Anne C. Bay-Jensen, Asger Billie, Peter Alexander Pedersen, Inger Bjyrjason, Jeppe Andersen, Bente J. Riis and Claus Christiansen. *Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, †Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, ‡Nordic Bioscience, Herlev, Denmark, †Center for Clinical and Basic Research, Vejle, Denmark.

There was a significant correlation between MRI score and muscle strength of the hip flexors (Spearman’s rho 0.26, p 0.028) but not between MRI score and overall muscle strength.

Conclusion: MRI is a useful tool to assess disease activity in myositis, especially in DM, where it can be identified as a sizeable number of patients who have normal sCK. Further studies of larger cohorts are warranted to confirm our findings.

Disclosure: E. J. Oberle, None; M. Bayer, None; D. O. Co, None; Y. Chiu, None.
Background/Purpose: To evaluate the structure-modifying and symptom efficay, as well as safety and tolerability of oral salmon calcitonin (sCT) formulated with a 5-CNAC carrier (a molecule based on Eligen® technology), in osteoarthritis (OA) patients with moderate to severe knee pain and joint structural damage classified as Kellgren-Lawrence 2–3.

Methods: This is the combined reporting of two randomized, double-blind, multi-center, placebo-controlled trials (CSM C021C2301 and CSM C021C2302), evaluating the efficacy and safety of oral salmon calcitonin in patients with painful knee OA, enrolling 1,176 and 1,030 patients, respectively. The subjects had painful knee OA with structural manifestations. Study subjects were randomized (1:1) to oral sCT 0.8 mg twice daily or placebo (PBO) for 24 months. The primary efficacy objectives were to examine the treatment effect compared to placebo on change over 24 months in joint space width (JSW) in the signal knee measured by X-ray, and to examine the change in pain and function using the WOMAC questionnaire. Other study parameters included patient and physician global assessment, cartilage volume measured by MRI technology, and biochemical markers of bone resorption (CTX-I) and cartilage degradation (CTX-II). The primary safety objective was to characterize the safety and tolerability profile based on adverse events incidence and changes in laboratory profiles.

Results: At the 24 month endpoint there was no statistically significant treatment effect on JSN in any of the two studies. In CSM C021C2301 there was a statistically significant (p<0.0001) treatment effect on WOMAC (sum of pain, function, stiffness, and total scores) as well as on the biomarkers of bone and joint metabolism (p<0.0003). None of the WOMAC scores or the biomarkers achieved a statistically significant treatment effect in the CSM C021C2302 study.

Conclusion: The present formulation of oral calcitonin did not provide reproducible clinical benefits in patients with symptomatic knee OA.

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 3; A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 1; A. Bihiet, Nordic Bioscience Diagnostic, 1; P. Alexandersen, CCBR, 3; J. Bjørgaard, Nordic Bioscience Diagnostic, 3; J. Andersen, Nordic Bioscience Diagnostic, 1; B. J. Riis, Nordic Bioscience Diagnostic, 1; C. Christiansen, Nordic Bioscience Diagnostic, 1.

2231

Combined Chondroitin Sulfate and Glucosamine Is Comparable to Celecoxib for Painful Knee Osteoarthritis. Results from a Multicenter, Randomized, Double-Blind, PHASE IV NON-Inferiority TRIAL. Marc Hochberg1, Johanne Marts-Pelletier2, Jordi Montfort3, Ingrid Moller4, Juan Raman Castillo5, Nigel K. Arden6, Francis Berenbaum7, Jean-Pierre Pelletier8, Francisco J. Blanco9, Philip G. Conaghan10, Yves Henrotin11, Thomas Pap12, Pascal Richette13, Allen Sawitzke14, Patrick du Souich15 and Moves Investigation Group16. 1University of Maryland School of Medicine, Baltimore, MD, 2Osteoarthritis Research Unit CR-CHUM, Notre-Dame Hospital 1560 Sherbrooke St East, Montreal, QC, 3Department of Rheumatology, Grup de recerca cellular en inflamació i cartil·lau, IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain, 4Instituto Poal, Barcelona, Spain, 5Head of Clinical Pharmacology Unit Hospital Universitario Virgen del Rocio, Sevilla, Spain, 6Sevilla, Spain, 7MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom, 8Sorbonne University, INSERM UMR 5938, UPMC, University of Paris 06, DHU I2B, Paris, France, 9Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, 10INIBIC Hospital Universitario A Coruña, A Coruña, Spain, 11Ecole d’Institute of Molecular Medicine, University of Leids & NIHR Leids mucuskoseletal Biomedical Research Unit, Leids, United Kingdom, 12Physical Therapy and Rehabilitation Department, Princess Paola Hospital, Marche-en-Famenne, Belgium, 13Institute of Experimental Mucouskeletal Medicine University Hospital Münster, Münster, Germany, 14INSERM 1332, Université Paris-Diderot, Hôpital Lariboisière, Paris, France, 15University of Utah Medical Center, Salt Lake City, UT, 16University of Montreal, Montreal, QC, 17Spain, France and Poland, Barcelona, Spain.

Background/Purpose: The multicentre Osteoarthritis interVENTion trial with Sysadoa (MOVES) compared efficacy and safety of Chondroitin sulfate (CS) and Glucosamine Hydrochondride (GH) with that of Celecoxib (CE) in patients with knee osteoarthritis (OA) and severe knee pain.

Methods: 606 patients with knee OA (Kellgren-Lawrence grade 2 or 3) and moderate to severe pain (WOMAC pain >30) were randomized to 400 mg CS + 500 mg GH tid or 200 mg CE qd for 6 months.

Methods: Primary outcome was decrease in WOMAC pain (0-500 scale) from baseline to 6 months; non-inferiority margin was set at 40 (corresponding to 8 mm on a 0-100 mm scale). Secondary outcomes included WOMAC function/stiffness, VAS pain, joint swelling/effusion, use of rescue medication, OMERACT-OARSI Responder Index and EuroQol-5D.

Patients were excluded if they had a history of known cardiovascular or gastrointestinal disease.

The main study analyses were performed using PP population. Primary efficacy analysis was also performed according to ITT to test the robustness of results.

Results: Mean age at baseline was 62.7 years, 83.9% were women, WOMAC pain was 37.1 (41.6) and 62.6% had KL grade 2. There were no differences between treatment groups.

A adjusted mean change (95% CI) from baseline to 6 months in WOMAC pain was -185.7 (-200.3; -171.1) (50.1% decrease) in CS + GH group and -186.8 (-201.7; -171.9) (50.2% decrease) in CE group (Figure 1). The mean difference at 6 months met non-inferiority margin: -1.11 (-22.0; 19.8). All sensitivity analyses confirmed the non-inferiority conclusion.

There were no differences at 6 months between treatment groups in the secondary outcomes, including WOMAC stiffness, with a decrease of 46.9% and 49.2% (P = 0.434); WOMAC function, 45.5% and 46.0% (P = 0.530); and VAS, 48.0% and 48.8% (P = 0.924); in GH + CS and CE groups respectively. Similarly, there were no significant differences in patient and physician global assessments of disease activity or response to therapy. Over 70% of patients in both groups fulfilled OMERACT-OARSI responder criteria at 120 days with ~ 80% response rate at 6 months. Both groups had a reduction (>50%) in joint swelling from baseline, from 12.5% to 5.9% for CS + GH, and from 14.0% to 4.5% for CE. Use of rescue medication was low and similar between treatments. There was no difference in proportion of patients with treatment-emergent or SAEs between groups; no deaths occurred in this study.

Finally, there were no significant subgroup by treatment interactions for either efficacy or safety confirming consistency of non-inferiority of CS + GH across clinically relevant subgroups.

Conclusion: The MOVES trial confirms that CS + GH is comparable to CE in reducing pain in patients with knee OA and extends results from GAIT. This fixed-dose CS + GH combination should offer a safe and effective alternative for those patients with cardiovascular or gastrointestinal conditions who have contraindications to celecoxib.

Disclosure: M. Hochberg, Consultant, 6; J. Martel-Pelletier, None; J. Montfort, None; I. Moller, None; J. R. Castillo, None; N. K. Arden, None; F. Berenbaum, None; J. P. Pelletier, None; F. J. Blanco, None; P. G. Conaghan, None; Y. Henrotin, None; T. Pap, None; P. Richette, None; A. Sawitzke, None; P. du Souich, None; M. Investigation Group, None.

2232

Cost-Effectiveness of Glucosamine, Chondroitin Sulfate, Their Combination, Celecoxib, Non-Selective Non-Steroidal Anti-Inflammatory Drugs, and Placebo in Treating Knee Osteoarthritis. Vinish Garg1, Dennis Raisch2, Ning Y. Gu3, Matthew E Borrego4, and Daniel O. Clegg5. 1University of New Mexico, Albuquerque, NM, 2George Wahlen VA Medical Center/University of Utah, Salt Lake City, UT.

Background/Purpose: Knee osteoarthritis (KOA) affects 13.8% of the US population aged ≥ 26, causing significant burden-of-illness. We compared the cost-effectiveness of conventional medicines such as non-steroidal anti-inflammatory drugs (NSAIDs) and celecoxib (CBX) with complementary and alternative medicines (CAM) therapies to treat KOA from the US health care payers’ and patients’ perspectives, with 24-week, 2-year, and 10-year time-horizons.

Methods: We constructed a Markov cohort model (10-year analysis) and a decision-tree model (24-week and 2-year analyses). All costs were obtained from...
the published literature (converted to 2012 USD) and included both direct and indirect health care costs of medications, drug-associated adverse events, and total knee replacement surgery. Clinical efficacies for treatment strategies were obtained from the Glucosamine/CS Arthritis Intervention Trial (GAIT). Effectiveness was measured using quality-adjusted life-years (QALY’s) gained, estimated from the SF-6D data collected during GAIT. Patients were stratified into mild pain only and moderate-to-severe pain groups based on their severity of knee pain. Published literature was used to obtain the rest of the modeling parameters. Base-case results were varied in both one-way and probabilistic sensitivity analyses.

Results: We found that, among the mild, moderate, and severe patients together (from time-horizon of 24 weeks and years 2 and 10), CAM therapies were cost-effective versus conventional medicines to treat KOA in the US, with CS being the most cost-effective treatment ($1,332 per QALY gained) and glucosamine the next most cost-effective ($203 per additional QALY gained). However, in a 24 week time-horizon among KOA patients with mild pain CBX was also incrementally cost-effective versus CS ($49,988 per QALY gained). A more moderate-to-severe pain patients from 24-week time-horizon, the combination of glucosamine and CS was the most cost-effective ($3,279 per QALY gained). A major driver of cost-effectiveness of CAM therapies versus conventional medicines in the 10 year time horizon was the lack of evidence of adverse events (AEs), compared to NSAIDS and CBX which have extensively documented AEs.

Conclusion: Our analysis indicates CAM therapies to be more cost-effective than conventional medicines in treating KOA, due to lack of known adverse events rates and lower drug utilization costs from CAM. Prescribers may want to consider the findings of our study; however, future research is needed regarding the long-term effectiveness and safety of CAM therapies for KOA.

Disclosure: V. Garg. AbbVie; 3; D. Raisch. None; N. Y. Gu. None; M. E. Borrego. None; D. C. Clegg. GAIT trial was supported by the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2.

2233

A PHASE II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy Study of Apremilast (CC-10004) in Subjects with Erosive Hand Osteoarthritis

Background/Purpose: We report on a phase II, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study in subjects with erosive hand osteoarthritis. Subjects must have had a minimum of 6 months’ history of EHOA immediately prior to enrolment to this study.

Methods: Subjects must have had a diagnosis of erosive hand osteoarthritis (EHOA), fulfilling the classification criteria of the American College of Rheumatology (ACR) and the OARSI 2010 classification criteria for RA. Subjects must have had erosive hand osteoarthritis of at least 6 months. The study included four phases: a pre-randomization phase for up to 35 days, a 91-days randomized, double-blind, placebo-controlled phase, a 77-days open-label treatment phase, and a 120-days follow-up phase. All patients received a single intra-articular injection of either MM-II or HA (Duro-Med®). Effectiveness measures included maximal global pain in the target knee, recorded by a 100mm VAS; WOMAC subscales; OMERACT OARSI responder criteria; PGA, PASS, PASE questions and consumption of paracetamol/acetaminophen, which was the only authorized rescue medication. Tolerability was assessed by local manifestation defined by an increase of at least 3 cm in knee circumference, measured at 2 cm above the upper border of the patella or local pain increase of more than 30 mm on a 100 mm VAS. A single adverse event was recorded through 90-days of follow-up.

Results: All patients completed the study. Results: relating to WOMAC A pain, summarized in Figure 1, show a faster response with MM-II, with maximal effect observed on day 14, which was maintained over time and was of a trend with a statistically significant difference from baseline pain from day 7. In the HA group, the onset of pain relief was slower, with an improvement statistically significant change from baseline observed only on day 90.

Conclusions: A statistically significant difference from baseline was observed in the HA group, with a reduction of more than 50% in the number of days and total dose of rescue medication consumption seen following MM-II administration, compared with HA injection. The percent of responders to treatment according to the OMERACT-OARSI responder criteria was 52.6, 66.7, 70 & 60 at the day 7, 14, 30 & 90 respectively compared to 30, 36.8, 25, 45 at the HA group (data not shown). Local adverse events (inflammatory flare) were observed in one patient at day 3 in the MM-II group and in 4 pts at day 1, 1 pt at day 3, and 1 pt at day 1 in the HA group.

Patient’s Relative Change in WOMAC A in Target Knee over Time

*statistically significant difference from baseline

Conclusion: Intra-articular injections of MM-II were found to be safe and effective. The pain-reduction action was more rapid and sustained up to 3 months compared with HA. Larger randomized controlled trials are needed to confirm these encouraging results.
2235

Cost-Effectiveness of Long-Term Opioid Use in the Treatment of Knee Osteoarthritis in Older Patients with Multiple Comorbidities. Jeffrey N. Katz1, Savannah Smith1, Jamie E. Collins1, Joanne M. Jordan1, David J. Hunter1, Edward H. Yelin1, Lisa Suter2, A. David Patel1 and Elena Losina3. Brigham and Women’s Hospital, Boston, MA. 1University of North Carolina Dept of Epidemiology, Chapel Hill, NC; 2Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia; 3University of California, San Francisco, San Francisco, CA. 4Yale School of Public Health, New Haven, CT.

Background/Purpose: Because older patients with osteoarthritis (OA) and multiple comorbidities face high risk of toxicity from nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and Cox-2 inhibitors, opiates (including tramadol) have been proposed as an analytical strategy. We evaluated clinical and economic outcomes of using prototypic medications (tramadol, naproxen, and celecoxib) in such patients.

Methods: We conducted the Osteoarthritis Policy Model, a validated computer simulation of knee OA, to project long-term clinical outcomes, costs and incremental cost-effectiveness ratios (ICERs) of OA treatment strategies in patients with mean age 70, knee OA, diabetes and coronary heart disease whose pain persists after initial therapy with acetaminophen, steroid injections and physical therapy (PT). We examined four treatment strategies: 1) continuing PRN acetaminophen; 2) tramadol; 3) naproxen and 4) celecoxib. Pain was the primary determinant of quality of life and its relief was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Scale. Treatment efficacies and toxicities were estimated from published literature and influenced time on regimen. Mean WOMAC change was 22 points for tramadol; 15 for naproxen and celecoxib. Annual medication costs and major toxicities for the first and subsequent years are shown in the Table. Toxicities included CVD and – for tramadol – fractures. We adopted a societal perspective, discounting outcomes at 3%, and assumed a willingness to pay (WTP) of $100,000 per quality adjusted life year (QALY) gained. ICERs below this threshold defined cost-effective strategies.

Results: Patients remained on tramadol for 1.98 years and the other regimens for 2.36 years. Twice as many experienced major toxicity with tramadol as with the other agents. The Table lists the cost-effectiveness results. The ICER for tramadol exceeded that for naproxen; thus, we compared naproxen directly to PRN acetaminophen and observed that naproxen had an ICER of $178,840/QALY. However, tramadol cost-effectiveness was highly sensitive to its toxicity. When tramadol toxicity was reduced by just 10% it became cost-effective (ICER $53,969/QALY), and ICERs for the naproxen-based strategy then exceeded the WTP threshold (ICER =$102,000/QALY) compared to the tramadol-based strategy.

Conclusion: In patients with OA and multiple comorbidities who have pain despite acetaminophen, steroid injection and PT, naproxen was cost-effective at a WTP $50,000. Tramadol became cost effective following a <10% reduction in its overall toxicity. The cost of celecoxib precluded its offering acceptable value. The impact of tramadol toxicity on these estimates underscores the need for further research on toxicity of opiates in frail patients; the limited number of years on regimen highlights the need for further research on toxicity of opiates in frail patients.

Table: Cost-effectiveness, toxicity and years on regimen among individuals treated with acetaminophen, tramadol, naproxen and celecoxib

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Toxicity attributable to regimen (%)</th>
<th>Costs</th>
<th>QALE</th>
<th>Cost</th>
<th>ICERs</th>
<th>Average years on regimen</th>
<th>Proportion of patients experiencing major toxicity attributable to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen PRN</td>
<td>0</td>
<td>$171</td>
<td>6,030</td>
<td>$111,558</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>12%</td>
<td>6,030</td>
<td>6,030</td>
<td>122,037</td>
<td></td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Naproxen</td>
<td>8%</td>
<td>6,642</td>
<td>6,410</td>
<td>112,983</td>
<td></td>
<td>13.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>9%</td>
<td>14,750</td>
<td>6,405</td>
<td>142,013</td>
<td></td>
<td>13.3</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Disclosure: L. Kallel, MM- II, 2; R. Dolev, Stock options, 1; R. Shimonov, None; G. Rivkin, None; M. Liebergall, None; Y. Mattan, None; X. Chevalier, MM- II, 6.

2236

Plant-Derived Products Are Effective for Treatment of OA Pain and Safer Than Other Active Therapies. Laura Laslett, Xiongzhong Jin and Graeme Jones. University of Tasmania, HOBART, Australia.

Background/Purpose: Osteoarthritis (OA) is a leading cause of chronic disability. There are no approved treatments for modifying the disease course, therefore disease management consists of symptom control, with patients often eventually requiring joint replacement. The controversy surrounding use of the COX-2 inhibitor class of NSAIDs and heightened cardiovascular risk highlights the importance of finding safer treatment options to minimise adverse side effects, such as natural therapies. Plant-derived treatments are traditionally used as medicines. However, such therapies have not typically been studied with the same rigor as pharmaceutical agents. This review summarises use of plant-derived products compared to placebo and active comparator for the treatment of OA pain and function.

Methods: 62 RCT’s of plant-based therapy for OA were identified from literature databases (PubMed, Embase), and summarised for pain (assessed using visual analog scores (VAS), numeric rating scales (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Knee Injury and Osteoarthritis Outcome Score (KOOS)). Pain scales, function and safety outcomes using standardised mean differences (SMD) and relative risks (RR), with trials grouped by class where possible.

Results: Overall, plant-derived therapies are effective for treating pain compared to placebo, assessed using VAS and NRS scores (SMD 1.08; 95% CI 0.72 - 1.44), or WOMAC OOS pain scales (SMD 0.98; 95% CI 0.62 - 1.35). Classes demonstrating overall efficacy in more than one trial for either VAS or WOMAC pain included Boswellia serrata, capsacin, and ginger; there was single trial evidence of efficacy for another 9 agents (pine bark, willow bark, NR-INF-02, UP446, E-OA-07, passion fruit peel, phytalgic, Aquamin-F, SK1306X). Plant-derived therapies have similar efficacy to active comparator (most commonly NSAIDs), assessed using VAS and NRS scores (SMD 0.32, p=0.08; or WOMAC OOS pain scales (< 0.08, p=0.14). Therapies are also effective for functional outcomes compared to placebo (SMD 0.52, p=0.001). However, significant heterogeneity remains for all pain and function outcomes, indicating results need to be interpreted with caution. Risk of adverse events was similar to placebo (RR 1.13, p=0.1), but reduced compared to active comparator (RR 0.75, p<0.001).

Conclusion: Plant-derived therapies may be efficacious in treating osteoarthritis pain and functional limitation and appear safer than other active therapies. However, quality trials and long term data are lacking, and the number of trials for each therapy is limited. Comparison of efficacy would be assisted by trial standardisation.

Disclosure: L. Laslett, Arthritis Relief Plus Pty Ltd 2; X. J. Jin, Arthritis Relief Plus Pty Ltd 2; G. Jones, Arthritis Relief Plus Pty Ltd 2.

2237


Background/Purpose: Osteoarthritis (OA) may comprise multiple phenotypes, each of which is inflammatory-driven OA. COX-2 inhibitors (i.e. celecoxib) are the most approved therapeutic options; a selected subpopulation of OA patients may benefit from optimally targeted anti-inflammatory treatment. Interleukin-1 (IL-1) is a potent catabolic cytokine thought to play a major role in the development and progression of OA both in terms of disease (structural progression) and symptoms (pain and functional deterioration). The anti-inflammatory effects of novel human DVD-Ig targeting IL-1α and IL-1β (ABT-981) were evaluated in knee OA patients using a panel of biomarkers that are elevated in the presence of tissue degradation secondary to joint inflammation.

Methods: This was a randomized, double-blind, placebo-controlled trial of the safety, pharmacokinetics, and pharmacodynamics of multiple subcutaneous injections of ABT-981 in knee OA patients (N=36). Three groups of patients (n=27) received 4 doses of ABT-981 or matching placebo (72) every other week (EOW) at 0.3, 1, and 3 mg/kg. Serum samples were collected on days 1, 5, 15, 19, 29, 33, 43, 47, and 57. The panel of inflammation and joint-degradation biomarkers included high-sensitivity C-reactive protein (hsCRP); matrix metalloproteinase (MMP)-9; vascular endothelial growth factor (VEGF); MMP degradation products of type I, II, and III collagen (C1M, C2M, and C3M) and CRP (CRP); and circulating levels of citrullinated and MMP-degraded vimentin (VIM). Biomarker response for patients on active drug in each group was compared with the pooled placebo group. Statistical analysis was performed on least-square means using SAS 9.2.

Results: Mean serum hsCRP levels in all ABT-981 groups were significantly decreased vs placebo (p value range, 0.003–0.031). Mean serum C1M levels decreased in a dose-dependent manner (p=0.062, 0.027, and 0.015 for 0.3, 1, and
3 mg/kg groups, respectively). Mean serum C3M levels exhibited a nonsignificant decreasing trend in the 1 and 3 mg/kg groups (p=0.062 and 0.090, respectively). Mean serum CRPM levels were decreased with ABT-981; however, a statistical difference was only established from day 33 on (p value range, 0.097–0.025; Figure). No other markers showed significant changes or trends.

Discussion: Through inhibition of IL-1α and IL-1β, ABT-981 significantly reduced serum hsCRP and markers of joint metabolism that are elevated in inflammatory-driven joint destruction diseases, suggesting a reduction in systemic inflammation. ABT-981 significantly decreased C3M, suggesting a damping of inflammation-mediated joint destruction by reducing connective tissue turnover. The observed serum C3M and CRPM decreases suggest the potential of ABT-981 to ameliorate inflammation-mediated tissue destruction and chronic tissue inflammation. Thus, ABT-981 may provide clinical benefit to a selected subpopulation of patients with inflammation-driven OA.

## 2238

### Exploratory Six Month Phase IIA Study of a Potential Disease Modifying Drug in Patients with OA of the Knee.

#### K etan Desai, Voltarra Pharma, Easton, PA.

**Background/Purpose**: No disease modifying drugs exists to treat osteoarthritis. Recently, a phase II study in Tasmania showed that Zoledronic Acid, a bisphosphonate, has an effect on decreasing bone marrow lesions in patients with osteoarthritis of the knee. However, this was associated with post-dose syndrome. At six months, after a single infusion, there was no difference in bone mineral density with a DEXA scan. VAS was evaluated at 1 month, 3 months, and six months. DEXA scan was repeated at six months to confirm no decrease in BMD.

**Results**: At six months, after a single infusion, there was no difference in bone mineral density in either cohort. The number of patients complaining of post-dose syndrome in the cohort treated with Zoledronic Acid was significantly worse that in those treated with Volt01 (9/16 versus 2/16). The improvement in pain as measured by VAS at six months was also significantly better in the Volt01 cohort than the Zoledronic Acid cohort (−35mm versus −10mm)

**Conclusion**: Zoledronic Acid has been recently shown to have disease modifying properties in a large phase II study in patients with OA of the knee. In the study presented in this abstract, Volt01, a new combination with Zoledronic Acid, was both safer and more effective than Zoledronic acid after a single infusion in patients with knee OA for at least six months. Volt01 thus has the potential to be a disease modifying drug for knee OA. Larger studies using MRI will need to be undertaken to confirm this observation.

Disclosure: K. Desai, Voltarra Pharma, 4;
weeks. Secondary objectives assessed changes in physical function, stiffness, global assessment of OA, and health related quality of life. **Methods:** Eligible patients, 40–80 years with Kellgren-Lawrence grade ≥2 and OA of ≥6 months duration required baseline average daily pain between 5 and 9 on the Numeric Pain Rating Scale (NPRS) following pain medication washout. Primary endpoint analysis of change from Baseline (Week 4) of weekly average daily NPRS used a mixed effects model with repeated measures yielding an overall 3-sided α = 0.025.

**Results:** A total of 164 patients (AF-219 n=78, placebo n=86) who received ≥ one dose of study medication and completed ≥50% of week 1 daily NPRS scores. 134 patients completed 4 weeks treatment (AF-219 n=56, placebo n=78) due to early discontinuations for taste-related adverse events (AEs) with active treatment and lack of efficacy in placebo. Reduction in weekly average daily NPRS in AF-219 treated patients was numerically greater than placebo at each week. This difference was greatest in week 2 (p = 0.0436).

Normalized pain, stiffness, physical function, and total WOMAC scores revealed larger numeric mean reductions at all end of treatment analyses; the Week 1 normalized total WOMAC score was significantly better in AF-219 treated patients (p = 0.0176). Patient (PGIC) and Clinician Global Impression of Change (CGIC) and Short Form-36 physical component summary and role physical and bodily pain domains at end of treatment were significantly improved compared with placebo. Placebo patients took significantly more rescue medication over all 4 weeks.

There were no deaths or SAEs during the treatment phase. AEs were generally mild. 88% AF-219 treated patients reported dysgeusia/hypogeusia and 19% discontinued treatment due to dysgeusia.

**Conclusion:** In patients with OA of the knee, treatment with the P2X3 antagonist AF-219 resulted in improvement in pain and symptoms compared with placebo.

**References:**

**Disclosure:** V. Strand, None; M. Ktt, None; A. Kivitz, None; A. Ford, None; P. Butera, None; B. McCarthy, None; T. Erfani, None; Y. Zhang, None; J. Makovey, None; B. Metcalf, None; L. March, None; K. Bennett, None; D. J. Hunter, None.

**Table: Association of Intermittent Analgesic Use and Risk of Pain Exacerbation**

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>P</th>
<th>OR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Analgesic</td>
<td>0.0007</td>
<td>7.02</td>
<td>1.70</td>
<td>29.1</td>
</tr>
<tr>
<td>Regular Use (n=411)</td>
<td>1.00</td>
<td>Ref</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>No Analgesic Use (n=574)</td>
<td>0.18</td>
<td>0.68</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=313)</td>
<td>0.10</td>
<td>1.57</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.06</td>
<td>5.82</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=48)</td>
<td>35.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.06</td>
<td>1.00</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=59)</td>
<td>1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.007</td>
<td>7.02</td>
<td>1.70</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=40)</td>
<td>1.26</td>
<td></td>
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<tr>
<td>Paracetamol</td>
<td>0.55</td>
<td>0.82</td>
<td>0.43</td>
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<tr>
<td>Intermittent Use (n=172)</td>
<td>1.56</td>
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<tr>
<td>tramadol</td>
<td>0.69</td>
<td>0.58</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=13)</td>
<td>8.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>celecoxib</td>
<td>0.09</td>
<td>0.19</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Intermittent Use (n=33)</td>
<td>1.26</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>diclofenac</td>
<td>0.30</td>
<td>2.48</td>
<td>0.44</td>
<td></td>
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<tr>
<td>Intermittent Use (n=35)</td>
<td>13.8</td>
<td></td>
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<td></td>
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</tbody>
</table>

**2242**

**Effects of Intraarticular (IA) Corticosteroid Injections on Bone Markers and Endogenous Cortisol in Patients with K nee Osteoarthritis (OA): A Randomized, Double-Blind, Placebo Controlled Trial.** M. Imran, A. Naru Baratham, J. Wok, B. L. Lutker and H. Lindsley

**Methods:** We describe a 2:2:1 randomized, double-blind, placebo controlled study. 25 subjects (20 females, 5 males) with knee OA, age range 45–83 years were identified from our clinical practice. Ten subjects (Group 1) were injected with Depo-methylprednisolone 80 mg plus lidocaine 20 mg, 10 additional subjects (Group 2) were injected with Depo-methylprednisolone 16 mg plus lidocaine 20 mg and 5 subjects (Group 3) were given normal saline with lidocaine 20 mg. Blood draws were performed 5 times (Days 0, 2, 3, 7, 14 and 28). Means and 95% CI were reported by time and group. All plots show mean (+/- SEM). Between and within-group comparison p-values were generated by t-tests. All parametric assumptions were verified.

**Results:** Mean levels of serum osteocalcin, a bone formation marker, reached a nadir (10.2 ng/mL (95% CI 9.3–11.2) from baseline of 15.5 ng/mL (95% CI 14.4–16.7) by Days 2–3 with recovery by Day 7 (14.9 ng/mL (95% CI 13.8–16.1)) after IA corticosteroids only for Group 1, with mean change of 5.3 ng/mL (95% CI 2.4–6.2) (p = 0.01). No change was seen in Groups 2, 3 (Fig 1, p > 0.05). In contrast, the bone catabolic marker Tartrate-resistant Acid Phosphatase Form 5b (TRACP-5b) showed no consistent change for any of the three groups over 28 days (range 1.7–2.7 U/L) (Fig 2). Mean baseline endogenous cortisol level reached a nadir by Days 2–3 for Group 1 (8.9 mg/dL (95% CI 8.0–9.8) and by Day 7 for Group 2 (8.9 mg/dL (95% CI 8.0–9.7)). Both returned at least to baseline by day 14. Baseline vitamin D levels did not differ significantly between groups (p > 0.05), though Group 1 levels were not as low (range 22–47 ng/mL) as Group 2 (range 8.3–51.5 ng/mL) or Group 3 (range 8.6–38.5 ng/mL). In control subjects, lower baseline levels of vitamin D were associated with greater decreases in

**Background/Purpose:** IA steroids are used to treat knee OA. Little is known about the systemic effect of intraarticular steroid injections on bone or the hypothalamic-pituitary-adrenal axis (HPA) Pathways.
osteocalcin at Day 2–3 (r = 0.9, p < 0.05). Low levels of vitamin D were associated with greater levels of suppression of osteocalcin at Day 7 in Group 2 (r = −0.7, p = 0.03).

Conclusion: IA corticosteroids have a transient adverse effect on bone formation with significant recovery of osteocalcin levels by one week and no change in bone catabolism. Cortisol levels decrease slightly at one week of IA administration and rebound above baseline by two weeks. In contrast to daily oral corticosteroids, single doses of IA steroids have no persistent adverse effect on bone or the HPA axis.

Disclosure: M. Imran, None; A. Baratham, None; J. Wick, None; B. Lukert, None; H. Lindsley, None.

2243

Comparison Between Two Diclofenac Diethylamine Gel Formulations, 1.16% Vs 2.32%: Is It Only Increasing the Strength of the Active Ingredient Enough? Giuseppa Quartarone1 and Nathalie Hasler-Nguyen2. 1Novartis CH R&D OU Italy Greece, Milan, Italy, 2Novartis CH Global R&D, Nyon, Switzerland.

Background/Purpose: Topically applied non-steroidal anti-inflammatory drugs (NSAIDs) can produce clinically effective drug concentrations at a peripheral site, but with low systemic concentrations and thus a lower risk of AEs. Various factors influence penetration and absorption of topical NSAIDs such as chemical properties of adjuvants included in the formulation and inter-individual variability in skin absorption. Modulating skin permeation is a pivotal factor in the development of new formulations as well as their dosing and duration of therapeutic effect. Diclofenac diethylamine (DDEA) 1.16% gel (Voltaren® Emulgel™ [VEG 1%], Novartis Consumer Health, Nyon Switzerland) is used topically to relieve pain and inflammation; it is applied to the affected site 3 or 4 times daily. We compared the in vitro skin permeation of VEG 1% with a new double-strength formulation of DDEA 2.32% [VEG 2%] including different doses of a permeation enhancer (PE) to assess the hypothesis of increased skin permeation that may result in delivering higher drug amounts to target tissues when applied every 12h.

Methods: In vitro skin penetration studies were performed at 35°C in glass Franz static diffusion cells (Bernard Gallas, Antibes, F; 1.54 cm²) using human skin. Samples of donor abdomens were obtained from the NDRI Institute (USA) and the WHRTB Institute (HU) and kept frozen at −80°C until use. The comparison of in vitro skin permeation of VEG 1% vs VEG 2% was performed. Then VEG 1% was tested against VEG 2% containing low (0.5%), medium (0.75%) and high (1.0%) amounts of a permeation enhancer. All samples were applied at 20 mg/cm² in a single dose, equivalent to the maximum daily dose of 4 applications of 5 mg/cm² under in use conditions.

Results: Addition of the PE at the VEG 2% gel resulted at a dose-dependent (up to 3-fold) increase in diclofenac’s skin permeation (Fig. 1). Medium and high PE concentration resulted in similar cumulative permeation.

Conclusion: Addition of PE to VEG 2% resulted in an up to 3-fold increased diclofenac skin permeation which correlated with the PE dose concentrations. The new gel is expected to have a lasting effect, e.g. up to 12h, potentially attributed to the release of a higher amount of drug at the application site as confirmed in a RCT (Predel 2012), where daily doses significantly reduced pain and improved joint function vs placebo. This could be useful when treating flares of peripheral joint conditions such as OA.

Disclosure: G. Quartarone, None; N. Hasler-Nguyen, None.

2244

Multimedia Patient Education Tool for Patients with Osteoarthritis. Aparna Ingleshwar3, Maria A. Lopez-Olivo4, Robert Volk3, Andrea Barbo3, Maria Jibaja-Wess6, Heather Lin2 and Maria E. Suarez-Almazor3, 1The University of Texas, MD Anderson Cancer Center, Houston, TX, 2Baylor College of Medicine, Houston, TX.
Background/Purpose: The use of video modelling in patient education can result in positive patient outcomes including informed decision-making and improved self-management. The purpose of our study was to test the efficacy of a multimedia patient education tool (M M-PiET) for patients with knee osteoarthritis (OA).

Methods: We randomized 219 participants to receive a MM-PiET including storylines and testimonials n=109) and 110 to receive a written booklet with the same content (n=210). Inclusion criteria were: (i) age ≥50, (ii) prior diagnosis of knee OA (unilateral or bilateral) by a physician, (iii) adequate cognitive status, and (iv) ability to communicate in English or Spanish language. Upon completion of the baseline questionnaire, participants reviewed the materials (MM-PiET or written booklet) to which they were allocated, and then completed a post-questionnaire. Primary outcome measures included: a) Disease knowledge and, b) Decisional Conflict Scale (DCS). Secondary outcomes included: a) Ottawa Acceptability Instrument, and b) Evaluation of the educational materials. Demographics and health literacy (Adequate vs Inadequate) were also collected at baseline. We compared difference in knowledge scores (pre-post randomization) between the intervention and control groups, and within the groups themselves. Linear regression was employed to assess the influence of the intervention and patient characteristics on the knowledge score adjusting by age, sex and pre-randomization knowledge score.

Results: Mean age was 65 ± 8 years, 76% were female, 82% had adequate health literacy, and 17% spoke Spanish. Mean difference in knowledge scores was higher in the MM-PiET group compared to controls (p = 0.03). No statistically significant difference was observed in DCS scores between groups (p = 0.03, for both scales). However, significant improvement in DCS scores was observed in both groups after the intervention; patients perceived being more informed (p = 0.001) with higher values clarity (p = 0.001). Regression analysis indicated that intervention group, female gender, and higher level of educational attainment were predictive of higher knowledge improvement scores (p < 0.05 for all, Adjusted R² = 0.11). Compared to control group, MM-PiET group participants were more likely to answer “Yes” to the following questions: (1) Did the video/booklet meet your needs for information about knee osteoarthritis? (94% vs 81%, p < 0.01), and (2) Did you like the explanation of the medical facts in the video/booklet? (100% vs 95%, p = 0.04). Compared to the control group, intervention group participants were more likely to rate the presentation of information about impact of OA and, self-care options as “Excellent” (47% vs 27% and 47% vs 32%, respectively; p < 0.05 for both questions).

Conclusion: The results of our study support the efficacy of the MM-PiET written booklet in improving disease knowledge in patients with knee OA.

Disclosure: A. Ingleshaw, None; M. A. Lopez-Olivo, None; R. Volk, None; A. Barbo, None; M. J. Bajza-Weiss, None; M. Lin, None; M. E. Suarez-Almazor, None.

2245
Characteristics of Conventional Footwear and Their Association with Reductions in Knee Loading with a Flexible Footwear Intervention. Naja Shakoor1, Roy H. Lidtke2, Chris Ferrigno2, Anjali Nair3, Markus A. Wimmer4, Laura E. Thorp5, K. Douglas Gross3, and Joel A. Block1. 1Rush University Medical Center, Chicago, IL, 2Rush University Medical Center, Chicago, IL, 3Boston Univ School Medicine, Boston, MA.

Background/Purpose: The peak external knee adduction moment (KAM) as measured through gait analyses has been associated with severity, progression and pain in medial knee osteoarthritis (OA); thus, biomechanical approaches to knee OA aim to reduce the KAM. We previously reported that flat flexible footwear may reduce the KAM compared to wearing conventional footwear. However, the characteristics of conventional footwear that influence the magnitude of this reduction remain unclear. Here we evaluate the footwear of participants with knee OA to identify the properties associated with a flexible footwear intervention.

Methods: Participants with medial compartment knee OA were provided with a flexible footbed (shoe previously described as “mobility shoe”) and were asked to wear these for approximately 5 months and to wear conventional shoes that they used most often for walking activities. Their own shoes were evaluated for stability/flexibility with the following 3 tests: 1) Sagittal stability: the shoe was held perpendicu-lar to a flat surface with the tip of the toe on the ground and approximately 5 pounds of load was applied vertically on the heel; 2) Torsional stability: the shoe was held parallel to the ground with a hand at the heel and the toe and about 5 pounds of torque was applied; 3) Heel counter stability: about 5 pounds of force was applied to the medial and lateral heel counter using the thumb and index finger. With all three tests, the resistance to deformation was classified on a 3-point grading scale: (0: rigid, 1: supportive, 2: flexible). The heel height of the shoes was also measured. Gait analyses were performed while walking in subjects’ own shoes and the flexible study shoes. Paired t-tests were used to evaluate overall percent reduction in the KAM with the flexible footwear compared to participants’ own shoes, and the association between reduction in the KAM and measures of their own shoe flexibility/ stability was evaluated using Spearman’s coefficient.

Results: 22 participants (15 women, mean age (SD) of 62 ± 11 yrs) were evaluated. Overall, the use of the flexible study shoes was associated with a significant 6% reduction in the KAM (2.55 ± 1.00 vs 2.40 ± 1.00 Nm/kg*ht, p = 0.007). The percent reduction demonstrated in the KAM was significantly associated with the stability of both the forefoot (rho = 0.470, p = 0.027), and heel counter stability (rho = 0.551, p = 0.008) of the partic- ipant’s own shoe, with more rigid footwear being associated with greater KAM reduction. The assessments for sagittal and torsional stability did not appear to provide unique information since they were strongly correlated (rho = 1.0) with one another. Interestingly, heel height was not associated the extent of KAM reduction (rho = 0.181, p = 0.488).

Conclusion: Footwear has been associated with knee joint loading and choice of footwear may be an important consideration in knee OA. This study suggests that those wearing more rigid footwear may expect the greatest benefit in medial knee load reduction with transition to flexible footwear and supports the concept that flexibility is an important load-reducing feature of footwear. Simple protocols to evaluate footwear such as those used in this study may be beneficial in helping patients make choices regarding footwear.

Disclosure: N. Shakoor, DIO and Dr. Comfort; 7. R. H. Lidtke, DIO and Dr. Comfort, 7. C. Ferrigno, None; A. Nair, None; M. A. Wimmer, None; L. E. Thorp, None; K. D. Gross, None; J. A. Block, None.

2246

Background/Purpose: Obesity is a modifiable risk factor of knee osteoarthritis (KOA). While medical treatments have limited benefit for RA effects, an alternative approach involves surgical weight loss to delay or avoid joint replacement. Limited retrospective data have shown improvement in KOA pain after bariatric surgery. We initiated a prospective study to evaluate painful KOA in the obese population, and track whether weight loss after bariatric surgery affects KOA-related pain and physical function.

Methods: We screened individual patients (n = 537) prior to laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy, or gastric bypass (RYGB). Patients age ≥21 with knee pain for ≥1 month and a visual analog scale pain score ≥ 30mm were enrolled, excluding lupus, inflammatory arthritis, or psoriasis. Baseline pre-op assessments included x-rays for OA severity by Kellgren-Lawrence (KL) grade, the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) with a Likert scale calculated from the KOOS. Patients are completing the questionnaires and being measured for BMI and % excess weight loss (%EWL) at intervals through 12 months post-op.

Results: In total, 307 patients reported knee pain, and of those, 175 met criteria and consented (89.7% female, mean BMI 43 kg/m², range: 32–60, mean age 42 ± 11, range: 18-73). X-rays were completed on 160 patients: KL0=38, KL1=31, KL2=33, KL3=33, KL4=25. The mean pre-op KOOS scores were 46 (0=worst, 100=best) for both pain and ADLs, the mean WOMAC pain score was 11 (0=best, 20=worst), and the mean overall WOMAC index was 52 (0=best, 96=worst). Higher KL correlated with symptoms: mean KOOS pain was 54, 49 and 37 for KL 0, KL 1, and KL 3–4 (p=0.0006 for KL1-2 vs 3–4), with similar trends across other KOOS and WOMAC scores. Higher BMI also correlated with worse pre-op knee symptoms, as the quantities with the lowest and highest BMI (32–36 and 49–61) had mean KOOS pain scores of 48 and 43. Thus far, 117 patients have had surgery (31 RYG, 66 sleeve, 22 LAGB). Improvement in average KOOS and WOMAC scores over baseline has been observed at all intervals (46, 36, 31 and 7 responses at 1.3-6.12 month visits), with more improvement farther after surgery. At 6 months, KOOS scores showed significant improvement in patients with the lowest BMI (p=0.015 vs. 49–61). In contrast, KOOS scores showed significant improvement in patients with the highest BMI (p=0.015 vs. 32–36) and further improved at 1 year. In addition, patients with a BMI of 32–36 and an %EWL of 45% or greater had significant improvement in symptoms across all WOMAC domains and KOOS pain and function. A BMI of 32–36 and an %EWL of 45% or greater was associated with significant improvement in KOOS pain and function. A BMI of 32–36 and an %EWL of 45% or greater was associated with significant improvement in KOOS pain and function.
months post-op, mean KOOS scores improved 29 points for pain, with mean WOMAC pain and index improving by 6 and 22 points. The %EWL correlated with knee symptoms at each interval and for all followups combined, as the smallest and largest %EWL quartiles (4–29%, 54–92%) showed mean improvements of 18 and 31 points (p<0.03) in KOOS pain - mirrored across KOOS and WOMAC scores. RYGB and sleeve yielded higher %EWL than LAGB (44%, 43% vs. 37%) across all intervals, and greater improvement in mean KOOS and WOMAC scores (e.g. mean KOOS pain increased by 28 and 29 and 8). Neither presence nor severity of KOA severity affected knee pain improvement from weight loss.

**Conclusion:** These data suggest that bariatric surgery improves patients’ KOA pain proportional to weight loss, with durability over time. RYGB and sleeve gastrectomy have more impact on knee symptoms than LAGB. While patients with worse KL grades report more baseline pain and disability, x-ray severity did not impact the response to weight loss.

**Disclosure:** A. Leyton-Mange, None; J. Lin, None; R. Flanagan, None; E. Wilder, None; J. Bhatia, None; F. Taufiq, None; L. Browne, None; M. Attur, None; R. La Rocca Vieira, None; M. Parikh, None; C. Ren-Fielding, Apollo Endosurgery, 5; S. B. Abramson, None; J. Samuels, None.

### 2247

**Bariatric Surgery Improves Quality of Life in Patients with Osteoarthritis and Obesity Compared to Non-Surgical Weight Loss.** Christopher Chong², Sangetea Kashyap³, Philip Schauer⁴, Colin O’Rourke⁵ and M. Elaine Husni⁶. “Cleveland Clinic, Cleveland, OH, “Cleveland Clinic Foundation, Cleveland, OH.

**Background/Purpose:** Numerous studies support obesity as a strong risk factor for development and progression of knee osteoarthritis (OA). The potential benefits of massive weight loss, as seen after bariatric surgery, have not been well studied. The study objective is to examine if massive weight loss after bariatric surgery is associated with improved OA symptoms and quality of life (QoL) compared with medical management alone in obese patients.

**Methods:** A total of 150 patients were screened for clinical and radiographic evidence of OA within the STAMPEDE trial (March 2007 - Jan 2011). The STAMPEDE trial examined the effects of bariatric surgery vs. medical management alone in obese patients with diabetes. 100 patients received bariatric surgery (50 sleeve gastrectomy and 50 Roux-en-Y gastric bypass) and 50 patients were medically managed. Clinical data, medication usage, and QoL scores were collected before and 12 months after intervention. OA was defined by physician diagnosis at an office visit and/or radiographic evidence of OA (joint space narrowing and osteophytes) of the hip, knee, ankle, or foot. The change in 12 month post-intervention SF-36 scores between the surgical group and medically managed group were compared. Scores were compared using linear regression models, adjusting for baseline score. Baseline scores were centered at their median value.

**Results:** 67 patients with OA had baseline and follow up data available for review. Demographics between the bariatric surgery and medical group were similar (mean age 51, female gender 44/56, mean BMI 36.6). 49 patients were in the surgery group and 18 in the medical group. There was a statistically significant difference in BMI change, over 12 months, between the surgical group and 18 in the medical group. There was a statistically significant difference (p<0.03) in KOOS pain - mirrored across KOOS and WOMAC scores, function (P 0.03), general health (P 0.001), and overall physical health scores (P 0.004) (Table 1). There was no significant difference between the groups in pain or role-physical scores.

**Conclusion:** Patients with OA who underwent massive weight loss after bariatric surgery had significant improvement in SF 36 physical functioning and general health scores when compared to patients treated with medical management of weight loss alone. There was also a trend suggesting improvement in bodily pain and role-physical.

**Table 1:** Adjusted SF-36 improvement in surgical compared to medical group at 12 months.

<table>
<thead>
<tr>
<th>SF-36 Scale</th>
<th>SF-36 difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>11.47</td>
<td>1.15–21.79</td>
<td>0.03</td>
</tr>
<tr>
<td>Role Physical</td>
<td>8.55</td>
<td>–7.12–24.21</td>
<td>0.28</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>9.44</td>
<td>–2.77–21.65</td>
<td>0.13</td>
</tr>
<tr>
<td>General Health</td>
<td>19.24</td>
<td>12.25–26.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Physical Health Summary](image)

**Figure 1:** Average SF-36 scores at baseline and 12 months.

**Disclosure:** C. Chong, None; S. Kashyap, None; P. Schauer, None; C. O’Rourke, None; M. E. Husni, None.

### 2248

**Clinical Outcomes, Neuropathic Pain and Patient Satisfaction over a 15 Year Period Following Primary TKA: A Repeat-Cross-Sectional Analysis.** Anne Lübke, Matthias Zingg, Daniel Fritschi, Pierre Hoffmeyer and Hermes Miozzari. Geneva University Hospitals, Geneva, Switzerland.

**Background/Purpose:** Studies evaluating patient-reported long term outcomes (>10 years) after primary TKA are lacking. Moreover, variability in patient satisfaction after TKA has been reported for the short and mid term, but has not been investigated over the long term and in relation to presence or absence of neuropathic pain.

**Objective was to assess pain, function, general health, and patient satisfaction at short, mid and long term following primary TKA.**

**Methods:** Patients eligible for this study were part of a prospective hospital-based cohort of all primary TKAs operated upon since March 1998. All patients operated in 2012, 2010, 2007, and 2004–1998, who were alive and still living in the area, received a postoperative questionnaire by mail between 2012 and 2013. We performed repeat cross-sectional analyses of pain, function, general health and patient satisfaction at the following time-points: prior to surgery, and 1, 2, 5, 9–11 and 12–15 years postoperative. Pain was evaluated with use of WOMAC and VAS score, neuropathic pain with DN4 (<neuropathic pain diagnostic questionnaire), function with WOMAC, general health with the SF-12, and satisfaction was evaluated with use of a five-item satisfaction rating.

**Results:** 1451 TKAs were eligible (68.4% women, mean age 71 (±9) years, mean BMI 29.6 kg/m²). Of those, 1021 returned the questionnaire (response rate 70.4%). Their mean age was 71 years, mean BMI was 29.5 kg/m² and 67.8% were women. Mean values of pain, function and general health were clinically significantly higher (effect sizes 0.22–1.71) one year postoperative as compared to prior to surgery (see Table). For pain and satisfaction there was an ongoing clinically significant “improvement” between 1 and 2 years postoperative. Results remained similar between 2 and 10 years with minimally lower (effect size <0.2) outcomes between 10 and 15 years. Neuropathic pain was reported in 12.4% preoperative, 14% at 1 year, 10% at 2 years and 5–7% 5–15 years after surgery. Its presence was significantly (p<0.001) associated with dissatisfaction.

**Conclusion:** Clinical outcomes and patient satisfaction were similar between 2 and 15 years after primary TKA. Neuropathic pain when present was strongly associated with dissatisfaction.

**Table 2:** WOMAC, VAS, SF-12 at 1, 5, 10, 15 years post TKA. Mean, standard deviation.

<table>
<thead>
<tr>
<th>WOMAC, VAS, SF-12</th>
<th>1 yr. post TKA</th>
<th>5 yrs. post TKA</th>
<th>10 yrs. post TKA</th>
<th>15 yrs. post TKA</th>
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<tbody>
<tr>
<td>Pain (VAS)</td>
<td>36.5 (26)</td>
<td>27.2 (22)</td>
<td>26.4 (26)</td>
<td>25.8 (25)</td>
</tr>
<tr>
<td>Function</td>
<td>78.0 (17.0)</td>
<td>76.9 (17.1)</td>
<td>74.9 (16.8)</td>
<td>73.8 (17.4)</td>
</tr>
<tr>
<td>SF-12, mean, SD</td>
<td>521 (7.8)</td>
<td>521 (7.8)</td>
<td>521 (7.8)</td>
<td>521 (7.8)</td>
</tr>
</tbody>
</table>
Criteria for Clinically Important Worsening in Knee and Hip Osteoarthritis.

Ellen A. M. Maher1, Alfons A. den Broeder2, Vincent J. J. F. Busch3, Johannes W. J. Bijlsma4 and Els van den Ende5.

1Sint Maartenskliniek, Nijmegen, Netherlands; 2University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Clinically important worsening in OA has not been well defined. Validated worsening criteria are important for research but also clinical practice to make informed treatment choices. The goals of this study are 1) to select candidate clinical worsening criteria and 2) to validate criteria for clinically important worsening.

Methods: Data were used from a cohort of knee and hip OA outpatients visiting our department who received standardised evidence-based tailored conservative treatment in a stepped-care format for 3 months. The development cohort comprised 218 patients with three-months follow up and the validation cohort consisted of 296 patients with two-years follow up. For this study baseline and three month data were used.

In the first round, an expert group (methodologists, orthopaedic surgeon, physical therapists, psychologist, rheumatologists) reviewed previously proposed criteria for clinical worsening and selected on the basis of consensus and face-validity the criteria that should be tested. Furthermore, the expert group decided that newly defined criteria of worsening should contain both pain and face-validity the criteria that should be tested. Furthermore, the expert group

Table 1. Sensitivity and specificity of newly developed worsening criteria, in the development and validation cohort

<table>
<thead>
<tr>
<th>Set</th>
<th>Development cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>1. Set 1: worsening in pain</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td>51%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>2. Set 2: worsening in function</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>50%</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<td>60%</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Conclusion: This study is the first to demonstrate, using qMRI, the response to conventional and Glu/Cs treatments in subjects with meniscal extrusion. Data first revealed that Glu/Cs prevented cartilage volume loss in patients with mild to moderate disease. However, in subjects with meniscal extrusion not taking analgesics/NASAIDs and those without meniscal extrusion but taking analgesics/NASAIDs. The non-effect on patients without meniscal extrusion not taking analgesics/NASAIDs, representing very mild disease, probably reflects that the cartilage volume loss was small and unlikely to provide an accurate estimate. Moreover, in subjects with meniscal extrusion who took the analysis/NASAIDs (severe disease), the non-effect observed likely reflects irreversible cartilage damage. The present data argue for MRI based diagnosis of meniscal extrusion in clinical practice to help physicians identify knee OA patients more susceptible to benefit from DMOAD treatment. These data also support the added benefit of using...
gMRI as an alternative to X-ray for the evaluation of DMOAD agents, especially in patients with less advanced disease.

**Disclosure:** J. P. Pelletier, Artrothlab, 9; C. Roubille, None; F. Abram, Artrothlab, 3; M. Dorais, Artrothlab, 5; P. Delorme, Artrothlab, 3; J. P. Raynauld, Artrothlab, 5; J. Martel-Pelletier, Artrothlab, 9.

**2251**

**Kneeling Disability Associated with the Treatment of Osteoarthritis: Analysis of a Copcord Study in Mexico.** Alexa Herández-Cáceres, 1Jacqueline Rodríguez-Amado, 2Ingris Pérez-Ballestas, 3David Vega-Moraless, 3Mario Garza-Elizondo, 4Roberto Negrete-López, 2Lorena Pérez-Barbosa, 2 and Janett Riega-Torres. 1Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario “Dr. José Eleuterio González”, Universidad Autónoma de Nuevo León, Monterrey, Tamaulipas, 2Departamento de Reumatología, Hospital General de México “Dr. Eduardo Liceaga”, Distrito Federal, Mexico, 3Hospital Universitario UANL, Monterrey, Mexico.

**Background/Purpose:** Osteoarthritis (OA) is the most prevalent rheumatic disease in Mexico. The core treatment, a combination of pharmaceutical and non-pharmacological modalities, is primarily performed in primary care.

**Objective:** To describe which are the most employed therapeutic resources for osteoarthritis and their associated factors in the urban and rural population of Nuevo León.

**Methods:** A cross-sectional study of patients with OA from a COPCORD study dataset that included the adult population ≥ 18 years of a representative sample of the State of Nuevo León who met the diagnosis of clinical OA and had information about the anatomical location of the disease. All variables in the COPCORD questionnaire were included and performed a descriptive analysis. For the univariate analysis, the population was divided between those who did and those who didn’t receive treatment. For the multivariate analysis, a regression logistic analysis of all the variables with statistical significance was performed.

**Results:** There were 696 patients with OA with an average age of 58yr (SD 14.1), 484 (69.5%) women and 579 (83.2%) patients were living in urban areas. Five hundred and two patients (85.1%) had pain in the last 7 days, with a mean VAS pain of 6 (IQR 3), 507 (72.8%) patients had a VAS pain ≥ 4. Functional disability was present in 133 (19%) patients and a mean HAQ of 0.37 (IQR 0.75) was found. The most common places of OA were knee (356, 51.5%), hand (224, 37%), and generalized OA (93, 13%); 259 (37%) patients already knew their diagnosis by the time of the examination. Four hundred and ninety-four (71%) patients reported having treatment for OA, being the most frequently prescribed NSAIDS by physicians (231/289, 79.9%) and of analgesics by 100 (20.2%) patients, mostly acetaminophen (73, 77%). There was more utilization of NSAIDS by physicians (231/289, 79.9%) and of analgesics by self-prescribes (35/100, 35%). In the univariate analysis, the variables associated with treatment were age ≥ 58yr (OR 1.3, 95% CI 1.1–1.4), female gender (OR 1.17, 95% CI 1.0–1.3), VAS pain ≥ 4 (OR 1.3, 95% CI 1.1–1.4), functional disability (OR 2.6, 95% CI 1.6–4.1), HAQ ≥ 0.35 (OR 1.9, 95% CI 1.5–2.4), and past diagnosis of OA (OR 5.1, 95% CI 3.3–8.0). In a multivariate analysis, VAS pain ≥ 4 (OR 1.9, 95% CI 1.2–2.8), kneeling disability (OR 3.15, 95% CI 1.3–7.4) and previous diagnosis of OA (OR 7.6, 95% CI 4.5–12.9) had statistical significance.

**Conclusion:** Associated factors with treatment of OA are VAS pain ≥ 4, kneeling disability and previous diagnosis of OA.

**Disclosure:** A. Hernández-Cáceres, None; J. Rodríguez-Amado, None; I. Pérez-Ballestas, None; D. Vega-Moraless, None; M. Garza-Elizondo, None; R. Negrete-López, None; L. Pérez-Barbosa, None; J. Riega-Torres, None.

**2252**

**Autoimmune Thyroid Disease Is Associated with a Higher Frequency of Spinal Degenerative Disc Disease.** Asha Shrestha, Hillel Cohen and Clement Tagoe. Albert Einstein College of Medicine, Bronx, NY.

**Background/Purpose:** Autoimmune thyroid disease (AITD) has been linked to a number of rheumatic syndromes including arthritis and generalized pain. Although AITD has been associated with back pain, the association with spinal degenerative disc disease (DDD) in particular is unknown. We therefore investigated the association between AITD and spinal DDD.

**Methods:** We identified adult patients with anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies tested from January 1997 through January 2014 in the Clinical Looking Glass database at the Montefiore Medical Center. We performed a cross-sectional analysis of patients with and without AITD. Main variable of interest was AITD, defined as abnormal levels of anti-TPO and/or anti-TG antibodies. Mean outcome measure was spinal DDD confirmed by radiological evidence of disc disease. Adjusted odds ratios were estimated with multivariate logistic regression model. The model was adjusted for covariates including age, gender, race, ethnicity, smoking, diabetes (DM), and body mass index (BMI). We did sub-analysis by stratifying patients according to BMI, thyroid stimulating hormone (TSH) levels, and by excluding patients with known connective tissue diseases.

**Results:** Out of 7094 patients with anti-TG and anti-TPO levels, we included 4383 patients with complete data on thyroid autoantibodies, spinal DDD, and the covariates. Of those, 1557 (35.5%) patients had AITD. Compared to patients without AITD, patients with AITD were more likely to be women (86% vs 81%, p < 0.001); more likely to be hypothyroid (24% vs 8%, p < 0.001); more likely to be on levothyroxine (31% vs 9%, p < 0.001); less likely to be euthyroid (50% vs 73%, p < 0.001); less likely to have DM (21% vs 27%, p = 0.02); and less likely to be black (25% vs 37%, p < 0.001). BMI in the 2 groups were comparable. There were no significant differences for age, smoking, and known connective tissue diseases between the 2 groups.

**Conclusion:** AITD is significantly associated with a higher frequency of spinal DDD, both in patients with and without known connective tissue diseases, independent of BMI and TSH levels. This finding is novel and suggests a possible important link between thyroid autoimmunity and spinal DDD. Further studies are needed to determine if AITD has a causal link with spinal DDD.

**Table 1:** Adjusted odds ratio for AITD and spinal DDD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Outcome = Spinal degenerative disc disease</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AITD</td>
<td></td>
<td>1.75 (1.49, 2.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.11 (1.12, 1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age squared</td>
<td></td>
<td>0.99 (0.99, 1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>0.93 (0.75, 1.15)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>1.01 (1.07, 1.63)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other race</td>
<td></td>
<td>0.73 (0.55, 0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>1.02 (1.00, 1.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>1.13 (0.93, 1.38)</td>
<td>0.19</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td>1.16 (0.99, 1.35)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>1.71 (1.45, 2.01)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Disclosure:** A. Shrestha, None; H. Cohen, None; C. Tagoe, None.

**ACR/ARHP Poster Session C**

**Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis: Osteoporosis: Treatment, Safety, and Long Term Outcomes**

**Tuesday, November 18, 2014, 8:30 AM - 4:00 PM**

**2253**

**Effect of Teriparatide in Patients with Osteoporosis with Prior Vertebral Fracture.** Guillermo Valenzuela, 1Douglas Yim, 2Douglas Beall, 3Michael Gordon, 4John H. Kriegel, 4 and Kelly D. Kohn. 4

**Background/Purpose:** The Direct Assessment of Nonvertebral Fracture in Community Experience (DANCE) study was an open-label, prospective, observational study that examined occurrence of nonvertebral fragility fractures in osteoporotic men and women
Results: Of 4085 patients who received ≥1 dose of teriparatide 20 μg/day, 715 had documented prior vertebral fractures of which 202 had previous vertebral augmentation. Patients with prior vertebral fractures vs. those without were older (mean [SD] age, 71.85 [10.66] vs. 67.07 [11.92] yr, respectively), more likely to have had prior fragility fractures (95.2% vs. 47.8%), had higher L1-L4 T-scores (−2.35 [1.47] vs. −2.50 [1.35]), had more baseline clinical conditions (2.21 [1.58] vs. 1.72 [1.37]), and a higher proportion had comorbid conditions (89.4% vs. 81.6%) (all p-values <0.04). Mean teriparatide exposure was similar for both groups (541.8 [283.1] vs. 542.3 [292.2] days). Bone density in the spine, total hip, and femoral neck increased similarly in patients with or without prior vertebral fracture (all p-values ≥0.06), with similar results in patients who did or did not have vertebral augmentation (all p-values ≥0.08). Compared with the first 6 mo., the incidence of nonvertebral fractures during months 6–24 was 52% lower (absolute difference 3.76%) in patients with and 37% lower (absolute difference 1.08%) in those without prior vertebral fractures. The reduced incidence of nonvertebral fracture over time was 52% lower (absolute difference 3.76%) in patients with and 37% lower (absolute difference 1.08%) in those without prior vertebral fractures. The reduced incidence of nonvertebral fracture over time was statistically consistent in both groups (effect of time by subgroup interaction p=0.38). Reduction in nonvertebral fracture during months 6–24–vs. the first 6 mo. of treatment was 62% lower (absolute difference 4.33%) for patients with prior vertebral augmentation and 41% (absolute difference 1.44%) for those without. Teriparatide was well tolerated.

Conclusion: Patients with prior vertebral fractures were older and had more fragility fractures and comorbid conditions at baseline than patients without previous vertebral fracture. In this post-hoc analysis, teriparatide improved bone density and reduced the incidence of nonvertebral fractures with >6 mo. vs. ≤6 mo. of therapy in osteoporosis patients with and without prior vertebral fracture, including those with prior vertebral augmentation.


2254

Changes in Subject Characteristics in the Denosumab Pivotal Fracture Trial and Its Extension for up to 8 Years

Methods: In FREEDOM, women were randomized to placebo or denosumab 60 mg every 6 months. All FREEDOM subjects who had not missed ≥1 dose of investigational product, completed the 3-year visit, and consented to enroll were eligible to receive open-label denosumab in the Extension. We assessed whether older age and incident fractures contributed to attrition at Year 5 of the Extension, representing 8 years of follow-up.

Results: In FREEDOM, 6478/7808 (83%) subjects completed the trial. Of 5928 subjects eligible for the Extension, 4530 (77%) enrolled. Through Year 5 of the Extension, 3004 (66%) remained on study. While baseline characteristics were similar in FREEDOM and Extension, all subjects were 3 years older at Extension baseline, prevalent vertebral fracture rate in placebo-treated subjects was higher at Extension baseline compared with FREEDOM baseline (25% vs 22%), and denosumab-treated subjects had higher mean BMD at Extension baseline. Age distribution after 5 years of Extension remained consistent with the antecedent 3 years in FREEDOM, with no preponderance of younger subjects (Figure). As expected, older subjects were more likely to discontinue, however, 62% of subjects who were ≥75 years at Extension baseline remained on study through Year 5. While subjects who fractured were more likely to discontinue in FREEDOM and in the Extension, 88% and 83% of placebo and denosumab fractured subjects, respectively, completed the 3-year FREEDOM trial, and 72% of fractured subjects in the Extension remained enrolled through Year 5.

Conclusion: In this large-scale, long-term study of denosumab, Extension population maintained similar characteristics to the original FREEDOM cohort. During Extension, a high percentage of subjects at increased risk for fractures due to older age and incident fracture remain on study. This suggests that the low fracture incidence and consistent safety profile reflect the long-term denosumab treatment effect.

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Figure. Age Distribution at FREEDOM Baseline (A) and Year 5 of FREEDOM Extension (B)

Background/Purpose: Understanding the effect of therapies in the vertebral compartments is relevant to bone biology and clinical practice. We developed an improved technique using cortical shell segmentation-based layering of high resolution quantitative computed tomography (HR-QCT) scans of T12 vertebral bodies to evaluate compartment-specific changes in BMD and microstructure.

Methods: In an international, randomized, phase 2 study (MClin et al., N Engl J Med. 2014), postmenopausal women with low BMD supplemented with calcium and vitamin D received subcutaneous (SC) romosozumab (210 mg monthly), teriparatide (20 mcg SC daily), or placebo (PBO). A subset of these women underwent HR-QCT scanning of T12 (N = 11 romosozumab, 12 teriparatide, 8 PBO) at baseline and month 12. For cortical HR-QCT analysis (blinded to treatment assignment), adjacent 200 micron thin films of the cortical shell were evaluated to determine changes from the outer soft tissue bordering the vertebrae to the medullary spongiosa (Figure). In addition to the standard cancellous compartment variables previously described (Graeff et al., J Bone Miner Res. 2007), this improved method allows accurate determination of cortical variables in the subregions, including apparent and corrected (deconvolved) cortical thickness, bone mineral content (BMC), and BMD. Changes in cortical thickness are modeled assuming an average 50% mineralization of newly added matrix.

Results: At baseline, mean (SD) apparent cortical thickness of 1.37 (0.13) mm was corrected to a cortical thickness of 0.29 (0.05) mm. At month 12, romosozumab significantly improved cortical BMC and BMD from baseline and in comparison to teriparatide or PBO (all P < 0.0003; Table). These gains were attained by both endosteal and periosteal bone matrix apposition. Improvements in cancellous BMD were similar between romosozumab and teriparatide.

Conclusion: Using HR-QCT scans of the spine, it is possible to evaluate changes across the cortical shell of the vertebral bodies and determine alterations in the endosteal and periosteal regions. The anatomical location and magnitude of these changes could impact changes in bone strength and thus affect fracture risk. Romosozumab administration was associated with significant increases in cortical thickness and improvement in all measured cortical parameters at 12 months compared with teriparatide or PBO. The clinical effect of romosozumab to reduce fractures is being evaluated in an ongoing phase 3 clinical program.

How Does Non-Compliance to Prolia® (DENOSUMAB) Impact the Change in Bone Mineral Density (BMD) in Osteoporotic Patients? 
Aashish K. Kalani1, Matt Wong-Pack1, Jacob Hordyk2, Arthur N. Lau, George Ioannidou3, Robert Bennett1, William G. Benson, and Jonathan D. Adachi1, 2
1McMaster University, Hamilton, ON, 3University of Ottawa, Ottawa, ON, 4Division of Rheumatology, McMaster University, Hamilton, ON, 5Rheumatology Health Team, Dr. Benson’s Rheumatology Clinic, Hamilton, ON.

Background/Purpose: Denosumab (Prolia®) has shown to be a safe and efficacious therapy for osteoporotic patients in many clinical trials. Unfortunately, few studies have explored its effectiveness in clinical practice. Currently, best practice guidelines suggest that denosumab should be administered subcutaneously every six months. However, in clinical practice, patients do not always receive subsequent denosumab as prescribed. This non-compliance may have a significant impact on the effectiveness of the drug. The objective of this study is to assess the impact on noncompliance with the regular dosing regimen has on bone mineral density (measured at the lumbar spine [LS] and femoral neck [FN]) compared to patients who receive their scheduled dosing regimen.

Methods: A retrospective cohort study was conducted from August 2012 to August 2013. We included all osteoporotic patients from a single academic center who received a minimum of two injections of denosumab with a follow-up BMD measurement since May 2010 for analysis. Patients who have only received their first subcutaneous injection and patients without a corresponding BMD score were excluded from the study. Patients were classified into 3 categories and analyzed in these groups: 1) subsequent injection less than five months, 2) between five to seven months, 3) more than seven months after their initial subcutaneous injection. Changes in BMD (at the LS and FN) over a 1-year follow-up period was analyzed between these three groups.

Results: Of the 924 charts examined, 436 patients met eligibility criteria. Multi-variable regression analysis was conducted comparing the change in BMD after one year of denosumab therapy at both the LS and FN for the three prespecified groups. The group receiving an injection 7 months after their initial injection was used as a reference. The change in BMD (95% confidence interval) after one year was -0.00008 (-0.01335 to 0.01168) and 0.02073 (-0.00697 to 0.04843) for patients receiving a subsequent injection between 5-7 months later, at LS and FN respectively. The change in BMD (95% confidence interval) after one year was 0.00515 (0.00619 to 0.01649) and 0.01474 (-0.00142 to 0.03390) for patients receiving a subsequent injection less than 5 months later, at LS and FN respectively. The relationship between the timing of drug administration and change in BMD over 1 year was not statistically significant (p>0.05).

Conclusion: This observational study proposes that the efficacy of denosumab (as measured by BMD measurements at the lumbar spine and femoral neck) has great efficacy in the treatment of osteoporosis especially when patient compliance was maintained. This emphasizes the importance of patient compliance and the need for programs available to patients to help ensure this compliance. However, in the small subset of patients who were unable to receive their subsequent denosumab injection within the 5 to 7 month window, there was no difference in BMD measurements. This suggests that although compliance is essential, a delay in a subsequent injection may be acceptable in extenuating circumstances. A follow-up study with a larger sample size and longer follow-up duration is required to further characterize this relationship.

Disclosure: A. Kalani, None; M. Wong-Pack, None; J. Hordyk, None; A. N. Lau, Amgen, Roche, 8, Amgen, Roche, 2, G. Ioannidou, None; R. Benson, None; W. G. Benson, None; J. D. Adachi, Amgen Inc, Astra Zeneca, Eli Lilly, GSK, M erck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, and Bristol-Mysers Squibb, 2, A. Ioannidou, None; R. Benson, None; W. G. Benson, None; J. D. Adachi, Amgen Inc, Astra Zeneca, Eli Lilly, GSK, M erck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, and Bristol-Myers Squibb., 2.

Background/Purpose: Osteoporosis is one of the serious complications of systemic glucocorticoid therapy. Reduced bone formation is the key process in patients with glucocorticoid-induced osteoporosis (GIOP), however, the significance of increased bone resorption in these patients is still under consideration. We reported that serum soluble receptor activator for nuclear factor-a ligand (sRANKL) level might be a predictive factor in patients under glucocorticoid therapy (Clin Endocrinol Metab. 97: E1909-917, 2012). Teriparatide, a recombinant form of parathyroid hormone, is an option of treatment for GIOP especially to the severe cases. Its daily injection stimulates bone formation, resulting in increase of bone volume and reduction of bone fracture. Thus, we observed the effect of teriparatide on serum sRANKL and osteoprotegerin (OPG) levels in bone resorption markers in patients with rheumatic disease under glucocorticoid therapy. The aim of this study is to evaluate the effect of teriparatide on serum sRANKL and OPG levels in patients under glucocorticoid therapy.

Methods: Patients: Patients were recruited at Toho University Otori Medical Center. This study was approved by the Ethics Committees at Toho University Otori Medical Center (approval number: 24-97). Twenty post-menopausal women (71±6 yr [mean ± SD]) with rheumatic diseases (rheumatoid arthritis 9, vasculitis syndrome 6, polymyalgia rheumatica 3, polymyositis 1, and systemic lupus erythematosus 1) were included in this study. All the patients were changed from oral bisphosphonates to daily s.c. injections of teriparatide (20 µg) for treatment of GIOP. Patients who received mean prednisolone at doses of 6.7±3.4 (SD) mg daily were eligible for this study. We measured serum sRANKL, OPG, bone formation markers (OC, ucOC, BAP, and P1NP), and bone resorption markers (TRACP-5b and NTX) during teriparatide treatment. The bone mineral density (BMD) was measured before and 6 months after start of teriparatide treatment. Data were expressed as the median with the interquartile range.

Results: Serum sRANKL levels were significantly decreased after teripar- atide treatment (0.066 [0.0-0.188] to 0.00 [0.0-0.008] pmol/L, p < 0.05). In contrast, serum OPG levels were not changed after the treatment (6.71 [5.79-8.13] to 7.17 [5.69-8.92] pmol/L, p = 0.584). All of serum bone formation markers (OC: 3.6 [2.9-5.8] to 10.0 [8.2-18.0] ng/ml; ucOC: 1.4 [0.9-4.6] to 5.2 [3.4-9.1] ng/ml; BAP: 10.9 [8.0-16.0] to 13.5 [11.6-22.3] nmol/mg; P1NP: 26.8 [17.5-56.9] to 47.0 [34.1-129.1] nmol/mg.) and resorption markers (TRACP-5b: 227 [171-506] to 353 [269-506] µmol/L and NTX: 12.7 [10.7-22.4] to 21.9 [16.9-26.6] mmol/Cr/L) were significantly decreased (p < 0.05) after teriparatide treatment. Mean BMD was significantly increased when compared to that of pretreatment value (0.65 [0.59-71] to 0.72 [0.65-0.84], p < 0.05).

Conclusion: It is suggested that the improvement of bone density by teriparatide might be explained not only by activation of bone formation but also by decreased bone resorption due to reduction of sRANKL in patients under glucocorticoid therapy.

Disclosure: M. Kaburaki, None; K. Kaneko, None; K. Shikano, None; M. Kawazoe, None; E. Shindo, None; H. Sato, None; N. Fujio, None; S. Murakatsu, None; N. Tanaka, None; T. Yamamoto, None; N. Kusunoki, None; T. Hasunuma, None; S. Kawai, None; S. Masuoka, None.

2260
Effects of Daily Teriparatide on the Spine and Femoral Stiffness Assessed By Finite Element Analysis of Clinical Computed Tomography in Rheumatoid Arthritis Patients. Kumiko Ono1, Satoru Ohishi2, Hiroyuki Oka3, Yuced Kadoho4, Tetsuro Yasui3, Tetsuro Yasui3, Naoko Shoda1 and Sakae Tanaka1. 1The University of Tokyo Hospital, Tokyo, Japan, 2Sagamihara Hospital, National Hospital Organization, Kanagawa, Japan, 322nd Century Medical & Research Center, faculty of medicine, the university of Tokyo, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) decreases bone mineral density and bone quality, and exposes patients to an increased risk of fracture. In RA treatment, improvement of systemic osteoporosis using anti-osteoporotic agents is important, as is suppression of fracture risk by controlling inflammation with a combination of disease-modifying anti-rheumatic drugs or biological agents. However, few studies have examined the effects of anti-osteoporosis drugs on patients with RA. Therefore, this study quantitatively evaluated the effects of daily teriparatide (TPTD) in RA patients at high risk of fracture over 6 months using several methods.

Methods: A total of 30 RA patients were enrolled in this prospective study. All patients receiving TPTD were evaluated according to changes in bone turnover markers from baseline to 1, 3, and 6 months. The markers used were serum procollagen type 1 N-terminal propeptide (P1NP) and...
Bisphosphonates are currently the drug of choice for treatment of osteoporosis. While anabolic agents like parathyroid hormone (PTH) have shown greater improvements in bone mineral density (BMD) in severe osteoporosis, their use is limited to a maximum of 2 years due to risk of osteosarcoma with rapid loss of gained BMD after cessation of treatment. Severe osteoporosis, their use is limited to a maximum of 2 years due to risk of osteosarcoma with rapid loss of gained BMD after cessation of treatment.

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**Methods:** We searched MEDLINE, the Cochrane Library, and ClinicalTrials.gov from inception to October 2013. We also reviewed reference lists of included studies and searched the abstracts of the last four years of relevant scientific meetings. We included randomized trials comparing combination therapy with bisphosphonate and PTH versus monotherapy with either agent in BMD in patients with osteoporosis.

**Results:** Of 332 studies identified, six met all inclusion criteria. Combination therapy led to small increases in % change in BMD at the total hip compared to PTH alone (WMD 0.38, 95% CI -1.41 to 2.18, I²=80%, 5 studies) and bisphosphonate alone (WMD 0.15, 95% CI -0.82 to 1.12, I²=38%, 5 studies). Similarly, combination therapy resulted in larger increases in % change in BMD at the spine compared to bisphosphonate alone (WMD 3.65, 95% CI 1.82 to 5.47, I²=67%, 5 studies), however PTH alone was superior to combination therapy at the lumbar spine (WMD −0.54, 95% CI −2.15 to 1.07, I²=46%, 5 studies). Based on 6 studies, there was a significant risk in developing hypercalcemia with combination therapy alone compared to monotherapy (11.83% vs. 7.04%, RR 1.68, 95% CI 1.18 to 2.41).

**Conclusion:** Combination therapy with PTH and bisphosphonates leads to greater improvements in BMD only at the lumbar spine compared to bisphosphonate therapy alone, however at the cost of increased risk of hypercalcemia.

**Disclosure:** Z. Kulcsar, None; L. Saleh, None; S. Gangidi, None; P. Khadka, None.

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**2262**

**Raloxifene for Osteoporosis in Postmenopausal Women with Rheumatic Diseases.** Won Seok Lee1, Y. Un Jung Choi2, Y. Un-Hong Cheon3, Myong-Joo Hong3, Chang-Hoon Lee4, Myeung Su Lee5, Sang-II Lee6 and Wan-Hee Yoo7. 1Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, 2Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, 3Department of Internal Medicine, Presbyterian Medical center, Jeonju, South Korea, 4Department of Internal Medicine, School of medicine, Wonkwang University, Iksan, Chonbuk, South Korea, 5Gyeongsang National University School of Medicine, Jinju, South Korea.

**Background/Purpose:** Raloxifene is a selective estrogen receptor modulator that has been extensively studied. We studied the efficacy of raloxifene on disease activity and bone mineral density (BMD) in postmenopausal women with rheumatic diseases receiving long-term glucocorticoids (GC).

**Methods:** Postmenopausal women with rheumatic diseases and osteoporosis were included. Patients with a history of thromboembolism or antiphospholipid antibody positivity were excluded. They were managed with raloxifene (60 mg/day) plus elemental calcium (1,200 mg/day). BMD of the hip and spine (primary outcome) was measured initially and at month 12, and disease activity (secondary outcome) was serially assessed using DAS28 and SELENA-SLEDAI.

**Results:** Between January 2010 and December 2013, 130 patients (86 assigned to receive GC and 44 patients not receiving GC, mean ± SD age 60.1 ± 9.0 vs. 59.3 ± 7.0 years) were recruited. 81 rheumatoid arthritis, 15 Sjogren’s syndrome, 11 scleroderma, 11 SLE patient’s disease, 7 lupus and 5 other rheumatic diseases were included. Demographic data, osteoporotic risk factors and BMD at various sites were similar between the two groups of patients. The duration and dose of prednisolone received was 72.5 ± 24 months and 3.3 ± 1.6 mg/day. At month 12, a significant gain in the lumbar spine (+3.9 ± 0.7%; p = 0.04 vs. +0.4 ± 0.1%; p=0.05) and total hip BMD (+1.1 ± 0.5%; p = 0.005 vs. 1.5 ± 0.7%; p > 0.05) was observed in patients receiving GC or not. However, femoral neck BMD was decreased in both groups. No patient had a major flare of lupus and rheumatoid arthritis. No fracture and thromboembolic events were reported.

**Conclusion:** Raloxifene was well tolerated in postmenopausal female patients with rheumatic diseases who had inactive disease and in whom hypercoagulability was not identified. Raloxifene increased total hip and lumbar spinal BMD in patients receiving corticosteroids or not.

**Disclosure:** W. S. Lee, None; Y. J. Choi, None; Y. H. Cheon, None; M. J. Hong, None; C. H. Lee, None; M. S. Lee, None; S. I. Lee, None; W. H. Yoo, None.
Continued Zoledronic Acid Use in a Large Healthcare System. Robert A. Overman1, Julie C. Lauffenburger1, Margaret L. Gourlay1 and Chad L. Deal1.

1University of North Carolina, Chapel Hill, NC, 2Cleveland Clinic, Cleveland, OH.

Background/Purpose: Oral bisphosphonates adherence has been reported as less than 50% at one year. With patients frequently having refill gaps greater than 30 days. Zoledronic acid (ZA) is a once yearly injectable bisphosphonate anti-osteoporosis medication (AOM) with 100% adherence for 12 months. We evaluated what proportion of patients who continued ZA after the first infusion and for those receiving a second dose how close to 365 days that dose was administered.

Methods: We identified new ZA users using billing data between January 1, 2010 and December 2012 from a large healthcare system based on healthcare procedure codes J3488 and Q2051, and linked to electronic medical record data. Included patients had at least two rheumatology office visits and first receipt of ZA was in or after 2010. We excluded patients who had received ZA before the study period but not other AOM. Results: are presented as mean (standard deviation [SD]) or %.

Results: There were 771 patients who met inclusion criteria. A second ZA infusion was given to 489 patients (63.4%) and 6.5% not continuing ZA were prescribed another AOM. Women (89.5%) and Caucasian (89.0%) race were the majority of the cohort with a mean age of 68.1 (10.9). The mean number of AOM used prior to ZA was 1.7 (1.3) with 18.7% not having an AOM prescribed within the health system. Previous fractures were present in 20.4%, mean Charlson Comorbidity score of 1.9 (2.5), and 29.7% had GERD or gastric ulcers at first ZA administration. Persistence of ZA is presented in Table 1. Of the 489 patients who received a second ZA infusion 307 (63%) were within 365 ± 30 days (a care gap of ≥30 days is defined as lack of persistence with oral agents). By 180 days 445/489 (91%) and 365 days 486 (99%) had received a second ZA infusion.

Conclusion: Although ZA adherence is by definition superior to oral BPs at one year, 36.6% of patients in our cohort did not receive a second infusion. Of those receiving a second infusion only 63% do so within the first 30 days although 99% had a second infusion at 365 days. Considering recent data suggesting that a single dose of ZA may reduce fracture for longer than one year, a gap of ≥30 days may be too strict a criterion for lack of persistence. ZA is approved for use at 24 month intervals for prevention. Since 36% of patient did not receive a second ZA dose, reasons for discontinuation and delay in a second infusion should be further investigated. Additionally, physician offices should have a method for scheduling yearly ZA infusions as a quality metric.

Table 1 Zoledronic Acid Treatment Gaps

<table>
<thead>
<tr>
<th>Treatment Gap</th>
<th>% Treated</th>
</tr>
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<tbody>
<tr>
<td>± 30 days</td>
<td>62.8%</td>
</tr>
<tr>
<td>+ 60 days</td>
<td>77.7%</td>
</tr>
<tr>
<td>+ 90 days</td>
<td>85.7%</td>
</tr>
<tr>
<td>+ 120 days</td>
<td>87.5%</td>
</tr>
<tr>
<td>+ 150 days</td>
<td>90.0%</td>
</tr>
<tr>
<td>+ 180 days</td>
<td>91.0%</td>
</tr>
<tr>
<td>+ 365 days</td>
<td>99.4%</td>
</tr>
</tbody>
</table>

ZA: Zoledronic Acid; 2nd ZA administration was assessed at 365 days after first administration.

Disclosure: R. A. Overman, None; J. C. Lauffenburger, None; M. L. Gourlay, None; C. L. Deal, None.

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Denosumab for Long-Term Glucocorticoid Users Who Have Inadequate Response to the Bisphosphonates: A 12-Month Randomized Control Trial. Chi Chiu Mok, Ling Yin Ho and Kwok Man Ma.

Background/Purpose: To evaluate the efficacy of denosumab on bone mineral density (BMD) in long-term glucocorticoid users who have inadequate response to oral bisphosphonate treatment.

Methods: Patients who were receiving long-term prednisolone treatment for their underlying medical illnesses were recruited. The inclusion criteria were: (1) Adult patients >= 18 years of age; (2) Daily dose of prednisolone >2.5mg within 3 months of study entry; (3) Inadequate BMD response (<2% increase in BMD or remaining osteoporotic) or the development of new fracture despite oral bisphosphonates for >=2 years. Participants were randomized to receive either: (1) Denosumab (60mg subcutaneously every 6 months) + discontinuation of bisphosphonates; or (2) Continuation of oral bisphosphonates (control group). Calcium (3g/day of caltrate), vitamin D (icaltrol 0.25ug/day) and other medications were continued. A baseline and follow-up BMD (femoral neck, femoral trochanter, total hip, lumbar spine and whole body) at 6 and 12 months were performed. Results: 42 women were recruited (age 54.7±12.9 years)- 21 shifted to denosumab and 21 continued on bisphosphonates. Underlying medical diseases were: SLE (76%) and RA (24%). The duration of prednisolone therapy was 101±66.3 months and the daily dose was 4.2±2.1mg. 30 (71%) patients were postmenopausal and the mean duration of menopause was 12.3±7.2 years. The mean body mass index (BMI) was 22.3±4.1kg/m² (21% patients had BMI≥30). The bisphosphonates being used by the patients were alendronate (79%), risedronate (12%) and ibandronate (10%). Pre-existing vertebral fracture was present in 7 (17%) patients and 3 patients (7%) had a family history of fragility fractures. Baseline demographic data, osteoporotic risk factors, and BMD at various sites were not significantly different between the two groups. At month 12, a significant gain in BMD at the lumbar spine (+3.4±0.9%; p=0.002) and the hip (+1.4±0.6%; p=0.03) was observed in denosumab-treated patients, whereas the corresponding change was +1.5±0.4% (p=0.001) and +0.8±0.5% (p=0.12) in the bisphosphonate group. The spinal BMD at month 12 was significantly higher in the denosumab than bisphosphonate group after adjustment for baseline BMD values, age and other parameters (p=0.03). No new fractures occurred in any participants at month 12. Minor upper respiratory tract infection was more commonly reported with denosumab treatment (33% vs 5%; p=0.045) while other adverse events occurred at similar frequency between the two groups. One patient from each group was withdrawn from the study because of non-compliance. None of the patients withdrew from study because of adverse events.

Disclosure: C. C. Mok, None; L. Y. Ho, None; K. M. Ma, None.

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Background/Purpose: Rheumatoid arthritis (RA) accelerates bone loss, increasing the risk of osteoporosis and osteoporotic fractures. We evaluated the effect of raloxifene and bisphosphonate on bone mineral density (BMD) and osteoporotic fractures in RA patients.

Methods: We retrospectively examined data of 112 seropositive RA patients who were diagnosed with osteoporosis and started on either raloxifene or bisphosphonate from January 2006 to December 2010 with no prior history of either medication. Patients with baseline BMD and at least one follow up BMD were included. The patients were examined for maximum of 3 years with a mean follow up period of 2.1 years. Bisphosphonates consisted of risendronate, alendronate or oral ibandronate. Vertebral fractures were defined using Genant’s semiquantitative classification.

Results: Forty-four patients were in the raloxifene group and 68 patients were in the bisphosphonate group. The patients in the raloxifene group were older and lighter in weight compared to the bisphosphonate group (Table 1). The patients in the bisphosphonate group consumed higher doses of calcium and vitamin D through medication compared to the raloxifene group. There was no significant difference in duration of RA, the daily dosage of prednisolone and medication possession ratio between the 2 groups. Thirty-six patients in the raloxifene group and 67 patients in the bisphosphonate group had follow up BMD at 1 year of treatment (Table 2). Nine patients in the raloxifene group and 40 patients in the bisphosphonate group had follow up BMD at 2 years of treatment. There was no significant difference in the yearly change of lumbar, total hip and femoral neck BMD from baseline and the number of vertebral fractures between the 2 groups at 1 year and at 2 years of treatment. Eighteen patients in the raloxifene group and 29 patients in the bisphosphonate group had follow up BMD at 3 years of treatment.
treatment. There was no significant difference in the mean change of lumbar and femoral neck BMD from baseline and the number of vertebral and non-vertebral fractures between the 2 groups at 3 years of treatment. However the mean change of total hip BMD was higher in the bisphosphonate group compared to the raloxifene group.

**Conclusion:** There was no significant difference in BMD changes and osteoporotic fractures in RA patients treated with raloxifene and bisphosphonate.

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Raloxifene (n = 46)</th>
<th>Bisphosphonate (n = 68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>45 (100)</td>
<td>48 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62 ± 9</td>
<td>68 ± 9</td>
<td>0.023</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.3 ± 13.3</td>
<td>55.8 ± 10.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>152.5 ± 7.2</td>
<td>157.9 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>1 (2)</td>
<td>11 (16)</td>
<td>0.026</td>
</tr>
<tr>
<td>Diabetic mellitus (%)</td>
<td>1 (2)</td>
<td>7 (10)</td>
<td>0.107</td>
</tr>
<tr>
<td>M-no. (%)</td>
<td>43 (98)</td>
<td>38 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatoid arthritis duration (mo)</td>
<td>70 ± 80</td>
<td>65 ± 57</td>
<td>0.666</td>
</tr>
<tr>
<td>Follow up duration (yr)</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>0.029</td>
</tr>
<tr>
<td>N -mote (no)</td>
<td>17 (39)</td>
<td>34 (65)</td>
<td>0.238</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1 (2)</td>
<td>5 (7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Selective serotonin nonpeptide inhibitors</td>
<td>0</td>
<td>0</td>
<td>0.896</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>2 (4)</td>
<td>3 (5)</td>
<td>0.973</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>253 ± 235</td>
<td>284 ± 89.2</td>
<td>0.012</td>
</tr>
<tr>
<td>Vitamin D (IU/day)</td>
<td>341 ± 310</td>
<td>535 ± 348</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**Methods:** A retrospective cohort study of 103 patients with RA and osteoporosis was conducted. Subjects were selected from patients who visited the Rheumatology Department of Chonnam National University Hospital between January 2002 and December 2012. All participants fulfilled the 1987 American College of Rheumatology revised criteria for RA and the World Health Organization criteria for osteoporosis. Baseline demographics, clinical characteristics, bone mineral density (BMD), laboratory results and treatment-related data were collected from the patients' charts retrospectively. Subjects were divided into two groups for comparison: those whose osteoporosis treatment was effective and those whose treatment failed. Risk factors for treatment failure were identified by univariate and multivariate logistic regression using variables that differed significantly between the groups.

**Results:** Osteoporosis treatment failed in 66 of 103 patients (64.1%). During 14.01 months of follow-up, non-adherence to bisphosphonate use (OR = 12.997; p = 0.003) was the most powerful risk factor for treatment failure. Daily glucocorticoid dosage ≥ 7.5 mg/day before the first BMD measurement (OR = 6.230; p = 0.015), immobilization > 3 months (OR = 4.773; p = 0.006), and DAS28 ≥ 3.2 (OR = 4.428; p = 0.009) were also significantly related to treatment failure.

**Disclosure:** Our findings indicate that osteoporosis treatment fails frequently in RA patients and adherence to bisphosphonate use, daily glucocorticoid dosage, immobilization, and DAS28 score should be taken into consideration when treating osteoporotic patients with RA.

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**Percentage of Women Achieving Non-Osteoporotic BMD T-Scores at the Spine and Hip over 8 Years of Denosumab Treatment.** S. Ferrari, C. Libardi, J.C.P. Lin, S. Adami, J.P. Brown, F. Cosman, E. Czerszynski, L.H. de Gregorio, J.M. Alouf, J.-Y. Reginster, N.S. Dazhade, A. Wang, R.B. Wagon, E.M. Lewiecki, M. Cummings. 1Geneva University Hospital, Geneva, Switzerland; 2Amgen Inc., Thousand Oaks, CA, 3University of Verona, Verona, Italy; 4Laval University and CHU de Quebec Research Centre, Quebec City, QC; 5Helen Hayes Hospital, West Haverstraw, NY; 6Krakow Medical Center, Krakow, Poland; 7CCBR, Rio de Janeiro, Brazil; 8Universitat Autonoma de Barcelona, Barcelona, Spain; 9University of Liège, Liège, Belgium; 10New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM; 11San Francisco Coordinating Center, CPMC Research Institute, and UCSF, San Francisco, CA.

**Background/Purpose:** Guidelines for the treatment of chronic conditions such as hypertension and diabetes include specific biomarker targets. This differs from osteoporosis treatment guidelines, which currently do not define treatment targets or goals. In general, absence of BMD loss and absence of fracture are considered treatment successes. This is far from ideal because success defined by the lack of a negative outcome does not set a real goal for therapy. Potential goals for osteoporosis treatment might include reaching a BMD T-score value somewhere above –2.5 which represents an acceptable level of fracture risk. To provide insight into T-score values achieved over time with denosumab (DMAB), we report on the percentage of women who achieved a range of possible target BMD T-scores at both the lumbar spine and total hip over 8 years of treatment.

**Methods:** For these analyses, women received 3 years of DMAB (60 mg subcutaneously every 6 months) during FREEDOM and 5 years of DMAB during the Extension for a total of 8 years of continued treatment. The percentage of women with T-scores > -2.5, > -2.2, > -2.0, and > -1.8 at both the lumbar spine and total hip, and T-scores > -2.5 at either the lumbar spine or total hip at baseline and over 8 years of DMAB treatment were determined. The influence of baseline T-score on subsequent T-score improvement was also explored.

**Results:** At FREEDOM baseline, mean (standard deviation) lumbar spine and total hip T-scores were −2.83 (0.67) and −1.85 (0.79), respectively, for the DMAB Extension participants (N = 2343). The percentage of women with T-scores > −2.5, > −2.2, > −2.0, and > −1.8 at both the lumbar spine and total hip progressively increased from baseline over 8 years of DMAB treatment as follows: 11% to 82% (> −2.5), 4% to 65% (> −2.2), 2% to 53% (> −2.0), and 1% to 39% (> −1.8) (Fig. 1). At individual sites, the percentage of women with a T-score > −2.5 increased from baseline over 8 years of DMAB treatment from 19% to 86% (lumbar spine) and from 75% to 94% (total hip). Baseline T-scores by quartile remained largely consistent throughout the 8 years of DMAB treatment, which showed similar trajectory in BMD across subjects regardless of initial BMD (not shown).

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**Risk Factors for Treatment Failure in Osteoporotic Patients with Rheumatoid Arthritis.** Kyung-Eun Lee, Lihui Wen, Dong-Jin Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea.

**Background/Purpose:** No available anti-osteoporotic medication has been shown to completely decline in bone mineral density (BMD) and the resulting increased risk of fracture. The objective of this study was to investigate the risk factors associated with treatment failure in osteoporotic patients with rheumatoid arthritis (RA).

**Disclosure:** K. J. None; L. W. None; D. J. None; S. S. L. None.
Conclusion: DMAb enables a substantial proportion of women with osteoporosis to achieve non-osteoporotic T-scores. The data reported here contribute insightful information to discussions on the topic of treatment goals for osteoporosis.

Discussion: S. Ferrari, Amgen Inc., MSD, 2; Amgen Inc., MSD, Lilly, GSK, Bioterca, 5; C. Libanati, Amgen Inc., 1, Amgen Inc., 3; C. J. F. Lin, Amgen Inc., 1, Amgen Inc., 2; Adam M. R. McClung, Amgen Inc., 1, Amgen Inc., 4; J. P. Brown, Amgen Inc., Eli Lilly, Merck, Novartis, 2; Actavis, Amgen Inc., E. Czerwinski, Amgen Inc., Pfizer, 2; Servier, Roche, Amgen Inc., 2; C. Libanati, Amgen Inc., 1, Amgen Inc., Pfizer, 2; Lilly, Merck, 2; Eli Lilly, 5; Eli Lilly, 8; F. Cosman, Amgen Inc., Lilly, Merck, 2; Amgen Inc., Lilly, Pfizer, 5; Lilly, Amgen Inc., 8; E. Czerwinski, Amgen Inc., Pfizer, 2; Servier, Roche, Amgen Inc., 2; L. H. de Gregorio, Amgen Inc., Merck, 2; J. Y. Reginster, Servier, Novartis, Ngma, Lyth, Amgen Inc., GlaxoSmithKline, Roche, Merck, Nycomed-Takeda, NPS, IBSA-Genoerier, Theramex, UCB, Asahi Kasei, 5; Bristol Myers Squibb, Merck Sharp & Dohme, Dohme Pharmaceuticals, Dohme Pharmaceuticals, 8; Teijin, Teva, Roche, Amgen Inc., Lilly, Novartis, GlaxoSmithKline, Amgen, Genoerier, Novartis, Novo Nordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, 9; S. Cummings, Amgen Inc., 1, Amgen Inc., 2; E. M. Lewiecki, Amgen Inc., Merck, Lilly, 2; Amgen Inc., Merck, 2; Amgen Inc., Merck, Lilly, 2; Radius Health, AgNovos, 5; S. Cummings, Amgen Inc., Merck, Lilly, 5.

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Results: A total of 16,713 participants were randomized at 387 centers in 40 countries, with 16,071 included in the analyses, and 642 excluded from all analyses due to study site closure (n = 483), duplicate randomization (n = 3), or failure to take any study drug (n = 156). At baseline, mean (SD) age was 72.8 (5.3) years, 57% were Caucasian, 46.3% had a VFa prior to study entry, and mean BMD T-scores were: lumbar spine = −2.7, TH = −2.7, and FN = −2.5. Both TTH and FN with hip fracture were estimated to provide statistical power. A prespecified interim analysis was performed when ~70% of targeted events had accrued. An external Data Monitoring Committee (DMC) reviewed these data and recommended that the base study be closed early due to robust efficacy and a favorable benefit-risk profile. The DMC noted that safety issues remained in certain selected areas. Both safety and efficacy continue to be monitored in the ongoing blinded extension trial. Data from an average follow-up of 40.8 months have been accrued from the base and extension studies, with 7,081 patients completing at least 4 years of follow-up. At the time this abstract was written, final data analyses were not complete.

Conclusion: The blinded, placebo-controlled base and extension study periods of LOFT will provide data on the efficacy of OND on fractures and BMD and general safety. A separate presentation will discuss in depth the safety profile for OND from this trial.

Disclosure: M. R. McClung, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Bristol-Myers Squibb, Corcept, Endo, Imagepace, Janssen, Lilly, Merck, Novartis, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, Novartis, 5; A. Santora, Merck, Allergan, Amgen, Eli-Lilly, Abiogen, Genentech, 5; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; A. Santora, Abbvie, Amgen Inc., Lilly, Merck, 2; N. Verbrugge, MSD Europe Inc., 3; A. M. Scott, Merck Sharp and Dohme Corp., 3; N. Verbrugge, MSD Europe Inc., 3; A. M. Scott, Merck Sharp and Dohme Corp., 3;
Efficacy and Safety of High Dose Infliximab in the Treatment of Uveitis in Pediatric Patients. Liza Mariel Bermudez1, Patricia Irigoyen2, Anca Askanase2, Michael Weiss2, Joyce Hui-Yuen2, Amy J. Starr2, Lisa F. Imundo3, Andrew H. Eichenfield4 and Josephine Isgrò1. 1Columbia University Medical Center, New York, NY, 2Pedi atric and Adult Rheumatology Columbia University Medical Center, New York, NY, 3Service College of Physician And Surgeons of Columbia University, New York, NY, 4Pedi atric and Adult Rheumatology Columbia University Medical Center, New York, NY.

Background/Purpose: Chronic uveitis, an inflammatory eye disease, is a leading cause of childhood blindness and often has a chronic recurrent course. This study reviews the efficacy and safety of high dose (>10–20 mg/kg) infliximab (IFX) in children with uveitis.

Methods: Retrospective chart review of 125 children and young adults with uveitis requiring systemic treatment. Data were collected on demographics, disease characteristics, infliximab dose, concomitant medications, treatment outcomes and side effects. Remission was defined as inactive eye disease ≥3 months after discontinuing all treatment; with ‘inactive disease’ was defined as grade 0 inflammatory cells. Descriptive statistics and Fisher’s exact test were employed.

Results: Of 125 patients with uveitis, 33 (26.4%) were treated with high-dose IFX (>10–20 mg/kg). An additional 19 patients received alternate TNF inhibitors (adalimumab 17/13.6%, etanercept 2 (1.6%). The median age at diagnosis was 10 years (IQR 2.22), 76 (61%) were female. The ethnic distribution was 78 (62%) Caucasian, 26 (21%) Hispanic, 4 (4%) African American, 3 (1%) Asian, and 14 (11%) not specified. Uveitis was associated with JIA (JIA-U) in 62 (50%); 56 (45%) oligoarthritis-JA, 4 (4%) poly-JA and 2 (2%) systemic-JA. Forty-nine (40%) patients had idiopathic uveitis; other causes included sarcoidosis 6 (5%), tuberculosis 1 (1%), Behcet’s 1 (1%), Vogt-Koyanagi-Harada 1 (1%). For the 33 patients on high-dose IFX, the median length of follow-up after initiation of treatment was 6 years, with a mean cumulative dose of 23 grams ± 16.7 (mean 7.2 mg/kg/dose ± 20.4). Fourteen were first started on methotrexate (MTX) and topical steroids (TS) with a median time to initiation of IFX of 17 months (IQR 7.26), 12 were started on MTX and IFX simultaneously, and 7 received IFX monotherapy. Twenty-one (64%) achieved inactive eye disease, while 12 (36%) who had persistently active disease. Of 73 patients treated with MTX/TS alone, 23 (32%) had inactive disease while 50 (68%) were active at last visit, showing increased inflammatory ophthalmic disease in patients not on IFX (p=0.0013). This difference was maintained when comparing all 52 patients on TNF inhibitors to those on MTX alone. 33 (63%) of patients on TNF inhibitors had inactive disease compared to 23 (32%) on MTX (p=0.0005).

Ophthalmologic complications of uveitis included band keratopathy in 13 (10%), cataracts in 9 (7%), posterior synechiae in 8 (6%), and glaucoma in 4 (3%). The majority of complications were seen prior to starting IFX. No significant differences were seen between patients on IFX and those on MTX.

No malignancies or serious infections requiring hospitalization were seen in these patients. One patient on adalimumab developed dilated cardiomyopathy and 1 herpes zoster. At the end of study, 28 (85%) patients remain on IFX and 3 on adalimumab, 1 on etanercept and 1 on leflunomide/rituximab.

Conclusion: This is the largest study assessing the efficacy and safety of high-dose infliximab in the treatment of pediatric uveitis. Our data demonstrate favorable outcomes in patients on IFX, with 64% achieving inactive disease vs 32% on MTX. Extended use of high-dose infliximab did not appear to be associated with increased risk of serious infection or malignancy.

Disclosure: L. M. Bermudez, None; P. Irigoyen, None; A. Askanase, None; M. Weiss, None; J. Hui-Yuen, None; A. J. Starr, None; L. F. Imundo, None; A. H. Eichenfield, None; J. Isgrò, None.
**Symptom and Treatment Characteristics of Juvenile Primary Fibromyalgia Syndrome: Are Males and Females Created Equal? Jennifer E. Weiss, Kenneth N. Schikler, Alexis Boneparth, Cara Hoffart, Mark Connolly and The CARRA Registry Investigators.**

**Background/Purpose:** Children and adolescents with persistent widespread musculoskeletal pain frequently present to pediatric rheumatologists for evaluation. Limited data are available on the characteristics and treatments used for these patients, particularly for males. Using the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, we sought to evaluate the overall demographic, symptom, and treatment characteristics of patients diagnosed with juvenile primary fibromyalgia syndrome (JPS) and to compare these characteristics as a function of gender.

**Methods:** Deidentified data on demographics, symptoms, functional measures and treatment characteristics were extracted from the baseline visits of JPS patients in the CARRA registry between May 2010 and May 2014.

**Results:** There were 181 patients (28 males), ages 8–21 years (M = 15.4, SD = 2.3) included. Patients were symptomatic for a mean of 1.7 years prior to their first visit to a pediatric rheumatologist, with no significant difference between males and females (M = 2.1 versus 1.6 respectively, t(173) = 1.06, p = .29). The most commonly reported symptoms at baseline included widespread pain (91%), fatigue (84%), disordered sleep (82%), headaches (68%), and extremity numbness/tingling (32%). Females were more likely to report numbness/tingling (36% versus 13% respectively, χ² = 5.09, p = 0.02). Table 1 lists treatments tried and recommended. Males were significantly more likely to have used gabapentin (25% versus 8%, χ² = 7.41, p < 0.01). Of the 64 patients using non-pharmacologic treatment, the most commonly used treatment was physical therapy (59%), with females significantly more likely to have used massage and yoga (Table 1). Less than 10% of patients tried opioids, serotonin norepinephrine reuptake inhibitors, craniosacral therapy, hypnosis, and biofeedback.

**Mean pain scores at baseline were moderate to severe (6.3/10) and were significantly positively related to CHAQ functional impairment scores (r = 35, p < 0.01), patient ratings of impairments in health-related quality of life (HRQOL) (r = .42, p < 0.01), and patient ratings of impairments in overall well-being (r = .64, p < 0.001). Males were found to be reliably more disabled based on subjective (patient/parent report) functioning measures (HRQOL and CHAQ), although no differences were observed on physician report measures (physician global assessment and ACR functional class).

**Table 1.** Treatments tried and recommended for JPS patients (N = 181)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Females (N = 154)</th>
<th>Males (N = 27)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical treatments tried (N = 117)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily non-steroidal anti-inflammatory drugs</td>
<td>42%</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>29%</td>
<td>14%</td>
<td>26%</td>
</tr>
<tr>
<td>Tri-cyclic antidepressants</td>
<td>27%</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>12%</td>
<td>33%*</td>
<td>16%</td>
</tr>
<tr>
<td>Non-pharmacological treatments tried (N = 64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical therapy</td>
<td>59%</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>Dietary supplements</td>
<td>12%</td>
<td>46%</td>
<td>27%</td>
</tr>
<tr>
<td>Therapeutic massage</td>
<td>29%*</td>
<td>8%</td>
<td>25%</td>
</tr>
<tr>
<td>Mindfulness/meditation</td>
<td>18%</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Cognition</td>
<td>18%</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Acutaneous/ulcer pressure</td>
<td>16%</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Yoga</td>
<td>14%*</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Treatments recommended/started at baseline visit (N = 181)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain education</td>
<td>92%</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>Graded aerobic activity</td>
<td>78%</td>
<td>67%</td>
<td>76%</td>
</tr>
<tr>
<td>Sleep hygiene</td>
<td>72%</td>
<td>57%</td>
<td>70%</td>
</tr>
</tbody>
</table>

**Conclusion:** Based on data from the largest known cohort of JPS patients, there appear to be few significant gender differences in disease characteristics and treatment. However, higher levels of disability are reported by male patients despite no comparable differences observed on physician severity measures, suggesting the need to consider gender on evaluation and treatment of JPS.

**Disclosure:** J. E. Weiss, None; K. N. Schikler, None; A. Boneparth, None; C. Hoffart, None; M. Connolly, None; T. CARRA Registry Investigators, None.

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**Assessment of Transition Readiness in Adolescents and Young Adults with Rheumatic and Other Chronic Health Conditions. Gabrielle Paul, Stephanie LaCount, Charles H. Spencer, Gloria C. Higgins, Karla Jones, Brendan Boyle, Manmohan K. Kambaj, Christopher Smallwood and Stacy P. Ardoin.**

**Background/Purpose:** The transition from pediatric to adult care is a vulnerable period. The lack of objective measures of transition readiness is a barrier to improving care. The Transition Readiness Assessment Questionnaire (TRAQ) is a disease-neutral, patient-reported tool with 33 questions across 2 domains (self-management and self-advocacy). Items are scored on a 1 to 5 ordinal scale representing stages of change model (precontemplation, contemplation, preparation, action and maintenance). The TRAQ has not previously been assessed in adolescents and children with rheumatic or gastrointestinal (GI) conditions.

**Methods:** 89 adolescents and young adults (16 – 25 years) with chronic rheumatic, endocrine or GI conditions at a single pediatric center were enrolled. Participants completed surveys including demographics, transition experience, TRAQ. Clinical information was obtained via chart review. Data were analyzed with descriptive statistics. Mean TRAQ scores were compared across specialty and age groups using one way ANOVA.

**Results:** The 89 participants were 65% female, 18.3 years, 72% Caucasian, 86% non-Hispanic and had rheumatic (54%), GI (21%) or endocrine (23%) conditions (Table 1). The 30 participants with rheumatic diseases had JIA/RA (25), SLE or MCTD (13), vasculitis (2) or other disease (6). Only 40% of participants reported discussing with current provider seeing an adult subspecialist provider in the future. Participants reported seeing subspecialist independently for part of visit never (31%), rarely (15%), sometimes (20%), often (24%) or always (8%). TRAQ self-management and advocacy scores did not differ significantly by specialty but the TRAQ self-advocacy score increased with age (Tables 2 and 3).

**Conclusion:** Despite guidelines that transition processes begin at age 14, fewer than half of these 16-25 year olds reported ever discussing future transition to adult providers and almost 1/3 had never seen provider independently for portion of clinic visit. Mean TRAQ scores for this group represented the preparation stage of change. The TRAQ is a promising tool for measuring transition readiness and can be used clinically and to assess intervention efficacy. These results underscore the need for improved transition processes for adolescents and young adults with chronic disease.

**Table 1: Transition Readiness Assessment: Participant Characteristics**

<table>
<thead>
<tr>
<th>Age, mean ± SD years</th>
<th>18.2 ± 1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%) female</td>
<td>58 (65)</td>
</tr>
<tr>
<td>Race, n (%) white</td>
<td>72 (81)</td>
</tr>
<tr>
<td>Ethnicity, n (%) Hispanic, Latino</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Current education status</td>
<td></td>
</tr>
<tr>
<td>Currently in school, n (%)</td>
<td>72 (82)</td>
</tr>
<tr>
<td>9th to 12th grade, n (%)</td>
<td>46 (52)</td>
</tr>
<tr>
<td>College/Technical School, n (%)</td>
<td>42 (47)</td>
</tr>
<tr>
<td>Highest Parental Education, n (%)</td>
<td></td>
</tr>
<tr>
<td>Some high school</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
Graduated high school 20 (22)
Some college/technical school 27 (30)
Graduated college/technical school 28 (31)
Graduate degree 9 (10)
Unknown or not reported 2 (2)
Annual household income, no. (%)<25,000 11 (12)
25,000 to 49,999 16 (18)
50,000 to 74,999 13 (15)
75,000 to 99,999 6 (7)
100,000 to 150,000 8 (9)
$150,000 7 (8)
Not reported/unknown 28 (31)
Employment
Not employed, no. (%) 47 (53)
Part time, no. (%) 36 (40)
Full time, no. (%) 6 (7)
Single, no. (%) 86 (97)
Insurance status
Parental private insurance, no. (%) 58 (65)
Personal private insurance, no. (%) 0
Public insurance, no. (%) 28 (33)
Other/Unknown, no. (%) 3 (3)
Health condition, no. (%)
Rheumatic 49 (56)
Endocrine 20 (22)
Gastroenterologic 19 (21)
Neurologic 15 (17)
Rheumatic 49 (56)
Duration of disease, mean ± SD
16 to 18 years (n=51) 3.10 ± 1.68
19 to 20 years (n=28) 3.38 ± 1.71
21+ years (n=4) 3.18 ± 1.65
F value
1.54 ± 0.52
P value
0.22
Table 2: Transition Readiness Assessment Questionnaire Scores by Specialty

Self-Management TRAQ Domain 1, mean ± SD
3.18 ± 1.70
3.14 ± 1.67
3.17 ± 1.72
0.09 ± 0.02
Self-Advocacy TRAQ Domain 2, mean ± SD
3.78 ± 1.56
3.97 ± 1.46
3.63 ± 1.61
1.32 ± 0.27

Table 3: Transition Readiness Assessment Questionnaire Scores by Age

Table 4: Transition Readiness Assessment Questionnaire Scores by Age

Table 5: Transition Readiness Assessment Questionnaire Scores by Age
patients who had started biologic therapy without uveitis kept uveitis free by the age of 14.6 or 15.3 years old at their last visit.

**Conclusion:** TNF inhibitors appear to be more effective than IL-6 inhibitor in the treatment of EOS, and may have a potential to prevent the onset of uveitis.

**Results**

A total of 82 children were recruited into the study. The median age was 11.7 years. The most common diagnoses were juvenile idiopathic arthritis (65%), systemic lupus erythematosus (9%), and juvenile dermatomyositis (5%). Fifty eight (71%) children were considered immunosuppressed.

**Vaccination database:** Patients received most recommended vaccines, with the exception of the Influenza (2013/2014) and Hepatitis B vaccines (recommended for age of 10 [grade 5] in Canada). Influenza was missed 40% of the time in the 1–3 years old group, 18% of the time in the 4–9 years old group, and 27% of the time in the 10–17 years old group. Hepatitis B was missed at a rate of 4% in the 10–17 years old group.

**Parent/parent questionnaire:** Nine patients reported previous adverse reactions to vaccination (Influenza [5], Mumps, Measles, and Rubella [M MR] [2], Hepatitis B [2] and Varicella [2]). In 38% at least one vaccination was withheld, most commonly for active disease (26%), recommendation against receiving vaccinations by health care provider (23%), uncertainty about whether or not a vaccine should be given (19%), concerns about disease flare (13%) and/or side effects post vaccination (5%). Several sources of information were utilized by patients and families for vaccination information, and satisfaction with this information was fairly high. Patients and parents identified the following information gaps: 1) risks and contraindications of vaccinations in childhood rheumatic diseases, 2) age-appropriate vaccination schedules and modalities, 3) best practice of vaccination documentation. Vaccination reminders were identified as useful, with several comments indicating that e-mail alerts, reminders, and a method to track this information would be useful.

**Conclusion:** The majority of children with rheumatic illnesses received the recommended vaccines. Immunization gaps were identified for Influenza and Hepatitis B. Knowledge regarding contraindications to vaccination is good. Concerns about perceived safety limit vaccination completeness.

**Immunization Status and Barriers in Childhood Rheumatic Diseases.**

**Disclosure:** S. Vazhappilly, None; O. Vanderkooi, None; S. Benseler, None; T. Gerschman, None; N. Johnson, None; N. Luca, None; P. Miettunen, None; D. Veeramreddy, None; H. Schmeling, None.

**Consensus Statement on the Transition Process from Pediatric Rheumatic Care to Adult Care in Patients with Chronic Inflammatory Rheumatic Diseases with Childhood-Onset.**

**Disclosure:** S. Vazhappilly, None; O. Vanderkooi, None; S. Benseler, None; T. Gerschman, None; N. Johnson, None; N. Luca, None; P. Miettunen, None; D. Veeramreddy, None; H. Schmeling, None.
discussed and to help define recommendations. A first draft of recommendations was generated and circulated for comments and wording refinements. Focal groups with adolescents, young adults and parents were separately. In a 2nd panel meeting the focus group results along with the input from invited psychologist was used to establish definitive recommendations. Then, a Delphi process (2 rounds) was carried out. A large group of 70 pediatricians and rheumatologists took part. Recommendations were voted from 1 (total disagreement) to 10 (total agreement). We defined agreement if at least 70% voted ≥7. The level of evidence and grade of recommendation was assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence.

**Results:** transition care was defined as a purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic inflammatory rheumatic diseases with childhood-onset as they move from child-centred to adult-oriented health care systems. The consensus covers: transition needs, barriers and facilitators, transitional issues (objectives, participants, content, phases, timing, plans, documentation, and responsibilities), physicians and other health professionals, knowledge and skills requirements, models/programs, strategies and guideline for implementation. Preliminary recommendations and agreement grade are shown in the table (1st Delphi round).

**Conclusion:** these recommendations are intended to provide pediatricians, rheumatologists, patients, families and other stakeholders with a consensus on the transition process from pediatric care to adult care in patients with chronic inflammatory rheumatic diseases with childhood-onset.

### RECOMMENDATIONS

<table>
<thead>
<tr>
<th>#</th>
<th>Recommendations</th>
<th>% ≥7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transition in pediatric rheumatology should be considered as a continuous, natural and flexible process</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>To standardize, plan ahead, and to define specific protocols related to transitional care</td>
<td>94%</td>
</tr>
<tr>
<td>3</td>
<td>To promote outpatient care during transition</td>
<td>47%</td>
</tr>
<tr>
<td>4</td>
<td>To endorse specialized nursing care during transition</td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td>During transitional care, health professionals should convey to patients and parents normality, optimism, sincerity, and should listen to and dialog with them efficiently</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>To support and reinforce patients autonomy and participation adapted to the age/maturity of them during transition</td>
<td>99%</td>
</tr>
<tr>
<td>7</td>
<td>To facilitate (evidence based) useful written information (electronic, paper) about disease most relevant issues, management and other aspects for patients and parents</td>
<td>91%</td>
</tr>
<tr>
<td>8</td>
<td>To actively involve patients and parents in all of the processes of the transitional care</td>
<td>94%</td>
</tr>
<tr>
<td>9</td>
<td>To inform patients and parents about the disease and transitional processes including adult care</td>
<td>99%</td>
</tr>
<tr>
<td>10</td>
<td>To monitor adherence (to treatments, visits, etc)</td>
<td>90%</td>
</tr>
<tr>
<td>11</td>
<td>To endurance effective communication, collaboration and coordination, among all health professionals involved in the transitional care</td>
<td>78%</td>
</tr>
<tr>
<td>12</td>
<td>To endurance effective communication, collaboration and coordination, between health professionals involved in the transitional care and patients educators</td>
<td>64%</td>
</tr>
<tr>
<td>13</td>
<td>To develop clinical sessions between pediatric rheumatologists and adult rheumatologists and with other specialists involved in transitional care</td>
<td>90%</td>
</tr>
<tr>
<td>14</td>
<td>Adaptations to patients academic needs should be considered</td>
<td>34%</td>
</tr>
<tr>
<td>15</td>
<td>A specific training on transitional care as a part of the pediatric training</td>
<td>58%</td>
</tr>
<tr>
<td>16</td>
<td>To promote multidisciplinary care by implementing a transitional care model based on each center characteristics, resources and needs</td>
<td>97%</td>
</tr>
<tr>
<td>17</td>
<td>The implementation of a transitional care model should be planned carefully as well as the strategies to assure the implementation</td>
<td>94%</td>
</tr>
<tr>
<td>18</td>
<td>When transferring a patient to the adult care, a full report on the disease course, impact, treatments, and other relevant aspects should be delivered</td>
<td>100%</td>
</tr>
<tr>
<td>19</td>
<td>To set up reference units of transitional care</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Disclosure:** M. I. Calvo-Penedes, Abbvie Spain S.L.U., 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Bristol-Myers Squibb, 2, Novartis Pharmaceutical Corporation, 2; J. A. Lopez, Abbvie, Novartis, Pfizer, 2, Novartis Pharmaceutical Corporation, 2; A. Abbie, Novartis, Pfizer, Roche, Sobi, 8; B. Buschedad-Reyes, None; M. Camacho, None; J. De Incoceno, Gebro, 2, Bristol-Myers Squibb, 8; A. Abbie, 8, Pfizer Inc, 8; M. L. Gamir Gamir, None; G. Graña, None; L. La Cruz, None; J. C. López-Rubidilla, None; M. Medrano, None; R. Merino, None; C. Medesto, None; E. Nuñez, None; M. J. Rua Elorduy, None; V. Torrente, None; C. Vargas-Lebrón, Roche Pharmaceuticals, 2, Pfizer Inc, 8; A. Abbie, 8; E. Loza, Roche Pharmaceuticals, 2, Merck Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2, Pfizer Inc, 2.
Association vasculitis (AAV) in the adult population, predominantly in granulomatosis with polyangiitis (GPA) with less frequency in Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA). There are several cases in the literature of pediatric patients with GPA presenting with orbital pseudotumor, however to our knowledge there are no published cases of this type of presentation in childhood CSS or MPA.

**Methods:** During the period between 2009 and 2014 three cases of orbital pseudotumor were diagnosed in our Pediatric Rheumatology Division. A thorough chart review was conducted on these patients regarding clinical presentation, laboratory data, imaging studies and pathology. A literature review was then conducted in PubMed looking for individual reports of pediatric ANCA-associated vasculitis, as well as previously reported cases of GPA.

**Results:** Four reports in PubMed were published regarding orbital pseudotumor and ANCA-associated vasculitis in pediatrics. Within these studies there were 15 cases of pediatric AAV presenting as orbital pseudotumor, all of which were limited to GPA. There was no published evidence of this initial presentation in either CSS or MPA in the pediatric population. The characteristics of our patients are listed below:

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Serology</th>
<th>Diagnosis</th>
<th>Disease Course</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>Female</td>
<td>p-ANCA</td>
<td>CSS</td>
<td>Biopsy of orbit</td>
<td>Steroids</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Female</td>
<td>MPO</td>
<td>CSS</td>
<td>Biopsy of orbit</td>
<td>Steroids</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Female</td>
<td>p-ANCA</td>
<td>CSS</td>
<td>Biopsy of orbit</td>
<td>Steroids</td>
<td>Remission</td>
</tr>
</tbody>
</table>

**MRI Brain Orbit** of one patient revealing an enhancing mass within the superolateral post-septal soft tissues of the right orbit, as well as signal abnormality along the pre-septal soft tissues involving the superior eyelid.

**Conclusion:** When pediatric patients present with orbital pseudotumor the differential should be widened regarding types of ANCA-associated vasculitides to include CSS and MPA. Recognizing these possibilities would allow for early screening and monitoring for potential multi-organ involvement.

**Disclosure:** A. Schiefler, None; M. Lettner, None; A. C. Brescia, None; C. D. Rose, None.

2279 Evidence Based Recommendations for Diagnosis and Management of Tumor Necrosis Factor Receptor-1 Associated Periodic Syndrome (TRAPS) Nienke ter Haar, Paul Brogan, Gilles Grateau, Jordi Aighton, Karel J. Carmans, Stefan Jost, Frank Kuemmerle-Deschner, Caroline Galeotti, Véronique Hentgen, Michael Hoffer, Tilman Kallinich, Isabelle Kone-Paut, Jasmin Kuijper-Kuiper, Huri Ozdogan, Seza Ozen, Ricardo Russo, Anna Simon, Yosef Uziel, Carine Wouters, Brian Feldman, Bas Vastert, Nico Wulffraat, Helen Lachmann and Marco Gattorno.

**Background/Purpose:** Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) is a rare hereditary autoinflammatory syndrome that can lead to significant morbidity. Evidence-based guidelines are lacking and management is mostly based on physician’s experience. Consequently, treatment regimens differ throughout Europe. A European initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for diagnosis and treatment of TRAPS.

**Methods:** Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric and adult rheumatologists. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement on the online survey or with relevant comments of the experts were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

**Results:** The literature search yielded 523 articles, of which 22 were considered relevant and therefore scored for validity and level of evidence. Eighteen were scored valid and used in the formulation of the recommendations. Seventeen recommendations were suggested in the online survey and discussed during the consensus meeting. Five general recommendations on management, two recommendations for diagnosis, seven for monitoring and eight for treatment were accepted with more than 80% agreement. Topics covered are the following:

- general recommendations: use of the multidisciplinary team, treatment goals and vaccinations
- diagnosis: TNFRSF1A screening, interpretation of R92Q and P46L variants
- monitoring: monitoring frequency and minimal assessments in TRAPS patients, the use of AIDAI score in clinical studies and risk assessment of amyloidosis

Evidence based recommendations were developed using the SHARE initiative provides recommendations for diagnosis and treatment for TRAPS and thereby facilitates improvement and uniformity of care throughout Europe.

Disclosure N. ter Haar, None; P. Brogan, Novartis, Roche, 2; Novartis Pharmaceutical Corporation, 5; G. Grateau, None; J. Antón, None; K. Barron, None; L. Cantarini, Novartis Pharma AG, SOBI, 2, Novartis Pharma AG, SOBI, 5, J. Frenkel, European Union ERA-NET, 2, Novartis Pharmaceutical Corporation, 5, SOBI, 8, C. Galeotti, Novartis Pharmaceutical Corporation, 2; V. Hentgen, Novartis Pharmaceutical Corporation, 5, Novartis, Pfizer, Roche, 9, M. Hofer, None; T. Kallinich, Novartis, SOBI, 8, Novartis Pharmaceutical Corporation, 2; I. Kone-Paut, None; J. Kuenemeren-Deschner, Novartis Pharmaceutical Corporation, 2, SOBI, 8; O. Ozdogan, None; S. Ozen, None; R. Russo, None; A. Simon, Sevier, 2, Novartis, SOBI, Xoma, 5, Y. Uziel, Novartis Pharmaceutical Corporation, 2, Abbvie, Abbvie, Pfizer, Roche, 2, Novartis Pharmaceutical Corporation, S. Abbvie, Novartis, Pfizer, Roche, 8, B. Feldman, None; B. Vaster, None; N. Wulfraat, None; H. Lachmann, None; M. Gattorno, None.

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Evidence based recommendations were developed using the SHARE initiative provides recommendations for diagnosis and treatment for TRAPS and thereby facilitates improvement and uniformity of care throughout Europe.

Disclosure N. ter Haar, None; P. Brogan, Novartis, Roche, 2; Novartis Pharmaceutical Corporation, 5; G. Grateau, None; J. Antón, None; K. Barron, None; L. Cantarini, Novartis Pharma AG, SOBI, 2, Novartis Pharma AG, SOBI, 5, J. Frenkel, European Union ERA-NET, 2, Novartis Pharmaceutical Corporation, 5, SOBI, 8, C. Galeotti, Novartis Pharmaceutical Corporation, 2; V. Hentgen, Novartis Pharmaceutical Corporation, 5, Novartis, Pfizer, Roche, 9, M. Hofer, None; T. Kallinich, Novartis, SOBI, 8, Novartis Pharmaceutical Corporation, 2; I. Kone-Paut, None; J. Kuenemeren-Deschner, Novartis Pharmaceutical Corporation, 2, SOBI, 8; O. Ozdogan, None; S. Ozen, None; R. Russo, None; A. Simon, Sevier, 2, Novartis, SOBI, Xoma, 5, Y. Uziel, Novartis Pharmaceutical Corporation, 2, Abbvie, Abbvie, Pfizer, Roche, 8, B. Feldman, None; B. Vaster, None; N. Wulfraat, None; H. Lachmann, None; M. Gattorno, None.

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Dissecting the Heterogeneity of Macrophage Activation Syndrome. Francesca Minio1, Sergio Davi2, AnnaCarin Homer2, Francesca Bovis3, ErkanDemirkaya4, AlessandroConsolaro5, JonathanAkiyusa4, Nury AhtayAya4, PatriziaBarone6, BiancaBica6, IsabelBoit6, LucianaBreda6, ZaneDavidson6, CarmenDe Cunto6, JaimeDe Incoccio6, SandraEnciso6, RominaGallizzi7, ThomasGriffin8, TeresaHennon9, GordHorneff9, MakaIoseliani19, MichaelJeng16, AgnezaMariaKapovic21, BiancaLatanzi1, JeffreyMLipton2, SilviaMagni-Mamonti23, ClarissaNassaf22, IngridaRumba-Rozenfeld23, ClaudiaSaad-Maghãhães24, SulaimanAlmayouth25, WafaAl-Suwairi26, KimoCStine29, OlgaVougiouka30, LehnK. Weaver31, NicolinaRuperto2, AlbertoMartin32, RandyQ. Cron32 and AngeloRavelli32.

Background/Purpose: The SHARE initiative provides recommendations for the management of CAPS and thereby facilitates improvement and uniformity of care throughout Europe.

Disclosure N. ter Haar, None; P. Brogan, Novartis, Roche, 2; Novartis Pharmaceutical Corporation, 5; G. Grateau, None; J. Antón, None; K. Barron, None; L. Cantarini, Novartis Pharma AG, SOBI, 2, Novartis Pharma AG, SOBI, 5, M. Gattorno, None; M. Hofer, None; I. Kone-Paut, None; J. A. Lopez, Abbvie, Abbvie, Pfizer, Roche, 2; Novartis Pharmaceutical Corporation, 5, Abbvie, Novartis, Pfizer, Roche, 8, B. Feldman, None; B. Vaster, None; N. Wulfraat, Abbvie, GSK, Roche, 2, Genzyme, Novartis, Pfizer, Roche, 5; S. Benseler, None; J. Kuenemeren-Deschner, Novartis Pharmaceutical Corporation, 2, SOBI, 8.
Evidence Based Recommendations for Diagnosis and Management of Muckle-Wells Syndrome (MKS). Nienke ter Haar1, Jerold Jeyaratnam2, Jordi Anton3, Caroline Galett4, Karyl Barron5, Paul Brogan6, Luca Cantarini7, Marco Gattorno8, Gilles Grateau9, Veronique Hentgen10, Michael Hofer11, Tilman Kallinich12, Isabelle Kone-Paut13, Jasmin Kjemmerle-Deschner14, Helen Lachmann15, Hui Ozdogan16, Seza Ozen17, Ricardo Russo18, Yosef Uziel19, Caroline Wouters20, Brian Feldman21, Bas Vastert22, Nico van der Heijden23, and Leo Forestilk†1. 1University Medical Center Utrecht, Utrecht, Netherlands; 2Pediatric Rheumatology Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; 3Bichêre Hospital, University of Paris SUD, Paris, France; 4NIH, Bethesda, MD, 5Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; 6University of Siena, Siena, Italy; 7Istituto Giannina Gaslini, Genova, Italy; 8Hospital Tenon, Paris, France; 9Versailles Hospital, Le Chesnay Cedex, France; 10Centre Multisite Romand de Rhumatologie Pédiatrique, Lausanne, Switzerland; 11Charité, University Medicine Berlin, Berlin, Germany; 12University Hospital Tübingen, Tübingen, Germany; 13University College London Medical School, London, United Kingdom; 14Cerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey; 15Department of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey; 16Hospital De Pediatría, Buenos Aires, Argentina; 17Tel Aviv University, Sackler School of Medicine, Tel Aviv, Israel; 18University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium; 19The Hospital for Sick Children, Toronto, ON, Canada; 20Wilhelmina Children’s Hospital and UMC Utrecht, Utrecht, Netherlands; 21Erasmus MC, Nijmegen, Netherlands.

Background/Purpose: Muckle-Wells Syndrome (MKS) is a rare hereditary autoinflammatory syndrome that can lead to significant morbidity. Evidence-based guidelines are lacking and management is mostly based on physician’s experience. Consequently, treatment regimens differ throughout Europe. In 2012, an European initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for diagnosis and treatment of MKS.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric and adult rheumatologists. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement on the online survey or with relevant comments of the experts were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 618 articles, of which 28 were considered relevant and therefore scored for validity and level of evidence. Fourteen were scored valid and used in the formulation of the recommendations. Sixteen recommendations were suggested in the online survey and discussed during the consensus meeting. Six general recommendations on management, three recommendations for diagnosis, six for monitoring and seven for treatment were accepted with more than 80% agreement. Topics covered are follow:

- general recommendations: the use of the multidisciplinary team, treatment goals, and vaccinations
- diagnosis: diagnostic value of Gaslini diagnostic score, IgD and urinary mevalonic acid excretion
- monitoring: the use of AIDAI in clinical studies, monitor frequency, minimal assessments in all MKD and additional monitoring in severe MKD patients, risk of infection and macrophage activation syndrome
- treatment: NSAIDs, glucocorticoids, IL-1 blockade, etanercept, switching biologicals, colchicine, statins and hematopoietic stem cell transplantation

Conclusion: The SHARE initiative provides recommendations for diagnosis and treatment for MKS and thereby facilitates improvement and uniformity of care throughout Europe.

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Background/Purpose: Cryopyrin-Associated Periodic Syndromes (CAPS) include a group of rare inherited autoinflammatory diseases consisting of FCAS, Muckle-Wells Syndrome and the most severe form, NOMID. Reduction in the use of steroids as concomitant medication is a treatment goal for anakinra-treated CAPS patients, since inappropriate use of steroids could lead to increased toxicity. Averse events (AEs) related to the cardiovascular system are along with infections most frequently reported in steroid-treated patients with rheumatic diseases (Hoes et al Am Rheum Di's. 2007;66:1560–67). A mong 16 patients with severe CAPS treated with anakinra and taking steroids at baseline, the mean daily prednisone-equivalent dosage has been reported to decrease from 0.80 mg/kg/day to 0.52 mg/kg/day after 6 months (Sibley et al. Arthritis Rheum. 2012;64:2375–86). The objective of the present analysis is to further evaluate the steroid-sparing potential and its consequences in an expanded cohort of patients with severe CAPS treated with anakinra.

Methods: A prospective, open-label withdrawal design study of anakinra treatment with long-term extension including 43 patients was conducted at the National Institutes of Health (Goldbach-Mansky et al NEJM 2006;355:581–92). The primary efficacy endpoint, Diary Symptom Sum Score (DSSS), collected daily up to 60 months, included 5 symptoms (fever, rash, joint pain, vomiting, headache); each scored from 0 (no symptoms) to 4 (severe symptoms). Use of steroid medication was obtained from the patient diary.
The prednisone dose was to be decreased by 20% at each study visit in which the subject’s disease activity was “moderately” or “significantly” improved. Different types of steroids were converted into prednisone-equivalent doses to enable comparisons. The AEs were analyzed with the infection rate (number of infections per patient years of treatment).

**Results:** During the study, the proportion of patients in the ITT population on steroids decreased from 47.1% at baseline to 33.3% at Month 60. Among the patients using steroids at baseline the mean (SEM) prednisone-equivalent dose was 0.76 (0.31) mg/kg at baseline, but a prompt tapering of their doses during the first 6 months to 0.15 (0.05) mg/kg was seen. At Month 36 and Month 60 respectively, a further decline in the prednisone-equivalent dose to 0.08 (0.02) and 0.05 (0.02) mg/kg, respectively. There was a rapid significant decrease of DSSS both in patients not using steroids at all and in patients reducing the steroids dose. The decrease was maintained up to Month 60 (p<0.001 in both subgroups at each follow-up visit). Among the patients reducing the steroid dose, the rate of infections was reduced from 3.4 events/patient year (1 year) to 1.4 (year 5).

**Conclusion:** The use of steroids expressed as mean prednisone equivalent dose decreased from 0.76 mg/kg to 0.05 mg/kg after 5 years of treatment with anakinra. The treatment effect evaluated by DSSS was maintained at the same low level throughout the study.

**Disclosure:** B. Halle, Swedish Orphan Biovitrum, 5; H. Olivecrona, Swedish Orphan Biovitrum; 3; H. Olivecrona, Swedish Orphan Biovitrum, 3; H. Olivecrona, Swedish Orphan Biovitrum, 3; M. Leinonen, Disclosure: B. Derfalvi, Gabor Bozsaki, Doloresz Szabo, Aron Csh, Kadalin Eszter Muller, Andrias Arato and Gabor Veres. Semmelweis University, Budapest, Hungary.

**Background/Purpose:** The incidence of arthritis and arthralgia in pediatric patients with Crohn’s disease (CD) is reported to be 2–15% and 22%, respectively. The aim of our study was to assess joint involvement with Pediatric CD Activity Index (PCDAI) and to assess quality of life (IMPACT-III). While arthritis in pediatric Crohn’s disease is associated with the enthesis-related JIA subgroup, subclinical sacroiliitis and HLA-B27-association may also be found.

**Methods:** A cross-sectional study was conducted in 82 pediatric patients with CD (age: 13.7±3.2 years, male:female ratio = 1.2:1, disease duration: 21.6±21, median: 15 months) to assess the prevalence of arthritis, lower extremity enthesis and arthralgia. Detailed joint physical examination and a modified JAMAR (juvenile Arthritis Multidimensional Assessment Report) were performed by a pediatric rheumatologist. Regarding disease activity, a PCDAI, IMPACT-III questionnaire and basic laboratory parameters including CRP and platelet count were determined, as well as sacroiliac MRI (n=62) and molecular genetic testing for HLA-B27 (n=72) were assessed.

**Results:** Altogether 35% (29/82) of the patients had arthritis. At the time of the examination, only 1 child had active enthesitis, 8/29 children had active arthritis indicated by swollen joint(s) – including 4 patients with also restricted range of motion in one or more other joints, suggestive of previous arthritis. Another 15/29 children had evidence of previous arthritis on joint examination. A nother 5 patients had a remote history of documented active arthritis. Hip (12/29) and knee (11/29) joints were most commonly affected. Cumulative incidence of arthralgia during the entire course of the disease was 48% (39/82), of whom 22% (18/39) had arthralgia, without arthritis, usually affecting the knee. There was a significant association between arthritis and lower quality of life (IMPACT-III score, p<0.01). In addition, incidence of arthritis and arthralgia correlated with higher CRP and PCDAI independent of age and sex. Arthritis was significantly more common in patients requiring infliximab treatment. None of the patients had sacroiliitis based on MRI, and HLA-B27 positivity was not related to arthritis.

**Conclusion:** The prevalence of joint involvement such as arthritis and arthralgia in pediatric CD was higher than previously reported when assessment is done by a pediatric rheumatologist. A arthritis was associated with more severe disease, as reflected by higher CRP, PCDAI score, as well as lower quality of life. Enthesitis was uncommon and sacroiliitis and HLA-B27 positivity were not significant associations in our pediatric CD cohort.

**Disclosure:** B. Derfalvi, None; G. Bozsaki, None; D. Szabo, None; A. Csh, None; K. E. Muller, None; A. Arato, None; G. Veres, None.

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**Safety and Efficacy of Rilonacept in Patients with Deficiency of Interleukin-1 Receptor Antagonist (DIRA).** Dawn C. Chapelle Neal, Adriana A Imdema de Jesus, Yan Huang, Yin Liu, Raphaella Goldbach-Mansky and Gina Monteleone.

**Background/Purpose:** Deficiency of interleukin-1 receptor antagonist (DIRA) is a neonatal-onset autoinflammatory syndrome caused by recessive mutations in IL1RN gene, the gene encoding the interleukin-1-receptor antagonist. It is clinically characterized by a perinatal-onset of pusular dermatosis, asymetrical multifocal osteoartymatitis, and marked elevation of acute phase reactants. In our treatment naive patients, IL-1 inhibition with anakinra leads to rapid and complete resolution of symptoms and normalization of the acute phase reactants. There is a need, however, for longer acting IL-1 blocking agents that are more convenient to administer and are less likely to cause injection site reactions.

**Objectives:** The primary objective of this study is to assess the ability of rilonacept to achieve/maintain remission in patients with DIRA who have shown response to anakinra. The secondary objective is to assess the safety of rilonacept in DIRA patients, and to assess its ability to prevent new organ damage.

**Methods:** Patients with a genetically confirmed diagnosis of DIRA and an adequate response to anakinra are eligible for the study. Per protocol, anakinra was discontinued 24 hours prior to first dose of study medication. A loading dose of rilonacept of 4.4 mg/kg/week was given and then decreased to a maintenance dose of 2.2 mg/kg/week. Patients who met flare criteria were subsequently escalated to 4.4 mg/kg/week with the option to increase to 6.6 mg/kg/week if needed. Diary and Dermatology scores in addition to ESR and CRP were collected at each visit. Paired t-test analyses were used to compare baseline and the most recent clinic visit data.

**Results:** Six Caucasian patients have been enrolled, 50% male, with a mean age of 4.8 years SD (±1.3). All patients were in remission on anakinra (diary score 0) with a mean dosage of 3.21 mg/kg/day SD (±0.48). The mean follow-up time has been 4.5 months. The diary scores have increased to 0.08 at the last visit, reflecting the onset of nail changes in one patient. All patients (except one) required an escalation in dosage from 2.2 mg/kg/week to 4.4 mg/kg/week due to a transient increase in micropustular lesions mostly in hyperkeratotic areas of the skin (elbow and knee). The micropustular lesions lead to the increase in dermatology scores from 3.3 to 3.2. Despite the mild skin lesions, no new bone lesions were detected and the acute phase reactants have decreased from baseline. No SAE’s have occurred and four adverse events have been reported.

**Conclusion:** Preliminary data in six DIRA patients suggest that doses of rilonacept at 4.4 mg/kg/week are required to achieve remission. Rilonacept treatment provides increased quality of life due to weekly injections. Long acting IL-1 inhibition with rilonacept seems to be a viable option in the treatment of DIRA.

**Disclosure:** D. C. Chapelle Neal, None; A. Imdema de Jesus, None; Y. Huang, None; Y. Liu, None; R. Goldbach-Mansky, Regeneron, 2; G. Monteleone, Regeneron, 2.

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**Food Allergy and Celiac Disease in Children with Juvenile Idiopathic Arthritis.** Trevor E. Davis*, M e-Sing Ong*, Diana M Iljoevic*, Jyoti Ramalingam* and Marc D. Natter*. *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, University of New South Wales, Sydney, Australia, 2Floating Hospital for Children at Tufts Medical Center, Boston, MA, 3Children’s Hospital Boston, Boston, MA.

**Background/Purpose:** There are multiple strong associations between gut pathology and rheumatologic diseases. This connection, between primary GI disease and rheumatologic diseases, is manifest in both autoimmune and infectious GI diseases. For example, arthritis is a component of several GI infections (Reactive arthritis following Salmonella, Shigella, Yersinia, or Campylobacter species, Whipples disease, and multiple parasitic infections) as well as inflammatory bowel disease and behcet’s. Arthritis is also a known extra-intestinal manifestation of celiac disease. There is controversy regarding the prevalence of celiac in adult arthritis and to date only a few small studies exist in children. Aditionally, both in children and adults, little is known regarding possible association of food allergies and arthritis. With this study, we endeavored to assess the risk of food allergy and celiac disease in a large population of children with juvenile idiopathic arthritis (JIA).
Methods: We analyzed electronic medical records from Boston Children's Hospital, between the years 1993 and 2014. Children with JIA, food allergy and celiac disease were identified, using tools of the National Center for Biomedical Computing “Infometrics for Integrating Biology to the Bedside” (i2b2). We assessed the risk of food allergy and celiac disease in JIA patients, in comparison with the children without JIA.

Results: A total of 1,933,719 children were included in our study. Of this total population 0.21% (n=4,128) had documented JIA, 1.14% had food allergy, and 0.18% had celiac disease (Table 1). Of the subjects with JIA 1.99% had documented food allergy and 1.02% had celiac disease. Children with JIA had an elevated risk of developing food allergy (OR 1.75; 95% CI 1.41 – 2.18; p<0.0001), and celiac disease (OR 5.58; 95% CI 4.11 – 7.58; p<0.0001).

Table 1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JIA</td>
<td>4,128 (0.21)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>21,953 (1.14)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>5,359 (0.19)</td>
</tr>
<tr>
<td>JIA population</td>
<td>4,128 (0.21)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>82 (1.99)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>42 (1.02)</td>
</tr>
</tbody>
</table>

Conclusion: We again find evidence of an association between the gut and rheumatologic disease. We clearly demonstrate an increased risk of celiac in JIA, consistent with the limited data on the subject. We also find a statistically significant increased risk of food allergies in JIA. In celiac evidence supports improvement or resolution of the associated arthritis with the removal of the trigger food, gluten. We do not yet know if the same holds for JIA.

Disclosures: T. E. Davis, None; M. S. Ong, None; D. Milojicic, Genentech and Novartis; S. J. Ramakrishna, None; M. D. Natter, None.

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Background/Purpose: The Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh Out) cohort is a multi-centre prospective inception cohort of newly diagnosed Juvenile Idiopathic Arthritis (JIA) patients. From our analysis of JIA associated new onset uveitis, we reported the first true incidence of uveitis of 2.9% per year and prevalence of 6.9%, the latter considerably lower than previously reported. We identified a positive ANA and young age at diagnosis of JIA (<7 years) as independent risk factors for uveitis. In this study, we examined the association between medications, uveitis and these independent risk factors.

Objectives: 1) to assess medications administered prior to uveitis and after diagnosis (2) to determine the association between the independent risk factors for uveitis and specific medication use and 3) their association with asymptomatic versus symptomatic presentation.

Methods: The ReACCh Out cohort recruited newly diagnosed JIA patients from 16 Canadian centres between January 2005 and December 2010. Prospective data was collected every 6 months for 2 years, then yearly. Clinical and laboratory data, medications, the presence of uveitis and complications determined by an ophthalmologist, was documented at each visit. Descriptive statistics characterize the uveitis cohort and frequencies were obtained for the medications used. We calculated the relative risk for certain medications, controlled for by the presence or absence of independent risk factors.

Results: 1104 newly diagnosed (<6 months) JIA patients with ≥1 follow-up visit were included. Patients were predominantly female (63%), median age at diagnosis of 9.3 (3.9, 13.0) years. Time from diagnosis to enrolment was 0.3 (0, 1.6) months. Follow-up to last visit was 34.2 (21.5, 48) months. 25 patients, uveitis status not available, were excluded. Patients with new onset uveitis were identified. Patients were on the following systemic medications prior to uveitis diagnosis: NSAIDs (71; 92.2%), Methotrexate (34; 44.2%), other DMARDs (7; 9.1%), systemic glucocorticoids (20; 26%), biologics (12; 15.6%). Following diagnosis: NSAIDs (45; 58.4%), Methotrexate (56; 72.7%), other DMARDs (10; 13%), systemic glucocorticoids (23; 30%), biologics (11; 14.3%).

Conclusion: In a large inception cohort of newly diagnosed, 77 patients with new onset uveitis were identified. Patients were on the following systemic medications prior to uveitis diagnosis: NSAIDs (71; 92.2%), Methotrexate (34; 44.2%), other DMARDs (7; 9.1%), systemic glucocorticoids (20; 26%), biologics (12; 15.6%). Following diagnosis: NSAIDs (45; 58.4%), Methotrexate (56; 72.7%), other DMARDs (10; 13%), systemic glucocorticoids (23; 30%), biologics (11; 14.3%).

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Cartilage Thickness and Bone Health in Children with Juvenile Idiopathic Arthritis. M Arinka1, Dan Pradsgaard, Anne Heene Spanno, Anne Horlyck, Carsten Heuck and Troels Herlin. Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Although treatment options have increased and morbidity has decreased in the last decade, Juvenile Idiopathic Arthritis (JIA) may still result in disability. Increasingly ultrasonography (US) has been used to measure cartilage thickness in children with JIA and normal values have been established. A thorough treatment of JIA has moved away from the use of long term steroids. Bone health remains a consistent worry in patients with JIA. The relation between cartilage thickness and bone health in patients with JIA has not been studied before. The aim of this study is to determine if there is a correlation between cartilage thickness and bone health in children with JIA.

Methods: We clinically examined joint activity in 68 children with JIA. Joint cartilage thickness was assessed by greyscale US in knee, ankle, wrist, metacarpophalangeal, and proximal interphalangeal (PIP) joints. Measurements were compared to reference values of a healthy cohort of a previous investigation.

Results: In total 68 patients (17 males, 51 females) with a median age at investigation of 11 years (range 5-15 years) and median disease duration of 42 months were included. Subtypes represented were: 26 oligoarticular persistent; 13 oligoarticular extended; 17 polyarticular rheumatoid factor (RF) negative; 4 polyarticular RF positive; 8 systemic onset. In total 680 joints were examined for cartilage thickness. Decreased cartilage thickness was present in 27% of the examined joints (181 joints). Most common joint with decreased cartilage thickness was the PIP, followed by the wrist, the least common was the ankle. Decreased cartilage thickness of the left wrist was found in 29 patients; 48% of these patients also have a decreased bone health index but only 17% have a decreased bone age.

Conclusion: Decreased cartilage thickness is a prominent and frequent feature in JIA. Decreased bone health and bone age is found in approximately half of the patients. Cartilage thickness seems to be correlated with decreased bone health, but less with decreased bone age. Further studies are necessary to study these correlations as decreased cartilage thickness might be an indicator for future bone health and steer treatment decisions.

Disclosures: M. Twilt, None; D. Pradsgaard, None; A. H. Spanno, None; A. Horlyck, None; C. Heuck, None; T. Herlin, None.
Accuracy of the Use of Administrative Diagnostic Codes to Identify Pediatric in-Patient Musculoskeletal Conditions in an African Tertiary Hospital. 

Rosie Scuccimarra1, Carol Hitchon2, Sasha Bernatsky3; Eugene Were4, Thomas Ngwiri5 and Ines Colmegna1. 1Montreal Children’s Hospital, Montreal, QC, 2University of Manitoba, Winnipeg, MB, 3McGill University Health Centre, Montreal, QC, 4Gertrude’s Children’s Hospital, Nairobi, Kenya.

Background/Purpose: The spectrum and frequency of pediatric rheumatic conditions in East Africa are unknown. Administrative data that is systematically collected using International Classification of Disease (ICD) codes can provide insight into this issue. The aim of this study was to assess the accuracy of using ICD-10 diagnostic codes in identifying either inflammatory or infectious musculoskeletal conditions requiring hospitalization at the largest pediatric center in East-Africa.

Methods: We reviewed the hospital records of all patients identified as having diseases of the musculoskeletal (M SK) system and connective tissues (CT) by ICD-10 diagnostic codes (M-codes) at discharge from Gertrude’s Children’s Hospital in Kenya, during a one year period from January to December 2011. ICD coding at this center is performed by medical records personnel based on the diagnosis provided by the treating physician. We evaluated the concordance rate between the physician’s diagnosis at discharge and the ICD-10 code assigned.

Results: The total number of admissions during 2011 was 8,011. Among these, 42 patients had an “M-code” diagnosis at discharge (0.5%) and 39 of these had charts available for review. Among those with M-code diagnoses, concordance rates between the ICD-10 code assigned by an administrator and the treating physician’s discharge diagnosis was 66.7% (26/39). Specifically, when only the infectious and inflammatory categories of M-codes were included (26 cases), concordance improved to 76.9% (20/26). The specific diagnosis in those with musculoskeletal infections (n=10) included septic arthritis (7/10), pyomyositis (2/10) and infective bursitis (1/10). Seven of these cases were coded correctly (70%). The diagnoses for those with inflammatory conditions (n=16) included 4 with Kawasaki disease; 2 with inflammatory arthropathies; and 10 with non-specific inflammatory M-codes such as unspecified arthritis, arthralgia or joint effusion. The concordance among the inflammatory M-codes was 81.3% (13/16) were coded correctly including all K.D cases.

Conclusion: Overall, the concordance of ICD-10 codes assigned in comparison to the physician’s discharge diagnosis for categories of inflammatory and infectious musculoskeletal conditions is acceptable. Inflammatory conditions are coded less specifically due to the physicians’ use of descriptive terms instead of definitive diagnoses at discharge. Therefore, administrative diagnostic codes could be used to estimate overall frequencies of rheumatic diseases in in-patients in East Africa however, their utility in estimating the frequency of specific inflammatory conditions is limited.

Disclosure: R. Scuccimarra, None; C. Hitchon, None; S. Bernatsky, None; E. Were, None; T. Ngwiri, None; I. Colmegna, None.

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Race and Other Risk Markers of Uveitis in a Prospective Cohort of Children with Juvenile Idiopathic Arthritis. Sheila T. Angeles-Han1, Courtney McCracken2, Steven Yeih3, Kirsten Jenkins4, Erica M Young4, Daneka Stryker5, Kelly A. Rouster-Stevenson5, Larry B. Voglg5, Christine Kennedy5, Sampath Prathalad5 and Carolyn Drews-Botsch6. 1Emory University School of Medicine, Atlanta, GA, 2Children’s Healthcare of Atlanta, Atlanta, GA, 3Emory University, Atlanta, GA, 4Emory Children’s Center, Atlanta, GA, 5Emory University School of Public Health, Atlanta, GA.

Background/Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) can lead to poor visual outcomes. American Academy of Pediatric guidelines recommend screening every 3 months in children with oligoarticular (oligo) or polyarticular (poly) rheumatoid factor (RF) (-) subtype. Uveitis positivity, <4 years of arthritis, and onset <7 years old. Identification of other risk markers could help modify current screening and improve outcomes.

Methods: In our prospective cohort of 250 JIA patients, rheumatology and ophthalmology medical record reviews and parent/patient based questionnaires were completed every 3-6 months (2011-2014). We collected data on demographics, arthritis, and uveitis, and quality of life function. We compared children with JIA and JIA-U, and African American (AA) and Caucasians (W) with uveitis.

Results: Our cohort was primarily W females with oligo persistent and poly RF (-) JIA. There were 45/250 (18%) with uveitis of whom 15.6% were AA (Table 1). Compared to JIA alone, JIA-U were more frequently of the oligo persistent JIA subtype (p < 0.001), younger at arthritis diagnosis (p < 0.001), ANA positive (p = 0.029), anti-CCP negative (p = 0.018) and had reduced vision related quality of life and function (p < 0.001). No children with JIA-U had psoriatic (p = 0.030), systemic (p = 0.029) or poly RF (+) (p = 0.133) JIA.

On regression analysis, young age at diagnosis (OR = 0.88, 95% CI 0.81-0.98, p < 0.001) and oligo persistent JIA (OR = 3.15, 95% CI 1.42-6.98, p = 0.011) were predictors for uveitis. AA race approached significance (OR = 2.56, 95% CI = 0.93-7.02, p = 0.068). ANA was not significantly after adjustment.

Comparing JIA-U by race, there were fewer AA children then W overall (7/40 (17.5%) vs. 33/40 (82%)) (Table 2). However, there was no significant difference in the frequency of uveitis between AA and W (7/33 (21%) vs. 33/190 (17%), p = 0.624). They were similar in age at arthritis diagnosis, JIA subtype, ANA positivity, arthritis characteristics, and treatment. AA were older at uveitis diagnosis (p = 0.018) with more ocular complications -synechiae (p = 0.027) and band keratopathy (p = 0.011). In our cohort, uveitis was less frequent in AA children overall. However, we found a similar likelihood of uveitis in AA compared to W (21% vs 17%). AA were older when diagnosed and suffered more ocular complications. We also confirmed known uveitis risk factors (young age at JIA diagnosis and JIA subtype). Further investigation into the role of race should be conducted as uveitis may be more common in AA but diagnosed later leading to increased visual complications, or may be more severe in AA.

Table 1: Characteristics of children with JIA and JIA-associated uveitis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>JIA</th>
<th>JIA-U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) Mean ± SD</td>
<td>11.1 ± 4.6</td>
<td>9.6 ± 4.9</td>
</tr>
<tr>
<td>Gender, female</td>
<td>144 (70.2%)</td>
<td>35 (77.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16 (7.8%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>157 (76.6%)</td>
<td>33 (73.3%)</td>
</tr>
<tr>
<td>African American</td>
<td>26 (12.7%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (10.7%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Disease Characteristics Age at arthritis diagnosis (yrs), Mean ± SD</td>
<td>8.1 ± 4.7</td>
<td>5.0 ± 4.9</td>
</tr>
<tr>
<td>Duration of JIA (yrs), Mean ± SD</td>
<td>2.9 ± 3.1</td>
<td>4.6 ± 4.0</td>
</tr>
</tbody>
</table>

JIA subtype
| Oligoarticular persistent | 45 (35.7%) | 45 (56.1%) |
| Oligoarticular extended | 12 (9.5%) | 1 (1.3%) |
| Polyarticular RF (+) | 55 (26.8%) | 6 (13.3%) |
| Polyarticular RF (–) | 13 (6.2%) | 0 (0.0%) |
| Systemic | 20 (9.8%) | 0 (0.0%) |
| Psoriatic | 10 (4.9%) | 0 (0.0%) |
| Enthesitis related arthritis | 27 (13.2%) | 4 (8.9%) |
| Undifferentiated | 2 (1.0%) | 0 (0.0%) |

Labs
| ANA (+) | 74 (37.8%) | 24 (55.8%) |
| RF (+) | 26 (12.7%) | 1 (2.2%) |
| Anti-CCP (+) | 23 (11.3%) | 1 (2.2%) |
| HLA-B27 (+) | 20 (14.3%) | 0 (0.0%) |

Quality of Life Function scores (child)
| PedsQL (Total), Mean ± SD | 76.4 ± 19.1 | 76.5 ± 20.5 |
| PedsQL (Psychosocial), Mean ± SD | 77.8 ± 16.1 | 75.0 ± 16.4 |
| CHAQ, Mean ± SD | 0.44 ± 0.46 | 0.43 ± 0.53 |
| EYE-Q, Mean ± SD | 3.60 ± 0.37 | 3.32 ± 0.41 |

Quality of Life Function scores (parent)
| PedsQL (Total), Mean ± SD | 73.9 ± 20.7 | 78.8 ± 18.6 |
| PedsQL (Psychosocial), Mean ± SD | 79.4 ± 16.3 | 80.3 ± 16.7 |
| CHAQ, Mean ± SD | 0.43 ± 0.45 | 0.35 ± 0.48 |
| EYE-Q, Mean ± SD | 3.70 ± 0.28 | 3.41 ± 0.41 |

1N(%) unless otherwise specified; 2Indicates missing data; 3Pediatric Quality of Life Inventory; 4Childhood Health Assessment Questionnaire; 5Effects of Youngsters’ Eyesight on Quality of Life

*p value <0.05
Canakinumab in Biologic-naïve Versus Previously Biologic-Exposed Systemic Jvenile Idiopathic Arthritis Patients: Efficacy Results from a 12 Week Pooled Post Hoc Analysis.

S999

Tuesday, November 18

Disclosure: A. Grom, Novartis, Roche, Novimmune, 5; P. Quartier, Abbvie, BMS, Novartis, 2, Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, Sobi, Medimmune, 5, Chugai-Roche, Novartis, 8; L. B. Vogler, None; L. B. Vogler, None; C. Drews-Botsch, None; C. Drews-Botsch, None.

Conclusion: In general, BE pts achieved aACR-JIA 50, 70 and 90 responses to CAN quickly in the first 2 weeks, and maintained their responses up to Week 12; albeit at a numerically lower level than BN pts. These data support the consistent efficacy of CAN across different subgroups of pts.

Reference:

Table 2. Comparison of Caucasian and African American children with JIA-associated uveitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Caucasian (n = 33)</th>
<th>African American (n = 7)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Mean ± SD</td>
<td>8.7 ± 4.1</td>
<td>13.5 ± 5.4</td>
<td>0.011</td>
</tr>
<tr>
<td>Gender, female</td>
<td>26 (78.8%)</td>
<td>4 (57.1%)</td>
<td>0.338</td>
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<tr>
<td>Hispanic</td>
<td>6 (18.2%)</td>
<td>0 (0%)</td>
<td>0.103</td>
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<td>Arthritis Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at arthritis diagnosis (yrs), Mean ± SD</td>
<td>4.4 ± 4.1</td>
<td>9.6 ± 7.6</td>
<td>0.169</td>
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<tr>
<td>Duration of JIA (yrs), Mean ± SD</td>
<td>4.5 ± 3.5</td>
<td>4.2 ± 5.7</td>
<td>0.916</td>
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<tr>
<td>JIA subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligo persistent</td>
<td>24 (72.7%)</td>
<td>3 (42.9%)</td>
<td>0.187</td>
</tr>
<tr>
<td>Oligo extended</td>
<td>1 (3.1%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Poly RF (-)</td>
<td>4 (12.1%)</td>
<td>2 (28.6%)</td>
<td>0.567</td>
</tr>
<tr>
<td>ERA</td>
<td>3 (9.1%)</td>
<td>1 (14.3%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Uveitis Disease Characteristics

| Age at uveitis diagnosis (yrs), Mean ± SD | 5.6 ± 3.9 | 9.9 ± 4.9 | 0.018 |
| Location | 27 (81.2%) | 5 (63.3%) | 0.611 |
| Bilateral involvement | 24 (72.7%) | 4 (66.7%) | 0.410 |
| Complications |                   |                          |         |
| Cataracts | 8 (24.2%) | 3 (42.9%) | 0.369 |
| Glaucoma | 2 (6.1%) | 0 (0%) | 1.000 |
| Synchiae | 8 (24.2%) | 5 (71.4%) | 0.027 |
| Band keratopathy | 4 (57.1%) | 3 (42.9%) | 0.011 |
| Cystoid macular edema | 2 (6.1%) | 2 (28.6%) | 0.134 |
| Labs |                   |                          |         |
| ANA (+) | 18 (58.1%) | 4 (50.0%) | 1.000 |
| HLA-B27 (+) | 5 (13.8%) | 0 (0%) | 0.545 |
| Medication use |                   |                          |         |
| Methotrexate all routes | 28 (84.5%) | 5 (71.4%) | 0.584 |
| Oral | 21 (63.6%) | 5 (71.4%) | 1.000 |
| Subcutaneous injection | 24 (72.7%) | 5 (71.4%) | 1.000 |
| Anti-TNF Use | 15 (45.5%) | 5 (71.4%) | 0.689 |
| Infliximab | 10 (30.3%) | 3 (42.9%) | 0.662 |
| A-dalumab | 2 (6.1%) | 1 (14.3%) | 0.448 |
| Quality of Life/Function scores (child) |                   |                          |         |
| PEDSOL2 (Total), Mean ± SD | 74.0 ± 16.5 | 78.7 ± 15.1 | 0.490 |
| PEDSOL2 (Psychosocial), Mean ± SD | 73.1 ± 16.7 | 78.7 ± 15.1 | 0.405 |
| CHAQ4, Mean ± SD | 0.45 ± 0.52 | 0.38 ± 0.62 | 0.790 |
| EYE-Q2, Mean ± SD | 3.33 ± 0.34 | 3.44 ± 0.63 | 0.741 |
| Quality of Life/Function scores (parent) |                   |                          |         |
| PEDSOL2 (Total), Mean ± SD | 79.2 ± 17.3 | 77.4 ± 16.9 | 0.804 |
| PEDSOL2 (Psychosocial), Mean ± SD | 79.9 ± 18.1 | 77.6 ± 14.9 | 0.753 |
| CHAQ4, Mean ± SD | 0.36 ± 0.46 | 0.43 ± 0.71 | 0.817 |
| EYE-Q2, Mean ± SD | 3.42 ± 0.33 | 3.37 ± 0.71 | 0.512 |

1(N%) unless otherwise specified; 2Indicates missing data; 3Pediatric Quality of Life Inventory; 4Childhood Health Assessment Questionnaire; 5Effects of Youngsters’ Eyeglass on Quality of Life

p value < 0.05

Disclosure: S. T. Angeles-Han, None; C. McCracken, None; S. Yeh, None; K. Jenkins, None; E. Myoung, None; D. Stryker, None; K. A. Rouster-Stevens, None; L. B. Vogler, None; C. Kennedy, None; S. Pralahad, None; C. Drews-Botsch, None.

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S999
Demographic, Clinical and Treatment Characteristics of the Childhood Arthritis and Rheumatology Research Alliance Registry Systemic JIA Cohort. Ginger L. Janow1, Laura Schanberg2, Soko Setoguchi3, Elizabeth D. Mollins4, Rayfel Schneider5, Yukiya Kikuma6 and The CARRA Registry Investigators. 1Joseph M Sanzari Children’s Hospital, Hackensack University Medical Center, Hackensack, NJ, 2Duke University, Durham, NC, 3Duke Clinical Research Institute, Durham, NC, 4Stanford University Medical Center, Stanford, CA, 5The Hospital for Sick Children, Toronto, ON, 6Hackensack Medical Center, Hackensack, NJ, 7Childhood Arthritis and Rheumatology Research Alliance, Durham, NC.

Background/Purpose: Systemic JIA (sJIA) is a rare disease whose treatment has changed in the past 10 yrs. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry contains a large cohort of sJIA pts. We aimed to: (1) describe the characteristics of the CARRA Registry sJIA cohort; (2) identify medication usage trends; and (3) identify subgroups at increased risk for poor outcomes.

Methods: 54 US/Canadian sites enrolled 528 sJIA pts as a cross-sectional convenience sample from 2010–2013. Only pts with complete datasets were included in this analysis. We tested binary and continuous variables for subgroup differences among or across groups, using a chi-square or ANOVA, respectively.

Results: 435 pts were included (Table 1). Disease activity was low: 15% had rash, 7% fever, median joint count 0, and median physician global assessment 1. Significant changes in medication usage occurred over the study period: DMARD and TNF inhibitor use decreased while IL-6 inhibitor (IL6i) use increased (Fig 1). 29% were on corticosteroids at enrollment. African Americans (AA) had higher CHAQ, worse quality of life and poorer ACR functional class (p = 0.0004). Pts diagnosed at a younger age (< 2 yrs) had more frequent biologic use and lower overall well being. Joint damage on imaging increased with younger age at diagnosis (p = 0.0003). 259 pts had follow-up visits at least 3 mos from enrollment, and disease activity measures improved in these pts. Of 234 pts without active systemic features, 91 had increased current IL6i, steroid and NSAID use and past biologic use compared to those without persistent arthritis.

Conclusion: This study describes the largest sJIA cohort reported to date. Significant changes occurred in medication usage over the study period, but corticosteroids are still frequently used. AA pts had more severe disease, as did pts diagnosed at a younger age. A significant proportion has persistent arthritis despite new treatments. Predictors of persistent arthritis are needed to improve treatment and outcomes in this subgroup.

Table 1. Demographic Features (n=435)

| Subject age at baseline visit, median (years) | 11.0 (6.8–14.6) |
| Subject age at onset of symptoms, median (years) | 4.6 (2.3–9.3) |
| Ethnicity, N(%) |  |
| ● Non Hispanic or Latino | 381 (87.6%) |
| ● Hispanic or Latino | 54 (12.4%) |
| Race, N(%) |  |
| ● White | 342 (78.6%) |
| ● Black or African American | 45 (10.3%) |
| ● Other | 48 (11.0%) |
| Gender, Male, N(%) | 197 (45.3%) |

Figure 1: Current Medication Usage By Year of Visit (baseline and follow-up visits)

Background/Purpose: Systemic JIA (sJIA) treatment has changed dramatically with the introduction of biologic agents, although treatment approaches may differ between countries. We characterized and compared patients,\(^1\) and is approved in Canada, UK and Russia. Given the nature of the disease (pediatric rheumatology) to first encounter with a pediatric rheumatologist (years, median, IQR) was 5.8 (3.2-10.7), 6.7 (3.5-10.6) and 7.8 (3.6-10.6) for the CAPS Registry (US), CAPS (UK) and CAPS (UK) respectively. Patients with juvenile idiopathic arthritis (JIA) are likely to be evaluated within 2 months of symptom onset. Differences in enrollment procedures precluded valid comparisons of disease activity measures. US patients were more likely to receive biologic agents (specifically anakinra) and systemic glucocorticoids in the first 12 months of disease compared to UK patients. Conclusion: Presenting features of children with sJIA were generally similar in the two countries. Compared to the UK, initial treatment of sJIA in the US more frequently included anakinra and, to a lesser extent, systemic glucocorticoids, which may represent differences in medication coverage.

Disclosure: Y. Kimura, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5, E. Morgan-DeWitt, None; K. L. Mieszalski, None; T. B. Graham, None; T. Beukelman, Novartis Pharmaceutical Corporation, 3, Genentech and Biogen IDEC Inc., 5, UCB, 5, Pfizer Inc, 2, M. F. Ibarra, None, N. T. Ilowits, Genentech and Biogen IDEC Inc., 5, Genentech and Biogen IDEC Inc., 8, Janssen Pharmaceutica Product, L.P., 5, Janssen Pharmaceutica Product, L.P., 9, Novartis Pharmaceutical Corporation, 5, Novartis Pharmaceutical Corporation, 9; M. S. Klein-Gitelman, None; K. Onel, None; S. Prahalad, None; M. G. Punaro, None; S. Ringold, None; D. Toib, None; H. Van Mater, None; P. F. Weiss, None; L. Schanberg, Novartis Pharmaceutical Corporation, 2, UCB Pharma, 5, Eli Lilly and Company, 5.

Table 2: Selection of CTP by Site

<table>
<thead>
<tr>
<th>SITE</th>
<th>CTP chosen (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GC (1)</td>
</tr>
<tr>
<td>2</td>
<td>IL6i (1)</td>
</tr>
<tr>
<td>3</td>
<td>IL6i (1)</td>
</tr>
<tr>
<td>4</td>
<td>MTX (1)</td>
</tr>
<tr>
<td>5</td>
<td>IL6i (3)</td>
</tr>
<tr>
<td>6</td>
<td>IL6i (3)</td>
</tr>
<tr>
<td>7</td>
<td>GC (1)</td>
</tr>
<tr>
<td>8</td>
<td>MTX (2)</td>
</tr>
<tr>
<td>9</td>
<td>IL6i (1)</td>
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<tr>
<td>10</td>
<td>MTX (1)</td>
</tr>
<tr>
<td>11</td>
<td>IL6i (1)</td>
</tr>
<tr>
<td>12</td>
<td>IL6i (1)</td>
</tr>
<tr>
<td>13</td>
<td>IL6i (3)</td>
</tr>
</tbody>
</table>

Table 2: Initial Medication Use in the First 12 Months of Disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>CARRA Registry (US) (N=70)</th>
<th>CAPS (UK) (N=74)</th>
<th>CAPS (UK) enrolled since 2009 (N=22)</th>
<th>P value for comparison between CAPS enrolled since 2009 and CARRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Glucocorticoid</td>
<td>60 (80%)</td>
<td>62 (84%)</td>
<td>62 (84%)</td>
<td>ns</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>46 (61%)</td>
<td>65 (88%)</td>
<td>16 (76%)</td>
<td>ns</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>6 (8%)</td>
<td>7 (10%)</td>
<td>1 (5%)</td>
<td>ns</td>
</tr>
<tr>
<td>A Biologic</td>
<td>46 (61%)</td>
<td>16 (22%)</td>
<td>6 (29%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Rilonacept</td>
<td>33 (44%)</td>
<td>3 (4%)</td>
<td>1 (5%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>28 (37%)</td>
<td>34% (5%)</td>
<td>1 (5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Total Biologic</td>
<td>6 (8%)</td>
<td>6 (8%)</td>
<td>8 (38%)</td>
<td>0.141</td>
</tr>
<tr>
<td>Any TNF Inhibitor</td>
<td>12 (16%)</td>
<td>11 (15%)</td>
<td>13 (58%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Disclosure: T. Beukelman, Novartis Pharmaceutical Corporation, 5, Genentech and Biogen IDEC Inc., 5, UCB, 5, Pfizer Inc, 2; R. Carrasco, None; Y. Kimura, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 3, L. Schanberg, Novartis Pharmaceutical Corporation, 2, UCB Pharma, 5, Eli Lilly and Company, 5; W. Thomson, None; K. L. Hyrich, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 9; F. the CARRA Registry Investigators, None; F. the CAPS Investigators Group, None.

Methodology: The US data source was the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, an observational registry established in 2010 that collects clinical data on children with incident or prevalent rheumatologic disease from >55 clinical sites throughout the US. Children with sJIA who were enrolled in the Registry within 9 weeks of their first encounter with PR were included in the analysis of initial treatment. The UK data source was the Childhood Arthritis Prospective Study (CAPS), an observational study established in 2001 that collects clinical data at regular intervals from a cohort of children with newly diagnosed JIA from 7 UK PR centers. All children with sJIA were included in the analysis of presenting features and children with clinical data available from the 12 month visit were included in the analysis of initial treatment. We also evaluated a subset of CAPS children enrolled since 2009 to match the CARRA enrollment period. Presenting features and initial treatments were compared using chi-square, Fisher's exact, and Wilcoxon ranksum tests.

Results: Presenting features are shown in Table 1 and medication use in the first 12 months is shown in Table 2. Disease manifestations were similar between the US and UK except hepatosplenomegaly was more frequent in the US (p<0.01). Elapsed time from first symptom to evaluation by PR was similar but slightly shorter in the US (p=0.011), and overall most children were evaluated within 2 months. Differences in enrollment procedures precluded valid comparisons of disease activity measures. US patients were more likely to receive biologic agents (specifically anakinra) and systemic glucocorticoids in the first 12 months of disease compared to UK patients.
population, rare condition), the phase III program only included limited placebo data. In such a context, the safety profile of CAN has been characterized via a model-based analysis of the dose-exposure-safety-event relationship. The purpose of the study is to explore the relationship between CAN concentration and the occurrence of adverse events of special interest (ESI) and related laboratory abnormalities.

**Methods:** The analysis considered the open-label, part I of phase III trial wherein SjIA patients received CAN 4 mg/kg (300 mg max) every 4 weeks for a maximum of 8 consecutive doses (n=188). Individual CAN concentration-time-profiles have been predicted for those patients, by combining the patients' CAN and IL-1β concentration-time data and an established population PK model. This model is a PK-binding model parameterized in terms of clearance of drug and ligand (IL-1β, central and peripheral volume for the drug, interstitial flow rate, ligand production rate and binding affinity which has been estimated using all the data available from the entire CAN program. The average serum CAN concentration (Cavg) was calculated from the concentration time profiles for each patient and dosing interval. In each dosing interval, Cavg were compared between patients with and without the following safety events of special interest: AEs of abdominal pain, cough, headache, infection, renal AEs, neuropsychiatric, and vomiting, as well as lab abnormalities of thrombocytopenia (3-ULNL [upper limit normal]), leucopenia (<0.8 X LLN [lower limit normal]), >200g/L decrease from baseline hemoglobin, neutropenia (<0.9 X LLN), transaminases elevation (>3 X LLN), elevated total cholesterol (>1.5 X ULN), triglycerides (>5.7 mmol/L), and >25% decrease from baseline estimated glomerular filtration rate for 2 consecutive visits.

**Results:** For all adverse ESI and related laboratory abnormalities, except neutropenia, Cavg was different for patients who experienced an event compared with those who did not. The mean Cavg for patients with neutropenia was comparable to the 74% percentile of those patients without neutropenia, however this higher Cavg was not found to be associated with more infection.

**Conclusions:** A pharmacometric based analysis in SjIA patients treated with a therapeutic dose of CAN, did not find, in the range of CAN exposure observed, any relationship between average CAN exposure and the occurrence of any safety ESI, except for neutropenia. This increased Cavg in patients with neutropenia was not associated with increased infections. These data support the effective and safe use of CAN 4mg/kg every 4 week for the treatment of SjIA in patients >2 years old.

## Table 1.10 and J27-related disease criteria applied to the analysis dataset (%)

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Baseline N = 178</th>
<th>D15 N = 172</th>
<th>D29 N = 157</th>
<th>D57 N = 131</th>
<th>D85 N = 125</th>
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<tbody>
<tr>
<td>J10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>0.0</td>
<td>18.0</td>
<td>26.8</td>
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</tr>
<tr>
<td>LDA</td>
<td>0.0</td>
<td>14.0</td>
<td>11.5</td>
<td>16.8</td>
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</tr>
<tr>
<td>MDA</td>
<td>0.6</td>
<td>19.2</td>
<td>19.7</td>
<td>20.6</td>
<td>16.8</td>
</tr>
<tr>
<td>HDA</td>
<td>99.4</td>
<td>48.8</td>
<td>42.0</td>
<td>26.2</td>
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</tr>
<tr>
<td>J27</td>
<td></td>
<td></td>
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<td>18.0</td>
<td>26.8</td>
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<tr>
<td>LDA</td>
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<td>14.0</td>
<td>11.5</td>
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<tr>
<td>MDA</td>
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<td>48.8</td>
<td>42.0</td>
<td>26.2</td>
<td>24.8</td>
</tr>
</tbody>
</table>
Conclusion: There was a dramatic reduction in disease activity from baseline to D85, with much of the reduction taking place by D15 onwards in both completers and in the full analysis dataset. An increasing proportion of CAN patients achieved ID or LDA — according to J10 and J27 — in the first 12 weeks of treatment, despite corticosteroid tapering, consistent with the previous ID definition from the phase III trials. These data confirm the early onset of effect as well as the short-term and sustained efficacy over 12 weeks of CAN, and suggest that JADAS may represent a useful tool to monitor treatment response.

References:

Disclosures: A. Ravelli, Pfizer, 2, Abbvie, Bristol Myers Squibb, Novartis, Pfizer. Roche and Johnson & Johnson, 8, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 8, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 5; H. I. Brunner, Roche, Novartis, 8, Novartis, Roche, BMS, Pfizer, Biogen, Boehringer-Ingelheim, Jansen, Astrazeneca, 5; N. Ruperto, Abbott, AstraZeneca BMS, Centocor Research & Development, Eli Lilly and Company, “Francisco Angelini”, Glaxo Smith & Kline, Itafarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Bionsciences GmbH, Xoma, Wyeth Pharmaceuticals Inc.; 2, A. Consolaro, Bristol Myers and Squibb, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biocin Technologies, 2, A. Consolaro, Bristol Myers Squibb, Novartis, Jansen Biologics B.V., Roche, WyethPharmaceuticals, P. Quarter, Abbvie, BMS, Novartis, 2, Abbvie, BMS, Novartis, 2, A. Consolaro, Novartis, Pfizer, MEDIUMUNE and SOBI, 5, Chugui-Roche, Novartis, 8; A. Consolaro, Novartis, 5; N. M. Wulfraaft, Novartis, Pfizer, 5, Abb Vie, 2; K. Lheritier, Novartis, 4, Novartis, 1; C. Galiez, Novartis, 4, Novartis, 4, A. Martini, Abbvie, Bristol Myers & Squibb, Francisco Angelini S.P.A., Glaxo Smith & Kline, Jansen, Biotech Inc, Novartis, Pfizer Inc, Roche, Sanofi Aventis, Schwarz, 2, A. Martini, Biogenedecrum Bristol MyersSquibb, Astellas, Behringer, Itafarmaco, Jansen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 5, A. Martini, Biogenedecrum Bristol MyersSquibb, Astellas, Behringer, Itafarmaco, Jansen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 8; J. D. Lovell, AstraZeneca, Centocor, Amgen, Bristol Myers Squibb, Abbott, Pfizer, Regeneron, Roche, Novartis, UBC, Forest Research Institute, Horizon, Johnson & Johnson, 5, Novartis, Roche, 8. National Institutes of Health- NIAMS, 2.

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Background/Purpose: Key objectives of biologic therapies in systemic juvenile idiopathic arthritis (SJIA) are to induce and maintain inactive disease, according to the ACR 2011 definition. Recent advances in the management of SJIA consider the induction or maintenance of inactive disease according to the JADAS 10-CRP (J10) or 27-CRP (J27) scoring system. The efficacy of SJIA are to induce and maintain inactive disease, according to the previous ID definition from the phase III trials. These data confirm the early onset of effect as well as the short-term and sustained efficacy over 12 weeks of CAN, and suggest that JADAS may represent a useful tool to monitor treatment response.

Table 1: J10 shift analysis table from D15 to D85*

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Disease state at Day 15*</th>
<th>ID</th>
<th>LDA</th>
<th>MDA</th>
<th>HDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>J10</td>
<td></td>
<td>ID</td>
<td>LDA</td>
<td>MDA</td>
<td>HDA</td>
</tr>
<tr>
<td>28 (100)</td>
<td>24 (85.7)</td>
<td>3 (1.36)</td>
<td>(3.10)</td>
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</tr>
<tr>
<td>20 (100)</td>
<td>10 (50.0)</td>
<td>10 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>15 (100)</td>
<td>15 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>10 (50)</td>
<td>10 (50.0)</td>
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<td>10 (50.0)</td>
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<td></td>
</tr>
</tbody>
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Disclosures: A. Ravelli, Pfizer Inc, 2, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 8, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 5; H. I. Brunner, Roche, Novartis, 8, Novartis, Roche, BMS, Pfizer, Biogen, Boehringer-Ingelheim, Jansen, Astrazeneca, 5; N. Ruperto, Abbott, AstraZeneca BMS, Centocor Research & Development, Eli Lilly and Company, “Francisco Angelini”, Glaxo Smith & Kline, Itafarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Bionsciences GmbH, Xoma, Wyeth Pharmaceuticals Inc.; 2, A. Consolaro, Bristol Myers and Squibb, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biocin Technologies, 2, A. Consolaro, Bristol Myers Squibb, Novartis, Jansen Biologics B.V., Roche, WyethPharmaceuticals, P. Quarter, Abbvie, BMS, Novartis, 2, Abbvie, BMS, Novartis, 2, A. Consolaro, Novartis, Pfizer, MEDIUMUNE and SOBI, 5, Chugui-Roche, Novartis, 8; A. Consolaro, Novartis, 5; N. M. Wulfraaft, Novartis, Pfizer, 5, Abb Vie, 2; K. Lheritier, Novartis, 4, Novartis, 1; C. Galiez, Novartis, 4, Novartis, 4, A. Martini, Abbvie, Bristol Myers & Squibb, Francisco Angelini S.P.A., Glaxo Smith & Kline, Jansen, Biotech Inc, Novartis, Pfizer Inc, Roche, Sanofi Aventis, Schwarz, 2, A. Martini, Biogenedecrum Bristol MyersSquibb, Astellas, Behringer, Itafarmaco, Jansen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 5, A. Martini, Biogenedecrum Bristol MyersSquibb, Astellas, Behringer, Itafarmaco, Jansen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 8; J. D. Lovell, AstraZeneca, Centocor, Amgen, Bristol Myers Squibb, Abbott, Pfizer, Regeneron, Roche, Novartis, UBC, Forest Research Institute, Horizon, Johnson & Johnson, 5, Novartis, Roche, 8. National Institutes of Health- NIAMS, 2.

2299

M-Ficolin and Masp-2 As Inflammatory Markers in Oligoarticular and Systemic Juvenile Idiopathic Arthritis. Christine Pertl 1, Steffen Thied 1, Jens Christian Jensenius 2 and Troels Herlín 1. Aarhus University Hospital, Aarhus, Denmark, 2Aarhus University, Aarhus, Denmark.

Background/Purpose: The lectin pathway of the complement plays a crucial role in the pathogenesis of various inflammatory processes. The lectin pathway proteins are activated through the recognition of pathogens by the pattern recognition molecules (PRMs), which include the mannan-binding lectin (MBL), and H- and M-ficolin in collaboration with MBL-associated serine proteases (MASP). PRMs reportedly play a role in rheumatoid arthritis (RA) indicating a correlation between the concentration of these proteins and RA disease activity. The aim was to evaluate the possible pathogenic role of the PRMs in Juvenile Idiopathic Arthritis (JIA).

Methods: We measured MBL, M-ficolin, H-ficolin, MASP-1, -2, -3, and the two alternative splice products, MASP4 and MASP1p, in plasma and synovial fluid (SF) of 109 children with persistent oligoarticular JIA and 19 children with systemic JIA. The concentrations of the eight proteins were measured by in-house time-resolved immunoflurometric assays (TRIFMA) using monoclonal antibodies.

Results: We observed significantly higher levels of M-ficolin and MASP-2 in all patients compared to healthy children with systemic JIA (p<0.001). Notably, higher levels of M-ficolin and MASP-2 were also found in synovial fluid from patients with systemic JIA (n=11) compared to SF from patients with oligoarticular JIA (n=36). Plasma/SF ratio of the lectin pathway proteins were calculated in paired samples for oligoarticular JIA (n=36) and systemic onset JIA (n=11). We observed significantly high plasma/SF for both subtypes for M- and H-ficolin, MASP-1 and MASP-2.
Biologic Treatment in Systemic Juvenile Idiopathic Arthritis: Single Center Experience. Buthaina Al adba, Rayfel Schneider and Earl Silverman. 1sickkids hospital, Toronto, ON, 2The Hospital for Sick Children, Toronto, ON, 3Hospital for Sick Children, Toronto, ON.

Background/Purpose: The prevalence of juvenile idiopathic arthritis (JIA) is approximately 3.3/1000 children and 10–15% have the systemic form (SJIA). Biologics, specifically anti-IL-1 and anti-IL-6 agents have been introduced to decrease the need for corticosteroids and therefore ameliorate the associated morbidity including growth failure, cataracts, fractures and body image problems.

Methods:
Study design:
Retrospective chart review of 306 patients diagnosed with SJIA at Hospital of sick children from January 1980 to December 2012. Exclusion criteria: Diagnosis not confirmed, <1 year follow-up, <1 visit per year and unable to obtain complete medical record.

Data analysis:
1) Number of patients treated with biologics.
2) Response of: i) Systemic features (fever or rash) and ii) Arthritis.

Results:
The cohort consisted of 306 SJIA patients which 38 of them (12%) have received biologic. 28/58 (48%) Since 2009. The main biologic used were anti-IL-1, anti-IL-6 and anti TNF. 41/58 needs one biologic, 10/58 two biologics and 7/58 three or more. Some patients used same biologic more than once. Anti IL-1 was used 47 times in the 58 patients (83%), Anti IL-6 used 14 times (24%) and anti TNF used 38 times (65%). The complete response of systemic features was about 70% in both anti IL-1 and anti IL-6 group, however it was 20% in anti TNF group. The complete response of arthritis was 64%, 48% and 31% in anti IL-6, anti IL-1 and anti TNF respectively.

SUMMARY:
1) 58/306 received biologic during the study- 28/58 (48%) since 2009. 2)The main biologics used were anti-IL-1, anti-IL-6 and anti-TNF agents. 3) A complete response of systemic features was found in about 70% for both anti-IL-1 and anti-IL-6 groups but only 20% in the anti-TNF group. 4) A complete response of arthritis was seen in 64%, 48% and 31% in the anti-IL-6, anti-IL-1 and anti-TNF groups respectively.

Conclusion:
1) Since 2009 there was a significant increase in the use of biologic therapies in SJIA. 2) Systemic features responded well to anti-IL-1 and anti-IL-6 but not anti-TNF treatment. 3) Arthritis improved by >66% with anti-IL-1 and anti-IL-6 in all patients but not with anti-TNF treatment. 4) Further studies with larger number of patients are needed to evaluate anti-IL-1 and anti-IL-6. 5) With anti-IL-1 and anti-IL-6 agents, a substantial proportion of patients were able to discontinue steroid.

Disclosure:
B. Al adba, None; R. Schneider, None; E. Silverman, None.

The New Proposal Classification Criteria for Juvenile Spondyloarthropathies. Ozgur K asapcopur, 1M elin Sezen, 1K enan Barut and Cengizhan A cikel. 1I stanbul University, C errahpasa Med ical Faculty, Istanbul, Turkey, 2G uhanie Military Medical Academy, Ankara, Turkey.

Background/Purpose: Juvenile spondyloarthropathies (JSpA) are a group of related seronegative rheumatic diseases characterized by involvement of the axial, peripheral large joints and entheses. Sets of classification criteria have been developed in adult patients with SpA. The ASAS classification criteria for axial and peripheral SpA have not been validated in pediatric populations.

Objectives: To assess the sensitivity[sen] and specificity[sp] of the ASAS criteria for patients with JSpA. To compare the performance of the ASAS criteria with that of ESSG classification criteria. To identify associations between criteria fulfillment and disease features.

Methods: Consecutive patients with JSpA (defined as ERA, PsA or UA according to ILAR) followed in our center with complete records were included. Clinical charts and databases were retrospectively reviewed. Randomly selected patients with oligoarthrits, systemic arthritis and polyarthrits were selected. Demographic and clinical characteristics, disease duration at first visit and follow up time were recorded. Items corresponding to the ASAS, ESSG, AMOR, spondenogative enthethesopathy and arthropathy (SEA) and MODified New York (NY) criteria for SpA and A nkylosing Spondylitis were obtained from first visit and during disease course. Descriptive, summary statistics [sen], [sp], positive predictive value [PPV],
negative predictive value [NPV]) and Wilcoxon Rank Sum test were used.

Results: 109 patients with JSpA (104 ERA, 2 JPA, 3 UA) were included (M:93), age at onset (10–15 years), disease duration at first visit (10–15 months, follow-up time 41–12 years). Controls: 69 patients with JIA (25 oligoarthritis, 24 polyarthritis RF negative, 20 systemic). At first visit cases showed: 106 (97%) arthritis, 89 (82%) asymmetrical oligoarthritis, 69 (63%) elevated CRP, 53 (49%) limitation of lumbar spine motion, 53 (49%) HLA-B27, 44 (42%) enthesitis, 44 (40%) tarsitis, 40 (37%) low back pain (LBP), 32 (29%) good response to NSAIDS, 27 (25%) positive family history, 21 (19%) radiographic bilateral sacroiliitis grade 2–4, 14 (13%) dactylitis, 8 (7%) uveitis, 7 (6%) unilateral sacroiliitis grade 3–4, 7 (6%) history, 21 (19%) radiographic bilateral sacroiliitis grade 2–4, 14 (13%) HLA-B27, 46 (42%) enthesitis, 44 (40%) tarsitis, 40 (37%) low back pain, 0.05 considered significant.

Conclusion: Gender advantage in JAS was more obvious, and JAS had onset more often with peripheral arthritis than with Spinal symptoms. Hip joint involvement was more common in JAS than AAS. The femoral neck BMD was reduced much seriously in JAS compared with that in AAS, while there was lower incidence of ophthalmia in JAS than AAS, clinicians should focus on the different manifestations in JAS and AAS, so as to make early diagnosis, provide aggressive treatment and prevent complications.

Disclosure: Z. Lin, None; J. Qi, None; J. Gu, None; P. Zhang, None.

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Positive HLA-B27 in Juvenile Spondyloarthropathies Is Associated to Early Sacroiliitis and Progression to Ankylosing Spondylitis. M. Ariana O. Perez1, Nadia E. Alkalawi2, Solange Carneiro3, Percival D. Sampaio-Barros4, Celso R. Gonçalves5, Carla G. S. Saad6, Julio C. B. Moraes7 and Claudia Goldenein-Schainberg8. 1University of Sao Paulo, Sao Paulo, Brazil. 2Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.

Background/Purpose: Juvenile spondyloarthropathies (JSpA) manifests with axial and peripheral involvement, enthesis and HLAB27+ in 60–90% children. Radiological sacroiliitis may occur within 10 years, representing an important prognostic factor. To determine initial and long term clinical profiles of JSpA patients from a single tertiary university center; HLAB27 prevalence and relationship with disease progression to ankylosing spondylitis (AS), according to ASAS criteria.

Methods: Descriptive cross-sectional study of a cohort of JSpA subjects. Demographic, clinical and radiological data were obtained by chart review and HLAB27 tested by flow cytometry (Becton Dickinson). Fisher and McNemar’s tests were used for statistical analyses and p<0.05 considered significant.

Results: Fifty patients with JSpA were evaluated, mean age=31.5±11.1yrs (15-60), mean age at onset=12.2±7.3yrs (7-16), mean age at diagnosis=19.8±9.6yrs (7-44), mean disease duration=18.9±11.4yrs (3-44). Most were males (44M:6F,88%) and whites (n=48,28%). Eleven (22%) children had a 1st-degree relative with SpA and 87% (34/39) were HLAB27+. At diagnosis (Table), peripheral manifestations prevailed, particularly asymmetric oligoarthritis while axial involvement was mainly inflammatory back and buttocks pain; 21 (42%) had enthesitis, all at the Achilles insertion; major extra-articular manifestation was anterior uveitis. After a mean follow up period of 12.8±9.1yrs (1-45), 5 patients were lost, axial involvement was predominant, none had uveitis and enthesitis remained in 13/21 (Table). Radiological sacroiliitis developed in 96% (n=48) patients: 41.7% (n=20) =5yrs, 16.7% (n=8) within 6–10yrs and 41.7% (n=20) >10yrs of initial symptoms. Remarkably, HLAB27+ children had earlier sacroiliitis =5yrs of diagnosis (p=0.02), high ESR at diagnosis (p=0.04) and developed AS (p=0.02). Sacroiliitis progression was not prevented (p>0.05) during daily NSAID therapy intake by all patients. Sulfasalazine was used by 86% and MTX by 72%. Currently 49% are receiving anti-TNF drugs.

Table: Clinical manifestations of patients with JSpA

<table>
<thead>
<tr>
<th>At Diagnosis (n=50)</th>
<th>Currently (n=45)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry oligoarthritis</td>
<td>24 (68.5)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Symmetry enthesitis</td>
<td>1 (2.1)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Symmetry tarsitis</td>
<td>10 (28.5)</td>
<td>5 (28.4)</td>
</tr>
<tr>
<td>Axial pain</td>
<td>29 (58)</td>
<td>43 (95.5)</td>
</tr>
<tr>
<td>Axial pain</td>
<td>22 (75.8)</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>25 (86.2)</td>
<td>18 (41.8)</td>
</tr>
<tr>
<td>Extra-articular</td>
<td>14 (28)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>12 (85.7)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (14.3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>21 (42)</td>
<td>13 (28.8)</td>
</tr>
<tr>
<td>Calcaneus</td>
<td>21 (100)</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>Hips</td>
<td>0</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Spinal process L5</td>
<td>0</td>
<td>2 (15.3)</td>
</tr>
</tbody>
</table>

Conclusion: Brazilian JSpA patients are typically white males with initial peripheral joint and enthesitic involvement that progress to axial disease. The high prevalence of HLAB27+ in JSpA associated to early sacroiliitis, elevated ESR at diagnosis and development of AS strengthen its role as a genetic marker of disease severity in children.
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Background/Purpose: Cardiovascular disease is the leading cause of mortality in the rheumatoid arthritis (RA) population. However, cardiovascular risk factors such as hyperlipidemia are undertreated in patients with RA compared to other high risk groups like diabetics. We examined the effectiveness of two interventions to increase screening for hyperlipidemia among patients with RA within the rheumatology practice of an academic medical center.

Methods: Interventions included a web-based survey regarding attitudes towards lipid screening in patients with RA sent to physicians in the division of rheumatology at the University of Pennsylvania on 1/6/14 and posters and flyers about cardiovascular risk in inflammatory arthritis posted in each clinic’s check-in area and exam rooms between 2/1-2/28/14. A query of our electronic health record was used to generate a list of patient visits with an ICD-9 code for RA seen in the practice between 7/1/13-4/15/14. Charts were reviewed for a random sample of 100 patient visits for the periods before and after the interventions (7/1-11/14 and 2/1-4/15/14 respectively). Patients were excluded if the rheumatologist had not documented a diagnosis of RA in the encounter note. If multiple visits for the same patient were found in the sample, the last visit in that period was used. The outcome was achieved if lipid screening was documented as performed in the encounter note or if results were recorded in the encounter note or in the laboratory section within 3 years of the visit date. The prevalence of up to date lipid screening in each period was assessed, and the groups were compared using the chi-squared test.

Results: Seventy-eight patients in the pre-intervention group and 82 in the post-intervention group satisfied inclusion criteria. Demographics are listed in the Table. Lipid screening was considered up to date in 39 of the 78 patients (50.0%) in the pre-intervention group and 57 out of the 82 patients (69.5%) in the post-intervention group (p=0.01).

Conclusion: Among patients with RA, the management of traditional cardiovascular risk factors, including lipid screening, is suboptimal. Flyers and posters increased the prevalence of documented lipid screening in the short term. The survey of physician attitudes towards lipid screening likely also increased awareness of practice patterns among rheumatologists. Further quality improvement initiatives are needed to identify long term solutions to improve the recognition and management of traditional cardiovascular risk factors among patients with RA.

Table. Demographics of the Pre and Post Intervention Groups

<table>
<thead>
<tr>
<th>Practice</th>
<th>Before N = 78</th>
<th>After N = 82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presbyterian Medical Center</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Perelman Center</td>
<td>61</td>
<td>51</td>
</tr>
<tr>
<td>Fellows’ Clinic</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Age- Median (Range)</td>
<td>60 (27-89)</td>
<td>60 (30-87)</td>
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<tr>
<td>Gender</td>
<td>Female</td>
<td>63 (81%)</td>
</tr>
<tr>
<td>Primary Care Physician Location</td>
<td>Outside of the University of Pennsylvania System</td>
<td>53 (68%)</td>
</tr>
<tr>
<td>Diabetic Disease Activity</td>
<td>Not Recorded</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Remission</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>9</td>
</tr>
<tr>
<td>Lipid Lowering Drugs Used</td>
<td>Statin</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Fish oil/Omega-3-acid ethyl esters</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Flaxseed oil</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate</td>
<td>1</td>
</tr>
</tbody>
</table>

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Quality of Care for Cardiovascular Prevention in RA: Compliance with Diabetes Screening Guidelines. Timothy J Schmidt1, J Antonio Avina-Zubia2, Eric C. Sayre3, Michal Abrahamowicz4, John M. Esdaile5 and Diane Lacaille6. 1University of British Columbia, Department of Experimental Medicine, Vancouver, BC, 2Arthritis Research Centre of Canada, Richmond, BC, 3M CIU University, MONTREAL, QC, 4University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, 5Arthritis Research Centre of Canada, Vancouver, BC.

Background/Purpose: Comorbidities are increasingly recognized as significant contributors of decreased quality of life, and increased mortality in RA. RA is associated with an increased risk of diabetes and cardiovascular mortality. Previous research suggests that RA populations receive suboptimal care for their non-RA health related issues.

Our aim was to evaluate the quality of care for cardiovascular disease prevention in RA by measuring compliance with general population diabetes screening guidelines in RA compared to the general population.

Methods: We conducted a retrospective matched cohort study among patients with RA who received care between Jan 1996 and Mar 2006 and followed up until Dec 2010. A case was selected if they had ≥ 2 MD visits more than 2 mos apart with an RA code. Cases were excluded if they had ≥ 2 subsequent MD visits for other inflammatory arthritis; if they saw a rheumatologist and RA diagnosis was never confirmed; or if there were no subsequent RA diagnoses over a follow-up > 5 yrs (N=36,458). Controls were selected from the general population and matched 1:1 to RA cases on gender, age, and calendar year. Administrative data was obtained on all physician visits, hospital admissions, tests ordered and medications.

Outcome: Compliance with current screening guidelines for diabetes defined as testing for plasma glucose (PG) at least once every 3 years for individuals ≥ 45 years, excluding individuals with previous diabetes. Individuals’ follow-up was divided into 3-year eligibility windows, when they were eligible for the screening guideline. Each individual could contribute up to four three-year eligibility windows. Compliance was measured as the proportion of eligible windows with at least one PG test performed within the time period. Compliance rates between RA and controls, using eligibility windows as the unit of analysis, were compared via a GEE model to account for the lack of independence of observations obtained from the same patient, adjusting for age and gender. Compliance rate per patient was also calculated.

Results: We identified 27,650 individuals with RA (68.8% female, mean [SD] age 62.5 (12.9) yrs), contributing 49,515 three-year eligibility windows; and 30,486 controls (68.6% female, age 62.5 (12.9) yrs), contributing 62,942 three-year eligibility windows. Overall, PG was measured in 71.2% of the eligible time windows in the RA sample and in 74.4% for controls (OR = 0.89 [95% CI; 0.86, 0.92], p<0.0001). RA individuals met the recommended screening guidelines in 72.1% (SD = 37.1%) of their eligible time windows, compared to 74.1% (SD = 35.3%) for controls (p<0.001).

Conclusion: Compliance with screening guidelines for diabetes was slightly lower in our RA cohort than the general population. Although the difference was statistically significant, it may not be a clinically relevant difference. Regardless, given the increased prevalence and burden of cardiovascular diseases in RA, diabetes screening is sub-optimal for RA individuals.

Disclosure: T. J. Schmidt, None; J. A. Avina-Zubia, None; E. C. Sayre, None; M. Abrahamowicz, None; J. M. Esdaile, None; D. Lacaille, None.

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Cardiovascular Disease Prevention in Rheumatologic Disease: Assessing Screening in a Primary Care Setting. Micaela Bayard1 and Magdalena Cadet2. 1New York Hospital of Queens/ Weill Cornell Medical Center, New York, NY, 2Duke University School of Medicine, Durham, NC.
**Background/Purpose:** To determine the proportion of patients diagnosed with rheumatologic disease receiving preventive cardiovascular care according to US Preventive Services Task Force recommendations with emphasis on hypertension, dyslipidemia, and glucose tolerance screening. Cardiovascular disease is the most prevalent co-morbidity for patients with Rheumatoid Arthritis, specifically ischemic heart disease. Studies have shown that more than half of premature deaths in people living with Rheumatoid Arthritis are attributable to cardiovascular disease. Studies also demonstrate a significantly increased risk of coronary artery disease in other inflammatory diseases including Systemic Lupus Erythematosus, Gout, and Psoriatic Arthritis. Enhanced atherosclerosis in rheumatic disease is a result of higher rates of systemic inflammation. Despite the recognized risk of cardiovascular disease in rheumatologic disease, little is known about cardiovascular risk management in these patients.

**Methods:** Clinical data from June 2013 to November 2013 was abstracted from outpatient electronic medical records of patients seen in rheumatology clinic with primary care follow-up with one of the following International Classification of Diseases, Ninth Revision (ICD-9) codes: Rheumatoid Arthritis (714.0), Systemic Lupus Erythematosus (710.0), Psoriatic Arthritis (696.0), and Gout (274.0). 69% had Rheumatoid Arthritis, 13% had Systemic Lupus Erythematosus, 18% had Psoriatic Arthritis, and 13% had Gout, this included patients with more than one of the 4 ICD-9 codes. Charts were reviewed for blood pressure testing at the most recent primary care visit, a lipid profile within the last year, and glucose or Hemoglobin A1C testing within the last year. These probabilities were summarized and compared between disease categories using Pearson's chi-square test.

**Results:** A total of 46 men and 121 women, with a mean age of 55.2 years, were identified. 79 were identified by having at least one of the four target ICD-9 codes. In this cohort, 100% were screened for hypertension, 24% for hyperlipidemia, and 27% for diabetes. Of the women, 100% were screened for hypertension, 24% for hyperlipidemia, and 29% for diabetes. There was no significant difference in screening between men and women. Rheumatoid Arthritis patients were more likely to be screened for diabetes, when compared to patients with Systemic Lupus Erythematosus, Gout, or Psoriatic Arthritis (49% vs 12%, p < .05).

**Conclusion:** This data suggests that patients with rheumatologic diseases known to accelerate risk for cardiovascular disease are not being consistently screened in primary care settings. The data also suggests that physicians may be more aware of recommendations for cardiovascular screening in rheumatoid arthritis and less in other rheumatologic diseases. Although traditional cardiovascular risk factors may be suboptimal screening tools for patients with rheumatologic disease, studies must first identify gaps in existing screening and intervention. Further research is needed to develop cardiovascular screening guidelines and risk stratification models, as seen in diabetes, which are specific to rheumatologic disease.

**Disclosure:** M. Bayard, None; M. Cadet, None.

### Quality of Care for Cardiovascular Disease Prevention in RA: Compliance Lipid Screening Guidelines

**Background/Purpose:** Previous studies quantifying delays in assessment of patients by rheumatologists have studied patients from rheumatology clinics and thus include all patients who ultimately had an rheumatologists. Our study estimates overall wait times for initial rheumatology consultations for patients referred by their primary care physician.

**Methods:** We employed a novel approach to identify first-time rheumatology referrals from the primary care Electronic Medical Record Administrative data Linked Database (EMRALD), representing comprehensive EMR data from 168 primary care physicians across Ontario, Canada (32 rural, 39 suburban and 97 urban physicians). We randomly sampled patients with rheumatology referral letters and performed linkage with administrative data to retrospectively confirm that patients had no prior rheumatologist assessments. Using a standardized data abstraction tool, the entire patient medical record was reviewed to categorize each patient according to their diagnosis: systemic inflammatory conditions, mechanical/degenerative/arthritis conditions, chronic pain, regional musculoskeletal (MSK) syndromes, osteoporosis/osseopathies, and other (e.g., abnormal diagnostic tests). Administrative data were then used to identify the date of the first rheumatologist visit subsequent to the date recorded on the referral identified in the EMR. The time in days from the date the first referral letter was sent to the date of the first rheumatologist visit was determined overall and for each diagnostic category.

**Results:** Among 1086 patients with first-time referrals, 99% of referrals analyzed occurred between 2006 and 2013. The majority of referrals were for mechanical/degenerative conditions (34%) and systemic inflammatory conditions (30%). Overall, 36% of patients were seen by a rheumatologist within 6 weeks from referral and 67% within 3 months. 68 (6%) patients were waiting longer than 12 months to be seen (Table). The average wait time to...
see a rheumatologist for any condition was 142 days (median 61) post-
referral. For patients with systemic inflammatory conditions, the median
time to be seen was 47 days (interquartile range 18–97). The median wait times
for individuals with conditions deemed non-urgent (osteoarthritis, chronic pain)
were roughly 2 weeks longer.

**Conclusion:** Using EMRs from a representative sample of Ontario primary
care practices revealed longer wait times to see a rheumatologist than previous
Canadian reports that sampled patients from urban rheumatology clinics. 33% of
patients were still waiting >3 months to be seen, exceeding current Canadian
recommendations. With individual systemic inflammatory conditions were seen
earlier compared to other types of referrals. A time series analysis of wait times across each
component of the care pathway is currently underway.

**Disclosure:** J. Widdifield, None; C. Bombardier, None; J. C. Thorne, None; R. L. Jaakkilainen, None; J. M. Paterson, None; S. Bernatsky, None; J. Young, None; L. Wing, None; N. Ivers, None; D. Butt, None; V. Poon, None; V. A. Ahluwalia, None; K. Tu, None.

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**2310**

**Improving Access to Health Care in Rheumatology Practices through Initiation of an Outpatient Urgent Care Clinic, a Paradigm Shift.** Ruchi Jain, Menashki Jolly, Theodore Pincus, Isabel Castrejon, Annie Huang and Joel A. Block. Rush University Medical Center, Chicago, IL.

**Background/Purpose:** Urgent care clinics are built into some primary
care practices, but no reports are available of urgent care clinics in rheumatology
settings. Many rheumatologists currently reserve slots in their sched-
ules to accommodate patients with urgent needs. However, this practice may
be inadequate as the slots may become filled by waitlisted, follow-up, or new
patients under care at an academic rheumatology setting who had
issues that could not wait until their next appointment, as well as for
recently discharged inpatients with need of early outpatient follow up. A control group of 100 patients seen sequentially in routine care was
identified, and compared to the urgent care group using t-tests and chi
square tests. Each patient in the control and urgent care group completed a multidimensional health assessment questionnaire (MD-HAQ) at each visit as part of routine care, with scores for physical
function, pain, patient global assessment, RA P A D 3 (routine assessment
of patient index data), and demographic data. Each physician scored a
contemporary physician global assessment. An additional survey for urgent care clinic patients queried if patients would have gone
to the ER if not seen today (Yes or No) and the level of the patients’
confidence that future urgent concerns would be met (0—no confidence
at all; 10—great confidence).

**Results:** Demographics of the 42 patients and 100 controls are in Table 1. Those seen in the urgent care clinic were older, less likely to work full time,
and more likely to have osteoarthritis than the controls. M D-H A Q scores were
significantly higher in the urgent care clinic vs controls (Table 1), 61% of
urgent care patients reported that they would have gone to the ER if the urgent
care clinic were not available, and mean confidence score of patients in the
urgent care clinic group was 9.75 on a 0–10 scale.

**Conclusion:** Patients seen in the urgent care clinic had poorer clinical
status than control patients, with higher patient and physician scores. 61%
would have gone to the ER had they not been seen in the urgent care clinic.
These patients also expressed high confidence that timely access would be
available in the future. Improved patient access for urgent needs may be met
by a dedicated urgent care clinic.

**Disclosure:** R. Jain, None; M. Jolly, None; T. Pincus, None; I. Castrejon, None; A. Huang, None; J. A. Block, None.

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**2311**

**Tele-Rheumatology: Despite Improved Access Could There be a Potential Delay in Care without a Skilled “Presenter”?** Zsolt Kulcsar1, Daniel A. Albert2, Krista Merrihew3 and John M. Chehella4. 1Dartmouth Hitchcock Medical Center, Lebanon, NH, 2The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, 3Dartmouth-Hitchcock Medical Center, Lebanon, NH, 4Giesel school of medicine and Dartmouth Hitchcock Medical Center, Lebanon, NH.

**Background/Purpose:** A tele-rheumatology initiative was implemented in New Hampshire (NH) by a large proportion of the population lives in rural areas
(60%) with limited resources and access to care. Tele-rheumatology services
developed at Dartmouth-Hitchcock Medical Center (DHMC) in partnership with
Weeks Memorial Hospital (Critical Access Hospital in Northern NH) bring
rheumatologists to rural areas, thus improving access. In addition to the
diagnosis and treatment of patients utilizing a “presenter,” an individual who sits
with patients at the remote site (medical assistant, nurse, etc.) to facilitate the visit.
We sought to learn what challenges and accomplishments our early tele-medicine
program has encountered since inception.

**Methods:** As part of a quality improvement initiative we performed an
IRB-exempt retrospective review of the charts for patients seen in the
tele-rheumatology clinic at DHMC from October 2011 to January 2013. We
evaluated the participants: including providers, presenters and patients
regarding their experience of care. We used descriptive statistics to summarize
our findings.

**Results:** In our cohort of 22 patients there were 63 encounters (18 initial
consults and 45 follow-up visits) with either of the two participating
rheumatologists. 27% (n=6) of the patients seen initially by tele-
rheumatology needed to be seen in-person for clarification of the joint exam.
83% (n=5) of the patients seen in-person had findings of synovitis not seen
together. The average time from initial consult to in-person evaluation
was 81 days. These patients without aggressive anti-inflammatory
therapy for longer than the recommended 42 days (6 weeks) according to
current guidelines. Providers expressed concern about being unable to lay
hands on patients, and the inability of the “presenter” to perform and convey
the findings of the joint exam which may have contributed to the delay in care.
The two top diagnosis that patients presented with during the tele-
rheumatology visits were inflammatory arthritis (n=10) and fibromyalgia
(n=9). 40% of the patients seen by tele-rheumatology were ultimately started
on high risk medications such as high dose steroids \( (>20\text{mg/daily}) \), biologics, and DMARDs (Table 1).

**Conclusion:** The use of tele-rheumatology has successfully increased access to arthritis care in rural regions of NH allowing for shorter travel and intensive anti-inflammatory therapy. The lack of musculoskeletal training for the presenter and inability of providers to lay hands on patients could lead to increased delay in initiation of this therapy for inflammatory arthritis. Initial strategies are being developed to improve the training of the presenters and to shorten this interval to meet current guidelines.

**Table 1. Dartmouth-Hitchcock Medical Center Tele-rheumatology Services Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providers</td>
<td></td>
</tr>
<tr>
<td>Patients seen by Provider #1</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Patients seen by Provider #2</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>Total # of Patients seen since inception</td>
<td>22</td>
</tr>
<tr>
<td>Total # of visits</td>
<td>63</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Age (avg. in years)</td>
<td>56.8</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>12 (54.5)</td>
</tr>
<tr>
<td>Avg. Distance from home to DHMC one way (miles)</td>
<td>9.96</td>
</tr>
<tr>
<td>Avg. Distance from home to Weeks Memorial (miles)</td>
<td>10.7</td>
</tr>
<tr>
<td>Visit Type (# of encounters)</td>
<td></td>
</tr>
<tr>
<td>Consult</td>
<td>18 (28.6)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>45 (71.4)</td>
</tr>
<tr>
<td>Required in-person follow up for joint exam</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Avg. time from initial visit to in-person follow-up (days)</td>
<td>80.8</td>
</tr>
<tr>
<td>Discrepancy in joint exam after in person visit</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Started on high risk medication</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Diagnosis Seen in Clinic</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Inflammatory Arthritis (RA, PsA, Ank Spon)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td>Osteoarthritis (DJD)</td>
<td>2 (9.0)</td>
</tr>
<tr>
<td>Crystal Arthropathy (Gout, CPPD)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

RA = Rheumatoid Arthritis, PsA = Psoriatic Arthritis, Ank Spon = Ankylosing Spondylitis, CPPD = Calcium Pyrophosphate Dihydrate Crystal Deposition Disease, DHMC = Dartmouth-Hitchcock Medical Center.

1. Miles calculated using zipcodes.com calculator.
2. Synovitis appreciated on exam which was not seen initially via telemedicine.
3. DMARDs (i.e., methotrexate), colchicine, high dose steroids (equivalent of prednisone >20 mg daily), denosumab.
4. Diagnosis is greater than 100% as some patients had overlapping diagnosis (i.e., both rheumatoid arthritis and fibromyalgia).

**Disclosure:** Z. Kulcsar, None; D. A. Albert, None; K. Merrihew, None; J. Mecchella, None.

**2312**

**Use of Physician Extenders to Improve Quality and Efficiency of Clinical Visits.** Cahill O’Rorke, Francis Young, Lorraine O’Neill, M. Airead Murray, Philip Gallagher and Douglas J. Veale.

**Background/Purpose:** Logistical difficulties associated with managing a large, publically funded secondary service, means that service delivery is costly in terms of physician time. Patients frequently do not have medication lists with them when they attend clinic. Recent results are not available to the physician at the time of clinical visit. Disease activity scores to assist in informing clinical decisions with a treat-to-target approach, are not calculated. Patient reported outcome measures (PROM) are rarely formally assessed and recorded, because these too are often time consuming.

**Physician Extenders (PE) have been used to improve efficiency in out-patient clinics.** In this action-research endeavour, we introduced changes both to the structure and process of how return patients are assessed, making use of a PE to prepare for patient visits.

**The specific aims were:**

1. To decrease the time physicians spend with inflammatory arthropathy (IA) return patients.
2. To perform a standardised and validated measurement of disease activity for all patients.
3. To increase the proportion of patients acquiring staging hands and feet plain film radiographs every two years in compliance with the consensus of rheumatologists at the hospital.

**Methods:** The PE recorded the results of the last inflammatory markers and plain film radiographs of hands and feet in a pro-forma. Where these results were not recent (2 weeks for blood results and 2 years for radiographs), the PE liaised with a physician, on a scheduled basis, to arrange for the latter to complete this required ordering forms.

The PE assembled and mailed the pro-forma and ordering forms to returning IA patients 2 weeks in advance of their clinic visit. The pro-forma included a patient global assessment; other PROMs, e.g., HAQ-DI, SF-36; as well as an accurate current medication list. Patients were asked to complete the pro-forma, and to have the bloods and radiographs taken a few days before their appointment.

Patients presented to clinic with a self-completed pro-forma as well up to date results.

**Results:** 125 patients (85 female) with IA were sent pro-forms before their clinic visit.

Mean time a physician spent at clinic per patient was decreased from 23 minutes to 15 minutes.

120 (96.0%), patients had DAS28-CRP scores calculated, 5 (4%) did not have scores calculated because of a piece of missing data.

68/125 (54.4%) had radiographs in the three 3 years before their clinic visit. Of the 68 who had no radiographs taken during this time, 49 (72.1%) had radiographs directly as a result of this action-research.

**Conclusion:** The use of a PE in preparation for clinical visits decreases the time physicians need to spend reviewing patients, and increases the quality of the visit as measured by the collection of DAS scores, and PROMs, and relevant radiological investigations. A cost analysis needs to be done to demonstrate that this approach is cost effective.


**Disclosure:** C. O’Rorke, None; F. Young, None; L. O’Neill, None; M. Murray, None; P. Gallagher, None; D. J. Veale, AbbVie, 2, MSD, 2, Pfizer Inc, 2, Roche, 2, Pfizer, 5, Roche, 5, Abbott, 6, MSD, 8, Pfizer, 8, Roche, 8.

**2313**

**Best Practices for Better Practice Alerts: Evaluation of a Best Practice Alert to Detect Chronic Glucocorticoid Use.** Mingyuan Zhang, Catherine Staas, Kara Kapp and Karia L. Miller.

**Background/Purpose:** Chronic glucocorticoid (GC) use is known to increase risk factors for osteoporosis and fracture. Patients with chronic GC use often receive suboptimal osteoporosis prevention, diagnosis, and treatment. We sought to create a best practice alert (BPA) to identify chronic GC users in our electronic health records (EHR) to recommend bone density testing. Daily dosage and duration of prescription data were not uniformly available for building the BPA. To improve identification of these patients, our objectives were to (1) describe the quality of medication data available for triggering a BPA, (2) to prompt bone density screening for patients on chronic GCs, and (2) assess alternative criteria using existing data.

**Methods:** Our target population was patients >50 years of age on chronic GCs defined as taking >7.5mg of prednisone daily or equivalent, for 30 days or more. We extracted medication orders from the University of Utah Healthcare clinical data warehouse for all GCs ordered between July 1 and December 31, 2013 for patients >50 years. The extract included refill number, quantity dispensed, difference between order start and end date, frequency, signature, and dosage per episode. We manually reviewed and classified each order as ‘yes’, ‘no’, or ‘unable to determine’ for chronic GC use. We assessed the frequency of data available for each data field, and stratified by records created using the structured versus free-text order template. We assessed the quality of medication data available for triggering a BPA, by prompting bone density screening for patients on chronic GCs, and 2) assess alternative criteria using existing data.

**Results:** Among the 1,699 GC prescriptions identified, 17% (292) were determined to be chronic GC use; 52% (881) were entered using a structured
In the absence of daily dosage and duration information, quantity dispensed \( \geq 30 \) tablets performed best with the highest sensitivity, and mid-range PPV (Table 1).

**Conclusion:** Medication data in the EHR are subject to variability and detecting chronic medication use requires adequate evaluation of medication data quality, available data fields, and clinician practice patterns. This is particularly challenging with GCs given their widespread use both chronically and in short-term tapers. Successful alert designers must evaluate both the accuracy of data used to generate an alert, and triggering criteria, to improve identification of the desired population.

**Disclosure:** M. Zhang, None; C. Staes, None; L. Kapp, None; K. L. Miller, None.

### 2314

**Dexa Testing in Long-Term Steroid Use.** Beth Scholz, University of Texas Health Science Center at Houston, Houston, TX.

**Background/Purpose:** Risk stratification in the ACR glucocorticoid-induced osteoporosis guidelines includes DEXA testing, which is not universally implemented at our rheumatology clinic. DEXA utilization should be increased to screen for this effect of glucocorticoid-induced osteoporosis guidelines includes DEXA test-

**Methods:** As a quality improvement project, institutional policy exempted this study from IRB review. As a baseline, charts were reviewed from 50 patients on steroids (equivalent to prednisone \( \geq 5 \) mg/day, \( \geq 3 \) months) seen in rheumatology clinic in August 2013. DEXA status was categorized as never, current, or out-of-date (\( > 2 \) years ago). Patient gender, menopausal status, steroid dose, and duration of steroid use were also recorded. Then a medication monitoring questionnaire (see Figure 1) was administered to all patients at the time of visit during the intervention pilot period in January 2014 with the intention of triggering more DEXA orders by providers. Other drugs and monitoring tests were included on the form for clinical utility but were not measured for this project. Charts from the 44 patients on qualifying steroid therapy seen during the pilot period were reviewed.

**Results:** During the baseline period, 32% of patients had a current DEXA. Status distribution was similar regardless of menopausal status or prednisone dose (\( > 5 \) versus \( \leq 5 \) mg/day). Of 9 male patients, 7 (78%) had current DEXA as opposed to 10 of 41 female patients (24%). During the intervention period, current DEXAs (including DEXAs ordered at the visit) increased to 48% (see Figure 2). The number of patients with "never" status was similar; most of the gain to "current" status resulted from updating DEXA testing.

**Conclusion:** A medication monitoring questionnaire at routine clinic visits can serve as a reminder to trigger appropriate DEXA orders in patients on long-term steroids. This intervention could be modified for other chronic medication monitoring parameters as well. Future interventions will target increasing FRAX calculation and documentation.

**Disclosure:** B. Scholz, None.

### 2315

**Glucocorticoid Induced Osteoporosis Screening and Treatment in a Cohort of Male Patients with Underlying Rheumatologic Diagnosis in a Tertiary Care Setting.** Hajra Shah, Narender Annapureddy, Joel A. Block and Ruchi Jain. Rush University Medical Center, Chicago, IL.

**Background/Purpose:** One-fourth of hip fractures occur in men. Three groups of men are at high risk for fracture: those who have already suffered a fragility fracture, those treated with androgen deprivation therapy for prostate cancer, and men treated with oral glucocorticoids for at least 3 months. Rapid bone loss occurs in the first 3 months of steroid use, peaks at 6 months and slows with continued use. In addition hypogonadism in chronic disease also may contribute to fracture risk. Men with rheumatic diseases taking glucocorticoids may not receive adequate screening or treatment compared to females. The American College of Rheumatology recommends that males over age 50 who take chronic glucocorticoids be screened for treatment and prevention of osteoporosis (OP). We assessed adherence to these guidelines in a busy academic practice.

**Methods:** A retrospective chart review identified male patients 50 years or older with a rheumatic diagnosis seen from 2010 to 2013. Inclusion criteria were 1. Patients who received any dose of prednisone...
for at least 3 months; and 2. Seen for at least 3 clinic visits. Exclusion criteria were 1. Recognized osteoporosis; and 2. Prior bisphosphonate use. Most patients had incident prednisone use. We collected demographic data, dose and length of steroid use, timing of DXA from initiation of prednisone use, T-score and calcium and vitamin D supplementation use. We defined appropriate care as screening with a baseline DXA within 6 months of initiation of prednisone, calcium and vitamin D supplementation and bisphosphonates with clinical evidence indicated. Patients not meeting these criteria were defined as receiving sub-optimal care. Fisher’s exact test was used to compare categorical variables.

Results: 100 patients met inclusion criteria; 50% were Caucasians with a mean age of 63.4 (SD 8.4 (51 - 85)) and had rheumatoid arthritis. 76% were taking >7.5 mg of prednisone or higher for at least 3 months and 62% for greater than 12 months. T-scores were available for 57 patients. 61% of patients were found to be abnormal. 53% were treated with calcium and vitamin D and only 31% with bisphosphonates when indicated. 78% of the patients received sub-optimal care for glucocorticoid induced osteoporosis (GIOP) management. 35% of junior faculty (< 5 years out of fellowship) compared with 13% of senior faculty (≥ 5 years from fellowship) managed patients appropriately (P = 0.014). OP screening for Vasculitis and PMR was more likely compared to other diseases (Figure 1).

Conclusion: The majority of patients who took significant amounts of prednisone for > 3 months received sub-optimal osteoporosis care. To our knowledge, this study is the first to analyze this problem, and identifies a potential gender gap in management of OP in a vulnerable population with inflammatory diseases taking steroids. More vigilance appears needed to

Methods: We identified new denosumab users billing data between June 2010 and October 2013 based on HCPCS code J0897 or J3590 with denosumab as the listed biologic. Patients had at least 183 days (6 months) follow-up and were administratively censored at two years post-denosumab initiation, for death, or on 6/1/2014 (end of study period). These data were linked to electronic medical record data and only included patients who had at least two office visits in a rheumatology clinic. Patient characteristics were assessed prior to first administration. A difference to denosumab was assessed with the proportion of days covered (PDC) follow-up period (censoring at 2 years, capping interval for denosumab). After initiation, PDC was calculated at a maximum of one and two years or censored at study end. We defined a patient as adherent if they had ≥80% of days covered. Results are presented as mean (standard deviation [SD]) or %.

Results: Five hundred patients met inclusion criteria. Included patients had a mean age of 71.9 (SD 11.0), 92.6% were women, and 88.8% Caucasian. Denosumab was the first AOM in 9.8% of patients. In those with a history of previous therapy, a mean of 2.3 (SD 1.5) AOM’s were prescribed. Prevalent fractures were present in 32.8%, mean Charlson Comorbidity score of 2.0 (SD 2.7), and 25% had diagnoses for either gastric ulcers or GERD at first denosumab administration. Eighty-three percent of patients had 12 months follow-up and 26% had 24 months of follow-up. Two denosumab injections were given in 82.3% of patients, 53% of patients received 3 injections, and 4 in 30% of patients. Of those that didn’t receive a second administration, 7% were prescribed another AOM. Mean 1 year PDC, 85.5% (SD 19.0), and 80.7% (SD 21.6) at 2 years. PDC ≥80% was achieved in 72.8% and 62.0% of patients at 1 and 2 years, respectively.

Conclusion: In patients treated with denosumab 72.8% of patients were adherent at 12 months and 62.0% were adherent at 24 months. Only 9.8% of patients started on denosumab were treatment naı ¨ve. Adherence rates were higher than those reported for oral bisphosphonates. Other studies have suggested that higher adherence rates for denosumab may be related to in-office administration, patient preference and convenience, and a favorable side effect profile. Since studies have suggested that adherence rates <50% are associated with little anti-fracture effect, the greater adherence with denosumab may have important implications for fracture prevention.

Disclosure: R. A. Overman, None; J. C. Lauffenburger, None; M. L. Gourlay, None; C. L. Deal, None.

2317
Towards Reliable Implementation and Optimal Use of Medication Decision Aid Cards for Shared Decision Making in Juvenile Idiopathic Arthritis

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Background/Purpose: The purpose of the study was to improve communication and shared decision-making (SDM) between clinicians and parents of patients with juvenile idiopathic arthritis (JIA), and patients with JIA, regarding the choice of medication. SDM aims to ensure medication choices match families’ goals and preferences. A treatment plan that is a good fit may be more reliably implemented at home, leading to better health outcomes. This project aimed to develop reliable care processes within a subset of centers in the Pediatric Rheumatology Care & Outcomes Improvement Network (PR-COIN) to 1) identify patients with JIA facing a decision to start or switch medicine, 2) provide SDM support during visits with our JIA ‘medication discussion cards’ that we developed and 3) measure the outcomes that accrue. Tests of implementation strategies across sites followed the Model for Improvement.

Methods: Volunteer PR-COIN sites employed iterative Plan-Do-Study-Act cycles to reliably implement the materials. To track the quality of interaction and the fidelity of use with the SDM cards, sites collected a short, voluntary, anonymous survey from parents after the visit. The post-visit survey contained information from two validated scales: 1) CollaborAte is a 3-item measure of SDM (scale range 0 - 100); 2) SURE is a 4-item measure of unmet decision support needs (scale range 0 - 4). The survey also contained 3 parent-report items that we developed with yes/no response options to assess the extent to which the decision aid cards were used as intended during the visit, or “fidelity of use.” The first fidelity item asks parents “Did you discuss starting or switching medicine to treat your child’s arthritis?” The

Figure 1. More

Figure 1.

Diagnosis

Percentage

Adherence

Non-Adherent

Adherent

(%)
second item shows a picture of the cards and asks “Did your clinician show you the tool (pictured) during your visit?” The third item asks, “If ‘yes’, did your clinician ask you to pick the first topic to discuss?” Outcomes were tracked on run charts including: proportion of eligible patient visits where ‘JIA medication discussion cards’ were used, percent of card use visits with cards used as intended. Separate run charts depict the weekly mean score for each proximal decisional outcome measure.

Results: 78 surveys were collected from 3 sites from March – June 2014. Decision aid cards were used in 33% of visits where a parent reported a medication start or switch. Cards were used as intended during 71% of visits. There was a ceiling effect with both outcome measures. CollobARATE scores were 100 for all but 3 parents, one who reported card use and two who did not. Of 78 parents had maximal SURE scores; the two parents with the greatest number of unmet decisional needs did not report use of the cards.

Conclusion: Uptake of decision aid cards was achieved in approximately 1/3 of visits where a parent reported a medication start or switch. When cards were used, there was moderate fidelity (71%) to intended use. Due to ceiling effects it was difficult to estimate if the use of cards was associated with improved proximal decisional outcomes. Next steps are to collect a different measure of decisional quality and expand the number of sites assessing outcomes, including a control site. We will develop and test new approaches with PDSAs to increase reliability and fidelity of use.

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2318
Increasing Rates of Remission in Juvenile Idiopathic Arthritis through a Quality Improvement Learning Network - the Pediatric Rheumatology Care and Outcomes Improvement Network.

Esi Morgan DeWitt1, Stacy P. Ardon1, C. a pri Bingham1, Beth S. Gottlieb4, Ronald M. Laxer2, Nancy Griffin3, Jesse Pratt4, Anne Paul5, Daniel Lovell6, Juddyn C. Olson7, Murray H. Passo8, Jennifer E. Weiss9, Tzielan C. Lee10, Sheetal S. Vora11, Melissa M. Hazen12 and Peter Margolis13.

Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 2Ohio State University College of Medicine, Columbus, OH, 3Penn State Hershey Children’s Hospital, Hershey, PA, 4Cohen Children’s Medical Center of New York, New Hyde Park, NY, 5The Hospital for Sick Children, University of Toronto, Toronto, ON, 6Division of Rheumatology, Cincinnati Children’s Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, OH, 7Medical College of Wisconsin, Milwaukee, WI, 8Medical University of South Carolina, Charleston, SC, 9Joseph M Sanzari Children’s Hospital, Hackensack University Medical Center, Hackensack, NJ, 10Stanford University School of Medicine, Stanford, CA, 11University of North Carolina Chapel Hill, Chapel Hill, NC, 12Boston Children’s Hospital, Boston, MA, 13Cincinnati Children’s Hospital, Cincinnati, OH.

Background/Purpose: The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) since 2011 has used quality improvement (QI) methods, chronic illness care model interventions, and a modified, sustainable, Breakthrough Series Collaborative approach to operations. As the network matures in use of population management and pre-visit planning interventions measureable improvements in remission outcomes for children with juvenile idiopathic arthritis (JIA) are being realized.

Methods: Teams conduct Plan-Do-Study-Act cycles using the Model for Improvement. Sites contribute data to a shared registry. Informed consent is obtained from patients for research uses. Data is displayed in run charts, funnel charts, and Pareto charts. Strategies for the Use of the Population Management Tool include peer review of patients with more than mild disease activity assessed by Physician Global Assessment >3 with decision support treatment algorithms. Pre-visit planning increases reliability of completion of process measures of care (medication safety lab tests, ultrasound eye screening) and flags patients for needed services such as PT, OT, or if there is inadequate disease control. Patients are being engaged at network and local levels to inform priorities and contribute to improvement work. Teams share resources, materials and best practices on monthly webinars, “Learning Labs”, and semi-annual face-to-face “learning sessions”.

Results: 26 of 11 participant sites submit data to the registry (ACR Rheumatology Clinical Registry). 1,457 patients contribute 7,040 encounters. Rates of clinical remission on medication for 6 months were statistically increased from baseline of 37.2% to 48.4% in the aggregate. There is variability in current site performance by >20%, with remission rates for May 2014 ranging from 39.4% – 62.7% at individual sites.

Conclusion: PR-COIN has marked a turning point from early improvement in process measures of care to demonstrable improvement in outcomes as teams are more experienced in QI methods and more reliably implementing pre-visit planning and using population management approaches. Variability in site performance provides opportunity for shared best practices. Challenges to growth have included delays in regulatory approval, and currently a single IRB model is being implemented. Double data entry is a barrier to efficient participation and teams are jointly developing “SmartForms” for electronic health records to facilitate standardized data collection and electronic data transfer. Patient engagement is a new direction expected to support enrollment and influence self-management initiatives.

Disclosure: E. Morgan DeWitt: None; S. P. Ardon: None; C. A. Bingham: None; B. S. Gottlieb: None; R. M. Laxer: None; N. Griffin: None; J. Pratt: None; A. Paul: None; D. Lovell: None; J. C. Olson: None; M. H. Passo: None; J. E. Weiss: None; T. C. Lee: None; S. S. Vora: None; M. M. Hazen: None; P. Margolis: None.

2319
Standardizing and Documenting Patient Education and Disease Indices in Childhood-Onset Systemic Lupus Erythematosus.

Julia G. Harris1, Elizabeth Roth-Wojcicki2, Marsha Malloy3, Kristyn I. Malaita4, Dominic O. Co1 and Judyann C. Olson5.

1Medical College of Wisconsin, Milwaukee, WI, 2National Outcomes Center, Children’s Hospital of Wisconsin, Milwaukee, WI.

Background/Purpose: Systemic lupus erythematosus (SLE) can affect many organ systems and lead to significant morbidities. Methods to standardize and improve care in this patient population have recently been established with development of quality indicators. Education is a common theme throughout many of the quality domains addressed. Our project sought to create a standard process for providers to educate SLE patients and their families and document its occurrence, in addition to collecting data pertaining to disease activity and damage. This pilot study will also establish baseline performance of these parameters that can lead to future quality improvement work.

Methods: Patient education materials were compiled pertaining to certain quality indicators: sun precautions, eye exams, vitamin D and calcium recommendations, smoking avoidance and cessation, risk of hypertension, risk of diabetes, weight management, exercise, and vaccination against influenza, pneumococcus, meningococcus, and Haemophilus influenzae. Previst planning identified SLE patients and what educational topics they were in need of. Teaching materials pertaining to the identified educational topics were given to the patient at each routine visit and education was provided. A SLE-specific flow sheet was created and incorporated into our electronic medical record where education was documented and tracked. Additional information including provider global assessment, parent/patient global assessment, disease activity score, and disease damage score were recorded in the flow sheet as well.

Results: Preliminary results have been recorded on 45 SLE patients during 99 clinic visits in a 15-week period from February to May 2014. A total of 162 separate educational variables (range 0–10 per person) were discussed in 88.9% of patients. The most common educational topics discussed (Table 1) and documented include: sun precautions (53.3% of patients), annual eye exams (51.1%), vitamin D recommendation (48.9%), calcium recommendation (46.7%), and pneumococcal vaccination (31.1%). Provider global assessment was recorded at least once in 93.3% of patients and patient/parent global assessment in 66.7%. Disease activity and disease damage scores were calculated in 64.4% of patients.

Conclusion: Our pilot study has been successful in developing an educational curriculum for our SLE patients, establishing a process for documenting and tracking educational topics, and creating a method for recording disease activity and disease damage parameters. Baseline performance on these measures is helpful to target areas for future quality improvement efforts.

Table 1

<table>
<thead>
<tr>
<th>Educational topics</th>
<th>Number of times discussed (range per person)</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun precautions</td>
<td>36 (0–4)</td>
<td>24 (53.3%)</td>
</tr>
<tr>
<td>Annual eye exams</td>
<td>30 (0–4)</td>
<td>23 (51.1%)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>26 (0–3)</td>
<td>22 (48.9%)</td>
</tr>
<tr>
<td>Calcium</td>
<td>24 (0–3)</td>
<td>21 (46.7%)</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>17 (0–3)</td>
<td>14 (31.3%)</td>
</tr>
<tr>
<td>Weight management</td>
<td>15 (0–2)</td>
<td>13 (28.9%)</td>
</tr>
<tr>
<td>Exercise</td>
<td>26 (0–4)</td>
<td>17 (38.9%)</td>
</tr>
<tr>
<td>Smoking avoidance</td>
<td>15 (0–2)</td>
<td>12 (26.7%)</td>
</tr>
<tr>
<td>Hypertension risk</td>
<td>7 (0–2)</td>
<td>5 (11.1%)</td>
</tr>
</tbody>
</table>
Diabetes risk  5 (0–1)  5 (11.1%)
Influenza vaccination  9 (0–4)  5 (11.1%)
Meningococcal vaccination  2 (0–2)  1 (2.2%)
Haemophilus influenzae vaccination  0 (0%)

Disclosure J. G. Harris, None; E. Roth-Wojcicki, None; M. Malloy, None; K. I. Malatta, None; D. O. Co, None; J. C. Olson, None.

2320
Initial Benchmarking of the Quality of Medical Care of Childhood-Onset Systemic Lupus Erythematosus. Ahmad I. Zaal 1, Rina Mina 1, Simone Appenzeller 1, Julia Harris 1, Marco F. Silva 2, Jilja Lee 2, Prachi Khendkar 1, Marat Aliyu 2, Josh B. Hendi 1, Anne J. Johnson 1, Jennifer L. Huggins 1, Raju Khubchandani 1, Stacy P. Ardoijn 1, M. S. Klein-Gitelman 1, Clovis A. Silva 1 and Herminie 1, Brunner 1. 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 2Facility of Medical Science, State University of Campinas, Sao Paulo, Brazil. 2Children’s Hospital of Wisconsin, Milwaukee, WI, 3Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil. "University of Cincinnati Medical Center, Cincinnati, OH," 4Askle Hospital and Research Center, Mumbai, India, 5Ohio State University College of Medicine, Columbus, OH, 6Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL.

Background/Purpose: Quality indicators (QI) are minimum standards of medical care in support of optimal disease outcomes. In childhood-onset systemic lupus erythematosus (cSLE), 26 QI’s, which are categorized into nine domains, have been developed based on international consensus and scientific evidence. The current level at which these QI’s are followed has not been well documented. Hence, the objective of this study is to assess the current quality of medical care received by patients with cSLE at tertiary pediatric rheumatology centers.

Methods: Cross-sectional data pertaining to the QI’s were acquired via chart review and analyzed collectively in 483 cSLE patients followed at seven international tertiary pediatric rheumatology centers - four in the United States, two in Brazil, and one in India. All cSLE patients followed in the participating centers were enrolled. The QI’s were adjudicated to be satisfactorily met if they were performed and documented for 80% cSLE patients they were applicable for.

Results: Adherence to the QI’s varied widely, ranging from 61 to 100%. The QI with the highest adherence (100%) fell under the Pregnancy domain. Most of the QI’s were satisfactorily met while six QI’s were not (Table 1). These six QI’s were classified under the following domains: Medication Management, General Prevention, Lupus Nephritis and Hypertension Management, Bone Health, and Education on Cardiovascular Risk Factors. A adherence to the QI’s was similar across centers, supporting the suitability and appropriateness of the current cSLE QI’s for international use.

Conclusions: In this benchmarking effort, the medical care of patients with cSLE at the participating international tertiary pediatric rheumatology centers is very good. Further efforts are warranted to improve the performance of several QI’s, especially those pertaining to Education on Cardiovascular Risk Factors.

Table 1  Adherence to the Quality Indicators

<table>
<thead>
<tr>
<th>Quality Indicators by Domain</th>
<th>Results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Testing at Diagnosis and Screening</td>
<td>96, 99</td>
</tr>
<tr>
<td>Obtained diagnostic/confirmatory labs within first two visits</td>
<td>96</td>
</tr>
<tr>
<td>Obtained lab surveillance of complete blood count, renal, liver function test every 12 months</td>
<td>99</td>
</tr>
<tr>
<td>General Prevention</td>
<td>85</td>
</tr>
<tr>
<td>Prescribed influenza and/or encapsulated organisms vaccination, unless contraindicated</td>
<td>85</td>
</tr>
<tr>
<td>Discussed and documented education on sun avoidance at least once in the medical record (e.g., wearing protective clothing, applying sunscreens whenever outdoors, and avoiding sunbathing)</td>
<td>82</td>
</tr>
<tr>
<td>Discussed transition plan to appropriate adult healthcare providers with patient age : 14 years</td>
<td>62</td>
</tr>
<tr>
<td>Lupus Nephritis (LN) and Hypertension Management</td>
<td>96</td>
</tr>
<tr>
<td>Kidney biopsy discussed/ordered/perform if developed proteinuria: &gt; 500 mg/day, or worsening glomerular filtration rate (GFR), or urinary sediment</td>
<td>96</td>
</tr>
<tr>
<td>Evaluated by a nephrologist in the last year for LN and of hypertension</td>
<td>67</td>
</tr>
<tr>
<td>Evaluated by rheumatologist every 3 months in last year if a patient has known LN regardless of disease activity</td>
<td>97</td>
</tr>
<tr>
<td>Received kidney biopsy when diagnosed with LN</td>
<td>80</td>
</tr>
</tbody>
</table>

If LN Class III/IV, treated with immunosuppressant and glucocorticoids within 1 month

Medication Management
If started new medications, discussed risk vs. benefit of therapy | 96 |
Currently prescribed any antimalarial therapy | 96 |
Attempted to taper a dose of steroids not acceptable for chronic use | 90 |
Attempted to taper and unable to decrease steroid; added/changed immunosuppressant therapy | 61 |
Surveillance for medication safety done at regular intervals | 99 |

Bone Health
Received at least one bone mineral density testing DEXA scan | 68 |
Repeat bone mineral density testing if baseline testing within normal limits (Z score < –2) | 80 |
Prescribed calcium/vitamin D if a patient is on any steroid therapy | 88 |

Ophthalmological Surveillance
Receives eye exams annually while on anti-malarial therapy | 82 |
Receives eye exams annually while on glucocorticoids | 82 |

Education on Cardiovascular Risk Factors
Education on cardiovascular risk factors (smoking, hypertension, high body mass index) every 1 year with patient and parent if patient is 13 years or older | 68 |
Discussed lifestyle modifications (smoking cessation, weight control, exercise) every 2 years with parent and patient 13 years or older | 70 |

Pregnancy
Anti-SSA, anti-SSB and anti-phospholipid antibodies have been assessed during pregnancy | 100 |

Neuropsychiatric Manifestations
Prescribed immunosuppressive therapy if patient has major neuropsychiatric manifestations in the last year of care (optic neuritis, coma, psychosis, etc.) | 94 |

Disclosure A. I. Zaal, None; R. Mina, None; S. Appenzeller, None; J. Harris, None; M. F. Silva, None; J. Lee, None; P. Khendkar, None; M. Centerville, None; H. Liu, None; J. D. Pendl, None; A. Johnson, None; J. L. Huggins, None; R. Khubchandani, None; S. P. Ardoijn, None; M. S. Klein-Gitelman, None; C. A. Silva, Fundacão de Amparo à Pesquisa do Estado de São Paulo (FAPESP 11/12471-2), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 302724/2011-7), F. Fedrico Foundation and by Núcleo de Apoio à Pesquisa “Saúde da Criança e do Adolescente, Z. H. I. Brunner, None, 2.

2321
Quality Improvement in the Identification of Crystals from Synovial Fluid: Hospital Laboratory Versus Rheumatology Department Evaluation. Joanne Szczypinski Cunha 1, Anthony Reginato 2, and Stuart Schwartz 2. 1The Warren Alpert School of Medicine at Brown University, Providence, RI, 2The Warren Alpert School of Medicine at Brown University, Providence, RI.

Background/Purpose: It has been well studied and accepted that the best method for evaluating joint disease is examination of synovial fluid. Synovial fluid analysis is critical to establish a definitive diagnosis, whether the patient has a septic joint or a crystal arthropathy. Our study aims at studying the consistency of crystal identification between the Rheumatology department and the hospital laboratories as well as identifying the factors contributing to the misidentification of crystals.

Methods: A retrospective study of synovial fluid analysis performed by the Rheumatology Department and the Rhode Island Hospital (RIH) laboratories was done over a year. Synovial fluid was gathered by arthrocentesis performed by the Rheumatology faculty for anyone with suspected crystal induced arthritis. Synovial fluid samples were analyzed by an attending physician with a compensated polarized microscope in the office and reviewed by another attending and/or fellow. Synovial fluid sent to the RIH lab was analyzed within the hour. A standard protocol was used for each sample which included cell count and differential. For this analysis the fluid was diluted with normal saline. Afterwards, part of the sample was dry centrifuged to examine for crystals. Both the wet prep of the sample as well as the dry centrifuged slides were examined by laboratory technicians for crystals. Within 24 hours, all dry centrifuged samples were reviewed by a pathologist. Results from the Rheumatology department were compared to the laboratory results on the same sample fluids.

Results: A total of 64 synovial fluid samples were examined. 18 discrepancies were found between the Rheumatology Department and the
hospital laboratories. 14 of the samples reviewed by the faculty were found to have crystals, while the laboratory reported these to be negative. A M-C
Nemar’s test was used to evaluate the data set. For each type of crystal, the p-value was not statistically significant (p-value MSU = 0.45, CPP = 0.07) but the p-value for both crystals was statistically significant at 0.02. Sensi-
tivity for each was calculated, with specificity being 100%, and compared between the faculty and the laboratory. The sensitivity for the detection of any crystals by the faculty was found to be 0.92, while for the laboratory it was 0.66. The sensitivity of MSU crystal detection by the faculty was 0.89 and by the laboratory, 0.74. Similar results were seen for the detection of CPP crystals by the Rheumatologists with the sensitivity being 0.90, while the laboratory’s sensitivity was much less, only at 0.57.

Conclusion: The results of our study are consistent with previous studies showing that there are still discrepancies in synovial fluid analysis. Many factors may be contributing to these variations including observer error, differences in time since sample collection, fluid, technician training and crystal concentration. When analyzed separately, not all of our findings reached statistical significance, but when examined together, statistical significance was met. We believe that this study has profound clinical significance. Errors in crystal detection can have serious impacts on disease management and patient care.

Disclosure J. Szczegiel Cunha, None; A. Reginato, None; S. Schwartz, None.

2322

Aim for Better Gout Control: A Retrospective Analysis of Preventable Hospital Admissions for Gout, Tarun S. Sharma¹, Thomas M. Harrington² and Thomas P. Olenginski³. Geisinger Medical Center, Danville, PA, ¹Geisinger Health System, Danville, PA.

Background/Purpose: ACR/EULAR guidelines have been published on the management of gout. Despite these guidelines, many patients with gout suffer recurrent flares and hospitalizations resulting in poor disease control and increased health care utilization. We aim to analyze the hospitalizations related to gout, determine whether these admissions were preventable and calculate imputed hospitalization costs.

Methods: A retrospective cohort of adult patients hospitalized at our institution with a primary diagnosis discharge of gout (defined as ICD-9 274, 275 or 712) from 01/01/2009 to 12/31/2013 was constructed (n=79). The primary diagnoses were validated and preventable admissions ascertained on chart review. A preventable admission was defined as an admission where the primary admitting diagnosis was a mono or polyarthritis subsequently diagnosed as gout on hospitalization and without any concomitant illness on presentation warranting admission. We reported demographic characteristics, including clinical diagnosis on admission, prior history of gout, possible risk factors for gout (Diabetes, Cardiovascular disease, chronic kidney disease, diuretic or low dose aspirin use), gout medications, serum uric acid levels within 1 year prior to admission, timing of arthrocentesis, if done, surgical procedures performed and hospitalization costs.

Results: Fifty six (56) of 79 patients were found to have adjudicated primary diagnosis of gout. Of these 56 gout admissions, 50 (89%) met the definition of preventable admission. On admission, the clinical diagnosis was septic arthritis (76%), inflammatory polyarthritis (14%) or cellulitis (8%). Of the 50 preventable admissions, 33 patients underwent arthrocentesis, 24 of which were performed in the Emergency Room. Thirty-five (35) patients (70%) had a previous history of gout and 21 (42%) had ≥3 risk factors for gout. Of the 35 patients with a prior history of gout, 74% were managed by primary care, whereas 26% were being managed by rheumatology. Of the 26 patients managed by family physicians, 8 (31%) were on urate lowering therapy (ULT) and 5 (19%) were on colchicine prophylaxis. Twenty three serum uric acid levels within 1 year of the date of hospitalization were recorded of which 18 (78%) were not at goal of <6 mg/dL. Of 15 patients on long term gout treatment, 33% were non-compliant. Thirty (3) patients underwent orthopedic procedures: toe amputation (1), arthroscopic debride-

ment (2) and were subsequently diagnosed as gout.

Total additive length of stay for the preventable admissions was 171 days (mean 3.42 days). Total hospitalization-related costs were $208,000 with average cost per admission of $4160.

Conclusion: We conclude that 89% of the hospitalizations with primary diagnosis of gout were preventable. Defined gaps in clinical care include: ACR/EULAR guidelines not followed, lack of crystal-confirmed diagnoses, patients presenting in emergency rooms with gout symptoms, and non-compliance. Consequently, this population incurred unnecessary health care costs in the emergency room and costly and preventable admission care expenditures. Steps to reasse the care of gout at our institution have begun as a direct result of these study findings.

Disclosure: T. S. Sharma, None; T. M. Harrington, None; T. P. Olenginski, None.

2323

WITHDRAWN

2324

Only 30% Rheumatologists Collect Basdai in Patients with Axial SpA in Daily Practice: The Potential Role of a Consensual Meeting to Improve It. Hélène Che1, Adrien Etcho1, Emmanuelle Denis Labous2, Hervé Natal2, Patrick Boumier2, Philippe Breuilard2, Marianne Durandin-Truffinet1, Jacques Fechtenbaum1, Veronique Gaud-Listrat1, Bernard Giraud1, Christophe Hudry2, Sylvain Le Babbe Alanoire2, Patricia Le Devic2, Patrick Le Gou2, Agnes Lebrun1, Emmanuel Mahé2, Bertrand Moura2, Minh Nguyen2, Antonioette Sacchi2, Xavier Ayal2, Anne Blanchais3, Severine Neveu4, Maxime Dougados5 and Anna Molto3. 1University Paris René Descartes and Hôpital Cochin, Paris, France, 2Réseau Hôpital et Ville en Rhumatologie (RHEVER) Net-
work, Paris, France, 3INSERM (U1153), Clinical Epidemiology and Biosta-

Background/Purpose: The current recommendations for optimal moni-
toring of axial spondyloarthritides (SpA) are to assess regularly disease activity. The two proposed tools comprise clinical aspects as well as laboratory abnormalities, e.g. BASDAI and C-Reactive Protein, or ASDAS [1]. To evaluate the tools used by rheumatologists in axial SpA patients in their daily practice and the potential impact of a meeting during which rheumatologists achieved a consensus on the tools to be used for such monitoring after a presentation of a systematic literature review (consensual meeting).

Methods: The medical chart of out-patients seen by rheumatologists (office-based or hospital-based) have been checked by an independent investigator. The patients had to have visited twice the same rheumatologist within one year (within six months before and after the consensual meeting) to be retained for this analysis. For each visit, the existence of the following informations in the medical chart (BASDAI score, CRP, ASDAS score) were collected.

Results: In total, 456 medical charts issued from 228 patients (mean age: 44.6 (±12.6) years old, 147 (64.5%) males, mean disease duration: 11.7 (±10.7) years) who visited 23 rheumatologists (1 9 (39.1%) hospital-based and 14 (60.9%) office-based, mean age 51.6 (±10.3) years old and with 22.2 (±10.1) median years of practice of rheumatology), visiting a mean of 62 (±37.1) patients per week of whom 17.8% were diagnosed with axial spondyloarthritides were reviewed.

Before the consensual meeting, the frequency of reported tools in the medical chart was 65 (28.5%), 117 (51.3%), 38 (16.7%) and 2 (0.9%) for BASDAI, CRP, BASDAI and CRP and ASDAS respectively. After the consensual meeting, these frequencies changed to 318 (57.7%), 119 (22.2%), 72 (31.6%) and 14 (6.1%) respectively.

An increase in the frequency of the reported tools, was more frequently observed in office-base rheumatologists (e.g. BASDAI score from 32 (23.2%) to 70 (50.8%) medical charts, before and after the consensual meeting, respectively).

Conclusion: This study suggests that 1) despite existing recommendations, tools permitting the evaluation of disease activity are not frequently collected in daily-practice and 2) a reminder through regular meetings could be considered in order to improve this situation.

Reference


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ACR/ARHP Poster Session C Rehabilitation Sciences (ARHP)
Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2325

Background/Purpose: Muscle power (MP) plays an important role in daily activities that require force generated at fast speeds such as climbing stairs. MP is decreased in individuals with arthritis and its contribution to disability has been suggested to be above that of muscle weakness. Yet, there is no consensus on testing parameters such as angular speed and muscle contraction curve to assess MP using isokinetic dynamometers. The purpose of this study was to investigate testing parameters used to assess quadriceps MP in subjects with arthritis. Aim 1 tested the associations of angular speed (or slope of angular speeds) and muscle contraction curve with a well-accepted performance-based measure of MP - the stair climbing test (SCT). Aim 2 investigated whether MP explains variability in SCT beyond that of demographic variables related to muscle performance and muscle strength.

Methods: A duals diagnosed with rheumatoid arthritis were invited to participate. This cross-sectional study used an isokinetic dynamometer to measure quadriceps maximal voluntary isometric contraction (MVIC) and MP. MP was measured using four angular speeds of contraction (240, 180, 120, and 60 degrees per second). Then, values of MP were retrieved from the dynamometer using 3 methods: 1) MP of the whole muscle contraction curve (maximum knee flexion to knee extension); 2) MP of partial curve up to peak torque (maximum knee flexion to peak torque), and 3) MP of partial curve deleting 10° of acceleration and deceleration from whole curve. We also calculated power slopes using MP of the 4 speeds for each curve method. SCT was measured in seconds as the time to go up 11 steps. Bivariate correlations were calculated to determine the associations between SCT and MP at the 4 angular speeds and power slope for each curve method. Separate hierarchical regression models were built to determine the contribution of each method to measure MP on SCT after controlling for age, gender, BMI, and MVIC.

Results: Fifty-one subjects participated (age 59 ± 1 years, 82% female, BMI 31 ± 0.9 kg/m²). All bivariate correlations coefficients between MP and SCT were significant and ranged from -0.35 to -0.54 (p < 0.001). Hierarchical regression analyses demonstrated that age, gender, and BMI explained 46% of variability in SCT. After adjusting for these variables, MP explained significant variability in SCT regardless of the angular speed or curve method used (7% to 17%). In separate regression models, after adjusting for demographics, MVIC was added and explained additional 15% of variability. Then, MP measures were added to the models. The only variable that contributed significantly to SCT in this model was the MP slope measured by the curve method that excluded acceleration/ deceleration (β = -0.326; p = 0.027).

Conclusion: The contribution of MP to SCT was beyond demographics and muscle strength only when measured as MP slope (combining all angular speeds) and used the curve method that discarded acceleration/deceleration. When measuring MP, utilization of MP slope rather than a single speed of contraction and carefully selection of the curve method are encouraged.

Disclosure: M. B. Catelani, None; S. S. Khoja, None; G. J. Almeida, None; S. R. Piva, None.

2327

Delivering ESCAPE-Pain (Enabling Self-Management and Coping of Arthritic Pain through Exercise) - an Online Guide for Healthcare Professionals - Michael V. Hurley1, Andrea Carter1, Das Carter1, Lonan Hughes2, Aoife Ni Mhuairi3 and Nicola E. Walsh3. 1Health Innovation Network South London, London, United Kingdom, 2Salaso Health Solutions, Tralee, Ireland, 3University of the West of England Bristol, Bristol, United Kingdom.

Background/Purpose: Worldwide, chronic joint pain is a major cause of suffering, impaired mobility, physical and psychosocial function, quality of life, dependency and healthcare expenditure. Enabling Self-management and Coping of Arthritic Pain through Exercise (ESCAPE-pain) is a programme that integrates the core interventions recommended by clinical management guidelines - patient education, self-management, coping strategies and exercise. Robust evaluation shows ESCAPE-pain is more effective and cost-effective than usual care, has sustained benefits, is popular with patients and therapists and reduces healthcare costs. Wide implementation would enable many more people to benefit from the ESCAPE-pain programme.

Objective: To facilitate implementation of ESCAPE-painby developing a “free to access” website that encapsulates the programme’s ethos, description, content and format for healthcare professionals (HCP) who want to deliver the programme.

Methods: Focus groups and interviews were held with approximately 30 HCPs to determine what information they required in order to deliver ESCAPE-pain. Using this information a clinical web and multimedia content development team constructed a prototype website describing the content, format and practicalities of delivering ESCAPE-pain. “Think aloud” interviews were conducted with 10 HCPs experienced in delivering ESCAPE-pain.
Background/Purpose: Chronic peripheral joint pain is extremely prevalent and a major cause of physical and psychosocial problems. Exercise improves pain and physical function, but the effect of exercise on psychosocial function (health beliefs, depression, anxiety and quality of life) is unknown. To improve our understanding of the inter-relationship between pain, physical and psychosocial function and exercise we conducted a Cochrane Review with meta-analysis of clinical trials that reported the effect of exercise interventions on psychosocial variables.

Methods: Twenty three clinical, public health, psychology, social care databases and 25 other relevant resources were searched. References of included studies were checked for relevant studies. Key experts were asked about unpublished studies. Quantitative synthesis of randomised controlled clinical trials of exercise-based rehabilitation programmes for chronic peripheral joint pain was conducted. Four of the authors independently assessed the content, format and resources required to implement ESCAPE-pain. HCPs and a major cause of physical and psychosocial problems. Exercise not only improves pain and physical function, but also has moderate benefits on psychosocial functioning and quality of life. However, the effect of exercise on health-related quality of life (HRQOL) is limited and a major cause of physical and psychosocial problems. Exercise reduced pain (SMD, 95% CI: 0.15 to 5.65), non-significant effect on role emotional (1.20, 0.86 to 1.54), in fatigue (2.90, 0.55 to 7.25). Conclusion: Exercise not only improves pain and physical function, but also has moderate benefits on psychosocial functioning and quality of life.
2330

Construct Validity of the Adult Myopathy Assessment Tool in Individuals with Inclusion Body Myositis. Michael Harris-Love1, Galen Joe, Todd Davenport5, Joseph Shradar5, Beverly McElroy2, Goran Rakocevic4, Olavo Vasconcelos5 and Marinus Dalakas4. 1VA Medical Ctr, Washington, DC, 2National Institutes of Health, Bethesda, MD, 3University of the Pacific, Stockton, CA, 4Thomas Jefferson University, Philadelphia, PA, 5Richmond Veterans Affairs Medical Center, Richmond, VA.

Background/Purpose: The Adult Myopathy Assessment Tool (AMAT) is a 13-item performance-based battery developed to assess function and anaerobic endurance in adults with muscle disease. The AMAT has been shown to be a valid assessment of physical status in people with neuromuscular disease, and has demonstrated intrarater and interrater reliability among clinicians rating patients with idiopathic inflammatory myopathy. The purpose of this study was to determine the construct validity of the AMAT in patients with sporadic inclusion body myositis (sIBM).

Methods: The AMAT was administered to 43 participants with sIBM (31 men, 12 women; age: 66.0 ± 7.5 years; disease duration: 9.9 ± 4.3 years) by a single practitioner at a Federal hospital. Peak isometric force measurements were obtained using quantitative muscle testing, and temporal characteristics of gait during habitual and fast walking conditions were measured using a portable gait analysis system. The participants also completed assessments for depression (Beck Depression Inventory), psychosocial fatigue (Fatigue Severity Scale), physical activity levels (Human Activity Profile), and self-reported physical status (36-item Short Form Health Survey, Ver. 2, Physical Component Summary).

Results: The participants attained a mean AMAT score of 30.1 (±5.7; range: 18–44). AMAT scores were significantly associated with strength (r = 0.40–0.43, p < 0.01), gait speed (r = 0.69–0.73, p < 0.001), physical activity levels (r = 0.67, p < 0.001) and self-reported physical status (r = 0.50, p < 0.005), but not depression or psychosocial fatigue (p > 0.05). These relationships were independent of age, disease duration, and age of onset. No floor or ceiling effects were observed as no participant attained the minimum or maximum score (0–45).

Conclusion: The construct validity of the AMAT is supported by its significant associations with muscle strength, functional performance, physical activity, and self-reported physical status. However, anaerobic endurance as measured by the AMAT differs from estimates of psychosocial fatigue in our sample. The AMAT is a standardized, performance-based tool that may be used to assess functional limitations and anaerobic endurance in patients with sIBM.

Disclosure: M. Harris-Love, None; G. Joe, None; T. Davenport, None; J. Shradar, None; B. McElroy, None; G. Rakocevic, None; O. Vasconcelos, None; M. Dalakas, None.

2331

People’s Views, Beliefs and Experiences of Exercise for Chronic Hip and Knee Pain: Cochrane Review with Qualitative Synthesis. Professor Mike Hurley5, Kelly Dickson3, Helen Hauari3, Dr Nicola E. Walsh3, Robert Grant3, Jo Cumming1 and Sandy Oliver5. 1St George’s University of London and Kingston University, London, United Kingdom, 2Institute of education University of London, London, United Kingdom, 3Institute of Education University of London, London, United Kingdom, 4University of the West of England, Bristol, United Kingdom, 5Arthritis Care, London, United Kingdom.

Background/Purpose: Chronic peripheral joint pain is extremely prevalent and a major cause of physical and psychosocial dysfunction. Exercise improves pain and physical function, but the effect of exercise on psychosocial function (health beliefs, depression, anxiety and quality of life) is unknown. To improve our understanding of the inter-relationship between pain, physical and psychosocial function and exercise we conducted a Cochrane Review of qualitative studies that reported people’s beliefs, feelings and experiences of exercise.

Methods: Twenty three clinical, public health, psychology, social care databases and 25 other relevant resources were searched for relevant studies. Two reviewers independently read and extracted data and used a thematic analysis to match the data against a conceptual framework and identify broad themes and sub-themes. Reviewers compared their individual coding, considered the extent to which each sub-theme was mutually exclusive and how they understood the data in relation to their individual coding. They reached a consensus on which a priori themes were supported by the data, and whether any new themes identified by the reviewers did actually map to the pre-existing broad theme. This approach has provided a clear path from the original research data, to individual study author’s descriptions and analyses to the findings of the qualitative review synthesis.

Results: Nine studies met the inclusion criteria. Their design, methodological rigour and reporting was good. Most of the studies gave clear descriptions of their methodology, clearly reported their findings, and took steps to ensure transparency and minimise the bias arising from researcher’s values and opinions in their reporting, interpretation and conclusions.

Chronic hip and knee pain affects all domains of people’s lives. Beliefs about chronic pain shaped people’s attitudes and behaviors about how to manage their pain. With little information or advice from healthcare professionals people attributed joint pain to “wear and tear”, age, processes and/or familial disposition. Physical activity was often associated with onset or increase in pain and interpreted as causing additional joint damage, so people avoided activity for fear of causing additional harm.

People’s views about their symptoms, health beliefs and psychosocial experiences revealed implications for practice which included: providing people with more and better information and advice about the safety and benefits of exercise; tailoring exercise to ensure they are enjoyable and seen by people as being relevant; challenging unhelpful health beliefs; providing practical support.

Conclusion: The uptake and effectiveness of exercise might be improved by challenging inappropriate health beliefs, providing better information and advice about the safety and value of exercise, tailoring exercise programmes to individual’s preferences, abilities and needs and provide better support.

Disclosure: P. M. Hurley, None; K. Dickson, None; H. Hauari, None; D. N. E. Walsh, None; R. Grant, None; J. Cumming, None; S. Oliver, None.

2332

Use of Wrist Hand Orthoses during Hand Function Skills and Functional Tasks By Adults with and without Rheumatoid Arthritis. Janet L. Poole1, Kelly Nunez2 and Patricia Burton2. 1University of New Mexico, Greenbank, WA, 2University of New Mexico, Albuquerque, NM, 3Veteran’s Administration Medical Center, Albuquerque, NM, 4University of New Mexico, Greenbank, WA.

Background/Purpose: To determine changes in muscle activation in the upper extremity using electromyography (EMG) when static and dynamic orthoses are worn by adults with and without rheumatoid arthritis (RA) during hand function skills and functional tasks.

Methods: Ten adults with Rheumatoid Arthritis and five controls were tested in four orthosis conditions (no, static, hinged, spiral) during hand function measures of grip, pinch and dexterity as well as functional tasks of drinking from a 12 ounce soda can, pouring from a 1 liter pitcher, turning a knob on a simulated door, and inserting a coin in a slot. Each participant completed three trials for the strength, dexterity and functional tasks. The order in which the orthoses were worn and was counterbalanced to control for effects of practice and fatigue. Muscle activity of eight muscles involved with reaching and grasp were recorded in the dominant upper extremity using surface electromyography (EMG) during execution of the hand function measures and functional tasks. Computer software calculated average integrated EMG of muscles for each participant in each orthosis condition for each measure and functional task which were converted to percentage of maximum voluntary contraction (%MVC). EMG data were expressed as combined %MVC during grip, pinch, dexterity and functional tasks and were compared across orthotic conditions using multivariate analyses of variance (MANOVAs).

Results: Orthosis use on individuals with RA and controls did not increase or hinder grip or pinch strength or increase speed in dexterity tasks.
Compared to the controls, adults with RA demonstrated lower strength on grip and pinch measures and took longer to complete the dexterity task in all orthosis conditions (p < .05). Other group differences were noted in muscle activation (% MVC in shoulder, elbow and wrist muscles) with individuals with RA having less muscle recruitment than controls in all strength, dexterity and functional tasks and in all orthosis conditions (p < .05). EMG differences varied when individuals wore orthoses. During grip, wrist and elbow muscle recruitment was greater than shoulder muscles in both groups in all orthosis conditions. Increased muscle activation in all muscles was noted during two point pinch in both groups when orthoses were worn (p < .05). When all subjects wore orthoses, muscle activation decreased at the wrist during drinking (p < .01). Similarly, individuals used more muscle activation in all muscles during pouring when no orthosis was worn (p < .05). There were no differences in EMG activity between the groups or orthosis conditions for turning the door knob or inserting a coin.

Conclusion: Adults with RA showed less muscle activation than controls during all strength, dexterity, and functional tasks. Both groups had greater EMG activity in the elbow and wrist as compared to the shoulder muscles in all orthosis conditions. Our findings suggest therapists might want to consider the type of tasks their patients need to perform when recommending orthoses as muscle activation may vary depending on the tasks.

Disclosure: J. L. Poole, None; K. Nunez, None; P. Burther, None.

2333

The Natural Use of Activity Pacing in Daily Life Does Not Result in Lower Symptoms in Osteoarthritis. Susan L. Murphy1, Anna Kratz2 and Mark P. Jensen1. 1University of Michigan, Ann Arbor, MI, 2University of Washington, Seattle, WA.

Background/Purpose: To examine the how individuals naturally use the behavioral strategy of activity pacing in daily life and how its usage relates to pain and fatigue within days among older adults with knee or hip osteoarthritis. Specifically, we hypothesized that pain and fatigue increases would precede increased natural use of pacing (i.e., pacing behavior would be symptom-contingent) and that individuals would experience a “pay-off” from pacing in that pain and fatigue would decrease after using pacing.

Methods: Participants (N = 147) were community-living adults 65 years and older who reported mild to moderate pain severity with evidence of osteoarthritis in a corresponding hip or knee joint. Participants were a wrist-worn accelerometer for 16 days and asked to report frequency of activity pacing behaviors (modified from the activity pacing scale of the Chronic Pain Coping Inventory), pain severity, and fatigue severity five times per day. Physical performance and survey data were also collected.

Results: Multi-linear mixed models (N = 147), including key demographic and clinical variables, showed that both pain and fatigue increases were associated with subsequent increased use of natural pacing. The increased use of pacing was associated with subsequent decreases in both pain and fatigue.

Conclusion: The natural use of pacing appears to be symptom-contingent which is different from how pacing is taught as part of behavioral treatment. Natural use of pacing was not shown to be adaptive in terms of short-term symptom reduction; rather self-reported pacing behaviors were related to increased symptoms. Future studies are warranted to further examine these relationships by capturing more complex contextual issues such as medication effects, social context, and momentary mood.

Disclosure: S. L. Murphy, None; A. Kratz, None; M. P. Jensen, None.

2334

Understanding the Experiences of Rural Community-Dwelling Older Adults in Using a New DVD-Delivered Otago Exercise Programme. Arun Agha, Teresa Liu-Ambrose, Catherine Backman and Linda C. Li. University of British Columbia, Vancouver, BC.

Background/Purpose: A rhritis is known to increase the risk of injurious falls. The home-based Otago Exercise Programme (OEP) has been shown to reduce the occurrence of falls in community-dwelling seniors. We recently developed a new OEP DVD that was designed to be delivered with minimal coaching by a physiotherapist (FT), for people living in rural communities. The current study aimed to: 1) understand older adults’ experiences in using the DVD-delivered OEP, and 2) explore barriers and facilitators to implementing the DVD-delivered OEP from the participants’ perspectives.

Methods: Thirty-two rural community-dwelling older adults (≥75 years old) who participated in a 6-month DVD-delivered OEP study were invited to participate in this qualitative study. Two small group interviews were initially conducted to explore the breadth of participants’ experiences with the program. These were followed by semi-structured individual interviews to gain an in-depth understanding of these experiences. An inductive constant comparison analysis involving coding of transcripts was performed. Methodological rigour was ensured through field note taking, journaling and maintaining an audit trail. Further, peer-review was performed to detect issues in the analysis such as overemphasized or underemphasized points, vague descriptions, and assumptions made by the researcher.

Results: Five participants partook in group interviews and 16 in individual interviews. Fifteen participants were female; eight participants received at least some university education. Participants’ ages ranged from 74 to 97 years. Three themes emerged. Theme 1, ‘The OEP DVD: Useful training tool but in need of more pep’, reflected participants’ experiences that the DVD provided important guidance at program onset, but was too slow and low-energy for longer-term use. Theme 2, ‘Providing greater control over one’s exercise regimen, but sometimes life gets in the way of staying active’, described participants’ appreciation of the program’s flexibility, but personal health concerns and everyday lives imposed challenges for adhering to the program. Theme 3, ‘Social creatures: Wanting greater human connection during exercise’, described how some participants desired further social interactions for enhancing motivation and sense of guidance.

Conclusion: In general, participants were positive about the OEP DVD, but it might not be needed once they are familiar with the program. Our findings also suggest that the program should be prescribed with strategies to address barriers to exercising and tips to increase adherence, such as encouraging older adults to exercise with family members or peers.

Disclosure: A. Agha, None; T. Liu-Ambrose, None; C. Backman, None; L. C. Li, None.

ACR/ARHP Poster Session C Research Methodology (ARHP)

Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2335

Reliability and Validity of the Arthritis Helplessness Index in Systemic Sclerosis. Shadi Ghollizadeh, Sarah D. Mills, Rina S. Fox, Philip J. Clements, Suzanne Kafaja, Vanessa L. Malcarme, Daniel E. Furst and Dinesh Kanna. 1SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, 2University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 3SDSU/UCSD Joint Doctoral Program in Clinical Psychology, Department of Psychology, San Diego State University, San Diego, CA, 4University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: The unpredictable and uncontrollable course of rheumatic diseases has made them an interesting area of study in the learned helplessness and health outcomes literature. The Arthritis Helplessness Index (AHI), a 15-item self-report measure of helplessness, was developed to address a gap in the understanding of psychological correlates of rheumatoid arthritis (RA). The AHI was initially conceptualized as a unidimensional measure, however subsequent factor analytic studies identified two subscales: Helplessness and Internality. Though developed and validated in RA patients, the AHI and its adaptation, the Rheumatology Attitudes Index (RAI), have been used across rheumatic conditions, including among patients with systemic sclerosis (SSc). The present study examines the reliability and validity of the AHI among SSc patients.

Methods: A sample of patients (N = 208) with physician-confirmed SSc completed the AHI as part of participation in the University of California Los Angeles (UCLA) Scleroderma Quality of Life Study. Baseline data from the study were used to explore the structural validity of the measure via confirmatory and exploratory factor analytic methods. Internal consistency reliability was evaluated with Cronbach’s alpha, and convergent validity was explored via Pearson product-moment correlations with measures of depression (CES-D), mental and physical functioning (SF-36v2 Physical and Mental Component Scores, HAQ-DI) and pain (SF-36v2 Bodily Pain).

Results: Because confirmatory factor analysis failed to demonstrate a tenable one or two factor solution, exploratory factor analysis using a geomin-rotated matrix was undertaken to examine the structure of the AHI among SSc patients. A revised two-factor model fit well statistically (χ² [19, N = 208] = 22.32, p = .269), and descriptively (CFI = .985, RMSEA = .029, SRMR = .032). Nine items were retained in the final solution, with the original five Helplessness items comprising Factor 1.
Helplessness, and four of the original seven Internality items comprising Factor 2, Internality. Internal consistency reliability was marginal for both subscales (five-item Helplessness factor: α = 0.634; four-item Internality subscale α = 0.634), and convergent validity was supported by significant correlations of AHI scores in the expected directions with the CES-D, SF-36v2 relevant subscale scores, and the HAQ-DI.

**Conclusion:** The present study derived a revised version of the AHI for use among patients with SSc. Several items that were appropriate for RA patients (e.g., regarding flares) dropped out of the revised version of the measure, suggesting that helplessness is not identical between the two conditions. Although the updated two-factor structure of the shortened nine-item measure fit the data well, it is unlikely that the present measure fully captures the construct of helplessness in SSc. Until future revisions of the measure incorporating patient involvement and input are completed, it is recommended that research examining helplessness in SSc use the updated 9-item, two-factor structure identified in the Arthritis Helplessness Index-Scleroderma version (AHI-SSc).

**Disclosure:** S. Gholizadeh, None; S. D. Mills, None; R. S. Fox, None; P. J. Clements, None; S. Kafaja, None; V. L. Malcarne, None; D. E. Furst, A Boott; A. Croft, A. Arthritis Consultation in Primary Care: Reaching Parts Other Methods

**Methods:** We assessed recruitment strategies, cost, and adherence from a clinical trial of Tai Chi and physical therapy among older adults with KOA in the Boston area. All participants met ACR criteria for symptomatic KOA and were recruited between Dec. 2010 and May 2013. Recruitment strategies included: 1) clinical referrals, 2) other referrals (studies, staff, and class members), 3) electronic ads (PatientslikeMe, Facebook, Clinical connections, clinicaltrials.gov, Craigslist, employee newsletter) and 4) paper ads (local newspapers, flyers). Costs were calculated by adding printing, posting, and personnel expenses. We calculated the percent of participants screened (# screened/prescreen), randomized (#randomized/screen), and able to complete their 12-week evaluation (#12 week/randomized). We also calculated the yield (# randomized) of prescreened, cost per randomized participant as well as median adherence to class schedule (# classes attended/total classes).

**Results:** 1195 people were phone prescreened. 822 were screened in person (mean age 59.7 years) and of these 72% were randomized; the cost per randomized participant was $178.43 (See Table). Sixteen participants were randomized who did not report recruitment source. Participant ads resulted in the highest number of prescreens and randomized participants. Clinical referrals and the senior expo generated the lowest number randomized. The yields for paper, electronic, and other referrals were highest. Clinical referrals resulted in the lowest yield. With the exception of clinical referrals, adherence was high for all recruitment methods as measured by attendance (>79%) and completion of a 12-week evaluation (>76%). Cost per participant was $253.51 for paper and $76.2 for electronic ads. There were no costs associated with referral methods.

**Conclusion:** Electronic ads are an effective tool in this older population but had minimal cost. Their effectiveness is likely to further increase with time. Paper ads still play a prominent role in effective recruitment. There were no costs associated with clinical referrals but this strategy was not the most effective given the low yield. Additional educational material for clinicians may encourage more referrals.

**Table 1. Yield and Cost of Recruitment Strategies in a Tai Chi and Physical Therapy Study for Older Adults with Knee Osteoarthritis**

<table>
<thead>
<tr>
<th>Method</th>
<th>Screening</th>
<th>Randomization</th>
<th>Attendance (Percent)</th>
<th>Total Cost</th>
<th>Total Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone recordings</td>
<td>855</td>
<td>189</td>
<td>148 (14%)</td>
<td>$118.51</td>
<td>1353</td>
</tr>
<tr>
<td>In person screen</td>
<td>96</td>
<td>29</td>
<td>21 (22%)</td>
<td>$204.51</td>
<td>1253</td>
</tr>
<tr>
<td>Randomized (Unscreened)</td>
<td>80</td>
<td>33</td>
<td>21 (27%)</td>
<td>$215.51</td>
<td>271</td>
</tr>
<tr>
<td>Randomized (Screened)</td>
<td>79</td>
<td>42</td>
<td>20 (26%)</td>
<td>$215.51</td>
<td>192</td>
</tr>
<tr>
<td>Total</td>
<td>1525</td>
<td>205</td>
<td>76 (22%)</td>
<td>$679.03</td>
<td>1822</td>
</tr>
<tr>
<td>Average attendance</td>
<td>83.3</td>
<td>73.3</td>
<td>78.2</td>
<td>383.3</td>
<td></td>
</tr>
</tbody>
</table>

**Background/Purpose:** Video-stimulated recall (VSR) is a method of enhancing participants’ accounts of a consultation using a video recording of the event to encourage and prompt participant recall in a post-consultation interview. VSR is used in education and research, and to a lesser extent in medical and nursing research, although little is known about the validity, utility and acceptability of the method. This abstract describes an evaluation of the use of VSR in a study of the Arthritis (OA) consultation in primary care in the UK.

**Methods:** With ethical approval and informed consent, 195 doctor-patient consultations were video-recorded with patients aged ≥ 45. Seventeen consultations in which OA was discussed were the subject of post-consultation interviews using VSR. VSR interviews were conducted with 17 patients and 13 General Practitioners (GPs). Evaluation of the method was achieved by thematic analysis of comments made during video playback, in addition to analysis of observations, field notes, consultation and interview transcripts. Empirical quotes will be presented to illustrate the findings.

**Results:**

**Validity**

There was evidence of the video altering both GPs’ and patients’ behaviour in the consultation with GPs particularly keen to demonstrate desirable behaviour. However, GPs frequently expressed surprise that their actions did not reflect what they felt was best practice, and so we conclude that any altered behaviour would not bias study findings and would likely help interpretation of clinical behaviour during VSR.

**Utility**

The method was useful to explore meanings behind specific sections of talk in the consultation and both patients and clinicians often adopted a more critical stance to the consultation following playback. VSR resulted in subtly changing participants’ accounts of consultations with GPs, suggesting that helplessness is not identical between the two conditions. Although the updated two-factor structure of the shortened nine-item measure fit the data well, it is unlikely that the present measure fully captures the construct of helplessness in SSc. Until future revisions of the measure incorporating patient involvement and input are completed, it is recommended that research examining helplessness in SSc use the updated 9-item, two-factor structure identified in the Arthritis Helplessness Index-Scleroderma version (AHI-SSc).

**Conclusion:** This study adds to the existing literature on VSR by describing specifically how this method enables a more critical, specific and in-depth response from participants to events of interest during clinical encounters, and in doing so, generates multiple perspectives on such encounters. The benefits of VSR for clinical and educational research need to be considered in conjunction with the important ethical considerations and the potential for this method to be intrusive.

**Disclosure:** Z. Paskins, None; T. Sanders, None; P. Croft, None; A. Hassell, None; V. Goldsmith, Lori Lyn Price, Jeffrey B. Driban, William F. Harvey and Chenchen Wang. Tufts Medical Center, Boston, MA.

**Background/Purpose:** In a large-scale clinical trial with a long-term outcome, it is essential to use recruitment strategies that are both cost-
Acute Rheumatoid Arthritis - Animal Models

Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2339

Detecting Inflammation in Vivo Using Activatable Fluorescence Contrast Agents in Inflammatory Arthritis. Mónica Guma¹, Beatriz Bartok², Viет A nh Nguyen Huu², Mathieu L. Viger¹, Jacques Lux¹, Shihanji Joshi-Barr¹, Adah Almutairi² and Gary S. Firestein². ¹University of California, San Diego, La Jolla, CA, ²University of California at San Diego School of Medicine, La Jolla, CA.

Background/Purpose: Current medical imaging technology detects structural rather than functional manifestations of disease. Imaging agents designed to enhance signal based on molecular mechanisms might permit earlier diagnosis and personalized treatment. We examined whether optical contrast agents whose fluorescence properties may be switched from OFF to ON in response to specific biological stimuli can identify inflammation in vivo in the murine serum transfer-induced arthritis model.

Methods: Mice were injected with 150 ml of K/BxN sera on day 0. At day 5, mice were injected intravenously with an imaging agent and visualized by IVIS® in vivo imaging system. Clinical arthritis scores were assessed. The imaging agent consists of H₂O₂ and acid-responsive polymeric particles (size: 250 nm) packed with a high concentration of near infrared (NIR) dyes. The close proximity of the dye molecules quenches their fluorescence, thus creating an “off-state”. The signal of this agent is “turned on” through the cleavage of protecting moieties on the polymer backbones upon exposure to either H₂O₂, or acidic pH, which reveals hydroxyl groups and thus increases the material’s hydrophilicity. After the hydrophobic switch, dye molecules diffuse out of the polymer matrix, relieving the particle from fluorescence quenching (“on-state”) (Figure 1).

Results: A after injecting particles (dose: 100 ml of 0.7 mg/ml Hy-Dex-IR780 in DPBS) intravenously on day 5 after arthritis induction, mice were imaged by IVIS®. Regions of inflammation exhibited significantly higher fluorescence intensity measured as an average of radiant efficiency of paws between non-arthritic and arthritic joints (1.91E +07 ± 1.5E +06 vs 4.44E+07 ± 1.85E +07; p<0.05). This activation results from inflammation-triggered release of dye molecules, as fluorescence was insignificant in healthy animals, and a non-responsive control version poly(lactic-co-glycolic acid)-IR780 was not activated by inflammation. Radiant efficiency in each paw significantly correlated with their clinical score. For example, a paw with a clinical score of 4 had radiant efficiency of 6.95E +07 while a paw with clinical score of 1 had 2.58E +07.

Conclusion: These results suggest that a novel activatable bioimaging agent can detect inflammation in vivo for clinical diagnosis of inflammatory conditions or to assess inflammation in animal models.

Disclosure: M. Guma, None; B. Bartok, None; V. A. Nguyen Huu, None; M. L. Viger, None; J. Lux, None; S. Joshi-Barr, None; A. Almutairi, None; G. S. Firestein, None.

2340

Human Osteoclasts Are Mobilized in Erosive Arthritis of Epstein-Barr Virus-Infected Humanized NOD/Shi-Scid/IL-2Rγ−/−Mice. Yosuke Nagasawa¹, Natsumi Ikumi¹, Takamasa Nozaki¹, Hirotaka Inomata¹, Kenichi Imadome², Noboru Kitamura², Mitsuhiro Iwata², Shigeoyoshi Fujimura² and Masami Takeda². ¹Nihon University School of Medicine, Tokyo, Japan, ²National Research Institute for Child Health and Development, Tokyo, Japan.

Background/Purpose: Various studies of the relationship between Epstein-Barr virus (EBV) and rheumatoid arthritis (RA) have not produced convincing evidence. Many human viruses do not infect mice; thus, it is difficult to conduct biomedical research. At this congress, we previously reported that EBV infection induces erosive arthritis that resembles RA in humanized NOD/Shi-Scid/IL-2Rγ−/− (NOD) mice. However, the mechanisms underlying arthritis in this mouse model are unknown.

In this mouse model, osteoclast-like cells are observed during bone erosion. To determine whether the human or mouse immune system activates bone erosion, we analyzed the origin of osteoclasts in this mouse model.

Methods: The NOD mouse is a highly immunodeficient mouse strain. Seven-week-old female NOD mice were intravenously injected with human CD34+ stem cells from cord blood (1.0 × 107 cells/mouse). Characterization of human hematopoietic system reconstitution (we termed it humanization) was then performed. Human CD4+, CD8+, and CD45+ cells in peripheral blood of these humanized mice were quantified every week using flow cytometry. The engraftment rate of human cells and characteristics of lymphocytes were determined. After 3 months of humanization, these mice were intravenously infected with EBV (1.0 × 107 TD50/mouse). EBV was purified from EBV-producing cells (AKATA or B95-8) and infected mice were sacrificed. The joint tissue samples were stained with hematoxylin-eosin, stained for tartrate-resistant acid phosphatase (TRAP) with an immunoenzyme method,

The NOG mouse is a highly immunodeficient mouse strain. Seven-week-old female NOD mice were intravenously injected with human CD34+ stem cells from cord blood (1.0 × 107 cells/mouse). Characterization of human hematopoietic system reconstitution (we termed it humanization) was then performed. Human CD4+, CD8+, and CD45+ cells in peripheral blood of these humanized mice were quantified every week using flow cytometry. The engraftment rate of human cells and characteristics of lymphocytes were determined. After 3 months of humanization, these mice were intravenously infected with EBV (1.0 × 107 TD50/mouse). EBV was purified from EBV-producing cells (AKATA or B95-8) and infected mice were sacrificed. The joint tissue samples were stained with hematoxylin-eosin, stained for tartrate-resistant acid phosphatase (TRAP) with an immunoenzyme method,
and immunostained for human cathepsin K (specific to humans and dogs). To let osteoclasts differentiate with progenitor cells, bone marrow cells from EBV-infected humanized NUG mice were cultured with human receptor activator of nuclear factor-κB ligand (RANKL) and human macrophage colony-stimulating factor (M-CSF) in slide chambers. These stimulated multinucleated cells were subjected to TRAP staining and immunostaining for human cathepsin K and human mitochondria.

**Results:** After humanization, >40% of peripheral-blood lymphocytes in these mice were human CD45+ cells. When the number of human CD8+ T-cells increased and surpassed the number of human CD4+ T-cells in peripheral blood, erosive arthritis was observed historically at a high rate (approximately 90%). Multinucleated cells present in the bone erosion zone were positive for human cathepsin K and TRAP staining. Multinucleated giant cells resembling osteoclasts were observed among cultured bone marrow cells stimulated with human RANKL and M-CSF. Human cathepsin K, mitochondrial, and TRAP staining were all positive in these multinucleated cells.

**Conclusion:** In this mouse model, we achieved a high engraftment rate. The relationship between the degree of arthritis and the ratio of CD4+ to CD8+ T-cell numbers in peripheral blood was evident. Osteoclasts present in the bone erosion zone originated from human cells. In addition, observed that multinucleated giant cells among bone marrow cells cultured with human RANKL and M-CSF were osteoclasts and originated from human cells.

**Disclosure:** Y. Nagasawa, None; N. Ikumi, None; T. Nozaki, None; H. Inomata, None; K. Imadome, None; N. Kitamura, None; M. IWata, None; S. Fujisawa, None; M. Takei, None.

**2341**

**The Combination Therapy of Cell Cycle Regulation Therapy Combined and TNF Blockade Ameliorated the Established Arthritis.** Tadashi Hosoya, K. kimoto Kawahata, Hitotsubaki Iwa, Hitoshi Koshawska, Japan Science and Technology Agency–CREST Program, Tokyo, Japan; “Tokyo Medical and Dental University (TMDU), Tokyo, Japan.

**Background/Purpose:** The pathogenesis of rheumatoid arthritis (RA) is characterized by infiltration of inflammatory cells to the synovial tissues and their hyperplasia. Activated synovial fibroblasts become another source of inflammatory cytokines and a platform inducing further recruitment of inflammatory cells. Cyclin-dependent kinases (CDK) are known to be key regulators of the cell cycle progression and targets in cancer treatment. We have revealed that a highly selective small-molecule CDK4/6 inhibitor (CDKI) ameliorated an animal model of RA, even with a dose one-fifth lower than the dose used in a cancer treatment model. Furthermore, CDKI combined with a cytokine blocker ameliorated early stage of arthritis additively without inhibiting antigen-specific immune responses.

In the clinical setting, we often treat RA patients with high disease activity. However, few agents were proven effective in treating established arthritis models. The drug effectiveness is usually estimated with early stage of arthritis in the pre-clinical study and is sometimes discrepant between animal models of arthritis and human RA. Therefore, it is difficult to predict which drug is promising in the patients with RA based on the results of arthritis models. However, the drug would be promising if it could ameliorate the established arthritis model. The present studies were carried out to discern if combination of CDKI and TNF blocker is effective in treating established arthritis.

**Methods:** DBA/1J mice immunized with bovine type II collagen emulsified in complete Freund’s adjuvant twice and evaluated for arthritis score and the joint deformity. Mice with collagen-induced arthritis (CIA) were divided into 4 groups equated the mean arthritis score of individual groups 30 days after the initial immunization and were treated with 20 mg/kg of CDKI 3 mg/kg of (ETN), a combination of both, or a vehicle solution from 30 days until 42 days after the initial immunization.

**Results:** The arthritis became established with 9.1 of the mean arthritis score 30 days after the initial immunization. Mice with CIA were treated with a vehicle solution or CDKI or ETN - separately or together. The mean arthritis score changed from 9.1 to 10.8, 8.4, 8.1, and 6.4 respectively 42 days after the initial immunization. The percentage of deformed limbs was evident. Osteoclasts present in the bone erosion zone originated from human cells. In addition, observed that multinucleated giant cells among bone marrow cells cultured with human RANKL and M-CSF were osteoclasts and originated from human cells.

**Conclusion:** In this mouse model, we achieved a high engraftment rate. The relationship between the degree of arthritis and the ratio of CD4+ to CD8+ T-cell numbers in peripheral blood was evident. Osteoclasts present in the bone erosion zone originated from human cells. In addition, observed that multinucleated giant cells among bone marrow cells cultured with human RANKL and M-CSF were osteoclasts and originated from human cells.

**Disclosure:** Y. Nagasawa, None; N. Ikumi, None; T. Nozaki, None; H. Inomata, None; K. Imadome, None; N. Kitamura, None; M. IWata, None; S. Fujisawa, None; M. Takei, None.

**2342**

**Redox Regulation of a New Autoimmune Mouse Model, Glucose-6-Phosphate Isomerase Peptide Induced Arthritis in Mice.** M. Yang and Rikard Holmdahl, K. Karolinska Institutet, Stockholm, Sweden; K. Karolinska Institute, Stockholm, Sweden.

**Background/Purpose:** Rheumatoid arthritis (RA) is a perpetuating disease, which affects approximately 1% of the population. Until now, the pathogenic mechanisms of RA remain elusive and currently no cure for the disease. Animal models of arthritis have provided valuable platforms to investigate the potential mechanisms of RA and test new therapeutic principles before initiating clinical trials in humans. Based on the well-known K/BxN model, a spontaneous arthritis mouse model, we have established glucose-6-phosphate isomerase (G6PI) peptide induced arthritis in mice. Since the G6PI peptide used in this model has two cysteines inside, therefore, we focus on how redox balance could affect antigen recognition and thereby affect the pathogenesis of autoimmunity.

**Methods:** G6PI peptide-induced arthritis is established by immunizing C57Bl/6N.Q (B6.N.Q) mice or Ncf1+/- mice with single injection of G6PI peptide emulsified in complete Freund’s adjuvant. Cysteine(s) in the peptide is substituted with serine to test whether redox can influence peptide itself. APCs from both wild type and Ncf1+/- mice are isolated, loaded with G6PI peptide or substituted peptide and cocultured with peptide-specific T cell hybridoma for 24hr. Supernatants are collected then to compare the IL-2 secretion level.

**Results:** Immunized B6.N.Q mice start to develop arthritis on day 10–12, reach to the peak value of severity on day 14–20 and then recover during following 7–10 days. Moreover, both female and male B6.N.Q mice could be induced arthritic diseases by G6PI peptide and the incidence is over 80%. Obviously, this peptide-induced arthritis mouse model represents an acute arthritic disease progression. To establish a chronic mouse model with this peptide, we inject pertussis toxin together with G6PI emulsion. It turns out that pertussis toxin not only increases the severity of the disease but also prolong the disease progression over two months. To investigate whether cysteine inside of the peptide is regulated by redox, Ncf1 mutant mice were used. Ncf1 encodes p47 phox subunit, which is an essential cytosolic subunit of NADPH oxidase 2 (No.2). The mutation of Ncf1 results in the deficiency of ROS production. The in vitro assay suggest that APCs from Ncf1+/- mice show higher capability to present G6PI peptide. However, when either one or both of the cysteine substituted with serine, there is no difference at all in antigen presenting between wild type and Ncf1+/- mice. Furthermore, peptide immunized Ncf1+/- mice exhibit more severe and chronic disease comparing with immunized wild type mice.

**Conclusion:** Taken together, we have established a peptide-induced arthritis mouse model. The model is induced with a defined peptide, leading to a high reproducibility and allowing a more precise investigation of the pathogenicity. Since the peptide per se is sensitive to ROS level, therefore, this model provides unique possibility to investigate redox regulation in autoimmune disease including RA.

**Disclosure:** M. Yang, None; R. Holmdahl, None.

**2343**

**Therapeutic Effects of Mesenchymal Stem Cells, Anti-Tumor Necrosis Factor and Anti-CD20 Treatment on Collagen Induced Arthritis.** Yue Sun, Xuebing Feng and Lingyun Sun, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

**Background/Purpose:** Tremendous progress has been made in the development of non-conventional therapies for rheumatoid arthritis (RA). In this study, the effects of mesenchymal stem cells (MSCs) transplantation on established...
collagen-induced arthritis (CIA) were evaluated and compared with two kinds of biologic agents, anti-tumor necrosis factor (TNF) and anti-CD20 antibody.

**Methods:** CIA was induced with the immunization of type II collagen (CII) and CFA in DBA/1J mice. Human umbilical cord derived MSCs (5×10⁶), anti-TNF antibody (100μg) and anti-CD20 antibody (200μg) were intraperitoneally injected into 3 groups of mice on day 28 after the immunization. The control group was treated with human fibroblasts (5×10⁶). All mice were sacrificed 3 weeks later and arthritis severity was assessed by clinical and histology scoring. The frequency of CD4⁺ T cell subsets, B cells, and plasma cells in spleen was analyzed by flow cytometry. Serum levels of autoantibody to mouse CII were determined by ELISA. The ability of MSCs to modulate Treg/Th17 cell percentages in CD3/CD28 stimulated DBA/1J T cells was assessed in vitro.

**Results:** MSCs treatment significantly decreased the severity of arthritis and pathology scores, which was comparable to anti-TNF or anti-CD20 treatment. Treatment depletion of nearly half of B220⁺ B cells and 39% of CD4⁺ T cells markedly reduced the frequency of plasma cells and serum levels of autoantibody compared to the control group (738±187 vs. 1817±447 U/ml, p<0.001). The decrease of autoantibody level was also detectable in those with anti-TNF treatment (663±336 U/ml) and MSCs treatment (1057±362 U/ml), but neither of the two treatments had an impact on the percentage of B cells or plasma cells. All of the three treatments resulted in a decrease in Th1 subset, but none of them altered the percentage of Th2 subset. Except anti-CD20 treatment, both MSCs and anti-TNF treatment significantly decreased the percentages of Th17 cells. Notably, only MSCs treatment increased the percentages of regulatory T cells (11.39±0.85 % vs 7.37±1.82 % in the control group, p<0.01). In vitro study confirmed that MSCs could induce the suppression of Foxp3⁺ T cells but reduce the percentages of pathogenic IL-17⁺Foxp3⁻ T cells.

**Conclusion:** MSCs exerted comparable therapeutic effects as biological agents on CIA through different mechanisms. MSCs may provide a promising approach for the treatment of RA.

**Disclosure:** Y. Sun, None; X. Feng, None; L. Sun, None.

### 2344

### Amelioration of Collagen-Induced Arthritis By Water-Soluble Fullerene C60(OH)₃₆ Nanoparticles through the Inhibition of Angiogenesis

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**Background/Purpose:** Our previous study has shown that injection of 13-nm gold nanoparticles ameliorates collagen-induced arthritis (CIA) through the inhibition of angiogenesis by binding to VEGF. Fullerene derivatives, strong scavengers of superoxide radicals, have been recently identified as potential therapeutic agents for arthritis, with the ability to inhibit proinflammatory mediators. In this study, we demonstrate amelioration of CIA by treatment with C60(OH)₃₆ nanoparticles through the suppression of proinflammatory cytokine production, bone erosion and synovial angiogenesis.

**Methods:** Physical properties of newly synthesized C60(OH)₃₆ nanoparticles were characterized by X-ray photoelectron spectrometer, infrared spectroscopy, fast-atom bombardment and matrix-assisted laser desorption/ionization mass spectrometry, transmission electron microscope and dynamic light scattering analysis. Their ability to remove superoxide radicals was confirmed by the electron paramagnetic resonance spectrometer and the inhibition of intracellular reactive oxygen species formation in RAW 264.7 cells. Eight-week-old male Sprague-Dawley rats were immunized with bovine type II collagen emulsified in complete Freund's adjuvant on day 0 and 7. Articular index was used to evaluate the therapeutic effect of the nanoparticles on arthritic joints receiving intra-articular injection of 10 mg nanoparticles or PBS as control (16 joints per group) on day 7. Histological and radiographic scores of arthritic joints were calculated upon sacrifice on day 21. Proinflammatory cytokines (IL-1β and TNF-a) and VEGF concentrations in homogenized synovium extracts were measured by enzyme-linked immunosorbtant assay. Synovial angiogenesis was examined by counting microvessel density without reduction of VEGF levels, and nanoparticle treatment inhibited VEGF-induced HMVEC-1 proliferation in a dose-dependent manner, suggesting that the mechanism of angiogenesis inhibition was through the interference in the signal transduction pathway rather than physical adsorption of the growth factor.

**Conclusion:** This study demonstrates that in vivo treatment of C60(OH)₃₆ nanoparticles ameliorates CIA through an anti-angiogenesis effect, further implicating a novel mechanism in application of certain fullerene derivatives as potential therapeutic agents in rheumatoid joints.

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### 2345

### Anti-IL-6 Receptor Antibody Prevents Deterioration in Bone Structure in a Mouse Model of Collagen-Induced Arthritis

**Authors:** Hiroto Yoshida, Mika Yago, Miko Suzuki, Keisuke Tanaka, Misato Hashizume and Yosihiro Matsumoto

**Institution:** Chugai Pharmaceutical Co., Ltd., Gotemba, Japan.

**Background/Purpose:** Rheumatoid arthritis (RA) is a disease that typically induces secondary osteoporosis, which increases the risk of bone fractures and, consequently, mortality. Bone fracture is induced not only by lower BMD but also by deterioration in bone structure. It is not clear whether anti-human IL-6 receptor antibody (tocilizumab) affects bone structure in RA patients, and the purpose of this study is to examine the changes in bone structure that occur when arthritis develops and the effects of anti-IL-6 receptor antibody on those changes, using a mouse model of collagen-induced arthritis (CIA).

**Methods:** CIA was triggered in DBA/1J mice by an intradermal injection of bovine type II collagen on Days 0 and 21. Mice were injected intraperitoneally either with anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21 or with TNF receptor-Fc (TNFR-Fc) 3 times per week from Day 0 to Day 56. Urine and serum were sampled on Day 35, the peak of swelling. Urinary CTX, a bone resorption marker, and serum PINP, a bone formation marker, were measured by ELISA. Femurs and lumbar spine were excised on Day 56, after swelling subsided. In the distal femur and L5 lumbar spine, the bone structure of trabecular bone and cortical bone was analysed by micro-computed tomography (μCT).

**Results:** In CIA mice, urinary CTX and serum PINP were significantly higher and lower, respectively, than in non-immunized mice. Trabecular bone volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), and cortical bone thickness (Ct) of the distal femur, and BV/TV and Tb. N of the L5 lumbar spine in CIA mice were significantly lower than in non-immunized mice. Both MR16-1 and TNFR-Fc suppressed the development of arthritis. An increase in urinary CTX during development of CIA was prevented by MR16-1 and TNFR-Fc. On the other hand, a decrease in serum PINP was prevented by only MR16-1. MR16-1 treatment significantly suppressed the deterioration in bone structure (BV/TV, Tb. N, Tb. Th, and Ct in the distal femur, and BV/TV and Ct in the L5 lumbar spine), TNFR-Fc treatment significantly suppressed the decrease of BV/TV and Tb. N in the distal femur.

**Conclusion:** We demonstrated that CIA induced severe deterioration in bone structure through an imbalance of bone turnover that was a result of not only increased bone resorption but also decreased bone formation. Moreover, our results indicated that proinflammatory cytokines such as IL-6 and TNF play an important role in bone structure deterioration. Our findings indicate that anti-IL-6 receptor antibody improves the imbalance in bone resorption and the decrease in bone formation and thus prevents the deterioration in bone structure.

**Disclosure:** H. Yoshida, None; M. Yago, None; M. Suzuki, None; K. Tanaka, None; M. Hashizume, None; Y. Matsumoto, None.

### 2346

### Specific Overexpression of FPR2 (FPRL-1) on Th1 Cells in GPI-Induced Arthritis and Patients with Rheumatoid Arthritis

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**Institution:** ¹University of Tsukuba, Tsukuba city, Ibaraki, Japan, ²Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, ³University of Tsukuba, Tsukuba City, Japan, ⁴University of Tsukuba, Ibaraki, Japan, ⁵University of Tsukuba, Tsukuba, Japan.

**Background/Purpose:** CD4⁺ T cells are critical to the pathogenesis of rheumatoid arthritis (RA). In glucose-6-phosphate isomerase (GPI) induced-arthritis (GIA), Th1 and Th17 cells are indispensable for both the induction and the effector phase. We recently identified the highly expression of formyl
peptide receptor 2 (FPR2) in splenic CD4+ T cells from GIA mice by DNA microarray. The FPR2 (human homologue: FPRL-1) is a G-protein coupled receptor showing pro- and anti-inflammatory effect. To clarify the function of FPR2 in CD4+ T cells in the generation of arthritis, we investigated the expression of FPR2 in GIA and FPRL-1 in patients with RA.

Methods:
(1) To confirm the results of DNA microarray, we analyzed the fluctuated expression of FPR2 mRNA on CD4+ T cells in GIA (day0, day 7: induction phase, day14: effector phase, day 28: contraction phase) by real-time PCR.
(2) To determine the Treg subsets expressing FPR2, we sorted FPR2+CD4+ T cells from lymph nodes of GIA (on day7), and the mRNA expression of various markers on CD4+ T cells subsets (Th1, 2, 17, Thf and Treg) was examined.
(3) We analyzed the expression of FPR2 on Th1 or Th17 cells in the polarized condition in vitro.
(4) In human, we analyzed the expression of FPR1 mRNA on peripheral blood mononuclear cells (PBMC) and CD4+ T cells from healthy subjects (HS), patients with Sjogren's syndrome (SS), and RA patients.
(5) We assessed the expression of FPRL-1 on human Th1 cells in the polarized condition in vitro.

Results:
(1) The FPR2 mRNA was significantly highly expressed on CD4+ T cells in GIA on day7 (p<0.05).
(2) The T-bet and IFNγ were higher expressed on FPR2+CD4+ T cells than those on FPR2−CD4+ T cells, whereas each marker for Th2, Th17, Tfh and Treg cells were not.
(3) The expression of FPR2 was frequently detected on Th1 polarized cells, but not on Th17 polarized cells.
(4) The expression of FPRL-1 on PBMC and CD4+ T cells was significantly higher in RA compared with HS and SS (p<0.05).
(5) FPRL-1 expression was significantly increased on human Th1 polarized cells.

Conclusion: We identified that FPR2+ T cells showed Th1 phenotype in mice and FPR2+ cells was highly detected on CD4+ T cells in patients with RA. Th1 polarized cells in mice and humans also expressed FPR2 and FPRL-1, respectively, suggesting FPR2+ (FPRL-1+CD4+) T cells might play a crucial role in the pathogenesis of RA.

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Therapeutic Effect of a Novel Histone Deacetylase 6 Inhibitor, CKD-L, on Collagen-Induced Arthritis and Peripheral Blood Mononuclear Cells from Patients with Rheumatoid Arthritis. Bo Ram Oh1, Hyojin Lim1, Daekwon Bae2, Nina Ha2, Yoon il Choi2, Hyun Jung Yoo1, Jin Kyun Park3, Eun Young Lee4, Eun Bong Lee3 and Yeong Wook Song1. 1Department of Molecular Medicine and Biopharmaceutical Sciences, BK 21 plus Graduate School of Convergence Science Technology, College of Medicine, Seoul National University, Seoul, South Korea, 2Department of Pharmacology and Toxicology, CKD Research Institute, CKD Pharmaceutical Company, Seoul, South Korea, 3Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, 4Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Epigenetic regulation plays an important role in inflammatory arthritis, including rheumatoid arthritis (RA). Histone deacetylase inhibitor (HDACi) has been recently reported to have therapeutic effect in collagen induced arthritis (CIA). CKD-L is a new HDAC6i developed by Chong Kun Dang Pharmaceutical Corporation. We investigated the therapeutic effect of selective HDAC6 inhibitors (CKD-L and Tubastatin A) on CIA, peripheral blood mononuclear cells (PBMCs) and regulatory T (Treg) cells.

Methods: CIA was induced by bovine type II collagen (CII) in DBA/1 mouse. Mice were treated with vehicle (n=10), CKD-L (15, 30 mg/kg, n=10, respectively) or Tubastatin A (30 mg/kg, n=10) by subcutaneous injection every day for 18 days. Arthritis score was assessed twice weekly after the onset of arthritis. Histological analysis was performed by H&E stain. CD4+CD25+ T cells were isolated from C57BL/6 mice spleen and activated with anti-CD3/CD28 beads, TGF-β and HDACi (1–10 μM) for 6 days. Cytotoxic T lymphocyte associated protein 4 (CTLA-4) expression in induced Treg (iTreg) cells was analysed by flow cytometry. Natural Treg (nTreg) cells and CD4+CD25+ (Teff) cells were isolated from C57BL/6 mice spleen, nTreg cells were incubated with anti-CD3/CD28 bead, HDAC6i (200–2000 nM) and carboxyfluorescein succinimidyl ester (CFSE)-labeled T eff cells for 3 days (Treg:Teff ratio=1:2). Proliferation of T eff cells was assessed by flow cytometry. RA PBMCs were stimulated with lipopolysaccharide 100 ng/ml and HDAC6i (10–5000 nM) for 24 hours. Multiplex cytokine assay was performed with supernatant. RA CD4+CD25+ T cells were cultured with anti-CD3 Ab, anti-CD28 Ab, IL-2, TGF-β and 1,25(OH)2VD3 for 5 days. iTreg cells were incubated for 3 days with CFSE-stained T eff cells in the presence of anti-CD3/CD28 beads and HDAC6i (10–5000 nM). Proliferation of T eff cells was analysed by flow cytometry.

Results: In CIA, CKD-L and Tubastatin A significantly reduced arthritis score and histological score. CTLA-4 expression in mouse iTreg cells was increased after treatment of CKD-L (P<0.001) and Tubastatin A (P<0.05). And mouse nTreg cells inhibited the proliferation of T eff cells after treatment with CKD-L (67.8%) and Tubastatin A (68.3%) compared to no treatment (80.1%). In RA PBMC, TNF-α was decreased after treatment with CKD-L (P<0.001) and Tubastatin A (P<0.001). IL-10 was increased after treatment CKD-L (P<0.05) and Tubastatin A (P<0.001). In cultured nTreg cells and T eff cells, CKD-L efficiently inhibited the proliferation of T eff cells (33.9%) compared to no treatment (32.6%). Tubastatin A had no effect on proliferation of T eff cells (30.1%).

Conclusion: CKD-L was effective on the suppression of arthritis in CIA. CKD-L increased CTLA-4 expression and function of Treg cells. These results suggest that CKD have beneficial effect in the treatment of RA.

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Activatory Fc Gamma Receptor IV Plays a Crucial Role in Pathogenesis of Experimental Immune Complex Mediated Chronic Arthritis. Irene Di Ceglie1, Arjen Blom2, Sjie Verbeek3, Peter van der Kraan4, Wim van den Berg5 and Peter L. van Lent1. 1Experimental Rheumatology, Radboud University, Nijmegen, Netherlands, 2Experimental Rheumatology, Radboud University Medical Center, Leiden, Netherlands, 3Human Genetic, Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Rheumatoid arthritis is characterized by Immune complex dependent chronic joint inflammation and severe cartilage and bone destruction. Earlier we found that in the absence of activatory FcγRII and III, joint destruction during the early murine phase of antigen-induced arthritis (AIA) was protected (1) but the role of FcγRIV has not yet been elucidated.

Methods: AIA was induced by injection of mBSA into the knee joint of FcγRI,II,III−/−, FcγRIII−/−, FcγRIIV−/− and wild type (WT) control mice previously immunized with mBSA/IFA. Histology of total knee joints was taken at day 7 and 21 after arthritis induction. Joint inflammation was scored using an arbitrary scale. Cartilage damage was measured as proteoglycan (PG) depletion. Bone destruction was determined using an arbitrary score. mBSA antibody titers were determined using ELISA.

Results: Both KO strains showed antibody titers against mBSA comparable to immunized control mice. In the early phase of AIA (day 7), joint inflammation was significantly higher in FcγRI,II,III−/− (infiltrate 47% and exude 107% higher) when compared to WT controls. In FcγRI,II,II,III−/− however, although comparable antibody titers, inflammation was significantly lower (infiltrate 30% and exude 46% lower) than in WT controls. Early cartilage destruction was protected in both strains reflected by significantly lower PG depletion (34% and 20% lower respectively) when compared to their WT controls.

During the chronic phase at day 21, joint inflammation in FcγRI,II,III−/− was still significantly higher (infiltrate 45% and exude 170% higher) when compared to WT controls. Protection of cartilage damage seen in early AIA was lost and PG depletion significantly increased in FcγRI,II,III−/− by 260%. Bone erosion also increased by 150%. These results suggest that FcγRI and III regulate destruction in the early phase whereas FcγRIV may be more important in chronic stages of arthritis.

In line with this we found that joint inflammation in FcγRI,II,III−/− was much lower when compared with FcγRIII−/− and remained at the same level as their WT controls, implying an active role of FcγRIV in inflammation during the chronic phase. The amount of PG depletion in FcγRI,II,III−/− was comparable to that observed in WT. In contrast erosion of cartilage matrix but also bone were found to be significantly lower when compared to WT controls (76% and 34% lower respectively).

Conclusion: Activatory FcγRIV is crucial in regulating joint inflammation during acute and chronic phase of AIA and became crucial in mediating cartilage and bone destruction during the chronic phase of the disease.

Disclosure: I. Di Ceglie None; A. Blom None; S. Verbeek None; P. van der Kraan None; W. van den Berg None; P. L. van Lent None.
Early Sympathectomy Inhibits Egress of Lymphocytes in Control and Arthritic Animals and Ameliorates Arthritis Disease. Susanne K. Klett and Rainer Straub. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: The sympathetic nervous system (SNS) plays an important role in course and development of autoimmune diseases like arthritis. In type II collagen-induced arthritis (CIA), early activation of the SNS is proinflammatory, but the SNS is anti-inflammatory in later stages of disease. Early sympathetic activation (SYX) prior to immunization ameliorates disease severity, but beneficial mechanisms of early SYX are not completely understood. The aim of this study was to determine how the SNS influences energy expenditure in lymph node parenchyma and egress of lymphocytes from draining lymph nodes/spleen of control and arthritic animals.

Methods: A new technique termed "spatial energy expenditure configuration (SEEC)" was developed to demonstrate bodily areas of high energy demand. SEEC is based on removal of tissue during the course of arthritis in DBA/1 mice, and subsequent determination of oxygen consumption in vitro as a measure of local energy expenditure (immune cell activation). SEEC was applied to healthy control animals, arthritic animals, and animals that underwent early SYX. We evaluated homing behavior of labelled donor splenocytes, expression of CCR7 on lymphocytes by flow cytometry, concentration of CCL21 in lymphocyte cell culture supernatants, and levels of sphingosine-1-phosphate (SIP) in serum of arthritic, sympathectomized arthritic, and control animals.

Results: In draining lymph nodes and spleens of arthritic mice, we observed a marked increase in oxygen consumption and organ weight during the course of arthritis. Although early SYX ameliorated later CIA, early SYX increased energy consumption and cell numbers in arthritic but also in control lymph nodes. This was interpreted as a probable sign of lymphocyte retention in lymphoid organs in healthy and arthritic animals. Splenocyte migration to the spleen was enhanced in early SYX compared to control mice. After early SYX, we observed an elevated expression of CCR7 on lymph node cells and a higher level of CCL21 in lymphocyte cell culture supernatants. This probably contributes to retention of T cells and dendritic cells within lymph node parenchyma and high at the exit site in the vascular lumen. The measurement of SIP in mouse serum revealed a significant higher concentration in CIA animals when compared to controls. Importantly, early SYX decreased SIP concentration in arthritic animals to control levels.

Conclusion: By using the SEEC technique, we identified draining lymph nodes as target organs of the sympathetic nervous system. SYX-induced disease amelioration is probably exerted by sequestration of lymphocytes in secondary lymphoid organs. This might prevent recirculation of immune cells to peripheral sites of inflammation.

Disclosure: S. Klett. None; R. Straub. None.

the attenuation of Th17 cells. This phenomenon may provide a new insight in the study of RA pathopoeis and clinical treatment.

Disclosure: X. Tang, None; S. Wang, None.

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**RORγt Expressing Fopx3**

Regulatory T Cells Regulates the Development of Autoimmune Arthritis in Mice.

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**Background/Purpose:** To determine the effect of RORγt overexpression in T cells on the development of collagen induced arthritis (CIA).

**Methods:** Arthritis was induced with chicken type II collagen (CII) in both C57BL/6 (B6) and C57/2 T cell-specific RORγt Transgenic (RORγt Tg) mice. An anti-CII antibody in sera was measured by ELISA. At 10 days after the first immunization of CII, lymph node (LN) cells were cultured with or without CII, and then the expression level of cytokine, transcription factor and chemokine receptor on CD4⁺ T cells were analyzed by flow cytometry and RT-PCR. Cytokine levels in culture supernatants were measured by ELISA. Joint infiltrating cells were also examined by flow cytometry. Cytokine production and suppressive function of Fopx3⁺ regulatory T cells was analyzed in vitro. Total draining lymph nodes cells or CD4⁺ cells were harvested from B6 mice or RORγt Tg mice at 10 days after the first immunization of CII, and cells were injected into B6 mice intravenously at 10 days after the immunization of CII. Mice were immunized with CII in CFA intradermally on 11 days after the cell transfer.

**Results:** CIA was significantly suppressed in RORγt Tg mice compared with B6 mice. An anti-CII antibody in sera was also reduced in RORγt Tg mice. RORγt expression and IL-17 production in CII reactive CD4⁺ T cells was significantly increased in RORγt Tg mice. Although there was no difference in IFNγ production and T-bet and Fopx3 expression between B6 mice and RORγt Tg mice. RORγt expression in Fopx3⁺ regulatory T cells were significantly higher in RORγt Tg mice than B6 mice. Most of Fopx3⁺ regulatory T cells expressed chemokine receptor 6, and which highly infiltrated in joints after the induction of CIA in RORγt Tg mice. Moreover, Fopx3⁺ regulatory T cells in RORγt Tg mice retain the expression of CD25, the suppressive function of effectors CD4⁺ T cells in vitro, and IL-10 production as well as Fopx3⁺ regulatory T cells in B6 mice. In adoptive transfer of draining LN cells or CD4⁺ cells from immunized mice arthritis was significantly attenuated in recipient B6 mice transferred with cells from RORγt Tg mice.

**Conclusion:** CIA was significantly suppressed in RORγt Tg mice, although IL-17 production and RORγt expression in CII reactive T cells was markedly higher than that of B6 mice. In vitro analyses and cell transfer experiments proposed the possibility that RORγt induced expression of CCR6 in Fopx3⁺ regulatory T cells, and these cells might regulate the development of CIA.

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**The Nitric Oxide Receptor Soluble Guanylyl Cyclase Is Found in Lymphatic Vessels of Arthritic Mice and Inhibition Alters Lymphatic Pulse.**

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**Background/Purpose:** Rheumatoid arthritis (RA) is a chronic erosive inflammatory condition that is characterized by episodes of "flare" due to synovitis of an affected joint. It has been shown in the tumor necrosis factor transgenic (TNF-Tg) mouse model of RA that the proliferative lymph node (PLN) can serve as a biomarker of arthritic flare. Prior to onset of knee flare, the PLN is expanded and an intramymphatic pulse is maintained, however, at some point following chronic ankle arthritis, the PLN suddenly collapses, the lymphatic pulse is lost, and knee arthritis occurs. Here, we show that the nitric oxide (NO) signaling pathway, known to be involved in blood vasculature contractility, is involved in lymphatic vessel contractility, and that the nitro receptor soluble guanylyl cyclase (sGC) may be a key regulator.

**Methods:** Immunohistochemistry was performed on fresh frozen histology sections of PLN from wild type (WT) and TNF-Tg mice stained for alpha (a1, a2) and beta (b1) subunits of sGC and co-localized with smooth muscle actin. In WT mice, near infrared indocyanine green (NIR-ICG) imaging was performed to determine and quantify lymphatic pulse. The sGC inhibitor NS2028 or control vehicle was injected into the footpads of mice, and lymphatic pulse was measured with NIR-ICG imaging 30 minutes later.

**Results:** Immunohistochemistry confirmed the presence of all sGC subunits in PLN from both WT and TNF-Tg mice. Of the six footpads injected with sGC inhibitor NS2028, a clear alteration in the lymphatic pulse with more frequent doublet and triplet spikes compared to control was observed (Figure 1). Quantification of the pulse showed an increased lymphatic pulse in the drug treated limb compared to control (2.66 vs 1.39 pulse per minute, respectively, p<0.05).

**Conclusion:** The presence of sGC receptor subunits in the lymphatic tissue of WT and TNF-Tg mice strongly supports a role for nitric oxide signaling in lymphatic contractility. Furthermore, local injection of sGC inhibitor in WT mice results in a dysregulated lymphatic pulse with an increased rate. This novel finding of increased lymphatic pulse rate with sGC inhibition suggests resumption of the lymphatic pulse in arthritic flare in mice via specific targeting of the sGC receptor may ameliorate flare in inflammatory arthritis.

Figure 1.

Disclosure: H. Rahimi, None; Y. Ju, None; E. M. Bauta, None; R. Wood, None; C. T. Ritchlin, None; E. M. Schwarz, None.

2354

**Efficacy of a Novel Orally Bioavailable J AK 1 Selective Compound in a Preclinical Rat Arthritis Model.**

Lily Y. Moy, Chi-Sung Chiu, Robert Faltus, Mark Zelstofff, Kalyan Chakravarthy, Sujal Deshmukh, Ilona Kariv, Joel K Lappenbach, Jason Brubaker, Duan Liu, Tony Siu, Jonathan Yong, Honghui Yu, Fiona Elwood and Milenko Cicmil. Merck Research Laboratories, Boston, MA.

**Background/Purpose:** Janus kinase (JAK) is a family of four tyrosine kinases that play a critical role in cytokine signaling and downstream lymphocyte activation and function. Inhibition of JAK enzymes as therapeutic candidates for rheumatoid arthritis (RA) has been validated by multi-JAK inhibitors that modify disease in clinical studies. However, there is also evidence from these trials that JAK inhibition with Tofacitinib increases the risk of infections as well as highlighting other potential toxicity concerns. These side effects are thought to be attributable to JAK 2 inhibition, suggesting that better therapeutic ratios might be achieved with selective JAK inhibitors that spare JAK2 activity. Here we report the in vitro and in vivo preclinical characterization of a highly selective JAK1 inhibitor (Compound B) as compared to the effects of a multi-JAK Inhibitor (Compound A).

**Methods:** Biochemical assays were used to determine JAK family kinase potencies. Cellular assays included: 1) IL-6 induced pSTAT3 driven gene expression in M*E-180 cells and 2) erythropoietin induced pSTAT5 driven gene expression in TF1 cells. Collagen-induced arthritis (CIA) in female Lewis rats was performed with a subcutaneous injection of bovine collagen on Days 1 and 8. Inflammation was monitored by measuring paw thickness, pCT imaging and histopathological evaluation were also performed in the ankle joint at the end of the study. Inhibition of baseline hematological parameters was assessed separately in naïve female Lewis rats following compound administration.

**Results:** Compounds A and B are reversible ATP competitive inhibitors of JAK1 and JAK2. Compound A has comparable activity in both enzymatic and cellular assays, whereas Compound B displays ~10X selectivity for JAK1 to JAK2 in the same assays. Therapeutic administration of both compounds dose-dependently inhibited the inflammation resulting from CIA in rats in vivo. Compound exposure levels corresponding to 50% inhibition were approximately 70µM/hr and 12µM/hr for Compounds A and B.
respectively. Inhibition of hematological parameters (reticulocytes, hemoglobin and hematocrit levels) in naïve rats was observed with compound administration at exposures comparable to that required for efficacy in the rat CIA model for the non-selective JAK inhibitor, Compound A. In contrast, for the JAK1 selective Compound B, changes in these parameters were not observed until >10X exposures of that required for efficacy in the rat CIA model were achieved. Furthermore, Compound B inhibited bone mineral density loss by µCT and attenuated inflammation, pannus formation, and cartilage damage by histopathology.

Conclusion: We identified a JAK1 selective compound using enzymatic and cellular assays where selectivity translated to in vivo selectivity in rats. These data demonstrate that a similar degree of preclinical efficacy is achievable with a JAK1 selective inhibitor as compared to a multi-JAK inhibitor. Importantly, the JAK1 selective inhibitor provided ~10X therapeutic window to adverse events. The optimal JAK selectivity profile to achieve maximal clinical efficacy with minimal side effects in patients remains to be determined.

Disclosure: L. Y. Moy, Merck Pharmaceuticals, 3; C. S. Chiu, Merck Pharmaceuticals, 3; R. F. Falust, Merck Pharmaceuticals, 3; M. Ziekstorf, Merck Pharmaceuticals, 3; K. Chakravarty, Merck Pharmaceuticals, 3; S. D. Shemshuk, Merck Pharmaceuticals, 3; I. Kariv, Merck Pharmaceuticals, 3; J. Klappenbach, Merck Pharmaceuticals, 3; J. Brubaker, Merck Pharmaceuticals, 3; D. Liu, Merck Pharmaceuticals, 3; T. Siu, Merck Pharmaceuticals, 3; J. Young, Merck Pharmaceuticals, 3; H. Yu, Merck Pharmaceuticals, 3; F. Elwood, Merck Pharmaceuticals, 3; M. Cicmil, Merck Pharmaceuticals, 3.

2355

Apremilast, a Novel Phosphodiesterase 4 Inhibitor, and Methotrexate Independently Prevent Inflammation in Vivo and in Vitro. Miguel Perez-Aso1, M. Carmen M ortelinos2, A ranzazu Mediero1, P eter H. Schafer3, and Bruce N. Cronstein1. 1New York University, New York City, NY, 2Universitat de València, València, Spain, 3NYU School of Medicine, New York, NY. Background/Purpose: Phosphodiesterase 4 (PDE4) inhibitors have clear immunoregulatory effects in laboratory studies, and the clinical application of this class of drug in the field of rheumatology is now beginning with the introduction of the novel PDE4 inhibitor apremilast, which was recently approved by the FDA for the treatment of psoriatic arthritides. Although apremilast is known to increase intracellular cAMP levels, less is known about its downstream signaling mediators. We therefore undertook this work to delineate intracellular signaling pathways for apremilast and to examine interactions between apremilast, methotrexate (MTX), and adenosine A2A receptors. Methods: After apremilast and lipopolysaccharide incubation, intracellular cAMP, TNF-α, IL-10, IL-6, and IL-1β were measured in the Raw 2647 mouse macrophage cell line. PKA, Epac1/2 (signaling intermediates for cAMP), and A2R knockdowns were performed by shRNA transfection and interactions with A2AR and A2BR. A premilast and MTX were tested with the cAMP-elevating effects of that receptor. Because A2AR is also involved in the anti-inflammatory effects of MTX, the mechanism of action of both drugs involves cAMP-dependent pathways and is therefore partially overlapping in nature.

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2356

Toluonesulfonylamido-Chalcone, 4-(p-toluonesulfonylamido)-4-Hydroxychalcone (TSAHC) Suppresses Inflammatory Response and Joint Destruction in an Experimental Arthritic Mouse and Fibroblast-Like Synovioctyes. Y. un-Hong Cheon1, W. An-Hee Yoo2, Y. un Sung Sunh2, M. Gyu Jeon1, Hyun-Ok Kim1 and Sang-II Lee1. 1Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, 2Chonbuk National University School of Medicine, Jeonju, South Korea, 3Geongosang National University School of Medicine, Jinju, South Korea. Background/Purpose: TSAHC, a toluonesulfonylamido-chalcone, 4-(p-toluonesulfonylamido)-4-hydroxychalcone is a compound to block proliferation and metastatic potential of cancer cells. Fibroblast-like synoviocytes of rheumatoid arthritis (RA-FLS) have inflammatory phenotypes and tumour-like characteristics such as abnormal proliferation, apoptotic resistance, migration, and invasion. Thus, this study was performed to determine whether TSA HC suppress inflammation and joint destruction in K/BxN serum transfer arthritis mice and RA-FLS.

Methods: TSAHC was synthesized with a purity > 99.0%. Treatment included intravenous injections of PBS, vehicle, or TSAHC (5mg/kg once every other day, n=9–10 for each group) for 10 days in K/BxN serum transfer model. Arthritis severity and ankle histology was evaluated using a semi-quantitative scoring system. The levels of inflammatory cytokines in the joints and serum were measured by ELISA and quantitative PCR. The NF-κB activation and cytokine expression were assessed by Western blotting and quantitative PCR using RA-FLS.

Results: The mice injected with TSAHC showed less severe arthritis than vehicle group in clinical score (5.4 ± 0.39 vs. 3.9 ± 0.79, mean ± SE, p < 0.05) and the change of ankle thickness (0.49 ± 0.04 vs. 0.29 ± 0.04 mm, p < 0.01). The pathologic analysis also showed decreased inflammation and bone erosion in TSAHC group. The levels of TNF-α, IL-1β, and sRANKL were decreased in serum and ankle tissues of TSAHC group than vehicle. In addition, IL-10 was increased nearly by 51% in TSAHC group than vehicle (p<0.05). 20µM of TSAHC, which observed as the highest non-toxic concentration on the cell viability, decreased IL-6 production with reduction of nearly 40% than vehicle (p<0.05) and inhibit nuclear translocation of NF-kB stimulated RA-FLS.

Conclusion: This study indicates that TSA HC inhibit inflammation and bone destruction in arthritis mice and decrease IL-6 production in RA-FLS via inhibition of NF-κB activation. Therefore, TSAHC may have therapeutic potential for the treatment of RA.

Disclosure: Y. H. Cheon, None; W. H. Yoo, None; Y. S. Suh, None; M. G. Jeon, None; H. O. Kim, None; S. I. Lee, None.
Methods: Arthritis was induced in C57BL mice (11 week old) by 2 injections within 21 days of chicken CII (cCII) emulsified in Adjuvant (CFA). Half of these mice (n=12) were fed with a hyperlipidic diet (HD) and the other half (n=12) with a standard diet. The control mice were not immunized (NI) but were fed either the standard diet (n=12) or HD (n=12). Aorta and synovial membranes were removed 15 weeks after the first immunization. We analysed VCAM-1, iNOS and IL-17 mRNA level in aorta by real time quantitative PCR (qRT-PCR). VCAM-1 localisation in the aortic sinus layers (intima, media and adventitia) was determined by immunohistochemistry (IHC).

Results: VCAM-1 expression was increased in aorta from CIA mice compared to NI mice, regardless of the fed diet (fig.1). Conversely, iNOS expression was increased in aorta from HD fed mice, whether immunized or not (fig.2). The expression of IL-17 in the aorta was not affected by collagen immunization or diet.

Conclusion: CIA in C57BL6 mice is accompanied by large vessel inflammation. Collagen immunization induced vascular dysfunctions marked by VCAM-1 overexpression independently of the diet. Conversely, HD diet induced a distinct profile of vessel inflammation characterized by high iNOS expression. CIA may be a pertinent model to study cardiovascular disease in RA.

Methods: We analyzed histological sections of K/BxN serum transfer arthritis as well as hTNFtg arthritis for the presence of CD11c+ cells by immunohistochemistry. We also performed synovial biopsies and analyzed the cellular composition of the inflammatory infiltrate with respect to DCs. We used CD11c-diphtheria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter, allowing for specific depletion of CD11c+ cells by administration of diphtheria toxin (DT). K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS. In addition CD11c DTR mice were crossed into hTNFtg animals and also received either DT or PBS. The severity of arthritis was monitored clinically and histologically.

Results: We show that CD11c+ cells are present in significant numbers in the synovia of K/BxN and TNF driven arthritids. Both myeloid dendritic subsets, CD8+ CD11c+ and CD11b+ CD11c+, can be found in synovial membranes of CD11c DTR transgenic mice of K/BxN arthritis. In addition local bone destruction and the number of osteoclasts was significantly reduced. Also in TNF-driven arthritis in CD11c-DTR/hTNFtg mice, depletion of CD11c+ cells led to a significant reduction of synovial inflammation, as well as local bone erosions. To exclude unspecific effects of DT in mice, wild type animals received DT showed identical clinical and histological signs of arthritis as PBS treated animals.

Conclusion: These data show that CD11c+ cells are involved in innate reactions leading to inflammatory arthritis and suggest that dendritic cells could be an important therapeutic target for patients suffering from rheumatoid arthritis.

Disclosure: A. Puchner, None; V. Saferding, None; E. Gonçalves-Alves, None; J. S. Smolen, None; K. Redlich, None; S. Blüml, None.
Conclusion: The therapeutic effect of CGEN-15001 in the CIA model of RA and in the humanized mouse model of psoriasis support its therapeutic potential for these diseases. These findings might also indicate a potential clinical value for psoriatic arthritis, a disease which combines both skin and joint pathologies and is underserved by current therapies. Its effect on key pathologic mechanisms of these and other autoimmune diseases, including downregulation of Th1 and Th17 inflammatory responses, induction of regulatory T cells and restoration of immune tolerance suggest a broad therapeutic potential with durable long-term effect.


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Glucocorticoids and Vascular Function in Arthritis: Benefic or Delete-
rious Effects? Study in Rat. Frank Verhoeven1, Katy M aguin-Gaté2, Perle Totoson3, Daniel Wendling4 and Céline Demougeot5. 1CHU jean Minjoz, Besançon, France, 2EA 4267 « Fonctions et Dysfonctions Épithéliales », Faculté de Médecine-Pharmacie, Besançon, France, 3EA 4267 "Fonctions et Dysfonctions Épithéliales", Besançon, France, 4CHU J Minjoz, Besançon, France, 5EA 4267 "Fonctions et Dysfonctions Épithéliales", Besançon, France.

Background/Purpose: Rheumatoid Arthritis (RA) is associated to an increase of cardiovascular (CV) risk explained in part by an accelerated atherosclerosis as a consequence of endothelial dysfunction. Glucocorticoids (GCs) are widely prescribed in RA patients. Surprisingly, despite the commonly held belief that glucocorticoids worsen the CV risk, data concern-

Methods: We isolated CD146+ cells from human umbilical cords mesenchymal stem cells by beads sorting and then investigated the chondro-
genesis and osteogenesis in a conditioned medium. The cytokine levels of IL-6 and TGFβ1 in CD146+/− cells and the effects of CD146+ cells on Treg/Th17 cell population were analyzed by flow cytometry. CD146+/− cells were injected intra-articularly (IA) in experimental mice model, and then analyzed the clinical scores and the histological findings.

Results: CD146+ cells showed significant higher chondrogenesis than CD146− cells. CD146+ cells also expressed lower levels of IL-6 than CD146− cells. Furthermore, TH17 cells were significantly induced post addition of CD146− cells in vitro and in vivo. Our data also showed that the intraarticular injection of CD146+ cells attenuated the disease progress in vivo. The immunohistological stains showed that only HLA-A− CD146− cells could be detected in the cartilage of CIA mice, and may preserve proteoglycans expression.

Conclusion: We firstly demonstrated that CD146+ cells have higher multilineage potency and can suppress the activation of TH17 cells in vitro and suppress disease activities in vivo. These data suggest that CD146+ cells have more therapeutic potentials than CD146− cells for inflammatory arthritis.

Disclosure: D. M. Chang, None; C. C. Wu, None.

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Enhanced Efficacy of Dexamethasone with Synovial Fibroblast Targeted Micelles in a Collagen-Induced Arthritis Mouse Model. Rebecca A. Bader, David R. Wilson, Arundhati Ramani and Patricia R. Wardwell. Syracuse University, Syracuse, NY.

Background/Profile: A number of conventional, disease modifying anti-rheumatic drugs (DMARDs) are associated with severe side effects due to non-specific targeting and impaired immune function. To improve thera-

Methods: A djuvant-induced arthritis (AIA) was induced in 6 weeks old male Lewis rats by injection of Mycobacterium butyricum in adjuvant at the baseline of the tail. At the onset of arthritis, rats were daily treated (i.p.) with prednisolone at 10 (high dose) or 0.1 mg / kg (Low dose) or saline (V vehicle) for 21 days. Arthritis score and tarsus diameter were daily monitored. At the end of treatment, thoracic aortas were harvested to measure the relaxation to acetylcholine on pre-constricted aortic rings in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), arginase (nor-NOHA), COX-2 (NS-398), EDHF (A-pamin/Charybotoxin), or a superoxide dismutase analog (Tempol). The relaxing effect of NO donor (sodium nitroprusside, SNP) was studied on endothelium-denuded aortic rings. Blood pressure and heart rate, glycaemia, triglyceride and total cholesterol levels and radiological score of hind paws were also assessed.

Results: Compared to “Vehicle”, AIA “High dose” exhibited reduced (p<0.05) arthritic score, paw diameters and radiological damage. This dose of GC significantly (p<0.05) improved AAI. A high dose of prednisolone significantly (p<0.05) improved the arterial response to acetylcholine, decreased the expression of COX-2 and increased the level of NO in the aorta. The relaxation observed in response to acetylcholine was significantly (p<0.05) higher in AIA “high dose”. By contrast, the low dose of prednisolone modified nor arthritis severity neither blood pressure, glycaemia and triglyceride levels. On the vascular side, this dose decreased the production of superoxide anions and increased EDHF, but failed to improve endothelial function in AIA rats. The response of rings to the NO donor was unchanged after GC treatment whatever the dose.

Conclusion: Our study demonstrates for the first time that a high dose of prednisolone during a short time is beneficial for endothelial function in case of arthritis, even though it induced deleterious cardiac-metabolic effects. From a clinical perspective, these results raise the question of the use of high doses of GC during a short period to reverse endothelial dysfunction along with a rapid disease control. Whether this beneficial vascular effect of GC depends of GC during a short period to reverse endothelial dysfunction along with a rapid disease control. Whether this beneficial vascular effect of GC depends on the reduction of disease activity or not deserves further investigations.

Disclosure: F. Verhoeven, None; K. Maguin-Gaté, None; P. Totoson, None; D. Wendling, None; C. Demougeot, None.

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the Role of CD146 in the Therapeutic Potential of Mesenchymal Stem Cells in Favor of CD146+ Cells for Experimental Arthritis. Deh-Ming Chang1 and Cheng-Chi Wu2. 1Taipei Veteran’s General Hospital, Taipei, Taiwan, 2National Defense Medical Center, Taipei, Taiwan.

Background/Purpose: To illustrate whether the subtypes of mesenchy-
mal stem cells (MSCs) have different cellular characteristics and therapeutic potentials, we separated CD146+/− mesenchymal stem cells and investi-
gated their effects on chondrogenesis, osteogenesis, the Treg/Th17 cells expression and arthritis model.

Methods: We isolated CD146+ cells from human umbilical cords mesenchymal stem cells by beads sorting and then investigated the chondro-
genesis and osteogenesis in a conditioned medium. The cytokine levels of IL-6 and TGFβ1 in CD146+/− cells and the effects of CD146+ cells on T reg/Th17 cell population were analyzed by flow cytometry. CD146+/− cells were injected intra-articularly (IA) in experimental mice model, and then analyzed the clinical scores and the histological findings.

Results: CD146+ cells showed significant higher chondrogenesis than CD146− cells. CD146+ cells also expressed lower levels of IL-6 than CD146− cells. Furthermore, TH17 cells were significantly induced post addition of CD146− cells in vitro and in vivo. Our data also showed that the intraarticular injection of CD146+ cells attenuated the disease progress in vivo. The immunohistological stains showed that only HLA-A− CD146− cells could be detected in the cartilage of CIA mice, and may preserve proteoglycans expression.

Conclusion: We firstly demonstrated that CD146+ cells have higher multilineage potency and can suppress the activation of TH17 cells in vitro and suppress disease activities in vivo. These data suggest that CD146+ cells have more therapeutic potentials than CD146− cells for inflammatory arthritis.

Disclosure: D. M. Chang, None; C. C. Wu, None.
Conclusion: This study demonstrated that our targeted, drug delivery platform can be used to enhance the therapeutic efficacy of hydrophobic DMARDS. DM loaded into the PSA-PCL-HA micelles was as effective as free DM when administered at 1/10th the dose to mice with CIA.

Disclosure: R. A. Bader, None; D. R. Wilson, None; A. Ramani, None; P. R. Wardwell, None.

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Leucine-Rich Alpha-2 Glycoprotein Is a Potential Disease Activity Marker Under IL-6 Suppression in Autoimmune Arthritis. Yusuke Takahashi1, M Moru Fujimoto2, Satoshi Serada3 and Tetsuji Naka2. 1Osaka University, Suita city, Japan, 2National Institute of Biomedical Innovation, Ibaraki, Japan, 3National Institute of Biomedical Innovation, Laboratory for immune signal, Japan, Ibaraki, Japan.

Background/Purpose: C-reactive protein (CRP) is frequently used to evaluate inflammation in patients with rheumatoid arthritis (RA). However, CRP is normalized when IL-6 function is potently suppressed by anti-cytokine biologics such as tocilizumab. Therefore, novel biomarkers are required for accurate and sensitive assessment of the inflammation during anti-cytokine therapy. By proteomic screening of sera from patients with rheumatoid arthritis (RA), we previously identified serum leucine-rich alpha-2 glycoprotein (LRG) as a potential biomarker that reflects disease activity in RA better than CRP.

This study is aimed to investigate the clinical significance of LRG as a biomarker of RA disease activity during anti-IL6 therapy.

Methods: As a preclinical testing, cynomolgus monkeys with collagen induced arthritis (CIA) were treated with anti-IL-6 receptor antibody (anti-IL-6R mAb) and joint swelling and rigidity were scored for clinical assessment of arthritis throughout the experiment. At the time of sacrifice, blood samples were collected to be subjected to the measurement LRG and CRP were evaluated.

Results: In CIA monkeys with anti-IL-6R mAb treatment, plasma LRG levels correlated better with disease activity than plasma CRP levels, presumably due to the fact that LRG levels were elevated in some animals with negative CRP in spite of high arthritis scores. Furthermore, among tocilizumab-treated patients for 6months with normalized CRP levels (<0.2mg/dL), serum LRG levels were significantly higher in patients with active RA (defined by CDAI>10) than those with RA with low disease activity (CDAI=10).

Conclusion: Our study indicates that LRG is a promising biomarker for monitoring disease activity in RA, even when CRP levels are reduced or normalized by anti-cytokine therapy.

Disclosure: Y. Takahashi, None; M. Fujimoto, None; S. Serada, None; T. Naka, None.

2364

PET-CT Imaging of Joints: A Quantitative Tool for Developing Novel Anti-Inflammatory Drugs. Siba Raychaudhuri1, A. M. M. Ibrah1, Smriti K. Raychaudhuri2 and Abhijit Chaudhari3. 1Univ California Davis/VA Sac Davis, CA, 2VA Sacramento Medical Center, Mather, CA, 3UC Davis School of Medicine, Sacramento, CA.

Background/Purpose: Mouse collagen induced arthritis (CIA) is the most commonly used preclinical model to screen new drug candidates for inflammatory arthritis. The conventional read out of this model is clinical score and histopathology. These read outs have several limitations including (i) longitudinal studies using the same mouse cannot be performed; (ii) clinical and histopathological scores are subject to observer bias; (iii) in vivo cellular events cannot be captured in its native environment. Thus, an in vivo drug screening tool is the unmet need of the day. Hence, we validated [18F]-FDG PET scan as an in vivo drug screening tool for new anti-inflammatory drugs using the mouse CIA model.

Methods: Animal handling was performed in accordance with the approved UC Davis IACUC protocol. Arthritis was induced using bovine type II collagen in 8-12 week old male DBA/2J mice (n=20), out of which 15 mice showed clinical signs of arthritis on day 28. After the disease progressed, on the day 42 to identify the pre-treatment histopathology 5 mice were sacrificed. In the remaining 10 mice, 5 mice received I.P. 300 g of anti-mouse TNF-α antibody (CNTO5048, Johnson Biotech, PA, USA) every alternate day for next 10 days, and 5 mice remained untreated (negative control). Mice were scored clinically and had [18F]-FDG PET scan on day 42 and 52. Histological score (HS) of the joint tissues were performed in all the mice.

Results: The pre-treatment mean clinical score (CS), histopathological score (HS), and [18F]-FDG uptake were 3.8±1.1, 9±1.1 and 340±22 KBq/cc (Mean±SD), respectively. In the untreated group, the CS, HS and [18F]-FDG uptake progressed on day 52 to 5.4±1.2 (p<0.05), 13.4±1.3 (p<0.05) and 480±32 KBq/cc (p<0.05), respectively. Anti-TNF therapy successfully arrested the disease progression as evident by CS and HS at day 52, 0.75±0.06 (p<0.01) and 2.5±1.1 (p<0.01), respectively compared to untreated group. [18F]-FDG PET uptake in this group was also significantly decreased at day 52 to 200±12 KBq/cc (p<0.01) (Figure 1). The PET uptake significantly correlated with changes in CS (r2=0.74, p<0.01) and HS (r2=0.59, p<0.01). A mong CS and HS, the correlation of [18F]-FDG PET with HS was higher than that observed with CS.

Conclusion: Our observation strongly suggest that [18F]-FDG PET scan can be considered as an in vivo preclinical drug screening tool for anti-inflammatory drugs of autoimmune arthritis. PET-CT imaging will reduce the number of animals required for a study and also the same animal can be studied at different stages of the disease, which will eventually reduce the effect of intra-species biological variations. The use of this in vivo imaging tool will allow longitudinal quantitative evaluation of the degree of joint inflammation in the same mouse.

Disclosure: S. Raychaudhuri, None; A. Mbra, None; S. K. Raychaudhuri, None; A. Chaudhari, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis - Clinical Aspects: Impact of Various Interventions and Therapeutic Approaches

Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

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Comparison of the Effects of a Pharmaceutical Industry Decision Guide and Decision Aids on Patient Choice to Intensify Rheumatoid Arthritis Therapy with Etanercept. Richelle Martin1, Ryan Eck1, Andrew J. Head1, James Birmingham2 and Aaron T. Eggebeen1. 1Michigan State University College of Human Medicine, Grand Rapids, MI, 2Michigan State University College of Human Medicine, Grand Rapids, MI.

Background/Purpose: To evaluate the comparative effects of a pharmaceutical industry decision guide (Pharm Booklet) and International Patient Decision Aids Standard (IPDAS) compliant patient decision aids (PIDA) on patient choice to intensify rheumatoid arthritis (RA) therapy.

Methods: We conducted a mail survey of 797 biologic naive RA patients in a community rheumatology practice. Patients were presented with a hypothetical decision scenario where they were asked to consider adding Enbrel® (etanercept) to their current regimen. Each was randomized to review 1 of 3 forms of etanercept specific decision support: a long 24 page PIDA (LONG DA), a short 2 page PIDA (SHORT DA), or the manufacture’s Enbrel® decision guide (Pharm Booklet). Each subject was evaluated for their decision to intensify therapy, beliefs about etanercept viewed through the Integrated Model of Behavioral Prediction, pre and post intervention etanercept related knowledge and decisional conflict.

Results: 402 anti-TNF naive RA patients participated (response rate 52%). 30.6% of patients randomized to Pharm Booklet elected to initiate etanercept. Only 14.6% and 14.0% of patients who reviewed the LONG DA or SHORT DA choose to take etanercept (Y2=15.7; P<.001). A binary logistic regression model explained 44.2% (R2=...
Strengths of the model included consideration of patient adherence and the potential for misclassification of the data. The model's performance was validated using a sensitivity analysis.

Conclusion: The model may provide an effective tool for predicting patient adherence to MTX. Further research is needed to validate the model's performance in different populations.

Disclosure: R. Mueller, AbbVie, Antares Pharma, Pfizer, Roche, and UCB, 5; Scientific grants: Bristol-Myers Squibb, Roche, and UCB, 2; J. von Kempen, AbbVie, Antares Pharma, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB, 5; Bristol-Myers Squibb, Roche, and UCB, 2; M. H. Schiff, AbbVie, Amgen, Antares Pharma, Bristol-Myers Squibb, Horizon, Lilly, Novartis, and UCB, 5; S. Haile, None.

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Effectiveness, Tolerability, and Safety of Subcutaneous Methotrexate in Early Rheumatoid Arthritis: Clinical Data from the St. Gallen Cohort

Background/Purpose: MTX is the cornerstone of RA treatment, although limitations of systemic exposure of oral MTX may affect its efficacy. Subcutaneous (SC) MTX has greater bioavailability than oral MTX, which may result in better efficacy and tolerability. Few clinical studies have assessed the efficacy and tolerability of SC MTX. We assess the clinical effectiveness and tolerability of SC MTX among pts with RA naïve at baseline to both conventional and biologic DMARDs at our center.

Methods: DMARD-naïve RA pts fulfilling the ACR/EULAR-2010 criteria and had > 1 follow-up visit were selected through sequential chart review until 70 were identified using a prospectively designed retrospective analysis. Pts received SC MTX at varying doses (10–25 mg/week, mean 18.2 mg) w/ 5 mg folic acid/ wk. The primary endpoint was a change in DAS28 (ESR); secondary endpoints included time to employment of the first biologic agent and cumulative MTX doses. Pts were followed until SC MTX administration was terminated or their last clinical visit. Decision for adding biologic agents was at the discretion of the treating physician.

Results: 70 pts remained in follow-up for a mean ± SD of 1.8 ± 1.6 years (range, 0.13–7.1) after initiating SC MTX treatment. During this time 33 (47%) required the addition of a biologic therapy (BIO + MTX), and 37 (53%) remained on SC MTX without any biologics (SC MTX). Mean weekly MTX doses were 19.1 mg for BIO + MTX pts and 17.4 mg for SC MTX pts. Compared to SC MTX pts, BIO + MTX pts were more frequently female (63.6% vs 51.4%), and less frequently ACPA-positive at baseline (33.3% vs 51.4%). Mean baseline DAS28 scores were 4.9 (range 2.42–7.1) for BIO + MTX pts and 4.7 (range 1.6–7.7) for SC MTX pts. During follow-up, BIO + MTX pts had a higher DAS28 score (mean ± SD 5.1 ± 1.1) than SC MTX pts (see figure). Both LDAS and remission were achieved by slightly fewer BIO + MTX than SC MTX pts (LDAS, 78.8% vs 81.1%; remission, 69.7% vs 75.7%). Among BIO + MTX pts, biologic therapy was required after a mean ± SD of 387 ± 404 days (range 54–2164). Over the study period, SC MTX was discontinued in 32 pts (46%). Most common discontinuation reasons were gastrointestinal distress (n = 7), inefficacy (n = 7), disease remission (n = 3), patient’s decision (n = 3), interstitial lung disease (n = 1), and cough (n = 1). Severe infections occurred in 3/33 (9%) of BIO + MTX pts and in 3/37 (8%) of SC MTX pts.

Conclusion: SC MTX is an effective, well-tolerated option for pts with RA in real life. Remission was achieved by a majority of pts following the initiation of SC MTX, and the addition of biologics was not needed throughout the study period for about half of pts. SC MTX delayed need for biologic therapy for about 1 year for almost half of the pts.

Disclosure: R. Mueller, AbbVie, Antares Pharma, Pfizer, Roche, and UCB, 5; Scientific grants: Bristol-Myers Squibb, Roche, and UCB, 2; J. von Kempen, AbbVie, Antares Pharma, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB, 5; Bristol-Myers Squibb, Roche, and UCB, 2; M. H. Schiff, AbbVie, Amgen, Antares Pharma, Bristol-Myers Squibb, Horizon, Lilly, Novartis, and UCB, 5; S. Haile, None.

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Physician Awareness of Suboptimal Patient Adherence to MTX: Results from a Large U.S. Rheumatoid Arthritis Registry

Background/Purpose: Most rheumatoid arthritis (RA) registries capture information about medication use data captured at office visits. The extent to which this information may be misclassified or over-estimated for RA medications, including methotrexate (MTX), is unknown.

Methods: In Q1 and Q2 2014, we conducted an Internet-based survey of RA patients participating in the comparative effectiveness CERTAIN sub-study (n = 2485 unique biologic initiations as of April 2014) nested within the Corrona RA registry. Patients were eligible if they had valid email addresses (n = 991 unique patients). Patients were asked whether they were taking methotrexate and if so, how many MTX doses in the last 4 weeks they had taken. Patient report from the survey was used as the gold standard and compared to the use of MTX routinely recorded in the registry at the previous and next office visits. A subgroup analysis was conducted for the additional patients who had not yet had a follow-up visit in the registry. A sensitivity analysis restricted the interval of time between the survey and the previous registry visit to <6 months to assess whether misclassification of MTX use was related to the interval of time between registry visits.

Results: A total of 433 patients answered the survey, a 44% response rate. Overall, survey respondents had mean (SD) age 53.5 (12.5) age, were 80.8% women, and 78.9% RF + or CCP+. Mean (SD) disease activity measured at the previous visit using CDAI was 17.4 (14.7). Of the subgroup of patients who were recorded at the prior and next registry visit as consistently being on MTX (n = 88), only 1 (1%) of patients indicated that they were not actually taking MTX. However, 10% of the remaining patients indicated that they had missed one or more doses in the last 4 weeks. Results were similar for the 111 additional patients who had not yet had a follow-up registry visit; 15% indicated that they had missed one or more doses in the last 4 weeks. Of the patients who missed one or more doses in the last 4 weeks, approximately one-third to one-half missed more than 1 dose. Results were robust in sensitivity analysis.

Conclusion: In this large U.S. registry, MTX use was generally ascertained accurately at office visits. However, up to 15% of patients recorded by their rheumatologist to be on MTX had missed doses in the last month. Clinicians need to be aware of potentially suboptimal adherence when assessing response to MTX. Further efforts to detect low adherence to MTX and identify reversible barriers to adherence are needed.

Disclosure: J. R. Curtis, RocheGenentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie, 2, RocheGenentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie, 5; A. Bharat, None; L. Chen, None; J. D. Greenberg, Corrona, LLC., 1, Corrona, LLC., 3, AstraZeneca, Celgene, Novartis and Pfizer, 5; J. M. Kremer, Corrona, LLC., 3, Corrona, LLC., 1, D. A. Pappas, Corrona, LLC., 3, Novartis Pharmaceutical Corporation, 9.
Impact of Physicians’ Adherence to Treat-to-Target Strategy on Outcomes in Early Rheumatoid Arthritis. Laura Kususalo1, Kari Puolakka1, Hannu Kautiainen2, Marjatta Leirisalo-Repo3 and Vappu Rantalaiho.2

1Turku University Hospital, Turku, Finland, 2South Karelia Central Hospital, Lappeenranta, Finland, 3Medicare Oy, Åboääsco, Finland, 4Helsinki University Central Hospital, Helsinki, Finland, 5Tampere University Hospital, Tampere, Finland.

Background/Purpose: We have previously shown that in early rheumatoid arthritis (RA) remission targeted, intensive combination treatment, regardless of initial infliximab, results in remission in most patients. Still, patient adherence to medication in RA is often poor and difficult to improve. Little attention, however, has been focused on the effect of physicians’ adherence.

Methods: In the Neo-RACo study 99 patients with early, active RA were treated with methotrexate, sulfasalazine, hydroxychloroquine and low-dose prednisolone for 2 years. Patients were randomized to receive either infliximab or placebo for 6 months from week 4. All swollen joints had to be injected with intra-articular glucocorticoids. After 2 years, medication could be tapered down in the case of remission. In non-remission, treatments were unrestricted, including the use of biologics. At all times, treatment aimed at strict Neo-RACo remission defined as no swollen or tender joints and presence of 5 out of the 6 following criteria: morning stiffness <15 minutes; no fatigue; no joint pain; no tender joints; no swelling in joints or tendons; and ESR <30 mm/h in women and <20 mm/h in men. During a 5-year follow-up, strict remission rates, disease activity score 28 (DAS28) levels, radiological changes, anti-rheumatic medication after 2 years, and cumulative days off work were assessed. Physicians’ (n=30) adherence during 15 study visits between 0 and 24 months was evaluated with a scoring system. On all visits, each patient was scored on 10 different items to assess the quality of their treatment. The total score for each patient varied between 0 and 100, with higher scores indicating better adherence. The primary outcome was the likelihood of developing SSI compared to patients in the TNF- group (pooled fixed-effects OR = 2.39; 95% CI = 1.72, 3.31; p < 0.0001). A smaller group of cases with only total hip and total knee replacement were also meta-analyzed; here patients in the TNF+ group had a 3.08-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled fixed-effects OR = 3.08; 95% CI = 0.87, 10.95; p = 0.08). The Begg-Mazumdar test and Egger test did not reveal any evidence of publication bias (p = 0.88 and p = 0.91, respectively).

Conclusion: Perioperative exposure to TNFi is associated with a higher risk of infection in all orthopedic surgery, although the risk in total hip and knee replacement is less clear. These data support withholding TNFi prior to orthopedic surgery.

Disclosure: L. Kususalo, None; K. Puolakka, Abbvie inc, BMS, Pfizer inc, MSD, Roche, UCB; H. Kautiainen, Abbvie inc, Pfizer inc, S; M. Leirisalo-Repo, MSD Finland, S; V. Rantalaiho, None.

Management of Perioperative Tumor Necrosis Factor α Inhibitors in Rheumatoid Arthritis Undergoing Arthroplasty: A Systematic Review and Meta-Analysis. Susan M. Goodman1, Indu M. Menon1, Rie Smethurst2, Paul Christos3 and Vivian P. Bykerk1.

1Hospital for Special Surgery, New York, NY, 2Hospital for Special Surgery, NY, NY, 3Weill Cornell Medical College, NY, NY.

Background/Purpose: Tumor Necrosis Factor α inhibitors (TNFi) are widely used in patients with RA (Rheumatoid Arthritis) undergoing orthopedic surgery, yet its optimal perioperative management is unknown. The objective of this study is to systematically review the available literature regarding perioperative TNFi management and post-operative infections and to formulate clinical practice recommendations for the optimum perioperative use of TNFi.

Methods: A librarian assisted search was conducted in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, with default date range of each database using the following key terms: Rheumatoid Arthritis, TNF-α, antirheumatic agent, surgical site infections (SSI), surgery/infection, arthroplasty, anti-TNF-α, infliximab, etanercept, adalimumab, risk factor, perioperative, postoperative. Studies were included if most patients had RA, age ≥ 18, and were undergoing orthopedic surgery. The intervention was use of TNFi. The comparison group was patients not treated with TNFi. The outcome of interest was surgical site infection. Study quality was assessed using Oxford Center for Evidence Based Medicine Levels of Evidence. No randomized controlled trials were available; high quality cohort studies (2b) and case control studies (3b) were included.

Results: A total of 2,004 studies were found. After abstract review, 30 studies met inclusion criteria. After detailed quality assessment, 11 studies met criteria with low risk of bias, representing 3730 RA patients with recent exposure to TNFi’s (TNF+ group) and 4307 with no recent exposure to TNFi’s at the time of surgery (TNF- group). These studies were included in the final analysis. There was no consistent reporting of corticosteroid use. If the non-comparability p-value was greater than 0.20, a fixed-effects model was used to estimate the pooled odds ratio (OR); if p<0.20, a random effects model was used to estimate the pooled odds ratio (a forest plot is presented). Patients in the TNF+ group for all orthopedic surgeries had a 2.39-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled fixed-effects OR = 2.39; 95% CI = 1.72, 3.31; p < 0.0001). A smaller group of cases with only total hip and total knee replacement were also meta-analyzed; here patients in the TNF+ group had a 3.08-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled random-effects OR = 3.08; 95% CI = 0.87, 10.95; p = 0.08). The Begg-Mazumdar test and Egger test did not reveal any evidence of publication bias (p = 0.88 and p = 0.91, respectively).

Conclusion: Perioperative exposure to TNFi is associated with a higher risk of infection in all orthopedic surgery, although the risk in total hip and knee replacement is less clear. These data support withholding TNFi prior to orthopedic surgery.

Disclosure: S. M. Goodman, None; I. M. Menon, None; R. Smethurst, None; P. Christos, None; V. P. Bykerk, None.
Methods: A librarian assisted search was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials, with defaulted date range of each database using the following key terms: Rheumatoid Arthritis, TNF-α, anti-rheumatic agent, surgical site infections (SSI), surgery/infection, arthroplasty, anti-TNF-α, infliximab, etanercept, adalimumab, risk factor, perioperative, postoperative. Studies were included if most patients had RA, age ≥ 18, and were undergoing orthopedic surgery. The intervention was use of TNFi. The comparison group was patients not treated with TNFi. The outcome of interest was surgical site infection. Study quality was assessed using Oxford Center for Evidence Based Medicine Levels of Evidence. No randomized controlled trials were available; high quality cohort studies (2b) and case control studies (3b) were included.

Results: A total of 2,004 studies were found. After abstract review, 30 studies met inclusion criteria. After detailed quality assessment, 11 studies met criteria with low risk of bias, representing 3730 RA patients with recent exposure to TNFi’s (TNF-+ and 4,307 with no recent exposure to TNFi’s at the time of surgery (TNF-)). These studies were included in the final analysis. There was no consistent reporting of corticosteroid use. If the non-combining p-value was greater than 0.20, a fixed-effects model was used to estimate the pooled odds ratio (OR); if p<0.20, a random effects model was used to estimate the pooled odds ratio (a forest plot is presented).

Patients in the TNF + group for all orthopedic surgeries had a 2.39-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled fixed-effects OR = 2.39; 95% CI = 1.72, 3.31; p<0.0001). A smaller group of cases with only total hip and total knee replacement were also meta-analyzed; here patients in the TNF + group had a 3.08-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled random-effects OR = 3.08; 95% CI = 0.87, 10.95; p = 0.08). The Begg-Mazumdar test and Egger test did not reveal any evidence of publication bias (p = 0.88 and p = 0.91, respectively).

Conclusion: Perioperative exposure to TNFi is associated with a higher risk of infection in all orthopedic surgery, although the risk in total hip and knee replacement is less clear. These data support withholding TNFi prior to orthopedic surgery.

Disclosure: S. M. Goodman, None; I. Menon, None; R. Smithurst, None; P. Christos, None; V. P. Bykerk, Amgen, S; Bristol-Myers Squibb, S; Pfizer Inc, S; UCB, S.

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Efficacy of First Line Biological Monotherapy in RA: Data from the Czech Registry Attra. Herman F. Mann, Sárka Forejtová, Katerina Jarosová, Ladislav Senolt, Michal Uher, Karel Hejduk, and Karel Pavelka.

Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Institute of Rheumatology, Prague, Czech Republic, Revmatologický ústav, Prague, Czech Republic, Charles University, Prague, Czech Republic. Institute of Biostatistics and Analyses, M. asyky University Brno, Czech Republic, Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Background/Purpose: The biological disease-modifying anti-rheumatic drugs (bDMARDs) should be used for the treatment of rheumatoid arthritis (RA) in combination with conventional synthetic DMARDs (csDMARDs). However a significant proportion of patients receive bDMARDs in monotherapy.

Methods: Baseline demographic data and efficacy parameters of the first bDMARD treatment of RA patients initiating bDMARD monotherapy (MONO) or combination (COMBI) therapy between 2007 and 2012 were retrieved from the national registry Attra. Attra is a centralized prospective computerized registry of patients receiving bDMARD therapy collecting data on efficacy, safety and quality of life of all patients treated with bDMARDs. bDMARD therapy was indicated after failure of at least 1 csDMARD (DAS28 ≥ 5.1).

Results: 1378 patients initiated bDMARD treatment after 2007, prospective data regarding disease activity were available for 924 of them and this subgroup was further analyzed. The 114 patients (12%) who were started on bDMARD monotherapy were older (58 versus 52 years; P = 0.001) with longer disease duration (10.1 versus 6.8 years; P = 0.002) and more failed csDMARDs in the past (4 versus 3; P = 0.002). The baseline DAS28 scores were similar in both groups (5.9 versus 5.8; P = 0.083). The most commonly used first line bDMARDs in both groups were anti TNF drugs (93.9% vs 94.4%; p = 0.8). 61.4% MONO patients remained on the same therapy after 12 months, further 21.1% had a csDMARD added to their initial bDMARD. 75.3% COMBI patients remained on the original therapy, 9.7% more were on monotherapy with the first bDMARD. Remission (DAS28 < 2.6) was reached by 37.8% MONO and 41.6% COMBI patients after 12 months. Longitudinal binary logistic regression model was used to calculate the likelihood of reaching remission for both groups at various time points.

<table>
<thead>
<tr>
<th>Month</th>
<th>Crude estimate</th>
<th>Adjusted estimate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>COMBI reference</td>
<td>MONO (0.35; 0.98)</td>
</tr>
<tr>
<td></td>
<td>reference</td>
<td>MONO (0.36; 1.02)</td>
</tr>
<tr>
<td>6</td>
<td>COMBI reference</td>
<td>MONO (0.37; 0.98)</td>
</tr>
<tr>
<td></td>
<td>reference</td>
<td>MONO (0.37; 1.01)</td>
</tr>
<tr>
<td>12</td>
<td>COMBI reference</td>
<td>MONO (0.44; 1.07)</td>
</tr>
<tr>
<td></td>
<td>reference</td>
<td>MONO (0.42; 1.07)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, age, disease duration, number of previous csDMARDs, glucocorticoid use and baseline DAS28.

The median survival on the first bDMARD was 42.3 months in the MONO and 56.5 months in the COMBI group (HR 1.29; P = 0.073) (Figure).

Figure: Survival on first bDMARD therapy

Conclusion: The results of this observational study suggest that bDMARD efficacy and retention is lower when used as monotherapy, however most observed differences did not reach statistical significance.

Acknowledgements: Supported by project 30023728 from M H CR

Disclosure: H. F. Mann, None; S. Forejtová, None; K. Jarosova, None; L. Senolt, None; J. Zavada, None; M. Uher, None; K. Hejduk, None; K. Pavelka, None.

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Fatigue and Related Factors in Patients with Rheumatoid Arthritis Treated with Tocilizumab in Daily Clinical. H Corominas, C Alegre de la Torre, M Rodríguez-Gómez, C Márquez Fernández-Cid, F M aceiras pan, and ACT AXIS Study Group.

Hospital de Sant Joan Despí, Ourense, Spain, Hospital Universitari Vall d’Hebron, Barcelona, Spain, Complejo Hospitalario Cristal Piñor, Ourense, Spain, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, Complejo Hospitalario Arquitecto Maride-Profesor Novoa Santos, A Coruña, Spain.

Conclusion: The results of this observational study suggest that bDMARD efficacy and retention is lower when used as monotherapy, however most observed differences did not reach statistical significance.
**Background/Purpose:** Fatigue in RA possibly resulting from alterations in the HPA axis like occurs with other RA symptoms as morning stiffness, and mood and sleep alterations. In addition, improvement of IL-6-induced anaemia noted in RA patients appears to be associated with disease activity, even with fatigue. This, together with the effect of tocilizumab (TCZ) in reducing morning stiffness, pain and fatigue, and improving Hb levels, has led us to investigate the correlation between the change in fatigue and related factors as serum Hb levels, SJC, morning stiffness, pain, sleepiness and depression.

**Methods:** A prospective, observational and multicenter study in patients with moderate to severe RA, non-responders or intolerants to DMARDs or TNF-inhibitors who initiated treatment with TCZ. Data were collected at the time of TCZ-beginning (baseline visit) and at 2 routine follow-up visits closest to the weeks 12 and 24. The variance of fatigue outcomes relative to associated factors was calculated by multiple regression analysis.

**Results:** Of 122 patients included, 120 were evaluable (87% female; mean age: 52.2 ± 12.6 years; mean disease duration: 9.1 ± 7.8 years). At baseline, Hb (g/dL), 12.4 ± 1.4; CRP (mg/L), 12.5 ± 16.9; DAS28 score, 5.6 ± 1.0; TJC, 8.6 ± 6.3; SJC, 5.9 ± 4.2; pain (visual analogue scale, cm), 6.7 ± 2.3; morning stiffness duration (hours), 1.3 ± 2.4; FACIT_F fatigue outcome, 23.7 ± 11.1; Beck depression score, 18.3 ± 13.0; Epworth sleepiness score, 6.1 ± 4.5. At 12 and 24 weeks, DAS28 had significantly decreased 2.5 ± 1.1 and 2.7 ± 1.4 points, respectively, fatigue scores had significantly fallen to 19.2 ± 10.6 and 18.8 ± 10.7, and 51% and 61% of patients were good EULAR responders. Significant improvements were also observed in the other RA-related factors evaluated (Table). Sleepiness and depression were significant correlates in the multivariable model explained 35% of the variance in fatigue scores.

**Mean changes (SEM) in fatigue outcomes and related factors from baseline**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 12</th>
<th>p-value*</th>
<th>Week 24</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT_F fatigue</td>
<td>-4.7 (0.9)</td>
<td>&lt;0.001</td>
<td>-5.2 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Hb levels (g/dL)</td>
<td>0.6 (0.1)</td>
<td>0.001</td>
<td>0.6 (0.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP levels (mg/L)</td>
<td>-10.7 (0.9)</td>
<td>&lt;0.001</td>
<td>-11.2 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SJC</td>
<td>-3.7 (0.5)</td>
<td>&lt;0.001</td>
<td>-4.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning stiffness (hours)</td>
<td>-0.9 (0.3)</td>
<td>&lt;0.001</td>
<td>-1.0 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain VAS (cm)</td>
<td>-2.6 (0.2)</td>
<td>&lt;0.001</td>
<td>-2.7 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>-0.6 (0.4)</td>
<td>0.16</td>
<td>-1.0 (0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Beck depression score</td>
<td>-3.6 (0.9)</td>
<td>0.001</td>
<td>-3.9 (1.1)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*Based on paired samples t-test. No multiple comparison adjustment was made. Abbreviations: SEM, standard error mean.

**Conclusion:** Tocilizumab improves fatigue outcomes in patients with RA, a benefit that may be mediated by its effect on disease activity as shown by the reduction of DAS28. Tocilizumab reduces the concentration of acute-phase reactants and improves Hb levels, which can also contribute to decreasing fatigue experienced by RA patients. However, if the improvements observed in morning stiffness duration, pain, and sleepiness and depression scores are the result of the improvement in patient’s fatigue cannot be concluded. Fatigue highly correlates with sleepiness and depression, having these RA-symptoms a significant role in explaining fatigue in RA.

**Disclosure:** H. Corominas None; C. Alegre de Miguel None; M. Rodriguez-Gomez None; C. Marras Fernandez-Cid None; F. Maceiras Pan None.

2374

**Use of Hydroxychloroquine Associated with Improved Lipid Profile in Rheumatoid Arthritis Patients.** Jose Felix Restrepo1, Inmaculada del Rincon2, Emily Molina3, Daniel Battaaran4 and Agustin Escalante5.

**Background/Purpose:** Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in rheumatoid arthritis (RA). CVD risk factor reduction, such as reducing cholesterol and plasma glucose may be beneficial for preventing CVD. Hydroxychloroquine (HCQ), a DMARD with a good safety profile and low cost, has been reported to improve lipid profiles and glucose level in RA. We aimed to examine the association between HCQ with plasma lipid and glucose levels in a large RA cohort.

**Patients and Methods:** We recruited RA patients from public, private, military, and rheumatology clinics, and invited them for yearly follow up evaluations in which we assessed demographic and laboratory features, as well as hydroxychloroquine use. We performed cross sectional analyses at baseline comparing fasting lipid profiles and plasma glucose between patients that were currently taking HCQ and those that were not. We subsequently used cross-sectional time-series regression models including all follow up visits, dividing patients into three groups based on hydroxychloroquine use (HCQ no use, HCQ use ≤ 6 months, HCQ use ≥ 6 months). The lipid and glucose levels in all large RA cohort.

**Results:** We studied 1261 patients (938 female, 323 male) with a mean ± SD age of 59.6 ± 11.5 years. At baseline 254 patients were on HCQ. After adjusting for age, sex, ethnicity and lipid lowering medications, patients taking HCQ had significantly lower total cholesterol (TC) (P-value = 0.001), LDL (P-values = 0.001), triglycerides (TG) (P-value = 0.013), and lipid profile ratios TC/HDL (P-value ≤ 0.001) and LDL/HDL (P-value ≤ 0.001). Furthermore, HDL was significantly higher in patients taking HCQ (P-value = 0.001). Plasma glucose level was not significantly associated with HCQ.

**Conclusion:** Subjects taking pills were less likely to be compliant than those having injections. Patients were equally likely to take active therapy and placebo therapy. Despite differences in compliance, treatment strategies were comparable and both strategies were well tolerated.


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**Compliance in the Rheumatoid Arthritis Comparison of Active Therapies Trial: Triple Vs Etanercept.** Sarah Leatherman1, Hongsheng Wu2, Edward K eyesten3, Mary B rappy4, and J oseph O’Dell5.1 VA Boston Healthcare System, Boston, MA, 2 Wentworth Institute of Technology, Boston, MA, 3Mount Sinai Hospital, Toronto, ON, 4University of Nebraska Medical Center, Omaha, NE.

**Background/Purpose:** In the 48-week, double-blinded, noninferiority RACTAT trial, 353 methotrexate suboptimal responders were randomized to two treatment strategies, either the addition of sulfasalazine and hydroxychloroquine (triple therapy) or the addition of etanercept. If subjects showed no clinical improvement in DAS28 at 24 weeks, their treatment strategy was switched. Compliance to the study medications as well as placebo is an important aspect for any clinical outcome and an important consideration for the application of results to treatment of patients. This is particularly relevant since many have questioned the tolerability of triple therapy.

**Methods:** Compliance with placebo and study medications was calculated using returned pill counts. Participants were defined as medication compliant if they took 80% or more of dispensed study medication. Baseline characteristics were compared between active drug compliant and non-compliant subjects for both the 24-week and 48-week follow-up periods. A administration method (pills versus injection) compliance, treatment strategy (active drug versus placebo) compliance, and the association between compliance and treatment response were also explored.

**Results:** Within active drug group, there were no significant differences at 24 or 48 weeks between compliant and non-compliant subjects for any of the baseline variables except that the Physician Global Assessment score for compliant was significantly better than that of non-compliant (p = 0.01 and p = 0.01, respectively). For active drug group, compliance was significantly higher than pill compliance at both 24 weeks (94.6% versus 86.4%, p = 0.0003) and 48 weeks (96.4% versus 90.6%, p = 0.0034). There were no differences in compliance of active and placebo medications at 24 weeks (90.0% versus 87.0%, p = 0.13) and 48 weeks (93.9% versus 92.8%, p = 0.08). Using other studies, we found no relationship between compliance and treatment response. Other factors previously found to be associated with good compliance, such as demographic variables, treatment assignment, and treatment response, were not significantly related.

**Conclusion:** Subjects taking pills were less likely to be compliant than those having injections. Patients were equally likely to take active therapy and placebo therapy. Despite differences in compliance, treatment strategies were comparable and both strategies were well tolerated.

Table 1. Pooled follow-up visits of 1,261 RA patients divided by HCQ exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Non Intermittent</th>
<th>Intermittent</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients/No of visits</td>
<td>880/2935</td>
<td>36/1411</td>
<td>108/301</td>
</tr>
<tr>
<td>Female, %</td>
<td>1,234 (72)</td>
<td>1,055 (69)</td>
<td>239 (79)</td>
</tr>
<tr>
<td>Hispanic White, %</td>
<td>1,234 (72)</td>
<td>1,055 (69)</td>
<td>239 (79)</td>
</tr>
<tr>
<td>Duration of RA, mean ± SD</td>
<td>15.3 ± 10.9</td>
<td>13.3 ± 9.3</td>
<td>11.9 ± 9.5</td>
</tr>
</tbody>
</table>

Laboratory

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>TC mg/dL, mean ± SD</th>
<th>TG mg/dL, mean ± SD</th>
<th>HDL mg/dL, mean ± SD</th>
<th>LDL mg/dL, mean ± SD</th>
<th>Glucose mg/dL, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC mg/dL, mean ± SD</td>
<td>185.6 ± 40.4</td>
<td>180.2 ± 38.0</td>
<td>180.1 ± 35.6</td>
<td>0.005</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL mg/dL, mean ± SD</td>
<td>106.5 ± 33.6</td>
<td>102.9 ± 30.7</td>
<td>97.5 ± 28.7</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>TG mg/dL, mean ± SD</td>
<td>322.1 ± 182</td>
<td>122.9 ± 62.7</td>
<td>115.1 ± 56.9</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL mg/dL, mean ± SD</td>
<td>3.8 ± 1.1</td>
<td>3.1 ± 0.8</td>
<td>3.0 ± 0.9</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose mg/dL, mean ± SD</td>
<td>103.0 ± 39.5</td>
<td>101.9 ± 37.6</td>
<td>95.1 ± 30.4</td>
<td>0.04</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*P-values were adjusted (Padj) for age, sex, ethnicity, and if the patients were currently on lipid lowering medications.

Conclusion: HCQ use was associated with significantly lower TC, LDL, TG, and TC/HDL and LDL/HDL ratios, and with higher HDL. The association of HCQ with plasma glucose was not as strong as that with lipids. These findings support the need for a randomized trial to establish the role of HCQ in CVD prevention in RA patients.

Disclosure: J. F. Restrepo, None; I. del Rincon, None; E. Molina, None; D. Battafarano, None; A. Escalante, None.

2375

Should Physician Reduce patients’ Glucocorticoids to Offset the Risk of Serious Infection Event Among RA Patients Who Switched from Non-Biologic DMARDs and Glucocorticoids to Biologics? Hufeng Yu, Lang Chen, George W. Reed, Joel M. Kremer, Jeffrey D. Greenberg and Jeffrey R. Curtis.

Background/Purpose: Using 2002–2013 Corrona RA registry data contributed by U.S. rheumatologists and their RA patients, we identified eligible index visits where patients were on a nbDMARD and GCs, but not on biologics. For patients on non-biologic DMARDs (nbDMARD) and GCs, it is unclear whether any increased risk for SIEs associated with adding a biologic might be offset if patients are able to reduce their GC exposure.

Methods: Using 2002–2013 Corrona RA registry data contributed by U.S. rheumatologists and their RA patients, we identified eligible index visits where patients were on a nbDMARD and GCs, but not on biologics. For patients on non-biologic DMARDs (nbDMARD) and GCs, it is unclear whether any increased risk for SIEs associated with adding a biologic might be offset if patients are able to reduce their GC exposure.

Results: Of 12,851 eligible index visits where patients initiated nbDMARDs and GCs, 23% were with GC <5mg/day and 77% with GC ≥5mg/day. Patients were treated with nbDMARD and GCs <5mg/day at the start of follow-up, 14.4% subsequently initiated biologics. For these individuals, 45.9% were able to discontinue GCs, 32.6% were on GC <5mg/day and 12.5% were on GC ≥5mg at the end of follow-up. Of 1,779 (20%) patients starting on nbDMARDs and GCs ≥5mg/day and then initiated biologics, 41.7% were able to discontinue glucocorticoids, and 9.8% were able to reduce GC dose to <5mg by end of follow-up. After excluding 7% of SIEs that could not be confirmed, we identified 2939 SIEs yielding an incidence rate for SIEs of 1.8 per 100 person years across all exposures. After adjustment and compared to exposure of nbDMARDs + GCs (≥5mg/day), patients on biologic DMARDs without steroid use were less likely to have a SIE (Table). Both age and CDAI at the index date were positively associated with SIEs (not shown).

Conclusion: Many RA patients treated with nbDMARDs and glucocorticoids who initiate biologics are subsequently able to discontinue glucocorticoids. These individuals are at reduced risk for serious infections.

Table: Events, absolute incidence rate and adjusted hazard ratio of serious infections by DMARD, biologic, and glucocorticoid exposure

<table>
<thead>
<tr>
<th>Biologic Exposures</th>
<th>Incidence rate per 100 person years</th>
<th>Adjusted Hazard Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nbDMARDs + GCs (≥5mg/day)</td>
<td>162</td>
<td>2.10</td>
</tr>
<tr>
<td>Biologic DMARDs + GCs (≥5mg/day)</td>
<td>47</td>
<td>2.71</td>
</tr>
<tr>
<td>Biologic DMARDs + GCs (&lt;5mg/day)</td>
<td>55</td>
<td>1.63</td>
</tr>
<tr>
<td>Biologic DMARDs + GCs (&lt;5mg/day)</td>
<td>12</td>
<td>1.56</td>
</tr>
<tr>
<td>Biologic DMARDs without GC</td>
<td>17</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, and CDAI at the index date DMARD = disease-modifying antirheumatic drugs

Disclosure: H. Yun, Amgen; L. Chen, None; G. W. Reed, Corrona, LLC; J. M. Kremer, None; J. D. Greenberg, Corrona, LLC; C. A. A. Trona, LLC; S. Novartis and Pfizer, S. J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, Abbvie, D. Roche, Genentech, UCB Pharma, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, Abbvie; S. A. Trona, LLC; S. Novartis, Pfizer, 5.

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Background/Purpose: Rituximab, a chimeric monoclonal anti-CD20 antibody, is approved to be infused over 4 hours and 15 minutes (first infusion), and 3 hours and 15 minutes (second infusion) due to the potential for infusion reactions. The risk of infusion reactions has been shown to be the greatest with the first infusion. Previously we reported our experience with rapid rituximab infusion in 10 rheumatoid arthritis patients, receiving a total of 26 rapid infusions. We now report a current safety analysis of 28 patients receiving a total of 132 rapid infusions in a single rheumatology practice. The objective is to evaluate the safety, tolerability, and practicality of a rapid infusion protocol for rituximab in RA patients (n=28) in a single community setting.

Methods: Patients, who were prescribed rituximab for the treatment of moderate to severe RA, were recruited from October 2006 to November 2013 and given the opportunity to participate in the rapid infusion protocol. All patients provided written informed consent. Each treatment course consisted of 2 rituximab 1000 mg infusions given 2 weeks apart. The first infusion followed the conventional infusion schedule. Rapid infusion protocol was administered on the second and/or all subsequent infusions over 2 hours. All patients received premedication. Vital signs were recorded at baseline and at 15, 30, 60, 90, and 120 minutes.

Results: A total of 57 patients received rituximab infusions (280 infusions) from October 2006 to November 2013. Out of these, 50 patients with a diagnosis of rheumatoid arthritis met the criteria to be followed on the short infusion protocol. A total of 28 patients agreed to be followed on rapid rituximab protocol. 132 infusions were included in this analysis with the mean treatment interval of 9.4 months. 93% of the patient population had failed or were intolerant to prior TNF-alpha inhibitors and 7% were biologic naïve. A total of 7 infusion reactions were reported over 132 rapid rituximab infusions (28 patients), as compared to 8 infusion reactions over 148 conventional infusions (22 patients). There was no significant difference in the incidence of infusion reactions between rapid and conventional infusions (p=0.97). In both rapid and conventional infusions, no patients discontinued rituximab due to infusion related symptoms or reactions. Overall, all symptoms reported were mild and resolved within 24 hours after the infusion. No serious infections or serious adverse events were reported in either rapid or conventional infusion groups.

Conclusion: The current analysis provides reassurance that rapid rituximab infusion is safe and well tolerated. Our experience of administering this protocol over 7 years proves that rapid infusion is as safe as the conventional infusion. In addition to safety, patients reported greater satisfaction with the short infusion duration. This data and previously reported data on rapid infusion in rheumatoid arthritis patients assures physicians that this strategy can be safely implemented in a single community practice setting.

Disclosure: R. Faarawi, None; K. Roth, None; S. Malik, None.
Background/Purpose: Smoking adversely influences comorbidities in rheumatoid arthritis (RA) and may affect progression of RA. The combination of negative health effects makes a compelling case for smoking cessation in RA. The aim of this pilot was to determine whether a targeted 3-month smoking cessation intervention for RA patients increases smoking cessation.

Methods: Thirty-eight RA patients who were currently smoking were recruited and randomized on a 1:1 ratio. All participants were given the current local care for smoking cessation (brief advice and subsidised nicotine replacement therapy: ABC). Participants randomized to the intervention arm (ABC +) received additional advice from trained Arthritis New Zealand educators for 3 months. Advice was tailored to participants’ specific needs from a range of intervention tools developed from previous qualitative consultation and focused on education about the relationship between smoking and RA, pain control, exercise, coping, and support. The primary outcome measure was smoking cessation at 6 months. The secondary outcome was sustained reduction in smoking at 6 months. The assessment was blind to intervention allocation. Disease and psychosocial characteristics of quitters and non-quitters were examined statistically.

Results: Thirty-five participants completed the 6-month trial; the 3 who withdrew were in the intervention arm. The overall smoking cessation rate was 24%. There was no significant difference in smoking cessation rate between the ABC + and ABC groups (26% vs 21%; P = 0.70). The mean number of cigarettes smoked per day reduced by 56% (P < 0.001) but did not differ between ABC + and ABC groups (mean reduction 59% vs 53%; P = 0.72). There was no difference in smoking cessation rates between participants with disease duration 2 years (22% vs 22%; P = 0.74). Successful quitters had a greater number of years in education beyond high school and had smoked less across their lifetime, but these differences were not statistically significant. The successful quitters did appear to have less severe disability and pain, and better psychosocial factors including less depression, perceived stress, and an enhanced quality of life but these did not reach statistical significance (Table 1).

Conclusion: This pilot randomized controlled trial evaluated the effects of an individually tailored smoking cessation programme in patients with RA. The smoking cessation rate and reduction in number of cigarettes smoked were high compared to previous smoking cessation studies. The lack of added benefit of the tailored intervention suggests brief advice is the best practice supporting RA patients who wish to quit smoking. RA patients with fewer years of education or longer history of smoking may require particular cessation support.

Table 1: Baseline disease and psychosocial factors associated with smoking cessation. All data are presented as mean (SD)

<table>
<thead>
<tr>
<th>Baseline disease and psychosocial factors</th>
<th>Successful Quitters (n=30)</th>
<th>Non-quitters (n=35)</th>
<th>Total (n=65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (years)</td>
<td>12.56 (1.88)</td>
<td>11.48 (1.33)</td>
<td>11.74 (1.52)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cumulative pack-years of smoking (years)</td>
<td>25.58 (10.44)</td>
<td>41.68 (24.47)</td>
<td>37.76 (22.86)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current age (years)</td>
<td>55.22 (12.34)</td>
<td>56.90 (11.83)</td>
<td>56.50 (11.80)</td>
<td>0.72</td>
</tr>
<tr>
<td>Socio-economic deprivation</td>
<td>5.00 (3.32)</td>
<td>5.31 (2.61)</td>
<td>5.24 (2.75)</td>
<td>0.77</td>
</tr>
<tr>
<td>ASES pain</td>
<td>6.87 (2.17)</td>
<td>6.15 (1.97)</td>
<td>6.32 (2.01)</td>
<td>0.36</td>
</tr>
<tr>
<td>ASES mood</td>
<td>7.54 (2.02)</td>
<td>7.12 (2.10)</td>
<td>7.24 (2.06)</td>
<td>0.62</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>6.67 (3.39)</td>
<td>6.72 (3.95)</td>
<td>6.71 (3.78)</td>
<td>0.97</td>
</tr>
<tr>
<td>HADS depression</td>
<td>3.67 (1.94)</td>
<td>4.79 (3.46)</td>
<td>4.33 (3.18)</td>
<td>0.36</td>
</tr>
<tr>
<td>PSS stress</td>
<td>19.00 (7.53)</td>
<td>22.48 (8.75)</td>
<td>21.66 (8.51)</td>
<td>0.29</td>
</tr>
<tr>
<td>HAD anxiety</td>
<td>0.56 (0.42)</td>
<td>0.87 (0.77)</td>
<td>0.80 (0.71)</td>
<td>0.26</td>
</tr>
<tr>
<td>PI HAQ</td>
<td>1.95 (1.36)</td>
<td>2.45 (2.18)</td>
<td>2.33 (2.01)</td>
<td>0.57</td>
</tr>
<tr>
<td>EQ VA S</td>
<td>76.33 (15.64)</td>
<td>70.76 (19.23)</td>
<td>72.08 (18.40)</td>
<td>0.44</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>0.73 (0.24)</td>
<td>0.85 (0.19)</td>
<td>0.86 (0.21)</td>
<td>0.22</td>
</tr>
<tr>
<td>Smoking self-efficacy</td>
<td>12.67 (5.49)</td>
<td>13.14 (6.35)</td>
<td>13.03 (6.18)</td>
<td>0.85</td>
</tr>
<tr>
<td>Smoking self-efficacy external</td>
<td>14.33 (4.66)</td>
<td>13.59 (4.15)</td>
<td>13.45 (4.15)</td>
<td>0.73</td>
</tr>
<tr>
<td>Fagerstrom Nicotine Dependence</td>
<td>3.78 (1.64)</td>
<td>4.03 (1.94)</td>
<td>3.97 (1.85)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*Abbreviations: ASES, Arthritis Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; HAQ, Health Assessment Questionnaire; PI-HAQ, Personal Impact Health Assessment Questionnaire; EQ-VAS, Euroqol visual analogue scale; EQ-SD, Euroqol health utility

Disclosure: P. Aimer, None; G. Treharne, None; S. Stebbings, None; C. Frampton, None; V. Cameron, None; S. Kirby, None; L. K. Stamp, Astra Zeneic, 5, Abbvie, 9, PHARMC, 6.

Ethnic Minorities with Rheumatoid Arthritis Achieve a Meaningful Clinical Response at 12 Months Despite Infrequent Use of Biologic Therapies.

Tuesday, November 18
2379
1Rush University Medical Center, Chicago, IL. 2Université Paris René Descartes and Hôpital Cochin, Paris, France. 3Hôpital Lapeyronie, Montpellier, France. 4Nancy University Hospital, Nancy, France. 5UPMC GRC08, Paris 06 University, Pitié Salpêtrière Hospital, Paris, France.

Background/Purpose: Remission has become a more achievable goal in rheumatoid arthritis (RA). Several criteria for remission are available in RA, including one based on RAPID3 (routine assessment of patient index data 3) with the smallest detectable difference (SDD). We analyzed radiographic progression according to remission status in the Espoir French early arthritis cohort, in which only 18.3% of patients received a biological DMARD over a 5-year follow-up as part of their routine care [2].

Methods: Radiographic progression over 1 year was analyzed in the Espoir cohort, which includes early arthritis patients who received routine care. Remission was assessed 12 months after baseline, according to 6 different criteria: ACR Boolean criteria; simplified disease activity index (SDAI) ≤3.3; clinical disease activity index (CDAI) ≤2.8; disease activity score (DAS28) ≤2.6; RAPID3 ≤3; and RAPID3=3≤S≤5. The numbers of patients whose radiographic progression according to the Sharp van der Heijde score was ≥5—the smallest detectable difference (SDD)—[3], ≥10 or ≥20 units at 12 months (12 months after the remission assessment) were analyzed, according to whether patients had been in remission 12 months earlier for each of the 6 criteria, using chi-square tests for statistical significance.

Results: Radiographic progression ≥5 units (SDD) was seen in 10.1%-11.8% of patients in remission compared to 13.0%-13.8% of patients not in remission; differences were not statistically significant (p>0.3) (Table). Progression ≥10 units was seen in 1.4%-4.3% of patients in remission versus 6.7%-7.6% of those not in remission, a 2-fold difference; only differences by DAS28 and RAPID3=3≤S≤5 were statistically significant (p<0.05). Progression ≥20 units was seen in 0.1%-1.1% of those in remission versus 2.6-3.1% of those not in remission, a 3-fold difference, statistically significant for SDAI, CDAI, DAS28, and RAPID3=3≤S≤5. A sub-analysis including 179 patients with radiographic damage at baseline and rheumatoid factor positivity was performed, with similar results.

<table>
<thead>
<tr>
<th>Remission criteria</th>
<th>Remission ≥5 units</th>
<th>Remission ≥10 units</th>
<th>Remission ≥20 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boolean</td>
<td>140 vs 492</td>
<td>10.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>SDAI ≤3.3</td>
<td>135 vs 467</td>
<td>10.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>CDASI ≤2.8</td>
<td>135 vs 467</td>
<td>10.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>DAS28 ≤2.6</td>
<td>247 vs 355</td>
<td>10.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>RAPID3 ≤3</td>
<td>187 vs 415</td>
<td>11.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>RAPID3=3≤S≤5</td>
<td>139 vs 463</td>
<td>10.1%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

*p < 0.05

Conclusion: Very little radiographic progression was seen in patients receiving routine care in recent years although only 18.3% of patients received a biological agent. Differences between patients in remission or non become apparent when applying higher cut-off points to define radiographic progression.

References:

Disclosure: I. Castrejón, None; M. Dougados, None; B. Combe, Roche France; F. Guillemin, None; B. Fautrel, None; T. Pincus, None.

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Durability of First Biologic Is Not Influenced By Initial/Early DAS28.
Gina Rohrkasten1, Blinu Jacob1, Janet E. Pope1 and Claire Bombardier2. 1St. Joseph's Hospital, London, ON, 2University Health Network, Toronto General Research Institute, Toronto, ON, 3Western University, London, ON, 4University of Toronto, Toronto, ON.

Background/Purpose: The Ontario Best Practices Research Initiative (OBRI) collects data on RA treatment in a real-world setting. Patients are enrolled and prospectively followed to assess response to biologic and DMARD therapy as well as to collect data on other factors. The objective of this study is to look at a real-world population and determine if initial disease activity influences the durability of the first used biologic in RA treatment.

Methods: Biologic-naïve RA patients were included if they started a biologic at baseline or at any time after entry into OBRI. For initial DAS, we used the DAS28 value when it was measured between 6 months before and 3 months after the start of the first biologic, whichever was closer to the date of biologic use. This was done so as the initial DAS28 would best reflect the patient’s DAS at start of biologic. Patients were censored at treatment stop date or discontinuation date, date of death, or up to 18 months after initiation of biologic, whichever occurred first. Persistence was defined as the length of time the patients continued to receive the drug, irrespective of change in dose, route, or addition of any other DMARD, steroids, etc. If the drug was stopped for <60 days after which the patient restarted the same medication, it was considered a continuation and the duration was calculated accordingly. Survival was first compared using KM curves and then again using Cox-regression analysis. Analysis was performed for all years and also censored at 1.5 years.

Results: 471 patients were included. At 1 year, the survival probability was 0.76 (95% CI 0.68–0.81). Median survival was 5.005 years (95% CI 3.466–8.337). Patients who were on biologic monotherapy, with no concomitant DMARD use, has worse persistence of their initial biologic.

Patients were divided into three groups for analysis based on initial DAS28 score (≤ 2.60, medium to high DAS28 2.61–5.10) and severe (>5.10). Figure 1 shows the KM Plot of survival on biologic stratified by DAS28.

Figure 1: Despite the initial trend towards better survival associated with lower initial DAS, this was not statistically significant. Similarly, type of insurance (public/private) did not impact survival. As seen in other studies, the only significant factor to impact survival on initial biologic was use of DMARD with the biologic.
Conclusion: Early/initial DAS28 score did not impact persistence on their initial biologic, nor did insurance type. This suggests that initial DAS28 score does not influence the durability of the initial biologic Combination of DMARD and biologic was more durable than biologic monotherapy.

Disclosure: G. Rohkar, None; B. J. Jacob, None; J. E. Pope, None; C. Bombardier, None.

2381

Adherence to a Treat-to-Target (T2T) Strategy in Early Rheumatoid Arthritis. Is It Feasible in Daily Clinical Practice? The most frequent strategy was addition/change of DMARDs (31%),

0.6 and 3.9

In our cohort, including patients with early rheumatoid arthritis in “real world”, the compliance with the T2T treatment recommendations were low. A change in drug treatment was registered in less than half of the visits where patients were not in remission.

Disclosure: C. A. Waimann, None; G. Citera, None; F. Dal Pra, None; M. C. Orozco, None; F. Ceccato, None; S. Paina, None; M. Gauna, None; A. Secco, None; M. Mamani, None; L. Marino, None; F. Caeiro, None; A. Alvarez, None; M. Haye Salinas, None; L. Encinas, None; J. Rosa, None; V. Scaglioni, None; E. R. Soriano, None; J. Marcos, None; M. Garcia, None; A. Salas, None; A. Martinez, None; R. Chaparro del Moral, None; O. L. Rillo, None; H. Berman, None; A. Berman, None; F. Colombes, None; E. Veloso, None; R. V. Juaquez, None; M. E. Crespo, None; A. Quinteros, None; M. Leal, None; G. Salviaterra, None; C. Ledesma, None; M. P. Sacnun, None; R. Quintana, None; M. Abdala, None.

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Adherence to Dmards in the First Six Months of Treatment in Early Arthritis Patients; Comparing Three Adherence Measures. Aneelke Pasma1, Ethan den Boer1, A. draan van ‘t Spijker2, Reiner Timman3, Jan van Busschbach1 and J.M.W. Hazes1.1Erasmus MC University Medical Center, Rotterdam, Netherlands, 2Erasmus University Medical Center, Rotterdam, Netherlands.

Background/Purpose: Non-adherence to DMARDs is an important indicator for the effectiveness of treatment in early arthritis patients. Reported non-adherence rates differ widely, because studies use different adherence measures. Electronic measurement is considered as a ‘gold standard’, but other measures have other attractive features. This study compared three methods to ascertain how non-adherence should be measured: the Compliance Questionnaire Rheumatology (CQR), the intracelluler uptake of methotrexate (MTX) in the form of methotrexate-polyglutamates (MTX-PGs) and Medication Event Monitoring Systems (MEMS).

Methods: Ault patients diagnosed with arthritis who started DMARDs were included in a cohort study. MTX-PGs were collected and the CQR was filled out after three and six months of treatment. Non-adherence was continuously measured with MEMS. When there was a discordance between the observed opening and the expected opening of the MEMS cap, this was assigned as a non-adherence event. The CQR and MEMS were compared with Pearson correlations. Sensitivity and specificity of adherence measured with MEMS against a CQR discriminant cut-off score was calculated at three and six months. To assess the influence of adherence measured with MEMS on MTX-PGs, a multivariate linear regression (backward selection) with MTX-PGs as dependent variable and with non-adherence measured with MEMS in the 12 weeks before MTX-PG measurement (continuous score), age, gender, time of treatment and dosage as independent variables was performed.

Results: Two hundred and one patients entered the study. As measured with MEMS, non-adherence rates varied over time and between different DMARDs (figure 1). For sulfasalazine and hydroxychloroquine, the non-adherence rates were highest. For all medicines, except for prednisone, the non-adherence rate rose over time. The CQR did not correlate with MEMS at any of the time points of therapy. At both time points, the ROC curves showed no discrimination between non-adherence measured with MEMS against the CQR cut-off score. Non-adherence (B 0.548, p=0.035), time of treatment (B 0.947, p=0.006) and age (B 2.052, p<0.000) significantly contributed to MTX-PGs, but only accounted for 18.8% of explained variance.

Conclusion: Non-adherence rates for prednisone are lowest and stable. This might be explained by the fact that patients immediately experience the effect of prednisone, and that most patients tapered prednisone. The non-adherence rate for MTX was low, probably because rheumatologists emphasize the necessity of MTX. The CQR is not associated with MEMS, but MTX-PGs are weakly associated with MEMS. This can be due to several reasons, such as individual differences in the uptake of MTX. We have to learn more about the uptake of MTX over time per patient, before we can use MTX-PGs in daily practice as a non-adherence measure.

Disclosure: C. A. Waimann, None; G. Citera, None; F. Dal Pra, None; M. C. Orozco, None; F. Ceccato, None; S. Paina, None; M. Gauna, None; A. Secco, None; M. Mamani, None; L. Marino, None; F. Caeiro, None; A. Alvarez, None; M. Haye Salinas, None; L. Encinas, None; J. Rosa, None; V. Scaglioni, None; E. R. Soriano, None; J. Marcos, None; M. Garcia, None; A. Salas, None; A. Martinez, None; R. Chaparro del Moral, None; O. L. Rillo, None; H. Berman, None; A. Berman, None; F. Colombes, None; E. Veloso, None; R. V. Juaquez, None; M. E. Crespo, None; A. Quinteros, None; M. Leal, None; G. Salviaterra, None; C. Ledesma, None; M. P. Sacnun, None; R. Quintana, None; M. Abdala, None.

Background/Purpose: The treat-to-target (T2T) strategy has become the new paradigm for the treatment of Rheumatoid Arthritis (RA); however the question is whether this strategy is feasible in daily clinical practice. The purpose of the study was to evaluate the adherence to a T2T strategy aiming at remission in a cohort of DMARD naive patients with early RA.

Methods: We included DMARDs naive patients with diagnosis of early RA belonging to a prospective cohort of patients with diagnosis of early arthritis (<2 years of disease duration). Data was collected every 3 months, including sociodemographic characteristics, functional status (HAQ), disease activity (DAS28) and medication. Clinical remission was defined as DAS28 ≤ 2.6. The primary outcome measure was the proportion of cohort visits in which therapy was adapted according to disease activity, stratified by remission state. Compliance with the T2T recommendations was defined as a change in drug treatment in patients failing to achieve clinical remission. Treatment strategies were stratified in seven groups: i) addition or dose escalation of NSAIDs, ii) addition/change of DMARDs, iii) dose escalation of DMARDs, iv) addition/change of biologic agents, v) addition or dose escalation of oral prednisone, vi) administration of parental corticosteroids, vii) administration of intra-articular corticosteroids. Compliance with T2T and treatment strategy was evaluated on each visit. The statistical analysis was carried out using STATA 12.

Results: We included 535 DMARDs naive patients with early RA. Mean age at inclusion was 48.2 ± 13.3 years. Female gender and disease duration was 7 ± 6 months. The patients contributed to a total of 3022 visits (mean follow-up = 24 ± 16 months). Mean HAQ and DAS28 score during follow-up were 0.9 ± 0.6 and 3.9 ± 1.2, respectively. Patients did not achieve remission in 2063 (68%) of the visits. A change in drug treatment was registered in 42% of these visits. The most frequent strategy was addition/change of DMARDs (31%), followed by addition/dose escalation of oral prednisone, addition/dose escalation of NSAIDs, dose escalation of DMARDs, intra-articular corticosteroids, parenteral corticosteroids and addition/change of biologic agents (9%, 9%, 8%, 3% and <1%; respectively).

Conclusion: In our cohort, including patients with early rheumatoid arthritis in “real world”, the compliance with the T2T treatment recommendations were low. A change in drug treatment was registered in less than half of the visits where patients were not in remission.

Disclosure: G. Rohekar, None; B. J. Jacob, None; J. E. Pope, None; C. Bombardier, None.

S1037 Thursday, November 18
The 12-Years Retention Rate of the First-Line TNF-Inhibitor in the Treatment of Rheumatoid Arthritis: Real-Life Data from a Local Registry.

Methods: We extracted data from a local registry that includes all RA patients (all fulfilling ACR/EULAR 2010 classification criteria) treated with biologic therapies between October 1999 and May 2014 in our Rheumatology Unit, limiting the analysis to patients treated with IFX, ETN, or ADA as first-line biologic drug. Data were collected through 31 May 2014. Drug survival up to 12-year follow-up was evaluated overall by the Kaplan-Meier method and corrected for patient variables, linear regression models were also used. Liver enzyme abnormalities were compared between patients on injectable and oral MTX who received MTX monotherapy for > 90 days; abnormal alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were defined as exceeding twice the upper limit of normal.

Results: Of the 7107 patients who were treated with injectable MTX monotherapy for > 90 days, 3910 required a therapeutic change (3808 were treated with oral MTX, 102 with injectable MTX). Patients treated with oral MTX remained on MTX monotherapy for a mean (SD) of 627 (365.5) days compared with 962 (786.6) days for patients treated with injectable MTX monotherapy (P < 0.001). Based on log-rank tests (see figure) and linear regression models, the use of injectable MTX was significantly associated with longer duration of MTX monotherapy (P = 0.0018 and P < 0.001, respectively). When adjusted for patient variables, the duration of MTX monotherapy was also significantly associated with age, race, starting MTX dose, and modified Charlson comorbidity score. These factors were assessed using a log-rank test and Kaplan-Meier curves; in order to correct for patient variables, linear regression models were also run. Liver enzyme abnormalities were compared between patients on injectable and oral MTX who received MTX monotherapy for > 90 days; abnormal alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were defined as exceeding twice the upper limit of normal.

Conclusion: Among patients identified in the VA database, the use of injectable MTX was associated with a significantly longer duration of MTX monotherapy compared with oral MTX. No significant differences in liver enzyme abnormalities were found between patients treated with injectable MTX and oral MTX.
Background/Purpose: Patients with inflammatory rheumatic diseases are at increased risk of infections when compared to healthy controls. Despite the fact that these infections could easily be prevented by available vaccines, vaccination coverage remains very low in France. The aim of this study was to evaluate the reasons why rheumatoid arthritis (RA) and spondyloarthritis (Sp) patients had not been vaccinated against influenza and streptococci infections.

Methods: In this French observational multicenter study, questionnaires were completed by RA and Sp patients referred to rheumatology departments from December 2012 to November 2013. The questionnaires consisted of questions about pneumococcal or influenza vaccinations, about the prescribing physician and, if applicable, about the reasons of non-vaccination. Clinical and demographic data were also collected.

Results: 268 RA patients and 189 Sp patients from 4 centers were included. Vaccination coverage was respectively 53% and 54.5% for pneumococcal vaccine and 59.7% and 47.1% for influenza vaccine. Lack of proposal was the major reason for non vaccination for pneumococcal (78.2% for RA and 78.9% for Sp patients; Figure 1) and influenza vaccine (48.1% and 61.1%; Figure 2). For pneumococcal vaccine, predictive factors for proposal were, history of RTX treatment (p = 0.0001) for RA patients and treatment with anti-TNFα (p = 0.006) for Sp patients. For influenza vaccine, predictive factors for proposal were: increased age (p = 0.01) and current biologic treatment (p = 0.002) in RA patients and presence of co-morbidities (p = 0.004) in Sp patients.

Conclusion: Despite the recognized usefulness of vaccination among patients with inflammatory rheumatic diseases and the current international recommendations, we found that the vaccination coverage of patients from 4 French centers is low, mainly due to the lack of vaccine proposal by the practitioners. These findings are consistent with data from other countries and highlight the need for pursuing information of the patients and their doctors.

Disclosure: C. Hua, None; J. Morel, None; B. Combe, None; C. Lukas, None.
2016

Tuesday, November 18

DAS 11 7 (29) 1 (100) - 3 (100)
Vienna, Austria, 4Medical University of Vienna, Vienna, Austria, 5Amsterdam Rheumatology Center, Amsterdam, Netherlands.

Table:

Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania,2Medical University of Vienna and Hietzing Hospital, Vienna, Austria,3Medical University of Vienna, Vienna, Austria, 4Austria M. Landewé, None; 5V. H. B. D. van Heijst, None.

Background/Purpose: Composite indices and single items are available to monitor disease activity in rheumatoid arthritis (RA). Their relation to radiographic progression is an important aspect to select the most appropriate as target. The objective of this study was to investigate the relationship between different disease activity indices (DAIs) and their individual components and radiographic progression in patients with RA.

Methods: A systematic literature review until July 2013 was performed by two independent reviewers using Medline and EMBASE databases. The research question was formulated according to the PICO method: Population (RA patients); Intervention (DAI including DAS, DAS28, SDAI, CDAI, RADAI and RAPID and individual items or scales including patients global health (GH), patientx5s global disease activity, pain, evaluationx5s global disease activity (EGA), all on a VAS, CRP, ESR, SJC and TJC); Outcome (radiographic progression). Longitudinal studies with 2 months of follow up assessing the relation between DAI and single items and radiographic progression were included. Risk of bias of the studies was evaluated according to Hayden tool (range 1-6). The results were grouped based on the means of measuring (baseline versus time-integrated) and analysis (univariable or multivariable).

Results: Fifty five studies from 1232 citations were included. Most of the studies were prospective cohorts and had an overall quality score 4 points. Radiographic progression was mainly assessed using the modified Sharp van der Heijde or Larsen scoring methods and the period to evaluate progression ranged between 12 and 240 months. The table shows a summary of the studies included in the SLR. All published studies that assessed the relationship between any time-integrated DAI and radiographic progression reached a statistically significant association. Among the single items, only SJC and ESR were associated with radiographic progression, while no significant association was found for TJC. Data with respect to CRP is conflicting. Data on patientsxGH, pain assessment and EGA is limited and does not support a positive association with progression of joint damage.

Conclusion: Published data indicates that composite disease activity scores including swollen joints are more related to radiographic progression than their individual components. Therefore, these are the optimal tools to monitor disease activity in patients with RA. The best performing single items are SJC and ESR.

Table: Summary of studies evaluating the relationship between disease activity indices and their individual components and radiographic progression; Data show total number of studies and the percentage of studies that reached statistically significance (% sig) based on the type of measure and analysis employed.

Disclosure C. Bledsoe, None; L. A. Davis, None; Y. Tran, None; A. Keniston, None; L. Caplan, None; I. Quinanzos, None; J. M. Hirsch, None.

2388

DMARD Use after an Initial Acute MI Is Associated with Reduced Risk of a Recurrent Event and Mortality.

Jie Zhang, Fengqiong Xie, Lang Chen, Huifen Yun, Paul M. Muntner, Emily Levitan, Monica Safford, Kenneth G. Saag, Jasvinder Singh and Jeffrey R. Curtis. 1 Univ. of Alabama at Birmingham, Birmingham, AL, 2University of Alabama at Birmingham, Birmingham, AL, 3University of Alabama at Birmingham School of Public Health, Birmingham, AL, 4The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Previous studies have suggested that disease modifying anti-rheumatic drugs (DMARDs) may reduce cardiovascular risk among patients with rheumatoid arthritis (RA). This analysis examined whether DMARD use after an initial acute myocardial infarction (MI) was associated with reduced risk of having a recurrent MI and mortality among older RA patients.

Methods: We identified Medicare beneficiaries (which covers more than 90% of all individuals 65 or older in the U.S.) and had an acute MI from 2006 to 2011. Eligibility criteria included the following: 1) had ≥2 rheumatologist visits with a diagnosis code for RA during a baseline period of at least 365 days prior to follow-up start; 2) had an acute MI defined as having an inpatient hospital claim with a discharge ICD-9 diagnosis code 410.X (excluding 410.X2) in any position and at least one overnight inpatient stay, unless the patient died. Follow-up started at time of discharge from the hospital after the initial MI. We used multivariable proportional hazard regression to examine the association between DMARD use after the initial MI and risk of having a recurrent MI and mortality, adjusting for factors ascertainment during baseline (socio-demographics and CHD risk factors [diabetes, hypertension, chronic kidney disease, abdominal aortic aneurism, peripheral arterial disease, atrial fibrillation, hyperlipidemia, tobacco use, overweight/obese, heart failure, chronic obstructive pulmonary disease]), and after M1 (medications for hypertension, hyperlipidemia, and RA). Exposure to DMARDs after M1 was categorized into the following exclusive hierarchical groups: 1) any anti-TNF biologic DMARD use; 2) any non-anti-TNF biologic DMARD use; 3) any methotrexate (MTX) use; 4) any non-MTX non-biologic DMARDs use (reference group, mostly hydroxychloroquine, sulfasalazine, and leflunomide use); and 5) no DMARD use.

Results: We identified 13,985 eligible RA patients with mean age 74.11 years. 74% of whom were women. Patients were grouped into one of five non-biologic and non-MTX DMARD use, non-TNF biologic DMARD use was associated with reduced mortality (hazard ratio [HR] 0.30 and; 95% confidence interval [CI] 0.14-0.68) and recurrent M1 (HR: 0.22, 95% CI: 0.07-0.69). Compared to the same reference group, any MTX use was associated with reduced mortality (HR: 0.71, 95% CI: 0.62-0.81) but not with recurrent MI. Oral glucocorticoid use (compared to no use) was significantly associated with increased mortality at doses ≥7.5mg/d (HR: 1.29, 95% CI: 1.12-1.48) and recurrent MI (HR: 1.73, 95% CI: 1.18-2.54) and high doses (>7.5mg/d [HR: 1.73, 95% CI: 1.30-2.26]) and with recurrent M1 at doses >7.5mg/d (HR: 1.29, 95% CI: 1.12-1.48).

Conclusion: Our findings suggest that among older RA patients, non-TNF biologic use and MTX use after an acute MI were associated with reduced risk of having a recurrent MI and mortality compared to non-biologic and non-MTX DMARD use, where glucocorticoid use was associated with increased risk of both outcomes. These results should be interpreted with caution given the possibility of residual confounding in observational studies.


2389

MRI Osteitis at Baseline Predicts the Development of Rapid Radiographic Progression at 2 Year Toward Patients with Early-Stage Rheumatoid Arthritis. Yishikazu Nakashima1, Mami Tamai2, Junko Kitatsu, Sousuke Tsujii4, Shoichi

Disclosure V. Navarro-Compañ, None; A. M. Gherge, None; J. S. Smolen, None; D. Alehata, None; R. B. M. L. Landewé, None; D. van der Heijde, None.
Background/Purpose: EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis (RA) states that magnetic resonance imaging (MRI) bone oedema (osteitis) is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. The development of rapid radiographic progression (RRP) is considered as a representative poor outcome in patients with RA. We have tried to examine whether MRI osteitis predict the further development of RRP in patients with early-stage RA from Nagasaki University Early Arthritis Cohort (NUEAC).

Methods: This is a 1-year observational study from seventy-six early-stage RA patients recruited consecutively from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrists and ankles. Of the patients, 15 variables were included during gender, age, disease duration, DAS28-CRP, CRP score, RAMRIS synovitis score, RAMRIS bone erosion score and Genant-modified Sharp score at entry (baseline) (RAMRIS = RAMRIS score × MRI wrist erosion score + MRI ankle erosion score). RAMRIS bone erosion score and Genant-modified Sharp score at entry were 9, 1, 0, 0, respectively. RRP was developed in 12 patients at 1 year. Fifteen variables including gender, age, disease duration, DAS28-CRP, CRP (mg/dl), matrix metalloproteinase-3 (mg/dl), presence of RF, presence of ACPA, initial therapy with MTX, use of biologic DMARDs within the first 6 months, HAQ, RAMRIS synovitis score, RAMRIS osteitis score, RAMRIS bone erosion score and mtSS were evaluated to explore the development of RRP at 1 year. Multivariate logistic regression analyses have identified that MRI osteitis at 1 year was the only independent predictor toward the development of RRP at 1 year (odds ratio: 1.12, 95% C.I.: 1.06–1.19, p = 0.0002).

Conclusion: Present data suggest that MRI osteitis is closely associated with poor radiographic outcome in patients with early-stage RA. Physicians should especially consider the tight control of disease activity if MRI osteitis is obvious in early RA patients.

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2390 Determinants and Impact of Early Initiation of Disease-Modifying Anti-Rheumatic Drug Therapy in Rheumatoid Arthritis: Chandana Keshavamurthy, K. Kevin Kuriakose, Deepak Chandra, A. Neet Kaur, Horace Spencer, and Nasim A. Khan, University of Arkansas for Medical Sciences, Little Rock, AR, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background/Purpose: Early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy is recommended to improve rheumatoid arthritis (RA) outcomes. The aim of this study was to determine whether characteristics associated with early DMARD initiation (< 6 month of RA symptom) and b) impact of early DMARD therapy on outcomes at one year.

Methods: This is a retrospective study of newly diagnosed RA patients at a single academic center. Eligibility criteria were RA diagnosis made by a board-certified rheumatologist, follow-up of at least 12 months and no prior history of DMARD use (except corticosteroids). Data on socio-demographics; dates of symptom onset, visit to referring healthcare provider (PCP), receipt of referral, Rheumatologist appointment and DMARD therapy initiation; functional status by M-segmental Health Assessment Questionnaires (MDHAQ) & disease activity by Routine Assessment of Patient Index Data 3 (RAPID3) and at initial and one year DMARD therapy were extracted in standardized manner from medical records.

Results:103 patients (71 (68.9%) females, 73 (70.9%) white; median (interquartile range, IQR) age of 50 (43–56) years, 74% anti-cyclic citrullinated peptide antibody-positive) were found eligible. 50 (48.5%) were uninsured, 37 (35.9%) had Medicaid or Medicare and 16 (15.5%) had private insurance. Median (IQR) time from RA symptom onset to DMARD initiation was 51 (26–83) weeks. 25 (24.3%) patients had early DMARD therapy initiation. The delay from symptom onset to PCP visit contributed most to non-early DMARD therapy initiation followed by duration for receipt of PCP referral to Rheumatology appointment (Table). Uninsured patients were significantly less likely to receive early DMARD therapy and were more likely to present with longer symptom duration to the PCP (p = 0.029), and have longer wait before getting Rheumatology appointment (p = 0.015). No other socio-demographic factor was associated with early DMARD initiation. There were no differences in MDHAQ, RAPID3, or initial DMARD agent for the early and late DMARD therapy groups. However, early DMARD therapy group had better functional status and lesser requirement of traditional and biological DMARDs after 12 month.

Conclusion: Only about one-fourth of RA patients received early DMARD therapy. Lack of insurance was associated with late DMARD therapy. Improved outcome and lesser need for intensive therapies were associated with early DMARD therapy. Our results supports need for improved insurance coverage as well improving awareness of early RA symptoms in general population and improving access to Rheumatology services.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early DMARD Therapy (&lt; 6 mo)</th>
<th>Late DMARD Therapy (≥ 6 mo)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>68 (67.2%)</td>
<td>60 (75.6%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Age, years</td>
<td>51 (36–65)</td>
<td>49 (45–55)</td>
<td>0.36</td>
</tr>
<tr>
<td>Race, white</td>
<td>86 (75.6%)</td>
<td>86 (89.2%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Education, &gt;12y</td>
<td>38 (34.6%)</td>
<td>30 (33.3%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Marital status, married</td>
<td>65.2 (59.3%)</td>
<td>64 (66.7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Insurance Private</td>
<td>32 (29.5%)</td>
<td>28 (31.1%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Uninsured</td>
<td>32 (30.0%)</td>
<td>18 (20.7%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Medicare or Medicare</td>
<td>26 (28.9%)</td>
<td>16 (18.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Private</td>
<td>8 (6.9%)</td>
<td>8 (9.1%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Patient’s home to Rheumatologist clinic, miles*</td>
<td>67 (42–132)</td>
<td>50 (37–102)</td>
<td>0.26</td>
</tr>
<tr>
<td>Symptom onset to PCP visit*, wks</td>
<td>4 (2–12)</td>
<td>4 (2–12)</td>
<td>0.89</td>
</tr>
<tr>
<td>PCP visit to referral placement*, wks</td>
<td>2 (0–4)</td>
<td>2 (0–4)</td>
<td>1.00</td>
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<tr>
<td>Referral receipt to Rheumatologist appointment*, wks</td>
<td>5 (0–30)</td>
<td>7 (5–14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rheumatologist 1st appointment to DMARD therapy*, wks</td>
<td>0 (0–30)</td>
<td>0 (0–32)</td>
<td>0.01</td>
</tr>
<tr>
<td>MDHAQ, 1st visit* (0–3)</td>
<td>1.3 (1.6–19.5)</td>
<td>1.3 (7.2–18.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>RAPID3, 1st visit* (0–3)</td>
<td>10.7 (4.9–23.3)</td>
<td>10.8 (4.1–23.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>RA treatment, 12 month</td>
<td>66 (72.4%)</td>
<td>64 (72.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>60 (71.8%)</td>
<td>62 (71.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>60 (71.8%)</td>
<td>60 (72.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>68 (78.6%)</td>
<td>64 (72.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>4 (5.9%)</td>
<td>2 (2.6%)</td>
<td>0.12</td>
</tr>
<tr>
<td>RA treatment, 24 month</td>
<td>84 (72.4%)</td>
<td>74 (72.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>60 (61.5%)</td>
<td>58 (59.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>60 (61.5%)</td>
<td>60 (61.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>62 (63.6%)</td>
<td>55 (56.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1All values in percentage (%), except variables with * represent median (IQR).
2p-values from Chi-square, Fisher’s exact test or Mann-Whitney U test.
3Early DMARD therapy is defined as therapy initiated within the first 6 months of RA onset.

Disclosure: C. Keshavamurthy, None; K. Kuriakose, None; D. Chandra, None; A. Kaur, None; H. Spencer, None; N. A. Khan, None.

2391 Sustained Rheumatoid Arthritis Remission and Low Disease Activity: Analysis of 13 Years of Follow up in Clinical Practice. G. Avila, A. Naranjo, M. Aria A. López-Lépiz-Lasanta, Andrea Pluma-Sanjurjo, C. Díaz, and Sara Marsal, University of O’Hebron Research Institute, Barcelona, Spain, University of O’Hebron, Barcelona, Spain.
Background/Purpose: Biological therapies (BTs) have greatly improved the outcomes in RA patients and nowadays clinical remission (REM) and low disease activity (LDA) have become realistic goals. Only few studies have examined sustained REM and LDA in clinical practice during large periods of time. Our objective was to analyze the duration of clinical REM and LDA in RA patients in clinical practice in a university hospital.

Methods: RA patients treated with ≥1 anti-TNF (infliximab, etanercept, adalimumab) during the period December 1999-March 13 were included. Only those treatments with ≥12 weeks of follow-up were analyzed. A large number of data were collected (gender, erosions, nodules, RF, ACPA, disease duration, previous BTs and concomitant corticosteroids/DMARDs...etc). DAS28 score was recorded every 3 months in all patients.

DAS28 records for each patient were interpolated to increase time resolution on the disease activity variations. We performed a parametric survival analysis in order to analyze the time until each patient reaches the first sustained period of low activity (LDA) and REM). Survival curves were analyzed according to (i) DAS28 threshold that determines a low activity, (ii) minimum period of time in which one patient must be below DAS28 threshold to be considered as sustained low activity. DAS28 thresholds were 2.6 for REM and 3.2 for LDA. The periods to consider sustained low activity were 12, 24, 48 and 96 wks. The Cox regression model was used to evaluate differences in survival times. To analyze the differences between anti-TNFs, the model included DAS28 at baseline, gender and disease duration.

Results: 222 RA patients were included (87% female, 78% erosive. 75% RF (+), 77% ACPA (+)). 452 BTs met the inclusion criteria and were analyzed. In the global survival analysis we found that 44%, 20% and 10% of patients started a sustained REM period of at least 12, 24 and 96 wks during the first year of treatment. The analysis stratified by clinical variables showed that the absence of erosions was associated with sustained REM for periods longer than 48 weeks (P-value = 7.94e-03, HR = 1.32 (1.02–0.71)). The differential analysis between anti-TNFs showed higher clinical remission rates in patients treated with Etanercept (ETN) compared to infliximab when longer periods were considered. Further HAQ scores were obtained at 1, 2, 3, 5, 7, 10, 12, 15 and 20 years follow up, and DAS28-CRP every 5 years. Generalized estimating equations (GEE) were used to test the association between anti-CarPA status and longitudinal HAQ and DAS28 scores including a time interaction term; then additionally adjusting for age, gender, smoking status; year of inclusion and ACPA status. The analyses were repeated in the ACPA positive and negative subgroups and in patients who fulfilled RA classification criteria without adjustment for ACPA.

Results: 1995 patients were included; 1310 (66%) were female, median age at onset (IQR) was 55 years (43–66) and median symptom duration (IQR) was 33 weeks (17–68). Anti-CarPA were positive in 460 (23%) patients and 1221 (61%) satisfied the 2010 ACR/EULAR classification criteria for RA, 539 (26%) were current smokers. ACPA were tested in 1465 patients, 373 (25%) were positive. Median follow up time (IQR) was 7 years (5–11). Baseline median HAQ and DAS28 were higher in anti-CarPA positive vs negative patients (1.125 vs 0.875 and 4.23 vs 3.73 respectively). In the GEE analysis, patients who were anti-CarPA positive had significantly more disability over time and higher levels of disease activity than those who were negative; multivariate model for the HAQ including adjustment for ACPA gave a β coefficient (95% confidence interval) 0.13 (0.03–0.23) (Table 1). Statistically significant associations were also seen in the ACPA negative subgroups. In the ACPA positive and RA subgroups there were significant associations with DAS28 and trends approaching statistical significance with HAQ scores.

Conclusion: The presence of anti-CarPA is associated with increased burden of disability and higher disease activity over time in patients with EIA. Our results suggest anti-CarPA may be useful in identifying ACPA negative patients with poor prognosis.

Table 1 Association between anti-CarPA positivity and HAQ and DAS28 throughout follow up

<table>
<thead>
<tr>
<th>Total cohort</th>
<th>ACPA-ve</th>
<th>ACPA+ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1995</td>
<td>n=1092</td>
<td>n=373</td>
</tr>
<tr>
<td>HAQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β coefficient (95% CI)</td>
<td>β coefficient (95% CI)</td>
<td>β coefficient (95% CI)</td>
</tr>
<tr>
<td>Univariate</td>
<td>0.20 (0.13-0.28)</td>
<td>0.16 (0.02-0.31)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.13 (0.03-0.23)</td>
<td>0.15 (0.02-0.29)</td>
</tr>
<tr>
<td>DAS28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β coefficient (95% CI)</td>
<td>β coefficient (95% CI)</td>
<td>β coefficient (95% CI)</td>
</tr>
<tr>
<td>Univariate</td>
<td>0.47 (0.33-0.61)</td>
<td>0.29 (0.03-0.55)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.31 (0.12-0.49)</td>
<td>0.37 (0.11-0.63)</td>
</tr>
</tbody>
</table>

2392

Anti-Carbamylated Antibodies (anti-CarPA) Are Associated with Long Term Disability and Increased Disease Activity in Patients with Early Inflammatory Arthritis: Results from the Norfolk Arthritis Register (NOAR).

2393

Similar Improvements in Physical Function, Quality of Life and Work Productivity Among Rheumatoid Arthritis Patients Treated with 2 Different Doses of Methotrexate in Combination with Adalimumab.
Background/Purpose: Methotrexate (MTX) is used in monotherapy or in combination with other DMARDs in the treatment of patients (pts) with rheumatoid arthritis (RA). We evaluated the effects of low and high MTX doses in combination with initiation of ADA on patient-reported outcomes (PROs), in MTX-irregular responders (MTX-IR) with moderate-to-severe RA.

Methods: MUSICA (NCT0185288) was a double-blind, randomized, controlled trial evaluating the efficacy of 2 different dosages of MTX, 7.5 or 20 mg/week (wk) in combination with ADA (40 mg every other wk) for 24 wks in MTX-IR RA pts. Pts entering the study had been receiving ≥15 mg/mg/week MTX for at least 12 wks. At each study visit, from baseline (BL) to wk 24, the following PROs were recorded: physical functioning, work productivity and activity impairment, and heath-related quality-of-life (HRQoL), using the health assessment questionnaire-disability index (HAQ-DI), work productivity and impairment (WPAI), and the short-form 36 (SF-36) questionnaires, respectively. Last observation carried forward (LOCF) was used to account for missing values.

Results: 154 pts were enrolled in the 7.5 mg/wk MTX + ADA arm, and 155 pts in the 20 mg/wk MTX + ADA arm. Both arms were similar for BL demographics (mean age 54.8, mean disease duration 5.3 years) and disease characteristics (mean DAS28 [CRP] of 5.8). In the low and high MTX dosage groups respectively, mean HAQ-DI scores were 1.5, mean percentages (%) of time in absenteeism at BL were 9.2 and 10.1; mean % of time in presenteeism at BL were 45.0 and 47.6; mean % of activity impairment at BL were 57.0 and 61.9. BL SF-36 (physical component) scores were 31.5 for both groups, and SF-36 (mental component) scores were 44.7 and 41.9 for the low and high-dosage groups respectively. After 24 wks, significant improvements from BL were observed for both MTX dosage groups, in the WPAI (except for absenteeism), HAQ-DI and the physical and mental components of the SF-36 (table). Differences in physical function, QoL and work productivity observed between the low and high MTX dosage groups were not statistically significant.

Table 1 Effect of treatment with ADA + low or high dose MTX on patient outcomes at week 24

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>n</th>
<th>Change from BL to wk 24, mean (95% CI)</th>
<th>P-value (BL and wk 24 main scores)</th>
<th>wk 24, mean score (95% CI)</th>
<th>P-value (between wk 24 main scores of dosage groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>153</td>
<td>-0.5 (-0.6, -0.4)</td>
<td>&lt;0.001</td>
<td>1.0 (0.0, 1.1)</td>
<td>0.476</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>154</td>
<td>-0.5 (-0.6, -0.4)</td>
<td>&lt;0.001</td>
<td>1.0 (0.0, 1.1)</td>
<td>0.476</td>
</tr>
<tr>
<td>WPAI-absenteeism</td>
<td>7.5mg MTX + ADA</td>
<td>63</td>
<td>-2.9 (-4.4, 2.5)</td>
<td>0.288</td>
<td>6.3 (1.9, 10.6)</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>61</td>
<td>-7.1 (-1.6, 0.2)</td>
<td>0.082</td>
<td>10.6 (4.7, 16.6)</td>
<td>0.261</td>
</tr>
<tr>
<td>WPAI-presenteeism</td>
<td>7.5mg MTX + ADA</td>
<td>66</td>
<td>-17.9 (-24.5, -11.3)</td>
<td>&lt;0.001</td>
<td>27.1% (20.9, 33.3)</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>63</td>
<td>-21.0 (-28.4, -13.6)</td>
<td>&lt;0.001</td>
<td>26.7% (20.0, 33.3)</td>
<td>0.700</td>
</tr>
<tr>
<td>WPAI-Overall Work Impairment</td>
<td>7.5mg MTX + ADA</td>
<td>63</td>
<td>-19.0 (-26.6, -11.4)</td>
<td>&lt;0.001</td>
<td>29.2% (22.9, 36.4)</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>63</td>
<td>-17.5 (-26.5, -8.4)</td>
<td>&lt;0.001</td>
<td>32.7% (24.7, 40.7)</td>
<td>0.580</td>
</tr>
<tr>
<td>SF-36-physical component</td>
<td>7.5mg MTX + ADA</td>
<td>137</td>
<td>-14.9 (-16.6, -10.2)</td>
<td>&lt;0.001</td>
<td>42.1% (37.0, 47.3)</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>143</td>
<td>-20.4 (-25.3, -15.5)</td>
<td>&lt;0.001</td>
<td>43.5% (36.5, 46.6)</td>
<td>0.278</td>
</tr>
<tr>
<td>SF-36-mental component</td>
<td>7.5mg MTX + ADA</td>
<td>150</td>
<td>7.2 (3.7, 10.7)</td>
<td>&lt;0.001</td>
<td>38.8 (37.0, 40.5)</td>
</tr>
<tr>
<td>20mg MTX + ADA</td>
<td>152</td>
<td>7.4 (3.1, 11.8)</td>
<td>&lt;0.001</td>
<td>38.9 (37.0, 40.6)</td>
<td>0.835</td>
</tr>
<tr>
<td>P-values between dosage groups at wk 24 determined by ANCOVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Similar to observations in pts with early RA, the addition of ADA to MTX in pts with moderate to severe disease and insufficient MTX response, led to improvements in physical function, work productivity and quality of life after 24 wks. The improvements were observed regardless of the MTX dosage. Similar improvements in the two MTX dosage groups support the hypothesis that MTX dose could be reduced in some MTX-IR pts while initiating ADA therapy.

Disclosure: J. T. Einarsson, None; M. C. Kapetanovic, None; P. Geborek, None.

2395

Understanding Patient Preferences Associated with the Use of T Therapies for Rheumatoid Arthritis: Results of a Conjoint Analysis.

K. Saverno¹, A. Louder¹, A. Singh¹, J. Cappelleri², A. Aten³, A. Koenig⁴ and M. Pasquale⁵. ¹Comprehensive Health Insights Inc, Louisville, KY, ²Pfizer Inc, Groton, CT, ³Pfizer Inc, New York, NY, ⁴Humana Inc, Louisville, KY, ⁵Pfizer Inc, Collegeville, PA.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib provides patients with a new oral alternative to biologic therapies; however, little is known about the
patient preference of modern treatments for RA. Here, we determined patient preferences for attributes associated with therapies used in the treatment of RA.

Methods: A choice-based conjoint survey was mailed to 1400 randomly selected Humana adult (21–80 years old) members diagnosed with RA (continuously enrolled and had ≥2 medical claims with an ICD-9-CM diagnosis code of RA [714.0] between 5/1/2012 and 4/30/2013) and no prior use of a biologic indicated for RA. Attributes included route of administration (ROA); monthly out-of-pocket cost; frequency of administration (FOA); ability to reduce daily joint pain and swelling; likelihood of serious side effects (SAE); improvement in the ability to perform daily tasks and activities; and medication burden (methotrexate co-administration). Mean attribute importance scores (AIS) were calculated after adjusting for various member demographics (e.g., age, gender, region, years since RA diagnosis). Mean AIS scores were used to rank order patient preferences for the attributes. An aggregate log analysis was implemented to estimate average utilities & preference shares for two treatments — twice daily oral and every other week self-injection.

Results: A total of 380 commercially enrolled members (response rate of 27.1%) in Humana returned the survey (mean ± standard deviation [SD] age 54.9 ± 9.3 years, 9.7% had a history of joint surgery due to RA, 81.6% female). After an adjustment for demographic and clinical characteristics, commercial members’ ranking of attribute importance was as follows in decreasing order (mean AIS > SD): ROA 34.08 ± 15.53; FOA 16.43 ± 6.69; SAE 12.01 ± 9.32; cost 10.12 ± 6.21; medication burden 9.75 ± 8.15; joint pain reduction 8.86 ± 3.82; and improvement in daily tasks 8.76 ± 4.70. Within the route of administration attribute, the oral formulation was the level with the highest part-worth utility (preference score) compared with subcutaneous and intravenous routes of administration. Based on the part-worth utility, it was estimated that 62% of RA patients included in the sample would prefer oral therapy.

Conclusion: Route of administration is an important consideration for those diagnosed with RA and naïve to biologic therapy. Given the variety of RA therapies available, gaining a better understanding of the attributes considered important to patients in their treatment may help inform payer and prescriber decisions in selecting therapies that will lead to higher patient satisfaction and improved medication adherence.

Disclosure: K. Saverno, Humana, 3; A. Louder, None; A. Singh, Pfizer Inc, 1; Pfizer Inc, 3; J. Cappelleri, Pfizer Inc, 3; Pfizer Inc, 1; A. Aten, Humana, 3; A. Koenig, Pfizer Inc, 1; Pfizer Inc, 1; M. Pasquale, Comprehensive Health Insights, a wholly-owned subsidiary of Humana Inc, 3.

2396

Treat to Target in Routine Clinical Practice. Mohammad Solaiman1, Olga Semenova2, Helen Thompson3, Joanne Cunnington3, Elaine Baguley1, Sahish K’alan2, Olanbambo Ogumbamb3 and Yusuf Patel3.1, Hull Royal Infirmary, Hull, United Kingdom, 2Hull Yoyal Infirmary, Hull, United Kingdom, 3Hull and East Yorkshire NHS Trust, Hull, East Yorkshire, United Kingdom.

Background/Purpose: In order to overcome obstacles with overbooked outpatient clinics and lack of capacity to see rheumatoid patients frequently for treatment escalation, we established a protocol-driven clinic run by a specialty doctor and nurse in 2010. All newly diagnosed patients with Rheumatoid Arthritis were seen on a 4–6 weekly basis by the team to escalate DMARD treatment according to disease activity as measured by DAS28-CRP. To assess DAS28-CRP remission rate in this cohort of patients after 1, 2 and 3 years of therapy. We also looked at rates of low disease activity (LDA) - DAS 28 CRP <2.6 but ≥3.2 and categorisation by DMARD monotherapy, combination therapy, or Biologic therapy.

Methods: Treatment escalation was done by agreed departmental protocol which included oral Methotrexate (up to 25mg/m2/week, followed by S/C injections if necessary). This was followed by addition of Hydroxychloroquine and then either Leflunomide or sulphasalazine if DAS28-CRP indicated activity. UK NICE guidelines allow use of Biologics if the DAS >5.1 at 6 months, hence this was the next step followed on the protocol. We collected additional outcome data for HAQ score, work stability data, and radiological erosion data. We enrolled 331 patients through the clinic to date and present outcome data for those completing year (172), 2 years (75) and 3 years (36).

Results: 127 patients have completed 1year, of which 20% achieved DAS28 scores <3.2 (LDA) and 60% <2.6 (remission). 6.4% needed combination DMARD therapy and 7 patients (5.5%) needed biologics, 30% remaining on DMARD monotherapy at 1 year. Mean HAQ scores reduced from 1.1 (+−0.01) to 0.32 (+−0.07) and radiological erosions progressed in only 10%. Job retention at one year was 90%.

75 patients completed 2 years of follow-up, 68% in DAS-remission and 16% LDA. 8% are on Biologics at end of year 2, 32% on DMARD monotherapy.

36 patients completed 3 years follow-up, with LDA in 25% and remission 61%. At year 3, Biologics use is 5.5%, with DMARD monotherapy in 20%.

Conclusion: Targeted protocol-driven treatment of early RA with rapid escalation of therapy using conventional DMARDs/biologics resulted in remission of 60% at 1 year and maintained remission of 68% and 61% at 2 and 3 years. The DAS28 remission rates and other outcomes achieved in this relatively ‘routine’ clinic are comparable to results achieved in controlled clinical trials. The innovative use of limited human resources and clinic appointments has provided good outcomes for patients with potential savings in expenditure on Biologic therapy.

Table: Comparison between Disease activity and therapy on consecutive 3 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapy</th>
<th>Combination</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>26 (20%)</td>
<td>15 (58%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Year 2</td>
<td>25 (20%)</td>
<td>14 (50%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Year 3</td>
<td>24 (20%)</td>
<td>15 (50%)</td>
<td>3 (11%)</td>
</tr>
</tbody>
</table>

Disclosure: M. Solaiman, None; O. Semenova, None; H. Thompson, None; J. Cunnington, None; E. Baguley, None; S. K’alan, None; O. Ogumbamb, None; Y. Patel, None.

2397

Improvement of Fatigue in Patients with Rheumatoid Arthritis Treated with Biologics: Relationship with Sleep Disorders, Depression and Clinical Efficacy. A Prospective, Multicenter Study. Marline Genty1, Marie Kostine2, Elodie Ardon3, Bernard Combe4 and Cédric Lukas2.1CHU Laparayonie, Montpellier, France, 2Rheumatology, CHU Pellegrin, Bordeaux, France, 3Rheumatology, Limoges University Hospital, Limoges, France, 4Hôpital Laparayonie, Montpellier, France, 5Hôpital Laparayonie, Montpellier, France.

Background/Purpose: The functional burden of disease in Rheumatoid arthritis (RA) patients, mainly caused by inflamed joints, is often worsened by extra-articular manifestations, among which asthenia remains the most frequently reported. Most biologics have shown overall efficacy on fatigue, but whether this is due to overall improvement of disease or to more specific aspects of the disease like sleep disorders due to overnight pain and awakenings remains unknown. The aim of this study was to evaluate potential predictive factors of improvement in related fatigue in RA patients newly receiving biologic therapy, and more specifically the potential influence of the improvement in sleep disorders.

Methods: We conducted a multicenter prospective study in RA patients (100% fulfilling ACR/EULAR classification criteria) requiring initiation or change of biologic therapy. The improvement in fatigue was assessed by the FACIT fatigue scale at inclusion (M0) and after 3 months (M3). Sleep disorders and evaluation of depression were respectively measured by Spiegel scale and Beck Depression Inventory. Potential confounders like presence of anemia, thyroid dysfunctions, iron deficiency, psychotropic or corticosteroids medications were adjusted for. The association between evolution of fatigue (improvement/no improvement according to predefined validated cutoffs) and...
other characteristics were evaluated by univariate (Chi2) then multivariate (logistic regression) analyses.

**Results:** We included and followed-up 99 patients (72.7% women, aged 58.2±12.1 with initially active disease (DAS28 5.1±1.4). FACIT scores at inclusion revealed frequently reported fatigue: 89% with scores more severe than expected in general population, high prevalence of sleep disorders (95%: abnormal 68%, pathologic 27%) and depression (67%: mild 33%, moderate 24%, severe 11%). Anti-TNF drugs were started in 50 patients, other biologics in 49 patients (tocilizumab N = 19, abatacept N = 16, rituximab N = 14). Clinical response was beneficial in most patients; 36% good EULAR response, 40% moderate, 24% no response. Improvement of fatigue, sleep quality and depression according to predefined cutoffs was observed in respectively 58.6%, 26.3% and 34.3% of cases. Factors associated with an improvement in fatigue at M3 were an elevated sedimentation rate at M0 (OR = 5.7 [2.0–16.0], p = 0.001) and a favorable EULAR response at M3 (OR = 4.8 [1.6–14.8], p = 0.006). Furthermore, a number of swollen joints > 5 at baseline (OR = 0.3 [0.1–0.8]) and the use of psychotropic drugs (OR = 0.2 [0.04–0.9]) were predictive of an absence of improvement in fatigue. No significant association with the improvement in sleep disorders could be demonstrated: of 29 patients with improvement in sleep quality, 17 (58.6%) considered their level of fatigue had decreased, while 41/70 (58.6%) could be demonstrated: of 29 patients with improvement in sleep quality, 17 (58.6%) considered their level of fatigue had decreased, while 41/70 (58.6%)

**Conclusion:** Continued participation during 10 year follow-up in the BeSt study was relatively high (62%), although impaired functional ability, higher age, experiencing severe adverse events and experiencing drug-free remission in the previous year were predictors for early termination. Motivators to continue participation were a wish to contribute to scientific research, to learn more about their disease and its treatment, personal benefit of available therapies, and a good rapport with the study nurse. By cultivating these motivators, early termination in future long-term follow-up studies might be reduced.

**Disclosure:** I. M. Markusse, None; L. Dirven, None; T. H. E. Molenaar, None; N. Rizayi, None; P. B. J. de Sonnaville, None; P. J. S. M. Kerstens, None; W. F. Lems, None; T. W. J. Huizinga, None; C. F. Allaart, None.

### 2399

**Non-Adherence to Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: An Italian Survey.**


**Background/Purpose:** Our study confirmed that fatigue in RA is frequent, as well as depression and sleep disorders, and is usually improved by effective treatment (i.e. via decrease in disease activity). Our results indicate that improvement of sleep disorders is more likely a surrogate of therapeutic efficiency rather than an independent outcome.

**Disclosure:** I. M. Markusse, None; L. Dirven, None; T. H. E. Molenaar, None; N. Rizayi, None; P. B. J. de Sonnaville, None; P. J. S. M. Kerstens, None; W. F. Lems, None; T. W. J. Huizinga, None; C. F. Allaart, None.

**Methods:** In 508 patients with early RA enrolled in the BeSt study, risk factors for premature study discontinuation were identified through univariable and then multivariable logistic regression analysis. In this analysis, for every patient ten endpoints were generated (still under follow-up at the end of a year, yes/no), and baseline characteristics and clinical characteristics as present at the preceding year of follow-up were entered as determinants. Patients who completed 10-year follow-up were asked to fill in a questionnaire on study experiences and possible motives for study adherence.

**Results:** In total, 313/508 patients (62%) attended the final visit, and 288 (92%) filled in the questionnaire. Mean age of completers was 61 years and 67% were female. Based on 508 included patients, risk factors for early termination were a higher age (odds ratio, OR 1.04, 95% confidence interval, CI 1.03 – 1.06), worse functional ability during the preceding year (measured with the health assessment questionnaire, OR 1.63, 95% CI 1.27 – 2.08), having achieved drug-free remission during the preceding year (OR 1.85, 95% CI 1.38 – 2.47) and suffering a severe adverse event during the preceding year (OR 1.71, 95% CI 1.18 – 2.49). In the first part of the questionnaire, the majority of patients mentioned contributing to scientific research (97% of patients agreed), helping other patients (91%), “I have nothing to lose” (80%), gaining understanding of new treatment strategies (84%) and of their disease (85%) as reasons to continue participation. Next, patients were asked to mark one or more possible reasons to continue participation. In total, 278 patients marked 912 reasons: tight disease control (202/278 patients), good treatment strategy (128/278), good medication prescribed by the protocol (117/278) and good half-time results (102/278) were most often mentioned. Over 95% of patients experienced participation as ‘expected’ or ‘better than expected’. In particular care by the study nurses was appreciated: 55 – 75% answered “better than expected” to 4 questions regarding this issue. Additional examinations during the yearly visits (additional questionnaires, imaging techniques) were mentioned “worse than expected” (10% of patients) as was filling in the 3-monthly questionnaires (7%). Most patients (74%) would participate in another trial and 94% would recommend participation to friends and family.

**Conclusion:** Continued participation during 10 year follow-up in the BeSt study was relatively high (62%), although impaired functional ability, higher age, experiencing severe adverse events and experiencing drug-free remission in the previous year were predictors for early termination. Motivators to continue participation were a wish to contribute to scientific research, to learn more about their disease and its treatment, personal benefit of available therapies, and a good rapport with the study nurse. By cultivating these motivators, early termination in future long-term follow-up studies might be reduced.

**Disclosure:** I. M. Markusse, None; L. Dirven, None; T. H. E. Molenaar, None; N. Rizayi, None; P. B. J. de Sonnaville, None; P. J. S. M. Kerstens, None; W. F. Lems, None; T. W. J. Huizinga, None; C. F. Allaart, None.
The demographic characteristics are summarized in Table 1.

### Table 1. Demographic Characteristics of 144 RA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>20 (67%)</td>
<td>15 (68%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>63 ± 15</td>
<td>62 ± 9</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15 (47%)</td>
<td>9 (38%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>61 (63%)</td>
<td>57 (70%)</td>
<td>10 (63%)</td>
</tr>
<tr>
<td>African American, n (%)</td>
<td>15 (16%)</td>
<td>10 (13%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>6 (6%)</td>
<td>5 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td><strong>Disease activity results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS28, mean ± SD</td>
<td>2.5 ± 0.8</td>
<td>2.5 ± 0.8</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td><strong>Smoking habit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker, n (%)</td>
<td>23 (77%)</td>
<td>15 (68%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>7 (23%)</td>
<td>8 (28%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (months)</td>
<td>11 ± 3</td>
<td>12 ± 4</td>
<td>6 ± 3</td>
</tr>
<tr>
<td><strong>Flares</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past 1 year, n (%)</td>
<td>2 (7%)</td>
<td>3 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>In the past 6 months, n (%)</td>
<td>5 (17%)</td>
<td>8 (29%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td><strong>Duration of disease prior visit 1 (years)</strong>*</td>
<td>6.8 ± 1.5</td>
<td>6.7 ± 1.3</td>
<td>6.9 ± 2.1</td>
</tr>
</tbody>
</table>

**Notes:**
- *CG* = Control group
- *D* = Disease activity
- *E* = Ethnicity
- *TG* = Tapering group
- *RF* = Rheumatoid arthritis
- *ACP* = Anti-cyclic citrullinated peptide antibodies
- *EA* = Early arthritis
- *S* = Smoking habit
- *S1* = Smoking status
- *H* = Hispanic
- *A* = African American
- *C* = Caucasian
- *F* = Female
- *M* = Male
- *E* = Ethnicity
- *S* = Smoking habit
- *S* = Smoking status
- *H* = Hispanic
- *A* = African American
- *C* = Caucasian
- *F* = Female
- *M* = Male

**Background/Purpose:** There is a growing interest about optimization of biological therapies but for now no strong evidence is available to support a tapering strategy in clinical practice. Our aim was to compare the clinical outcomes of a tapering strategy to the standard dosing regimen of TNF inhibitors (TNFi) in patients with rheumatoid arthritis (RA) and low disease activity during long-term follow-up.

**Methods:** In this retrospective observational study, two groups of RA patients on TNFi with DAS28 <3.2 were compared: the tapering group (TG: 67 pts from Spain) and the control group with the standard therapy regimen (CG: 77 pts from the Netherlands). DAS28 was measured at different time points: visit 0 (prior starting TNFi), visit 1 (prior to starting tapering in TG and at least 6 months with DAS28 <3.2 after starting TNFi in the TG and CG), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (the last visit available after visit 1).

**Results:** The demographic characteristics are summarized in Table 1. Despite an overall reduction of administered drug at visit 4 in the TG (an interval elongation of 32.8% in infliximab, 52.9% in adalimumab and 52.6% in etanercept), no significant differences were found in the clinical activity between the groups at the end of the study (DAS28: 2.7 ± 0.9 in TG vs. 2.5 ± 1 in CG, p = 0.1) (Figure 2). The number of patients with flares was similar in both groups [28/67 (42%) in TG vs. 36/75 (48%) in CG, p = 0.5]. No significant differences were seen in the proportions of patients who dropped out [10/67 (15%) in TG vs. 6/77 (8%) in CG, p = 0.17].

**Conclusion:** The tapering strategy of TNFi in RA patients with low disease activity results in an important reduction in the amount of drug administered, while the disease control remains similar to that of patients on the standard dosing regimen.

**2400**

Compared to the Standard Dosing Regime of TNF Inhibitors in Patients with Rheumatoid Arthritis in Remission or with Low Disease Activity, Chamiada Piasencia-Rodríguez, G. J. Wolbink, Charlotte L. M. Kriebkaert, Christine A. Peschken, Liam O’Neil, Carol A. Hinchon, David B. Robinson, Janet Dhindsa, Hani El-Gabalawy and Christine A. Peschken.

**Background/Purpose:** Severe disease and poor outcomes have been described in First Nation (FN) patients with Rheumatoid Arthritis (RA). We examined the contributions of interrupted and delayed care to the outcomes of FN RA patients compared with Caucasian (CA) patients with RA.

**Methods:** Our academic Arthritis Centre maintains a prospective database on all patients seen since 1990, with records of more than 10,000 patients. The database includes patients’ diagnoses, demographics, year of disease onset, and date of first and subsequent clinic visits, and self-reported ethnicity. At each visit, patients complete a modified health assessment score (H11021) and an adverse events checklist (H11021). A Lansbury Index (LBI), a weighted joint count, is calculated each visit. Complete joint counts, physician global VAS, and current treatment information are recorded. A modified HAQ index (H20841) is calculated at each visit.

**Results:** In this retrospective observational study, two groups of RA patients on TNFi with DAS28 <3.2 were compared: the tapering group (TG: 67 pts from Spain) and the control group with the standard therapy regimen (CG: 77 pts from the Netherlands). DAS28 was measured at different time points: visit 0 (prior starting TNFi), visit 1 (prior to starting tapering in TG and at least 6 months with DAS28 <3.2 after starting TNFi in the TG and CG), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (the last visit available after visit 1).

**Fig 1**

`Fig 1` shows the comparison of HaQ between the tapering and control groups in each year. The clinical activity was measured by DAS28. (n, mean ± SD: *p* < 0.05). The clinical activity was not measured after year 7 in the tapering group (*n* = 15 patients). Between the groups at the end of the study (DAS28: 2.7 ± 0.9 in TG vs. 2.5 ± 1 in CG, p = 0.1) (Figure 2). The number of patients with flares was similar in both groups [28/67 (42%) in TG vs. 36/75 (48%) in CG, p = 0.5]. No significant differences were seen in the proportions of patients who dropped out [10/67 (15%) in TG vs. 6/77 (8%) in CG, p = 0.17].

**Conclusion:** The tapering strategy of TNFi in RA patients with low disease activity results in an important reduction in the amount of drug administered, while the disease control remains similar to that of patients on the standard dosing regimen.
Results: Records of 154 CA and 150 FN patients were abstracted. Disease duration and gender distribution were similar in CA compared to FN (9 ± 4 vs 8 ± 5 years; and 79% vs 85% female respectively). Mean distance from care was 73 km for CA and 408 km for FN, with 35% of FN living >500 km away compared to 1% of CA, (p < 0.001). FN patients were younger at disease onset than CA, (40 ± 13 vs 49 ± 17 years; p < 0.001). At clinical presentation, FN were more likely to be seropositive for both RF and ACPA compared to CA, (59% vs 46%; p = 0.02) and had higher RF titers (405 ± 551 vs 276 ± 68; p = 0.005), and ACPA titres (114 ± 88 vs 61 ± 82; p = 0.001). The two groups did not differ in mHAQ, ESR, CRP, VAS, tender, or swollen joint counts at first visit, but FN had higher LBI scores (40 ± 36 vs 28 ± 33; p = 0.012). FN had greater delays from symptom onset to first DMARD (19 months ± 26 vs 15 ± 35; p = 0.02), and first biologic (57 months ± 34 vs 46 ± 45; p = 0.06), but had more total DMARD trials over their disease course (5 ± 1.3 vs 3.7 ± 2.5; p = 0.001), and were off DMARD therapy for longer periods in total (36 months ± 30 vs 25 ± 40; p = 0.009), had fewer clinic visits/year (5 ± 12 vs 3 ± 7; p = 0.072), and received more frequent intramuscular steroid injections (IMS) for flares. 21% of FN had received 3-5 IMS vs 12% of CA, and 11% had received ≥ 6 IMS vs 3% of CA; p < 0.001. At the last visit, FN had higher mHAQ scores (.71 ± .47 vs .42 ± .52; p < 0.001), higher LBI (34 ± 37 vs 20 ± 30; p = 0.003), and more frequent joint damage/defority, (85% vs 74%; p = 0.02).

Conclusion: The young age at onset, more frequent seropositivity, and higher LBI suggest biologically more severe disease, but our data suggests differential care delivery with modifiable factors over the disease course that likely impact outcomes, including treatment delays, missed appointments, and interrupted care delivery models, particularly incorporating outreach care, have the potential to improve care substantially for this population.

Disclosure: L. O’Neil, None; C. A. Hitchon, None; D. B. Robinson, None; N. Dhinda, None; H. El-Gabalyaw, None; C. A. Peschken, None.

2402

Evaluation of Perceived Self-Efficacy, Learned Helplessness and Functional Capacity in Patients with Rheumatoid Arthritis. Facundo Ver gara1, Emmanuel Bertiller2, Celeste Orozco2, Javier Rosa1, Erika Catay1, Maria de los Angeles Gallardo1, Emilce Schneeberger1, Maria Victoria Garcia1, Gustavo Citera1, Marcos G. Rose moff2, Mirtha Sabelli2, and Enrique R. Soriano1.

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4Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
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6Instituto de Rehabilitacion Psicosofica, Buenos Aires, Argentina.
7Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
8Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: Rheumatoid Arthritis (RA) is an inflammatory chronic disease that involves cognitive and emotional aspects of patients, from the beginning of diagnosis. One relevant cognitive factor is perceived self-efficacy, which is defined as the individual’s abilities to cope with the disease. Another important cognitive factor in the perception of RA control is the learned helplessness. We could define it as an inadequate perception of the disease generating feeling of defenselessness, behaviors of passivity, loss of self-esteem and belief that nothing you do can improve your situation.

It has been reported that patients with high levels of self-efficacy have less pain, learned helplessness and functional disability. On the other hand patients with higher learned helplessness, have more pain and functional disability. Our objective was to assess the association between perceived SE and LH with disease activity, functional disability, and educational level.

Methods: Consecutive patients, older than 18 years, with definite diagnosis of RA according to 2010 ACR/EULAR criteria, seen at the outpatient rheumatology unit between March and April 2014, were included. During the inclusion visit the following data were collected: Demographics; socio-economic status (Gratfran scale); educational level; disease duration; swollen and tender joint counts (28 joints); CDAI (Clinical Disease Activity Index); HAQ-DI (Health Assessment Questionnaire/simplified Argentinean validation); pain by visual analogue scale (VAS); fatigue (VAS); patient and physician global assessment of disease activity (VAS); morning stiffness (VAS); depression screening measured by CES-D-7; perceived SE measured by Arthritis Self-auto-efficacy Scale; LH measured from Rheumatology Attitudes Index (RAI) (spanish validation).

Descriptive statistics were calculated. Correlations were calculated using Pearson test. SE and LH were compared between patients in remission and with active disease.

Results: One hundred and two patients were included. Patient’s characteristics are shown in table 1. There was a significant positive correlation between LH and pain (r = 0.67; p < 0.001); HAQ (r = 0.64; p < 0.001), and CDAI (0.41; p < 0.001); and a negative correlation between SE and pain (r = −.43; p < 0.001); HAQ (r = −.41; p < 0.001); and CDAI (r = −.34; p < 0.001). Patients on remission (n = 90) according to CDAI, had significantly higher SE (70.3 vs. 56.8; p < 0.001) and lower LH (7.2 vs. 11.6; p < 0.001) than patients not in remission. There was a poor correlation between LH and SE with educational level (years of education) (r = 0.39 and −0.19, respectively).

Features

Female, n (%) 85 (83, 3)
Age, media (DS) 59 (12, 7)
Years from diagnosis, media (DS) 12,7 (10, 7)
Nacionality (n=100)
Argentine, n (%) 94 (94)
Foreign, n (%) 6 (6)
Education level (n=102)
Incomplete elementary school, n (%) 6 (5, 9)
Completed elementary school, n (%) 20 (19, 6)
Completed high school, n (%) 11 (10, 8)
Completed high school, n (%) 30 (29, 4)
Tertiary, n (%) 16 (15, 7)
University, n (%) 19 (18, 6)
Marital status (n=100)
Married 55 (55)
Divorced 13 (13)
Widowed 12 (12)
Positive RF, n (%) 46 (70, 2)
Positive Anti-CCP, n (%) 57/70 (81, 4)
Methotrexate, n (%) 80 (78, 4)
Biologic agents, n (%) 37 (36, 3)
Corticosteroids, n (%) 21 (20, 6)
Socio-economic level (Gratfran)(n=9)
I, n (%) 5 (5)
II, n (%) 31 (31)
III, n (%) 42 (42)
IV, n (%) 21 (21)
CDAI, Median (IQR) 5.2 (2, 12, 5)
HAQ, Median (IQR) 0.5 (0, 1, 25)
Pga (VAS), Median (IQR) 20 (10, 30)
Pga (VAS), Median (IQR) 19.5 (5, 47)
Pain (VAS), Median (IQR) 22 (5, 50)
Stiffness (VAS), Median (IQR) 7 (0, 30, 5)
Fatigue (VAS), Median (IQR) 12.5 (1, 45)
SE, Median (IQR) 62 (53, 73)
Ces-D7, Median (IQR) 3 (1, 7)

Conclusion: LH and SE are potentially modifiable cognitive factors that correlate with functional disability and disease activity. This might have potential clinical implications.

Disclosure: F. Vergara, None; E. Bertiller, UCB; C. Orozco, None; J. Rosa, None; E. Catay, None; M. D. L. A. Gallardo, None; E. Schneeberger, None; M. V. Garcia, None; G. Citera, None; M. G. Rosenmoff, None; M. Sabelli, None; E. R. Soriano, None.

2403

From Early Arthritis Clinic to Remission Clinic: Short-Term Outcome and Ultrasoundographic-Synovitis Dynamics in Rheumatoid Arthritis Patients in DMARD-Induced SDAI-Remission during Drug-Free Follow-Up. Antonio Manzo, Francesca Benaglio, Garifalla Sakellarious, Martina Scarabelli, Elisa Bindia, Barbara Vitolo, Serena Bugatti, Roberto Caporali and Carlomaurizio Montecucco. Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Pollicino S.Matteo Foundation/University of Pavia, Pavia, Italy.

Background/Purpose: The introduction of DAS-driven intensive treatment strategies in early rheumatoid arthritis (RA) has considerably improved outcome and patients’ quality of life. Previous studies have also suggested the possibility, in selected cases, of maintenance of an acceptable clinical status for prolonged periods following treatment suspension. Despite these observations, three critical issues remain partly unexplored: 1) whether systemic
suppression of inflammation can coincide with reversal of the pathogenic process; 2) the possibility to define exploitable parameters able to predict in which patients treatment can be suspended; 3) the primary dynamics as well as the anatomic-biologic substrate of relapse. The aim of the current study was to investigate the clinical-radiographic-functional outcome and ultrasonographic-synovitis dynamics of RA patients in DMARDs-induced SDAI remission, during 12 months drug-free follow-up.

**Methods:** From December 2011, all RA patients followed at our Early Arthritis Clinic achieving stable clinical remission and candidate to treatment suspension are referred to a dedicated Remission Clinic. Referral criteria: 1) introduction of DMARDs treatment within 12 months from symptoms’ onset, 2) ≥24 months DMARDs treatment with a DAS28-driven intensive protocol, 3) stable DAS28 remission (DAS28≤2.6) and 40% (8) achieved low disease activity for reasons of tolerability. Amongst these: Mean DAS28 improved by 18% (44%) patients with an inadequate response to oral MTX for reasons of range 26–83 yrs and mean disease duration was 8.3 years (range 0.5–46 yrs). 49 of 395 adults with RA were surveyed with a mean age of 61 years, 89% were female, 46% white, 31% Latino. Nearly one-third (31%) had limited health literacy (LHL) and 17% had limited English language proficiency, disease characteristics (duration, fatigue, disease activity), depression (score ≥10 on the Patient Health Questionnaire 9), and insurance.

**Results:** 40 consecutive RA patients in DAS28 and SDAI remission (SDAI=3.3) at the baseline visit have been follow-up for 12 months in drug-free regimen and monitored every 3 months. Maintenance of stable DAS28 remission (T0-T12) was observed in 18/40 patients (45%), while treatment re-introduction due to disease relapse was required in 13/40 patients (32.5%). No significant radiographic progression (SHS) and functional impairment (HAQ) was detected at a group level during drug-free follow-up. Ultrasonographic stratification at baseline showed the absence of power Doppler signal (hands-wrists) in 29/40 (72.5%) (SDAI≤3.3; PD=0). Despite stringent remission and absence of sub-clinical signs of synovitis at recruitment, 8/29 (27.5%) patients relapsed, while in 12/21 (57.1%) a transient or persistent reappearance of defined PD signal (PD>0) was detected during follow-up despite the lack of requirement of DMARDs re-introduction according to study criteria.

**Conclusion:** Suspension of DMARDs with short term maintenance of good clinical status is an achievable goal after treat-to-target and tight control strategies in early RA. However, despite stringent clinical and ultrasonographic criteria, relapse signs of disease reactivation can occur early after drug withdrawal, supporting the requirement of additional patho-biologic insights for a more specific stratification of RA remission phase.

**Disclosure:** A. Hammond, None; M. Batley, None.

### 2405

**Quality of Patient-Clinician Communication in a Diverse Cohort of Adults with Rheumatoid Arthritis.** Jennifer Barton², Chris Tonner³, Laura Trupin³, Patricia P. Katz³ and Edward H. Yelin³. ¹University of California, San Francisco, San Francisco, California, ²University of California, San Francisco, CA.

**Background:** To assess correlates of the quality of patient-clinician communication in a diverse cohort of adults with rheumatoid arthritis (RA).

**Methods:** Data were obtained through structured 30-minute telephone interviews conducted in English or Spanish. Subjects were enrollees of the Rheumatoid Arthritis Outcomes Study (RA OS), a longitudinal cohort of adults with RA. Two questions from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) were used to assess RA patients’ experience of communication with their rheumatologist: “How often did this doctor check to be sure you understood everything?” and “How often did this doctor spend enough time with you?” Responses options consisted of 5 choices ranging from “never” to “always.” We report the proportion of subjects who responded “always” which is considered by CAHPS as the “Top-box” score. Logistic regression was used to model the quality of communication as a function of demographics (age, gender, race/ethnicity), education, health literacy (single-item literacy screener), English language proficiency, disease characteristics (duration, fatigue, disease activity), depression (score ≥10 on the Patient Health Questionnaire 9), and insurance.

**Results:** 395 adults with RA were surveyed with a mean age of 61 years, 89% were female, 46% white, 31% Latino. Nearly one-third (31%) had limited health literacy and 17% had limited English language proficiency (LEP). Mean disease duration was 23 ± 12 years, 39% reported moderate fatigue and 18% severe, and 17% had a PHQ-9 score ≥10. In multivariate models controlling for disease activity, fatigue, and depression (see table), RA patients with LHL and LEP were more likely to report that their rheumatologist always checked for understanding. However, patients with LEP were less likely to report that their doctor always spent enough time with them, as were Latinos (compared to all other race/ethnic groups).

**Conclusion:** Despite the finding that over 90% of RA patients with limited English language proficiency perceive that rheumatologists always check for understanding, only 38% of these same patients and 40% of Latinos report that doctors spend enough time with them. These results were independent of disease activity and depression. Providing high quality, patient-centered care in RA is important for all patients, especially those with barriers to communication. Awareness and interventions to enhance quality of communication and that address cultural expectations for care are needed for vulnerable populations.

### Table

**Table Proportion of subjects who responded “always” to communication questions about rheumatologists among 395 adults with rheumatoid arthritis, from multivariate models**

<table>
<thead>
<tr>
<th>Overall percent (95% CI)</th>
<th>Check to be sure you understood</th>
<th>Spend enough time with you</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>74 (69, 78)</td>
<td>59 (54, 63)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>71 (52, 89)</td>
<td>65 (51, 87)</td>
</tr>
<tr>
<td>African American</td>
<td>75 (61, 89)</td>
<td>76 (64, 90)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>74 (64, 84)</td>
<td>40 (29, 50)</td>
</tr>
<tr>
<td>Islander</td>
<td>71 (52, 89)</td>
<td>69 (51, 87)</td>
</tr>
</tbody>
</table>

**Disclosure:** A. Hammond, None; M. Batley, None.
2406

Background/Purpose: Injectable biologics are commonly used to treat patients (pts) with moderate to severe rheumatoid arthritis (RA); the frequency with which they are prescribed but not filled is unknown. This exploratory analysis aimed to evaluate filling of newly prescribed injectable biologics for RA and characterize pt outcomes.

Methods: In a retrospective cohort design, pts (age ≥18 years during study period) with an RA diagnosis (ICD-9: 714.XX) in 2007-2013 were selected from a de-identified database of clinical information from electronic health records (EHR; Humedica) linked to healthcare claims (Optum) from commercial and Medicaid advantage health plans. First injectable biologic prescription date in EHR was the index date. Pts without continuous pharmacy coverage for ≥6 months pre- and post-index, with evidence of pre-index injectable biologic administration in EHR or claims, or with hospitalization within 30 days post-index were excluded. Pts were categorized as filling the biologic prescription within 30 days (early fillers), 31-180 days (late fillers), or not at all within 180 days (non-fillers) of index. Pt baseline characteristics, including claims-based index of RA severity, RA prescribing patterns, and pt-reported pain scores (0-10; provider-determined scales) from EHR were assessed across all pts; 6-month post-index healthcare resource utilization (including biologic fills) and costs as identified within claims were assessed in pts with continuous medical and pharmacy coverage.

Results: Of 381 pts meeting inclusion criteria, 171 (45%) and 60 (16%) filled an injectable biologic prescription within 30 days and 31-180 days of index, respectively; 90% of prescriptions were written for TNF inhibitors (TNFi). Early fillers were younger, more likely to be female, had higher baseline RA severity, and filled more prescriptions for any reason pre-index. Of non-fillers, 65% were Medicare pts vs 18 and 37% of early and late fillers, respectively. Filling of nonbiologic DMARD prescriptions within 30 days of index was highest in early biologic fillers (45.6%) and lowest among non-fillers (23.3%); however, during days 31-180, the rate was 5.9% in early biologic fillers vs 34.0% in non-fillers. Of early fillers, 14% did not have another biologic prescription filled after 30 days. In the small subgroup of pts with both pre- and post-index pain scores, mean pain scores decreased in early fillers (−1.6; n=11), but increased in late fillers (0.5; n=6) and non-fillers (1.1; n=7). In pts with pharmacy and medical coverage for 180 days post-index (n=375), early fillers had greater RA-related pharmacy (84% of cost difference) and medical resource use and costs than late and non-fillers combined.

Conclusion: Over half (55%) of pts prescribed injectable biologics (90% TNFi) did not fill the prescription within 30 days; 40% had not filled by 180 days. For evaluation of clinical outcomes, documentation of pain scores in the EHR was limited for structured analysis. As expected, healthcare resource use/costs were higher in early fillers over short-term observation. Future research will need to focus on long-term consequences of under-treatment on clinical and economic outcomes.

Disclosure J. Harnett, Pfizer Inc, 1, Pfizer Inc, 3; D. Wiederkehr, Pfizer Inc, 1, Pfizer Inc, 3; R. Gerber, Pfizer Inc, 1, Pfizer Inc, 3; D. Gruben, Pfizer Inc, 1, Pfizer Inc, 3; J. Bourret, Pfizer Inc, 1, Pfizer Inc, 3; A. Koenig, Pfizer Inc, 1, Pfizer Inc, 3.

2407

Background/Purpose: It is generally thought that the early treatment of patients with rheumatoid arthritis (RA) leads to improved patient outcomes over time. Our study aims to better understand if early treatment alone is sufficient to achieve these goals and assess whether measures such as DAS, joint count and perceived severity are sufficiently sensitive for this purpose.

Methods: We used data collected as part of an online treatment survey conducted among a panel of 500 European rheumatologists between April 2009 and July 2014 across EUS (Fr, Ge, It, Sp, UK). In order to assess whether earlier treatment has an effect on patients current disease status we ran a linear regression using patients’ current DAS, current disease severity (as perceived by their physicians) and the number of joints affected by their disease as dependent variables (DV) and included the following as independent variables (IV):

- Time from cDMARDs initiation until first bDMARDs initiation (β1)
- Time from diagnosis until cDMARDs initiation (β2)
- Severity at diagnosis (β3)
- Number of cDMARDs before bDMARDs initiation (β4)
- Current bDMARDs (Brand) (β5)

We focused our analyses on patients diagnosed post 1998 to ensure patients had access to bDMARDs and only considered those currently prescribed their first line of bDMARD therapy to avoid any confounding effects caused by patients’ treatment history. We also accounted for possible differences in patients’ disease severity, both at diagnosis and at the time of their first bDMARD treatment, as well as the length of time they had been on their current bDMARD treatment.

Results: We considered data from a sample of 43,769 patient record forms and on average, our patients had a DAS of 2.9 with 85.8% classified as having moderate to severe RA. In addition, the mean time from diagnosis to cDMARD initiation and bDMARD initiation was 12.1 and 45.5 months, respectively.

Preliminary results from the regression analysis show that we can explain very little of the variability in our DV with an adjusted R square of just 5% for DAS, 2% for current severity and 5% for the number of affected joints. Therefore, we considered the coefficients of each model to measure the effect of our IV.

β1 and β2 have a low positive effect on DAS and current disease severity however, the choice of Enbrel, Humira and RoActemra as a first bDMARD has a strong negative effect on these two DV. In addition, β3 and β5 both have a strong positive effect on patients’ number of affected joints, while β4 has a low positive effect.

Finally, we see that patients who have been on their first bDMARD for a shorter period of time (up to 2 years) better explained the variation seen in our DV.

Conclusion: Our analyses demonstrate that simply initiating treatment with cDMARDs and bDMARDs early in patients’ disease is not enough to optimise patient outcomes. Instead, early treatment must be combined with close monitoring and aggressive step-up treatment strategies such a treat-to-target to maximise patients’ response to treatment and control their disease. In addition, our data also suggest that the impact that early treatment may have could be limited in time with disease statuses becoming more similar as the duration of bDMARD therapy increases.

Disclosure L. Chanroux, None; J. Casellas, None.
Methods: This is a prospective randomized controlled trial involving 37 RA patients (fulfilling ACR 1987 classification criteria). Patients were assigned to n-3 FA supplements (n=11) or MedDiet (n=8) and compared to a control group (n=15), during a 6 month follow-up period. Demographic characteristics, number of tender and swollen joints, global health status, ESR, CRP, and DAS-28 were obtained before and after the intervention. The analysis of dietary intake was performed with a semi-quantitative food frequency questionnaire. Patients were further stratified according to biological therapy. The statistical analysis was performed by Wilcoxon and Kruskal-Wallis tests with a significance level of 0.05.

Results: A significant reduction in ESR was noted after 6 months of n-3 FA but there was no significant variation in the remaining measures after 6 months, independently of the study group and the ongoing therapy for RA. However, a trend towards a reduction in DAS-28 and VAS was noted (Table 1).

Table 1: Evaluated parameters at the beginning and after 6 months of intervention.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n-FA</th>
<th>Beginning</th>
<th>6 months</th>
<th>p</th>
<th>MedDiet</th>
<th>Beginning</th>
<th>6 months</th>
<th>p</th>
<th>Control Group</th>
<th>Beginning</th>
<th>6 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>31.8±9.42</td>
<td>16.8±12.37</td>
<td>11.3±7.55</td>
<td>0.50</td>
<td>28.0±9.23</td>
<td>21.3±12.0</td>
<td>13.2±5.5</td>
<td>0.12</td>
<td>0.02</td>
<td></td>
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</tr>
<tr>
<td>CRP</td>
<td>2.5±2.24</td>
<td>1.4±1.24</td>
<td>1.1±0.75</td>
<td>0.05</td>
<td>2.3±1.18</td>
<td>1.9±1.02</td>
<td>1.5±0.55</td>
<td>0.05</td>
<td>0.03</td>
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<tr>
<td>DAS-28</td>
<td>3.65±2.28</td>
<td>1.35±1.26</td>
<td>1.0±0.65</td>
<td>0.05</td>
<td>3.5±1.26</td>
<td>2.9±1.08</td>
<td>1.6±0.25</td>
<td>0.05</td>
<td>0.01</td>
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<tr>
<td>EVA GH</td>
<td>39.6±24.75</td>
<td>31.0±18.0</td>
<td>22.8±6.25</td>
<td>0.04</td>
<td>46.8±30.85</td>
<td>51.0±18.53</td>
<td>25.8±3.5</td>
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<tr>
<td>Tender joints</td>
<td>3.5±0.62</td>
<td>1.8±0.53</td>
<td>1.1±0.36</td>
<td>0.05</td>
<td>4.9±0.48</td>
<td>5.1±0.48</td>
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<tr>
<td>HAQ-DI</td>
<td>5.0±2.80</td>
<td>5.0±2.80</td>
<td>1.0±0.45</td>
<td>0.05</td>
<td>5.0±2.80</td>
<td>4.9±2.80</td>
<td>0.05</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s productivity (WPAI)</td>
<td>0±0</td>
<td>0±0</td>
<td>0±0</td>
<td>0.05</td>
<td>0±0</td>
<td>0±0</td>
<td>0.05</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-FA vs MedDiet</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
<td>3.8±0.01</td>
<td>3.5±0.01</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Omega-3 fatty acids supplements were associated with a reduction in the ESR after 6 months in accordance to other studies. The trend towards a reduction in DAS-28 observed in this study encourages the need for further studies in larger samples.

Disclosures: A. C. Araújo, None; M. F. Moraes-Fontes, None; L. Santos, None; N. Riso, None.

2410

Working Status and Improvements in Work Productivity over Time in an Early Rheumatoid Arthritis (ERA) Cohort. Bindeé Kurjia*, Daming Lin*, Cheryl Barnabe, Gilles Boire, Boulos Harouei, Carol Hitchon, Keystone and Vivian P. Bykerk. 1University of Toronto, Toronto, ON, 2Western University, London, ON, 3University of Manitoba, Winnipeg, MB, 4Vancouver Coastal Health, Vancouver, BC, 5Southlake Regional Health Centre, Newmarket, ON, 6University of Manitoba, Winnipeg, MB, 7University of Calgary, Calgary, AB, 8CHUS - Sherbrooke University, Sherbrooke, QC, 9Centre Hospitalier de l’Université de Montréal, Montréal, QC, 10University of Manitoba, Winnipeg, MB, 11University of Toronto, Toronto, ON, 12University of Montreal and Montreal Children’s Hospital, Montreal, QC, 1 University of Toronto and Southlake Regional Health Centre, Newmarket, ON.

Background/Purpose: To describe working status in an ERA population in the first year of disease, and factors associated with improved work productivity.

Methods: Patients in the Canadian Early Arthritis Cohort who completed the Work Productivity and Activity Impairment (WPAI) questionnaire at baseline and month 12 (commencing in 2010) were included. Differences in working status at baseline were compared using chi-square or student’s t-tests. A change in employment status and overall activity impairment was calculated as change from baseline to month 12. A change in absenteeism (work hours missed) and presenteeism (impact of RA on work productivity) was only calculated for those working at baseline. Multivariate logistic regression analyses tested whether age, sex, symptom duration, DAS28 score, HAQ-DI and previous biologic failures were associated with improvements in WPAI.

Results: Of 2524 patients in the cohort, 729 had completed at least one WPAI questionnaire. Of these, 190 were eligible (423 did not have serial DAS28 and 306 were missing month 6 variables for analysis). Of these, 190 patients had mean age 56 years, symptom duration 5.6 months, baseline DAS28 score 4.85; 110 were in paid employment at baseline. Individuals not in paid employment at baseline less frequently had high school or college education, had lower income, were older, had moderate-to-high DAS28

Discloser: A. C. Araújo, None; M. F. Moraes-Fontes, None; L. Santos, None; N. Riso, None.

2409

Omega-3 Fatty Acids and Mediterranean Diet As Complimentary Therapies for Rheumatoid Arthritis. Ana Carolina Araújo, Maria Francisca Moraes-Fontes, Lélia Santos and Nuno Riso. Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the synovial joints, often with a progressive and destructive course, leading to disability. Nowadays, there are several drugs available to treat this condition. However, in some patients the disease can be quite difficult to manage, due to refractoriness and expense of therapy. Complimentary therapies to manage RA may contribute to this unmet need. The anti-inflammatory effect of the Mediterranean diet (MedDiet) has been increasingly recognized in the last forty years together with the anti-inflammatory properties of omega-3 fatty acids (n-3 FA).

This study aimed to evaluate the effects of n-3 FA supplements and MedDiet upon disease activity and laboratory measures of a cohort of RA patients.
scores, and demonstrated higher HAQ-DI scores. Improvements in WPAI domains were shown (Table). Among working individuals, by 12 months, 78% had an improvement in working hours missed, 67% reported improved productivity and 72% had reduced activity impairments. The largest change occurred for absenteeism (9.57 fewer hours/week missed). Y ounger age (OR 0.93, CI 0.89–0.98), DA258 remission (OR 10.52, CI 1.4–79) and higher HAQ-DI at month 6 (OR 4.01, CI 1.2–13.1) were associated with gaining employment by month 12. DMARD or biologic use at month 6 was not associated with change in WPAI domains but corticosteroid use was negatively associated with presenteeism (OR 0.23, CI 0.06–0.89).

Conclusion: Differences in demographic and disease-related variables exist between ERA patients who are working versus those who are not. The majority of working individuals show improvements in WPAI domains over time but maintaining the minimum clinically important difference for these domains is needed to help guide clinical interpretability. The impact of disease activity and functional ability on work productivity warrants further exploration in larger samples.

Table. Mean (SD) in WPAI domain scores at baseline, month 12 and change from baseline to month 12.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ-DI</td>
<td>0.89 (0.51)</td>
<td>0.38 (0.55)</td>
<td>0.51 (0.44)</td>
</tr>
<tr>
<td>Work Productivity</td>
<td>0.71 (0.46)</td>
<td>0.42 (0.44)</td>
<td>0.29 (0.34)</td>
</tr>
<tr>
<td>Social Function</td>
<td>0.43 (0.30)</td>
<td>0.28 (0.33)</td>
<td>0.15 (0.24)</td>
</tr>
</tbody>
</table>


2412

Regime of Use of Rituximab in Patients with Rheumatoid Arthritis in Daily Clinical Practice. Letícia M. M. M. Mendes,4 Irene Lorente,4 Santos Castañeda,4 Teresa Velasco,1 Luis Sala-Icardo,1 Rosario García-Vicuña,1 Alberto García-Vadillo,1 Juan P. López-Bote,4 Federico Herrera,4 Cecilia M. Urroz-Calleja,4 J. M. Álvarez-García and Isidoro González-Alvaro,4 1Hospital Universitario de La Princesa, Madrid, Spain, 2Hospital Universitario de La Princesa, IISP, Madrid, Spain, 3Hospital Universitario de La Princesa, IIS Papal, Madrid, Spain, 4Hospital Universitario de La Princesa, IIS La Princesa, Madrid, Spain.

Background/Purpose: The recommended therapeutic regime for Rituximab (RTX) in Rheumatoid Arthritis (RA), according to prescribing information, includes two 1000-milligram infusions given two weeks apart, every 6 months. However, this is often not the case in clinical practice, since both consensus documents and information from clinical trials consider other alternatives. Our objective in this study was to analyze the pattern of use of RTX in RA in daily clinical practice.

Methods: This is a retrospective study that includes patients treated with RTX between 1998 and 2013 in a single university hospital. We reviewed medical records and collected demographic data, number of cycles, doses and intervals of RTX administered to the patients, response duration, as well as frequency and reasons of treatment discontinuation. Descriptive analysis was performed using the statistical package Stata v. 12 and HAQ-DI (PSA: 0.01; RA: 0.001; 0.05; 0.01; 0.001).

Results: Ninety-three patients were studied, of which 83% were women. Median age at disease onset was 51 years with an interquartile range (IQR) of 39 to 60 years. Median age at the start of treatment with RTX was 60 (IQR: 51–70) years. Out of the 93 patients, 11 had negative rheumatoid factor. The number of cycles of RTX administered to each patient ranged from one to nine. Treatment was discontinued in 33% of the patients. The reasons for discontinuation were inefficacy (16%), adverse effects (7%) and others (10%). RTX was most commonly withdrawn during the first two cycles. The main data related to use of RTX in our study are summarized in the following table.

<table>
<thead>
<tr>
<th>CYCLE OF RTX</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>93</td>
<td>78</td>
<td>53</td>
<td>45</td>
<td>35</td>
<td>25</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>156</td>
</tr>
<tr>
<td>Fixed regime (%)</td>
<td>16</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11.3</td>
</tr>
<tr>
<td>_response duration (months)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>8</td>
<td>102</td>
</tr>
<tr>
<td>Administration interval (months)</td>
<td>10</td>
<td>11.6</td>
<td>10.3</td>
<td>11.4</td>
<td>13</td>
<td>14</td>
<td>13.6</td>
<td>8.9</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>7</td>
<td>12</td>
<td>25</td>
<td>36</td>
<td>50</td>
<td>56</td>
<td>44</td>
<td>44</td>
<td>35</td>
<td>156</td>
</tr>
<tr>
<td>Fixed regime (%)</td>
<td>36</td>
<td>33</td>
<td>12</td>
<td>16</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Discontinued (%)</td>
<td>10</td>
<td>19</td>
<td>16</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Administration interval (months)</td>
<td>10</td>
<td>11.2</td>
<td>10.7</td>
<td>11.3</td>
<td>10</td>
<td>11</td>
<td>13.6</td>
<td>11.1</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>7</td>
<td>12</td>
<td>35</td>
<td>50</td>
<td>56</td>
<td>44</td>
<td>44</td>
<td>35</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Fixed regime (%)</td>
<td>36</td>
<td>33</td>
<td>12</td>
<td>16</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Discontinued (%)</td>
<td>10</td>
<td>19</td>
<td>16</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

1Fixed regime: administration of two 1000-milligram infusions given two weeks apart, every 6 months.
2Mean value.
3Calculated percent saving in direct yearly drug cost compared to the fixed regime.
4All unspecified data are given in median value.
Response duration in males tended to be longer [12 months; IQR: 8–13] than in females [10 months; IQR: 7–12], but this didn’t reach statistical significance (p = 0.011, Mann-Whitney’s test). Longer response duration was observed in patients with a longer RA history (r = 0.24, P = 0.001, Pearson’s test). RTX dose per cycle did not modify the response duration (1 vs 2 grams, 9.5 and 10 months respectively).

**Conclusion:** Our data show that, in daily clinical practice, RTX is more frequently used on demand, tending to abandon the fixed regime of 2 grams every six months. In addition, we observe a tendency to an increased use of 1 gram cycles with time. This results in cost savings without apparent decrease in healthcare quality.

**References:**

**Disclosure:** L. Merino-Méndez, None; I. Llorente, None; S. Castañeda, None; T. Velasco, None; L. Sala-Icardo, None; R. García-Vicuña, None; A. García-Vadillo, None; J. P. Lopez-Bote, None; J. López-Lope, None; P. Herrera, None; C. Muñoz-Calleja, None; J. Álvaro-Gracia, None; I. González-Alvaro, None.

**2413**

**Similar Response Rates to Anti-Tumor Necrosis Factor and Non-Anti-Tumor Necrosis Factor Biological Therapies in Ethnic Minority Patients at 6 Months.** Gail S. Kerr1, Yusuf Y acilci1, Christopher Swearingen2, Luis R. Espinoza3, Edward L. Treadwell4, Yvonne Sherrer5, Angela Mosley-Williams2, Ignacio García-Valladares6, Rodolfo Perez Alamino7, Sharon Dowell8, Mercedes Quinones9, A. Kugan Ince10, Theresa Lawrence Ford11, Chunqiao Luo12, Adrian Godoy10 and John A Amatruda10.

**Washington DC VAMC, Georgetown and Howard University, Washington, DC, New York University School of Medicine, New York, NY, University of Arkansas, Little Rock, AR, LSU Medical Center, New Orleans, LA, East Carolina University, Greenville, NC, Centre Humain Immuno Arthritis, Fort Lauderdale, FL, Detroit VAMC, Detroit, MI, Hospital General de Occidente, Zapopan, Jal., Mexico, LSUHSC, New Orleans, LA, Howard University Hospital, Washington, DC, St Louis University, St. Louis, MO, North Georgia Rheumatology Group, PC, Lawrenceville, GA, University of Arkansas for Medical Sciences, Little Rock, AR.

**Background/ Purpose:** Biological therapies have expanded the treatment options and strategies for rheumatoid arthritis (RA). While anti-tumor necrosis factor (anti-TNF) biologic response rates are well established, in multi-ethnic populations, the response to anti-TNF and non-anti-TNF agents is unknown. Hence, we evaluated the response rates to RA biologic therapies in a diverse ethnic and racial group.

**Methods:** Ethnic Minority RA Consortium (EMRAC) patients with follow up data were evaluated. Comparisons of patient socio-demographic (age, gender, race, education, smoking), RA disease status (disease duration, RF, ACPA, nodules/erosions), DMARD use, and disease activity (RAPID3) were made between anti-TNF and non-anti-TNF therapies using chi-square test of categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. A logistic regression analysis associating RAPID3 outcome (low/moderate disease vs severe disease) at last follow-up encounter with anti-TNF and non-anti-TNF therapies adjusting for age, disease duration, gender, smoking, race and baseline RAPID3 was performed.

**Results:** EMRAC analysis of biologic responses in 350 subjects with an average follow up of 8 months was performed (Table 1). More Caucasians received biologic therapies and anti-TNF use was most common. Anti-TNF patients were similar to non-anti-TNF patients in all demographic and clinical characteristics, including use of DMARD therapy. While, baseline RAPID3 was significantly higher in non-anti-TNF than anti-TNF patients, there was no significant difference in proportions of patients achieving RAPID3 outcome between biologic groups (P = 0.969), adjusting for age, duration, gender, smoking, and baseline RAPID3. Moreover, no differences between races were observed in achieving RAPID3 outcome (P = 0.688, regression).

**Conclusion:** There is a similar prevalent use of and response to anti-TNF and non-anti-TNF biologic agents in ethnic minority RA patients in routine clinical care. Follow up analyses are needed to assess sustained clinical response and outcomes to the varied biologic armamentarium, inclusive of ethnic subsets.

**Patient Characteristics of Biologic Use in EMRAC Cohort**

<table>
<thead>
<tr>
<th>Race</th>
<th>Low/Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>121 (46.4%)</td>
<td>37 (53.6%)</td>
</tr>
<tr>
<td>African-American</td>
<td>48 (20.3%)</td>
<td>12 (74.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>51 (21.1%)</td>
<td>18 (26.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (12.1%)</td>
<td>5 (22.9%)</td>
</tr>
</tbody>
</table>

* Logistic Regression adjusting for Age, Duration, Race, Smoking and Baseline RAPID3.

**Disclosure:**
- G. S. Kerr, Genentech and Biogen IDEC Inc., 2, Bristol-Myers Squibb, 2.
- Y. Acilci, Genentech and Biogen IDEC Inc., 2, Pfizer Inc, 2, Bristol-Myers Squibb, 2.
- A. Godoy, None.
- J. Amatruda, None.

**2414**

**Etanercept in Mono Therapy or in Combination with MTX: Results from a Sub Analysis of a German Non-Interventional Study.** Karl Heinz Goeltl1, Markus Gauß2, Andreas Krause3, Udo Lendl4, Ralph Lippe5, Thomas Mönisch6, and Peter-Andreas Loeßnich7.


**Background/ Purpose:** Although a combination with MTX is recommended for all biologics, data from different registries around the world show that in real life around 30% of all RA patients are treated in mono therapy. However, data on safety and efficacy of Etanercept (ETN) as mono therapy in daily practice are rare.

**Methods:** A dults with RA newly initiating ETN have been included into this non-interventional study. Data collection and safety parameters have been recorded. We describe characteristics of patients treated with ETN or ETN + MTX for up to 52 weeks. Safety, efficacy as well as health outcome parameters have been assessed.

**Results:** 4871 patients have been included into this study. 1090 of these have continuously been treated with ETN and 1441 with ETN + MTX. There have been no statistically differences regarding all baseline characteristics. The mean disease duration was 10.6 ± 10.3 years in the ETN and 9.7 ± 8.9 years in the ETN + MTX group. They have been pretreated with 2.9 ± 1.6 and 2.7 ± 1.2 DMARDS respectively. From a mean baseline value of 55.5 ± 13.
and 5.3±1.3 score points, the DAS28 continually decreased to 3.4±1.4 and 3.2±1.3 at visit 7. At week 52 slightly less patients with ETN reached DAS28 remission (DAS28<2.6) as with ETN+MTX (32.5% [29.0–36.1%] vs. 35.4% [32.5–38.3%]). Concurrently with the DAS28 also the mean disease activity (patient global assessment, visual analogue scale VAS), pain (VAS) and fatigue (VAS) improved in both treatment groups. Duration of morning stiffness decreased in the ETN group from 78±81.1 to 26.2±50.6 min and in the ETN + MTX group from 72.6±81.1 to 21.8±50.6 min. 38.4% [35.1 – 41.7%] of patients with ETN reached a functional remission (FFR) at week 52 (vs. 44.3% [41.5 – 47.2%] under ETN+MTX therapy). In both groups the treatment was well tolerated and no new safety signals were observed.

Conclusion: Etanercept rapidly reduces disease activity in combination with MTX as well as in mono therapy. About half of the patients stayed on the treatment was well tolerated and no new safety signals have been observed.

Disclosure: K. H. Goedt, Pfizer Inc, Roche, Janssen -Cilag, MSD, 5, Pfizer Inc, Abbvie, 8; M. Gaubitz, Pfizer Inc; Abbvie; Chugai, MSD, Roche, BMS, 5, Pfizer Inc; Abbvie, Chugai, MSD, Roche, BMS, 5, Pfizer Inc; Abbvie, Roche, BMS, 5, Pfizer Inc, Abbvie, Roche, BMS, MSD, 5, Pfizer Inc, Abbvie, Roche, BMS, MSD, UCB; B. U. Lendt, Pfizer Inc; 3; R. Lippe, Pfizer Inc; 1; Pfizer Inc, 3; T. Meng, Pfizer Inc, 1; Pfizer Inc, 3; P. A. Loeschmann, Pfizer Inc, 1; Pfizer Inc, 3.

2415 Characteristics of Rheumatoid Arthritis Patients Not Receiving Early Initiation of Disease Modifying Therapy. Dimitrios A. Pappas1, Jeffrey D. Kent2, Jeffrey D. Greenberg, Marc Mason, Joel M. Kremer, Amy Y. Graham, R. J. Holt, C. Columbia University, New York, NY, 3New York University School of Medicine, New York, NY, 4Corona, LLC, Southborough, MA, 5Albany Medical College and the Center for Rheumatology, Albany, NY, 6University of Illinois - Chicago, Chicago, IL.

Background/Purpose: Early and aggressive therapy of Rheumatoid Arthritis (RA) with Disease Modifying Anti-Rheumatic Agents (DMARDs), glucocorticoids, and biologic agents is recommended by current treatment guidelines and supported by interventional studies with treat to target principles. However, delays in initiation of therapy might be observed in real life. The objectives of this analysis was to evaluate how frequently RA therapy is instituted promptly and to describe the characteristics of patients who are not treated early upon diagnosis.

Methods: The percentage of patients who at the time of enrollment in the Corona Registry were not receiving any RA directed therapy was evaluated and their characteristics were summarized. The time to subsequent initiation of any RA directed therapy was also estimated.

Results: Out of the 35,485 patients enrolled in CORRONA, 20,317 (57.3%) had no prior use of prednisone, 18,299 (51.6%) had no prior biologic use, 16,930 (47.7%) had no prior DMARD use (excluding MTX), 16,335 (45.2%) had no prior MTX use, 2,166 (6.1%) had no prior nbDMARD use, and 750 (1.2%) had no history of receiving any RA directed therapy at the time of enrollment. For the patients without any history of RA directed therapy: age at the time of enrollment (mean ± SD) was 57.5±14.7 and age at RA onset was 52±15.4 years. 69.4% were seropositive for RF and 60.6% for CCP antibodies. Patients had an overall established disease duration of 5.5±9.0 years with only half (50.7%) having early disease (duration ≤1 year). CDAI was 18.3±15.0; 34.3% of the patients had high and 27.6% moderate disease activity by CDAI. Subjects graded their fatigue as 35.6±15.1 on a visual analog scale (0–100). Patients with no history of directed RA therapy did not have lower disease activity at enrollment compared with those receiving directed therapy. These patients were followed for a median (95% CI) time of 29.5 months (24.6–33.8). During the follow-up period, only 372 out of 750 (49.6%) patients initiated any RA directed therapy. The median time to initiation of any DMARD was 15.9 months (12.2–18.4) and to initiation of any RA directed therapy was 12.1 months (9.3–14.8).

Conclusion: In this registry analysis, a high percentage of patients with RA did not have a history of receiving directed therapy within a mean of approximately 5 years of RA onset. In those patients that had not received any RA directed therapy previously, approximately 50% did not initiate any therapy in 12 months of registry follow-up.


1University of Saskatchewan, Saskatoon, SK, The Mary Pack Arthritis Centre, Vancouver, BC, Arthritis Research Centre of Canada, Richmond, BC, 2Private Practice, Scarborough, ON, 3Clinical Research and Arthritis Centre, Windsor, ON, 4University of Ottawa, Ottawa, ON, 5Centre de Rhumatologie de l’Est du Quebec, Rimouski, QC, 6Naanimo Regional General Hospital, Nanaimo, BC, 7Emorial University of Newfoundland, St Johns, NF, 8SS Medical Research, Montreal, QC, 10Janssen Inc., Toronto, ON.

Background/Purpose: This analysis aimed to describe the pattern of specific joint involvement (tender and/or swollen) pre- and post-TNFi treatment and the impact of specific joint pattern involvement on composite score outcomes and pain.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or Psa with infliximab (IFX) or golimumab (GLM). In this analysis, RA patients included those treated with IFX between 2003-2014 or with GLM between 2010-2014. Based on joint involvement 7 groups were created: shoulder(s), elbow(s), metacarpophalangeal (MCP(s)), wrist(s), proximal interphalangeal (PIP(s)), knee(s), and thumb(s). The impact of specific joints on disease activity indices and pain was assessed with the independent-samples t-test; linear regression produced adjusted estimates.

Results: A total of 1030 RA patients were included with 577 assessments. At baseline, MCP(s) (84.8%) and wrist(s) (66.1%) were the most commonly swollen joints. Tenderness was most frequent at baseline in these two joint types (81.1% and 70.9% of patients, respectively). Swelling/ tenderness rates in all joint groups were significantly lower (Table 1) among patients enrolled in 2010-2013 vs. those enrolled in 2002-2005; no significant differences, however, were observed in joint involvement pattern. Swelling and tenderness in all joint groups were associated significantly (P<0.001) higher pain. Upon adjusting for age, gender and the total number of swollen (S) C28 and tender (T) C28 joints, swollen shoulder(s) and knee(s), and tender shoulder(s) and elbow(s) had the biggest impact on pain. Swollen MCP(s), knee(s) and thumb(s) had the greatest impact on DAS28, while for CDAI and SDAI swollen thumb(s) and swollen thumb(s) and...
knee(s), respectively, showed the highest association. Tender wrist(s), shoul-
der(s), and knee(s) showed the highest association with DAS28, while tender MCP(s) had the greatest impact on CDAI and SDAI. However, all indices were significantly higher among cases with swollen thumb(s) (unstandardized coefficient (B): B_{DAS28} = 0.25, P = 0.006; B_{CDAI} = 0.29, P = 0.001; B_{SDAI} = 0.26, P = 0.001).

**Conclusion:** Although joint swelling/tenderness documented at anti-TNF initiation has decreased over time, the profile of affected joints has remained stable. Swelling/tenderness in specific joint groups was differentially associ-ated with PD, with larger joints having the greatest impact. Furthermore, differences were observed in levels of disease activity based on the type of affected joint which could be attributed to their impact on patient global assessment. These results suggest that location of joint involvement, in addition to the number of affected joints, has an independent impact on pain.

**Table 1:** Pattern of Swelling or Tenderness by Enrolment Period

<table>
<thead>
<tr>
<th>Swelling/Tenderness by Joint</th>
<th>2002-2005 (N=412)</th>
<th>2010-2014 (N=278)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen Knee(s)</td>
<td>13.1 (7.1)</td>
<td>7.4 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen PIP(s)</td>
<td>22.1%</td>
<td>12.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen MCP(s)</td>
<td>35.7%</td>
<td>19.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Wrist(s)</td>
<td>76.7%</td>
<td>51.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Finger(s)</td>
<td>75.0%</td>
<td>48.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Knee(s)</td>
<td>24.5%</td>
<td>14.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen PIP(s)</td>
<td>42.0%</td>
<td>21.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen MCP(s)</td>
<td>72.3 (4.0)</td>
<td>64.7 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Wrist(s)</td>
<td>65.0%</td>
<td>40.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Finger(s)</td>
<td>76.7%</td>
<td>48.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swollen Knee(s)</td>
<td>46.8%</td>
<td>31.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


**2417**

**Is Remission Really Achievable in EARLY Rheumatoid Arthritis?** Olga Addimanda1, Pierluigi Macchioni2, Andrea Caruso 1, Niccolo` Possemato1, Naonobu Sugiyama M.D., Ph.D., 1, Tatsunori Murata, M.S.2, Yosuke Morishima1, Yuji Fukushima2, Yoshiyuki Shibasaki3 and Lisa Marashli1.

**Biologics such as etanercept (ETN), adalimumab (ADA), infliximab (IFX) and tocilizumab (TCZ) have led dramatic improvement in the treatment of rheumatoid arthritis (RA), but the impact of their high drug costs on medical expenditure remains a concern. The aim of this study is to characterize the treatment patterns of patients with RA treated with biologics and evaluate the direct biologics cost and medical cost using Japanese claims data provided by Japan Medical Data Center Co., Ltd.**

**Methods:** Patients with RA (defined by ICD10 code) treated with ETN, IFX, ADA, and TCZ between January 2005 and March 2013 were included. Annual costs of the biologics per patient, based on average daily dose and NHL discount price, were calculated from 2009 to 2012 for ETN, IFX, ADA, and TCZ. Patients were grouped based upon their initial prescription for either ETN, IFX, ADA, or TCZ. One year biologics cost including all biologics (including second or more, e.g. golimumab) and total medical cost following initial prescription were compared between ETN and the other treatment groups. Discontinuation and switching event rates to other biologics in each group were estimated using Kaplan-Meier survival analysis. Dose changes, based on +/-50% change in average dose per administration, at 3 month intervals were also evaluated up to 4 years following initial prescription.

**Results:** A total of 524 patients were identified for longitudinal analysis, with 45% (n=238) initiating ETN, 41% (n=217) initiating IFX, and 13% (n=69) initiating ADA. The cross-sectional annual biologics cost was $8,000 in 2009 and $7,200 in 2012 in patients with ETN, $10,000 both in 2009 and in 2012 in patients with ADA, $12,000 in 2009 and $16,000 in 2012 in patients with ADA, $9,000 in 2009 and $8,000 in 2012 in patients with ADA, $12,000 in 2009 and $16,000 in 2012 in patients with ADA, and $20,000 in 2009 and $24,000 in 2012 in patients with ADA, and $20,000 in 2009 and $24,000 in 2012 in patients with ADA, and $20,000 in 2009 and $24,000 in 2012 in patients with ADA, and $20,000 in 2009 and $24,000 in 2012 in patients with ADA.

**Conclusion:** The biologic and total medical costs, along with discontinuation and switching event rates were lowest in ETN group. Although there are limitations such as channeling bias, these findings might imply the clinical cost reductive benefits in ETN first line treated group.
Methods: Using PRISMA methodology, a pre-specified search and review strategy was devised to answer the question “what are the EULAR response rates for biologic medications in adults with active RA?” MEDLINE and EMBASE were searched for Rheumatoid Arthritis (Both M e sh term and free text) in Title/Abstract AND Name of biologic drug (free text) in TitleAbstract OR Biologic Therapy (M e sh term) OR “Biologic” (free text) in TitleAbstract AND EULAR response (free text) in Entire Document AND Adult (free text) Entire Document. All articles were reviewed independently by 2 experts; duplicates and non-primary research articles were removed along with those using medication doses outside of the approved Australian indications, and only patients with ≥ moderate DAS or tender/swollen joint count ≥ 4 were included. Whether the patients were naïve to biologic DMARD and whether the response assessment was at 3 (2.0 – 4.5) months or 6 (4.5 – 7.0) months was recorded. The percentage of patients achieving a moderate, good, or either EULAR response was calculated overall and for subgroups.

Results: Overall, 27,280 patients were included representing 62 studies. Mean baseline DAS28 was 6.0 (SD = 0.6). Good (G) and moderate (M) EULAR responses were achieved in 25.6% and 47.3% respectively, with 28.1% failing to achieve a Good or Moderate EULAR response when all patients were pooled. Response rates were similar for patients who were naïve to biologics (G-24.0% & M-47.5%), those who had failed to respond to at least 1 biologic (G-28.1% & M-47.1%) and at both 3 months (G-27.1% & M-50.4%) and 6 months (G-25.2% & M-46.3). Sufficient data was present for separate analyses of adalimumab (ADA), etanercept (ETN) and tocilizumab (TCZ) and EULAR response rates were similar, however tocilizumab had a higher rate of good EULAR response [37.4% (TCZ), 28.2% (ADA), 27.6% (ETN)].

Conclusion: A systematic review of studies reporting EULAR response rates for biologic medications in active RA showed that only 28.1% of patients fail to achieve at least a moderate EULAR response. Response rates were similar for patients who were naïve or had previous exposure to biologics, for 3 and 6 months assessment time points, and for different biologic medications. Comparison of these controlled trial data with real life response rates reported in clinical registries will be of interest.

Disclosure: L. Roberts None; K. Tynns None; J. de Jager None; G. Littlejohn None; H. Griffiths None; D. Nicholas None; P. Bird None; J. Young An employee of Roche Products Pty. Limited; 3; J. Zochling None.

2420

Quality Assessment of Controlled Trials Evaluating Chinese Herbal Medicine in Patients with Rheumatoid Arthritis: a Systematic Review. Xin Pan, Maria A. Lopez-Olivo, Pratibha Nayak and Maria E. Suarez-Almazor. The University of Texas, MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Chinese herbal medicine (CHM) is a mainstay in the treatment of rheumatoid arthritis (RA) in China. We conducted a systematic review to appraise the methodological quality of controlled clinical trials evaluating the efficacy and safety of CHM in patients with RA.

Methods: We searched electronic databases (Medline, EMBASE, The Cochrane Library, and Web of Science) from inception until May 2014 for controlled trials (randomized or not) evaluating the use of CHM including herbs and decoctions (i.e., “tang”), in patients with RA. The search was not limited by language, year of publication or type of publication. Study selection was performed by 2 independent reviewers. Data extraction and the methodological quality of the trials was assessed using the Cochrane risk of bias tool for randomized trials and Newcastle Ottawa Scale for controlled non-randomized studies. Descriptive statistics were used to report on risk of selection, performance, detection, attrition, reporting biases and others (i.e., conflict of interests) for randomized trials and selection, comparability and outcome biases for cohort studies.

Results: Out of 2,125 unique citations only 54 studies were included (51 randomized trials and 3 non-randomized studies) including 7,792 patients. Only one study was conducted in the US, the rest were conducted in China. There were 3,446 patients receiving CHM. In the control groups 2,283 patients received a disease modifying anti-rheumatic drug (DMARD) (i.e., methotrexate, leflunomide, sulfasalazine, and etanercept), 182 non-steroidal anti-inflammatory drugs (NSAIDs), and 164 inert placebo. Additionally, 1,717 received combined CHM + either DMARD or NSAID. In 23 studies patients were described as having active disease, 13 included patients with more than 1 year disease duration, 1 included patients with RA and anemia, and 17 included patients with one or two traditional Chinese medicine (TCM) ‘pathological factors’ (i.e., feng, shi, and/or han). Discontinuations were not reported in 31 studies, but ranged from 0 to 55% in the remaining studies. For the randomized studies, when evaluating selection bias 54% of the studies were judged to have an adequate random sequence generation, but 77% had inadequate allocation concealment. 79% had a high risk of performance bias (not blinding participants and/or personnel) and detection bias was unclear in 56% of the studies; 62% of the studies reported how missing data was handled, therefore attrition bias was judged to be low. In 87% no disclosure of interest or source of founding was reported. For non-randomized studies, all the studies were representative of RA patients, had an adequate ascertainment of intervention with comparable groups, but only one demonstrated that the outcome of interest was not present at start of study or provided the rate of lost to follow-up.

Conclusion: Studies evaluating CHM often fail to meet expected methodological criteria, and high quality evidence is lacking. Future studies of CHM should be methodologically robust and adhere to reporting guidelines such as the CONSORT statement for TCM.

Disclosure: X. Pan None; M. A. Lopez-Olivo None; P. Nayak None; M. E. Suarez-Almazor None.

2421

Patient Treatment Goals in Rheumatoid Arthritis: Results of Focus Groups Among Rheumatologists, English and Spanish-Speaking Patients. Jennifer Barton1, Christopher J. Koening2, Diana Martinez3, Gina Evans-Young2, Patricia P. Katz2 and Edward H. Yelin2. University of Washington, Seattle, WA. 1; University of Miami, Miami, FL. 2; University of Texas, MD Anderson Cancer Center, Houston, TX. 3; University of Texas, MD Anderson Cancer Center, Houston, TX.

Background: Treatment goals for patients with rheumatoid arthritis (RA) have included patient- and disease-related factors, such as the presence of active disease, the presence of disability, and the ability to perform daily activities. The Patient Treatment Goals scale (PTG) measures treatment goals across 4 dimensions: activity limitation, pain and stiffness, functional limitation, and social activities. While the instrument has been validated only in English-speaking countries and in a rheumatologist sample, it has not been validated among Spanish-speaking patients.

Purpose: We conducted a series of focus groups in English and Spanish among English and Spanish-speaking rheumatologists and patients with RA to: (1) identify factors that are important to RA patients when considering treatment, (2) determine the extent to which the PTG scale meets the needs of RA patients in English and Spanish-speaking countries, (3) test the feasibility of implementing the scale in clinical practice.

Methods: As part of this larger study, 35 focus groups were conducted in English (n = 13) and Spanish speaking (n = 22) in the United States (n = 31) and Spain (n = 4). Groups were conducted among 35 rheumatologists and 114 patients with RA. Focus groups were audio recorded.

Results: The mean age of patients was 60 years, and 75% were female. The mean DAS28 score was 3.0. Patient groups discussed factors that are important when considering RA treatment, including pain, joint swelling, fatigue, mood, physical function, and family roles. Rheumatologists discussed factors that influence their treatment decisions, such as the presence of disease activity, disease history, and comorbidities. The PTG scale was considered useful by both patients and rheumatologists, with 92% of patients and 94% of rheumatologists reporting that they would consider using the PTG scale in clinical practice.

Conclusion: The PTG scale is useful among both English and Spanish-speaking patients with RA and rheumatologists, and is likely to be useful in clinical practice.

Disclosure: None; None; None; None; None; None; None; None; None; None; None; None; None; None; None; None.
Research/policy goals
- More access to drugs/more affordable drugs X
- Develop a more sensitive/functional Visual Analog Scale for pain
- Longer visits to allow for full discussion of RA

Treatment goals
- More information around nutrition X
- Less surgeries X

Disclosure: J. Barton, Pfizer; Z. C. J. Koening, None; D. Martinez, None; G. Evans-Young, None; P. P. Katz, None; E. H. Yelin, None.

2422
A Tailored Approach to Reduce Dose of TNF Inhibitors Is Equally Effective, but Substantially Less Costly Than Standard Dosing in Patients with Rheumatoid Arthritis over One and Two Years: A Prospective Cohort Study.

Background/Purpose: To compare effectiveness and costs of standard versus individually tailored reduced doses of TNF inhibitors (TNFi) in patients with Rheumatoid Arthritis (RA) after achieving low disease activity.

Methods: This was a single center prospective observational study performed within the national biologics registry. The TNFi dose tapering strategy was chosen by treating physicians, without pre-specified protocol. Patients with RA treated for at least 6 months by TNFi who reached low disease activity (LDA) were eligible for this analysis. LDA was defined as DAS28<3.2. Firstly, we selected one "baseline" visit for each patient in the standard dosing group, which would be most comparable to baseline visits in the reduced dosing group (=start of dose reduction) using 3 parameters (duration of TNFi treatment, DAS28 and HAQ) to find the best match. Secondly, a propensity score (PS) was used to control for all other confounders associated with starting TNFi dose reduction. The co-primary outcomes were change (D) in HAQ and loss of LDA (defined as DAS28 > 3.2 & DDAS28 ≥ 0.6). Secondary outcomes were DAS28 area under the curve (DAS28 AUC), HAQ AUC, and annual cost of anti-TNF therapy. The outcomes after one and two years of treatment (since baseline visit) by standard vs reduced doses of TNFi were assessed by generalized linear regression after adjustment on PS.

Results: In the reduced dosing group the mean dose of TNFi corresponded to 0.64, 0.66 and 0.69 of the standard dose initially, at 12 and 24 months resp. After PS adjustment, baseline demographic and clinical characteristics between the groups were well balanced (table 1). 48 (32) and 136 (76) patients in the reduced vs standard dosing group after 1 year (2 years) resp. were available for analysis. Both co-primary outcomes were similar between both groups after one and two years since baseline (table 2 and 3). Annual cost of TNFis per patient was lower by ~4,000 € in the reduced dosing group.

Conclusion: In RA patients after reaching LDA, a tailored approach to reduce doses of TNFi produced similar clinical outcomes at 1 and 2 years resp., but was substantially less costly.

Acknowledgements: This work was supported by IGA grant NT12437.

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard dosing group n=136</th>
<th>Reduced dosing group n=48</th>
<th>Crude p value</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>135 (84.6 %)</td>
<td>34 (70.8 %)</td>
<td>0.040</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>52.9 (11.1)</td>
<td>51.4 (11.8)</td>
<td>0.416</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD)</td>
<td>72.7 (15.5)</td>
<td>73.5 (15.7)</td>
<td>0.446</td>
</tr>
<tr>
<td>Smoking</td>
<td>n (%)</td>
<td>47 (42.4 %)</td>
<td>17 (35.4 %)</td>
<td>0.766</td>
</tr>
<tr>
<td>Working or unemployed</td>
<td>n (%)</td>
<td>70 (52.5 %)</td>
<td>24 (50.0 %)</td>
<td>0.861</td>
</tr>
<tr>
<td>Disease duration prior to start of anti-TNF therapy (years)</td>
<td>Mean (SD)</td>
<td>13.4 (8.5)</td>
<td>17.7 (6.2)</td>
<td>0.537</td>
</tr>
<tr>
<td>Duration of anti-TNF therapy (months)</td>
<td>Mean (SD)</td>
<td>33.1 (22.0)</td>
<td>46.4 (30.6)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

S1056
Table 2  Primary and secondary outcomes after 1 year of standard vs reduced dosing of TNFis

<table>
<thead>
<tr>
<th></th>
<th>Standard dosing group</th>
<th>Reduced dosing group</th>
<th>Adjusted difference (95% CI) reference</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ at baseline (Mean (SD))</td>
<td>0.77 (0.62)</td>
<td>0.64 (0.65)</td>
<td>-0.03 (0.03; 0.06)</td>
<td>0.024</td>
</tr>
<tr>
<td>HAQ at 12 months (Mean (SD))</td>
<td>0.88 (0.65)</td>
<td>0.72 (0.70)</td>
<td>-0.06 (0.04; 0.08)</td>
<td>0.007</td>
</tr>
<tr>
<td>Change in HAQ after 12 months (Mean (SD))</td>
<td>0.11 (0.38)</td>
<td>0.08 (0.30)</td>
<td>-0.03 (0.02; 0.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>Difference (95% CI) reference</td>
<td>-0.00 (0.00; 0.00)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>DAS28 baseline (Mean (SD))</td>
<td>3.29 (0.59)</td>
<td>3.28 (0.59)</td>
<td>-0.01 (0.00; 0.02)</td>
<td>0.023</td>
</tr>
<tr>
<td>Change in SUA after 12 months (Mean (SD))</td>
<td>0.02 (0.17)</td>
<td>0.01 (0.20)</td>
<td>-0.01 (0.00; 0.02)</td>
<td>0.017</td>
</tr>
<tr>
<td>DAS28 AUC during 12 months (Mean (SD))</td>
<td>0.70 (0.17)</td>
<td>0.72 (0.18)</td>
<td>-0.02 (0.00; 0.04)</td>
<td>0.031</td>
</tr>
<tr>
<td>Change in HAQ after 12 months (Mean (SD))</td>
<td>0.03 (0.01; 0.05)</td>
<td>0.00 (0.00; 0.00)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Difference (95% CI) reference</td>
<td>0.00 (0.00; 0.00)</td>
<td>&lt;0.001</td>
<td></td>
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</table>

Table 3  Clinical and ultrasound scores

<table>
<thead>
<tr>
<th></th>
<th>Standard dosing group</th>
<th>Reduced dosing group</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ at baseline (Mean (SD))</td>
<td>0.83 (0.62)</td>
<td>0.63 (0.68)</td>
<td>0.888</td>
</tr>
<tr>
<td>HAQ at 24 months (Mean (SD))</td>
<td>1.01 (0.72)</td>
<td>0.72 (0.75)</td>
<td>0.583</td>
</tr>
<tr>
<td>Change in HAQ after 24 months (Mean (SD))</td>
<td>0.38 (0.45)</td>
<td>0.09 (0.29)</td>
<td>0.237</td>
</tr>
<tr>
<td>Placebo</td>
<td>Difference (95% CI) reference</td>
<td>-0.120 (0.34; 0.086)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS28 baseline (Mean (SD))</td>
<td>3.29 (0.59)</td>
<td>3.28 (0.59)</td>
<td>-0.01 (0.00; 0.02)</td>
</tr>
<tr>
<td>Change in SUA after 24 months (Mean (SD))</td>
<td>0.02 (0.17)</td>
<td>0.01 (0.20)</td>
<td>-0.01 (0.00; 0.02)</td>
</tr>
<tr>
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</tr>
<tr>
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<td>0.03 (0.01; 0.05)</td>
<td>0.00 (0.00; 0.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>Difference (95% CI) reference</td>
<td>0.00 (0.00; 0.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.

2) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.

Table 1  Clinical and ultrasound scores

<table>
<thead>
<tr>
<th></th>
<th>Prior to EIA ultrasound</th>
<th>After EIA ultrasound</th>
<th>Adjusted difference (95% CI) reference</th>
<th>Adjusted p-value</th>
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<tbody>
<tr>
<td>HAQ at baseline (Mean (SD))</td>
<td>0.83 (0.62)</td>
<td>0.63 (0.68)</td>
<td>0.19 (0.03; 0.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>HAQ at 24 months (Mean (SD))</td>
<td>1.01 (0.72)</td>
<td>0.72 (0.75)</td>
<td>0.28 (0.04; 0.04)</td>
<td>0.012</td>
</tr>
<tr>
<td>Change in HAQ after 24 months (Mean (SD))</td>
<td>0.38 (0.45)</td>
<td>0.09 (0.29)</td>
<td>0.237 (0.03; 0.03)</td>
<td>0.023</td>
</tr>
<tr>
<td>Placebo</td>
<td>Difference (95% CI) reference</td>
<td>-0.120 (0.34; 0.086)</td>
<td>&lt;0.001 (0.00; 0.02)</td>
<td>0.023</td>
</tr>
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<td>-0.02 (0.00; 0.04)</td>
<td>0.031</td>
</tr>
<tr>
<td>Change in HAQ after 24 months (Mean (SD))</td>
<td>0.03 (0.01; 0.05)</td>
<td>0.00 (0.00; 0.00)</td>
<td>&lt;0.001 (0.00; 0.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.
Acknowledgements: This work was supported by a grant from Fundación Española de Reumatología.

Disclosure: J. M. Senabre-Gárgano, None; J. Rosas-Gómez de Salazar, None; E. Salas-Heredia, None; G. Santos-Soler, None; F. Llinares-Tello, None; C. Santos-Ramirez to M. M. Sanchez-Barrioluengo, None; X. Barber-Vallejo, None; R. Ortega, None; A. Pons, None; C. Cano, None; M. L. Lorente-Betoret, None.

2424
Comparison of Medication Use in Rheumatoid Arthritis Patients Between University and Private Settings - Results from Ontario Best Practice Research Initiative. Thomas McKeown1, Binu Jacob1, Xiuying Li2, Sandra Couto2, William Lensen3, Vandana Ahuwalia3, Arthur Karasik4 and Claire Bombardier4. 1University Health Network, Toronto General Research Institute, Toronto, ON, 2St Josephs Hospital and McMaster University, Hamilton, ON, William Osler Health Center, Brampton, ON, 3University of Toronto, Toronto, ON, 4University of Toronto, Toronto, ON.

Background/Purpose: The objective of this study was to compare the characteristics and patterns of medication use among rheumatoid arthritis (RA) patients in university and community settings.

Methods: Descriptive analyses were performed using data collected from the Ontario Best Practice Research Initiative (OBRI), a clinical registry of RA patients followed in routine care. Patients were categorized as university if their rheumatologist worked in a teaching hospital, mentored medical students and/or had their Research Ethics Board (REB) located at a hospital. The patients were affiliated with an academic site, but practiced at a community site were excluded from the analysis. Patient baseline demographics, clinical characteristics, socioeconomic features and treatment regimens were compared between university and community patients using chi-square and t-tests.

Results: Among 1583 RA patients, 512 (32%) were from university and 1071 (67%) from community sites. Compared to community patients, university patients were younger (35.5 ± 12.9 vs. 57.9 ± 13.3 yrs, p<0.004), had longer RA disease duration (11.3 ± 10.9 vs. 6.9 ± 8.5yrs, p<0.0001), and were highly educated with higher household incomes. Prevalence of depression was higher among community patients (26%) compared to university (21%), p=0.04. The disease activity measures and functional status at baseline were similar between the two groups. The use of Biologics was more in university patients (31% vs. 17%, P<0.0001) with fewer use of DMARDS (61% vs. 73%, P<0.001).

Conclusion: RA patients in community settings appeared to be older with longer disease duration, had lower socio-economic status and a lower utilization of biologics. The results do not represent the clinician practice patterns as the referral criteria might have biased the patients enrolled in the study. Further analysis is required to evaluate whether the care gap due to differential utilization of biologics have an impact on disease severity in subsequent years.

Disclosure: T. McKeown, None; B. Jacob, None; X. Li, None; S. Couto, None; W. Lensen, Jansen Inc, S; V. Ahuwalia, None; A. Karasik, None; C. Bombardier, None.

2425
Rheumatoid Arthritis Stable Follow up Visits – 3 Month Versus 6 Month Intervals. Mark C. Fisher and Deborah S. Collier. Massachusetts General Hospital, Boston, MA.

Background/Purpose: Specialist visits are a contributing factor to the rising cost of healthcare and payment models increasingly encourage decreased outpatient specialty visits.

Methods: Due to monitoring of methotrexate, sulfasalazine, or lefunamide, many rheumatologists see patients with stable Rheumatoid Arthritis (RA) every 3 months for routine follow up. We hypothesized that decrease in utilization and cost of outpatient specialty services can be achieved without compromising patient care or safety by seeing these patients every 6 months, with a lab check every 3 months.

Results: Patients with RA on either methotrexate or sulfasalazine in stable remission or low disease activity were offered visits every 6 months instead of every 3 months, with labwork done at 3 months. This was part of a Quality Improvement initiative to decrease healthcare costs.

Outcomes included number of eligible patients for two full time providers over a 6 month period, percent of total established RA patients for these providers deemed appropriate for inclusion, percent of patients who had their labs done, percent of patients with new cytopenia or liver function test (LFT) abnormality, percent of patients who had problems requiring a follow up visit during the 6 month interval, and estimated cost savings.

Results: Over 6 months, 21 eligible patients were identified. Clinical features are noted in Table 1. Overall, 14/21 patients were seropositive, either for RF or CCP antibodies, and 12 were positive for both. 10 patients were on combination therapy with a biologic. The 21 RA patients were out of 184 established RA patients seen for follow up visits by two full time providers (11.4%) during the study period (Table 2). 14 of 21 patients (66.7%) had their labs drawn at 3 months. There were no new cytopenias or LFT abnormalities. No patients required additional follow up for RA. One patient required a follow up visit during the 6 month interval for new diagnosis of Giant Cell Arteritis. Each saved visit equaled an estimated cost savings of between $92 and $356, depending on the insurer, with an average of $161 savings per visit and $352 per patient annually.

Conclusion: Patients with RA in stable remission or low disease activity can safely and cost effectively be seen at 6 month intervals with labs drawn at 3 months. There were no new RA issues between visits, and no new laboratory abnormalities. Patient compliance was good, but could be improved. This intervention saved an average of $362 per patient annually.

Table 1: Clinical Characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender (female)</th>
<th>Ethnicity</th>
<th>White</th>
<th>Hispanic</th>
<th>RF</th>
<th>CCP</th>
<th>Erosive disease</th>
<th>Disease duration (years)</th>
<th>On MTX</th>
<th>On SSZ</th>
<th>On Lefunamide</th>
<th>On Plaquenil</th>
<th>On prednisone</th>
<th>On biologic (in combination)</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Golimumab</th>
<th>Abatacept</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.8</td>
<td>82.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Outcomes

<table>
<thead>
<tr>
<th>Total Established RA Patient Visits</th>
<th>Eligible RA patients</th>
<th>Labs done</th>
<th>New Cytopenias</th>
<th>New LFT abnormalities</th>
<th>Interval Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>184</td>
<td>21 (11.4%)</td>
<td>14/21 (66.7%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Disclosure: M. C. Fisher, None; D. S. Collier, None.

2426
Comparison of Patient Self-Reported and Physician Reported Rheumatoid Arthritis Medication Use - Results from the Ontario Best Practices Research Initiative. Binu Jacob1, Xiuying Li2, Angela Cesta3, Bindée Kurita4, Edward Keystone4 and Claire Bombardier4. 1University Health Network, Toronto General Research Institute, Toronto, ON, 2University Health Network, Toronto, ON, 3University of Toronto, Toronto, ON, 4Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Patient self-reported medication histories may be prone to misclassification and recall bias. We aimed to assess the agreement between patient (Pt) and physician (MD) reported medication use in a cohort of RA patients.

Methods: Patients enrolled in the Ontario Best Practices Research Initiative (OBRI), a clinical registry of RA patients followed in routine care, were included. Following patient consent, data were extracted from physician charts using a structured questionnaire on patient demographics, comorbidities, disease activity and use of RA medications. Patients are assessed every 3 months through telephone interviews according to a standardized protocol to collect additional socio-economic characteristics, disease activities measures, and medication use. We examined the concordance of reporting
medication names and the level of agreement between Pt and MD reported RA medications. RA medications (only DMARDs and BIOLOGICS) were categorized as (yes/no) for both self-reported and physician reported data and kappa statistics with 95% confidence intervals were computed at baseline and 12 month period to assess chance-corrected agreement between the two sources of data. Percent agreement was also calculated as a measure of agreement. In addition, dose reported for various drugs were compared at baseline and one year. Wilcoxon signed rank test was used to compare the mean difference of doses reported.

Results: Of the 2347 patients included in the study, 77% of patients were female with a mean (SD) age of 57.4 (12.9) years, and the majority (85%) were Caucasian. Patients had moderate disease activity according to both mean (SD) DAS28 scores 4.5 (1.5) and CDAI scores 21.0 (14.0). At baseline, substantial agreement was found between Pt and MD reported medication use (kappa=0.78, 95% confidence interval (CI), 0.71-0.8) and use of specific BIOLOGIC and DMARDs with agreement ranged from 88 to 100% (Figure, kappa range 0.50–0.85). The degree of substantial agreement was found between Pt and MD reported medication use (95% CI 0.83–0.85) and there was no significant difference in reported dose between Pt and MD.

Conclusion: Similar level of agreement between patients and physicians suggest that differential misclassification is unlikely in the reporting of RA medication use. Furthermore, the accurate reporting of doses at one year suggests that patient's ability to report their medications improves over time.

Methods: In the HOPEFUL-1 study, patients with early RA were randomized to receive ADA 40 mg every other week (EOW) plus weekly MTX 6–8 mg, or only MTX 6–8 mg every week for 26 weeks. Thereafter, all patients received open-label ADA 40 mg EOW plus weekly MTX for 26 weeks. At week 52, patients could enroll in HOPEFUL-2, an observational follow-up study, where they received ADA plus MTX (ADA-continued group) or MTX alone (ADA-withdrawn group) for 52 weeks based on investigator and/or patient decision. At week 104, patients could enroll in HOPEFUL-3, a 104-week follow-up extension. Data at week 156 were used in this interim analysis. Using multivariable analysis, factors associated with remaining in ADA-withdrawn group as well as sustaining LDA in the ADA-withdrawn group at week 156, were analyzed. The 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR), Health Assessment Questionnaire Disability Index (HAQ-DI), and modified total Sharp score (mTSS) were also examined.

Results: Among the 220 HOPEFUL-2 patients, 172 were enrolled in the HOPEFUL-3 study, 79 from ADA-continued and 93 from ADA-withdrawn. Patient characteristics at the baseline of HOPEFUL-2 were similar in the ADA-continued and -withdrawn groups, except for SJC, which was significantly higher in the former group. At week 156, 73 patients out of 93 (78%) remained in the ADA-withdrawn group with the remainder of patients either discontinuing from the study or continuing/restarting treatment with ADA. At week 156, there were no differences in clinical, functional, and structural outcomes between the patients in ADA-withdrawn group and the remainder of patients (Table). The predictive factors for remaining in the ADA-withdrawn group at week 156 were level of CRP at week 0, as well as SJC, CRP, and titer of rheumatoid factor at week 52 (cut-offs = week 0 CRP, 2.04; week 52 CRP, 0.21; week 52 SJC, 0). Moreover, DAS28-ESR 2.6 at week 52 distinguished 44 patients, those who were able to sustain LDA without using ADA at week 156.

Conclusion: The attainment of low disease activity based on serological markers at the onset and at the time of ADA withdrawal was the key determinant for maintenance of biologic-free disease control for up to 2 years in early RA patients.

Table 1.

<table>
<thead>
<tr>
<th>ADA-withdrawn</th>
<th>Others (n=93)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA S28-ESR</td>
<td>2.63</td>
<td>2.81</td>
</tr>
<tr>
<td>HA Q-DI</td>
<td>0.26</td>
<td>0.45</td>
</tr>
<tr>
<td>Percentage of patients with SJC ≤ 10</td>
<td>66.7%</td>
<td>71.2%</td>
</tr>
<tr>
<td>Percentage of patients in LDA</td>
<td>62.0%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Percentage of patients in remission</td>
<td>42.3%</td>
<td>52.6%</td>
</tr>
<tr>
<td>HA Q remission</td>
<td>83.8%</td>
<td>84.6%</td>
</tr>
</tbody>
</table>

2427

Attainment of Low Disease Activity Is Predictive of Maintenance of Disease Control over Adalimumab Discontinuation for Two Years Following Combination Therapy in Japanese Patients with Early Rheumatoid Arthritis. Yoshiba Tanaka1, Hisashi Yamanaka2, Naoki Ishiguro3, Nobuyuki Miyasaka4, Katsuyoshi Kawana5, Katsutoshi Hiramatsu5, Aki Kuroki5, and Tsutomu Takeuchi6. 1University of Occupational and Environmental Health, Japan, 2Kakuda City Hospital, Japan, 3Juntendo University, Tokyo, Japan, 4Kagawa University, Kagawa, Japan, 5Kagoshima University, Kagoshima, Japan, 6Teijin Pharmaceutical Ltd.

Disclosure: B. Jacob, None; X. Li, None; A. Costa, None; B. Kuriya, None; E. Kastane, A Biotest, AstraZeneca, BMS, F. Hoffmann-La Roche, Genentech, Jansen, Lilly, Novartis, Pfizer Sanofi-Aventis, UCB, 5, Abbott Laboratories, AstraZeneca, Biocodex, BMS, F. Hoffmann-La Roche, Genentech, Jansen, Lilly, Merck, Pfizer, UCB, 5, Abbott, AstraZeneca, BMS Canada, F. Hoffmann-La Roche, Jansen, Pfizer, UCB, Amgen, B; C. Bombardier, None.

Background/Purpose: A though available data has suggested successful withdrawal of a monoclonal antibody TNF blocker after achieving remission in patients with early rheumatoid arthritis (RA), longer term follow-up data is needed to predict maintenance of biologic-free disease control. The purpose of this study was to identify the factors associated with maintenance of disease control for 2 years of adalimumab (ADA) discontinuation after treatment with ADA plus methotrexate (MTX) in patients with early RA.
Machado\textsuperscript{a}, Jaime C. Branco\textsuperscript{a}, João E. Fonseca\textsuperscript{a} and José Pereira Da-Silva\textsuperscript{a},
\textsuperscript{a}Hospital Santa Maria, Lisboa, Portugal, \textsuperscript{b}Portuguese Society of Rheumatology, Lisboa, Portugal, \textsuperscript{c}Hospital Garcia de Orta, Almada, Portugal, \textsuperscript{d}Clínica de Reumatologia de Lisboa, Lisboa, Portugal, \textsuperscript{e}Centro Hospitalar do Alto Minho, Hospital de Ponte de Lima, Ponte de Lima, Portugal, \textsuperscript{f}Leiden University Medical Center, Leiden, Netherlands, \textsuperscript{g}Leiden University Medical Center, Lisbon, Portugal, \textsuperscript{h}Hospital Academic Medical Center, Lisbon, Portugal, \textsuperscript{i}Hospitais de la Universidad de Coimbra, Coimbra, Portugal.

**Background/Purpose:** Our aims were to assess disease activity states using DAS28ESR, CDAI and SDAI and to compare their outcomes in two rheumatoid arthritis (RA) populations of METEOR database.

**Methods:** A total of 64605 visits from 5870 Dutch patients and 20120 visits from 3385 Portuguese patients were analyzed. We also collected and replicated the same analyses in a subset of one random visit per patient.

**Results:** Disease activity was very similar with CDAI, SDAI and ACR/EULAR remission criteria. Concomitantly, using DAS28ESR, a significant higher proportion of Dutch visits was classified as “in remission” was lower in Dutch visits and this component was determinant for lowering DAS28 scores in this group of patients.

**Conclusion:** DAS28ESR was used. SDAI and CDAI attenuated those differences. The percentage of Dutch and Portuguese visits classified as “in remission” was very similar with CDAI, SDAI and ACR/EULAR remission criteria. Concomitantly, using DAS28ESR, a significant higher proportion of Dutch visits was classified as “in remission” was lower in Dutch visits and this component was determinant for lowering DAS28 scores in this group of patients.

**Table - Comparing means of the components of the disease activity indices within each disease activity state between Dutch and Portuguese populations**

<table>
<thead>
<tr>
<th></th>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>6.73</td>
<td>&lt;0.0001</td>
<td>4.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TJC28</td>
<td>6.24</td>
<td>&lt;0.0001</td>
<td>6.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SJC28</td>
<td>3.65</td>
<td>0.0003</td>
<td>1.94</td>
<td>0.0520</td>
</tr>
<tr>
<td>ESR</td>
<td>14.13</td>
<td>&lt;0.0001</td>
<td>9.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DAS28</td>
<td>7.34</td>
<td>&lt;0.0001</td>
<td>6.04</td>
<td>0.0024</td>
</tr>
<tr>
<td>B. CDAI</td>
<td>1.99</td>
<td>0.0048</td>
<td>1.99</td>
<td>0.0002</td>
</tr>
<tr>
<td>MDGA</td>
<td>10.63</td>
<td>&lt;0.0001</td>
<td>11.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TJC28</td>
<td>1.37</td>
<td>0.0232</td>
<td>3.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SJC28</td>
<td>4.19</td>
<td>&lt;0.0001</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDAI</td>
<td>5.87</td>
<td>&lt;0.0001</td>
<td>1.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C. SDAI</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Disclosure:** R. Nagamine. None.

**ACR/ARHP Poster Session C**
Clinical Practice/Patient Care (ARHP)
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

**2429**

**Seasonal Changes May Influence Activity of Rheumatoid Arthritis.**
Ryuji Nagamine. Sugioka Memorial Hospital, Fukuoka, Japan.

**Background/Purpose:** RA activity during the year was assessed to investigate whether seasonal changes influenced parameters of RA activity.

**Methods:** This study was performed in Fukuoka, a Japanese city with four distinct seasons. From September 1 to August 31, 2011, parameters of RA activity were assessed in a total of 3811 visits by 348 patients (mean age, 62.1 years; mean duration of RA, 10.8 years), including 2174 visits by 140 patients treated with biologics (mean age, 63.0 years; mean duration of RA, 11.9 years). The following parameters were assessed: C-reactive protein (CRP); erythrocyte sedimentation ratio (ESR); matrix metalloproteinase (MMP)-3; rheumatoid factor; DAS28-CRP and DAS28-ESR. All parameters in each month in the first two years were assessed and results were compared among months. Monthly mean temperature and mean atmospheric pressure in Fukuoka in the years of the study are shown in Fig. 1.

**Results:** For all cases, mean CRP level was 0.65 mg/dl from October to December, and 0.53 mg/dl from July to September. In cases treated using biologics, mean CRP level was 0.67 mg/dl from October to December and 0.50 mg/dl from January to March. These differences were significant (P<0.05). CRP level from April to June (mean, 0.70 mg/dl) was also significantly higher than that from January to March (P<0.01). CRP was significantly higher in autumn and spring and than in summer and winter, even in patients treated with biologics. Seasonal changes thus clearly influenced CRP levels. No significant differences in other parameters were found, although MMP-3 levels were also higher from October to December and from April to May compared to other months (Fig. 2).

**Conclusion:** The results clearly show that seasonal changes significantly influence CRP levels. In the city, the temperature rapidly fell and atmospheric pressure rose in autumn to early winter, and the reverse occurred in spring. RA activity may correlate with changes in temperature and atmospheric pressure.

**2430**

**Serological and Clinical Characteristics of a Large Collection of Incomplete Lupus Erythematosus Patients.**
Teresa Aberle\textsuperscript{a}, Virginia C. Roberts\textsuperscript{a}, Julie M. Robertson\textsuperscript{a}, Joel M. Guthridge\textsuperscript{b}, Kathy L. Sivils\textsuperscript{b}, Astrid Rasmussen\textsuperscript{c}, David R. Karp\textsuperscript{c} and Judith James\textsuperscript{a}, 1Oklahoma Medical Research Foundation, Oklahoma City, OK; 2University of Oklahoma Health Sciences Center, Oklahoma City, OK; 3University of Texas Southwestern Medical Center, Dallas, TX.

**Background/Purpose:** Incomplete lupus (ILE) is defined as a condition in which patients present with signs of systemic autoimmunity and clinical manifestations compatible with systemic lupus erythematosus (SLE) but do not fulfill the American College of Rheumatology (ACR) classification...
ELISA or by multiplexed assay were also measured. ANA with titer/pattern, anti-dsDNA by IIF, anti-cardiolipin (aCL), and connective tissue screening questionnaires (CSQ), detailed clinical questionnaires were reviewed to assess for ACR SLE classification criteria and medications; some of these individuals may transition to classified SLE or another systemic autoimmune rheumatic disease. However, many will remain ILE patients without major organ involvement. Differentiating between these groups is clinically challenging and better clinical, demographic and molecular biomarkers which define ILE patients would be clinically helpful and would also allow better identification of high-risk individuals for prevention trials or for closer monitoring.

Methods: For this analysis, we examined participants enrolled to the Lupus Family Registry and Repository (LFRR). Medical records were reviewed to assess for ACR SLE classification criteria and medications; individuals who met only 3 ACR classification criteria were designated as ILE for this study (n = 443). Additionally, each participant completed connective tissue screening questionnaires (CSQ), detailed clinical questionnaires, demographic and therapeutic information. Autoantibody testing for ANA with titer/pattern, anti-dsDNA by IIF, anti-cardiolipin (aCL), and autoantibodies against Ro, La, Sm, nRNP and ribosomal P by precipitin, ELISA or by multiplexed assay were also measured.

Results: In this cohort, individuals with ILE (n = 443) were most commonly European-American or African-American females on average 46.0 ± 13.9 years of age with an average CSQ score of 6.03 ± 2.39. Among the 443 individuals meeting 3 ACR classification criteria, 311 (70%) never took an immunomodulating drug (methotrexate, azathioprine, hydroxychloroquine/ chloroquine, corticosteroids) and 375 (85%) never took a major immunosuppressant (cyclophosphamide, mycophenolate mofetil, cyclosporine, biological). The most prevalent ACR classification criteria that ILE individuals presented with were ANA (97.2%), immunologic criteria (62.3%), arthritis (44.2%), photosensitivity (24.6%), and hematologic criteria (25.3%). aCL (46.5%), anti-dsDNA antibodies (27.3%), leukopenia (14.6%), and lymphopenia (12.4%) were the most prevalent ACR sub-criteria present. When 13 autoantibodies were examined using a high-throughput multiplex assay, anti-chromatin (34.5%), anti-Ro (27.7%), anti-RNP (24.3%), anti-Sm/RNP (20.9%), anti-dsDNA (14.9%), and anti-Sm antibodies (11.5%) were the most prevalent autoantibodies.

Conclusion: Large numbers of individuals with ILE can be identified and their clinical presentation is characterized by immunologic and hematologic findings, as well as arthritis and cutaneous disease. Multiple lupus-associated autoantibodies are enriched in these patients. Longitudinal studies are warranted to better understand the individuals at the highest risk of transition to systemic autoimmune rheumatic disease, as well as to understand the biologic processes which help prevent individuals from progressing to major organ involvement.

Disclosure: T. Aberle, None; V. C. Roberts, None; J. M. Robertson, None; J. M. Guthridge, None; K. L. Sivils, None; A. Rasmussen, None; D. R. Karp, None; J. James, None.

2432


Background/Purpose: Recent research suggests that mind-body physical activity such as yoga and Tai Chi can significantly improve physical function in rheumatoid arthritis (RA). Yoga and Tai Chi are gentle physical activities that promote strength, flexibility, balance and positive mental health. However, it is difficult to assess the effectiveness of these activities given that prior studies have small sample sizes. Therefore, we conducted a systematic meta-analysis to assess the effectiveness of these exercises on improvement of physical function in adults with RA.

Methods: Medline was searched using the keywords: Yoga, Tai Chi, Physical Function, and Rheumatoid Arthritis. Included articles were those that measured the pre-intervention and post-intervention physical function scores using a validated physical function measurement tool for adults with a clinical diagnosis of RA who participated in a yoga or Tai Chi intervention lasting at least 6 weeks. Articles were excluded if the population was younger than 18, if the physical function measure was not a validated tool and if the reported results combined disease conditions such as RA and lupus. Effect sizes with confidence intervals were calculated using a fixed effects model for each intervention study by comparing the mean pre-intervention physical function score to the mean post-intervention score.

Results: The Medline search retrieved 219 English articles. The final analysis included 6 articles. There were 3 tai chi studies, 1 RCT and 2 pre/post intervention assessments, with a total of 22 participants. There were 3 yoga studies, 2 controlled clinical trials and 1 pre/post intervention assessment, with a total of 30 participants. There is strong evidence for the effectiveness of Tai Chi (standardized mean difference (SMD) = 1.20, 95% confidence interval (CI) = 0.13, 2.31) and for yoga (SMD = 1.22, 95% CI = 0.10, 2.27) on improving physical function in adults with RA who have participated in a physical activity program for at least 6 weeks. See Forrest plot.

Conclusion: Our data suggest that Tai Chi and Yoga are largely effective in improving physical function in adults with RA. Providers may be able to assist in improving the physical function of this population by discussing health promotion strategies such as yoga or tai chi physical activity programs.

Disclosure: H. Greysen, None. K. Lee, None.

2432

Nutritional Assessment in Patients with Systemic Lupus Erythematosus and Systemic Sclerosis. Sabrina Vagnani1, Chiara Tani2, Linda Cari2, Francesca Querci1, Alessandra Della Rossa3, Anna d’Ascanio3, Ilaria Emerini4, Marco Cerobi5, Saviero Caini2, Domenico Palli2, Stefano Bombardieri1 and Marta Mosca. 1Rheumatology Unit, University of Pisa, Pisa, Italy, 2Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute, ISPO, Florence, Italy, 3Florence, Italy, 4Rheumatology Unit, Pisa, Italy.

Background/Purpose: Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SSc) can be both associated with various degrees and types of malnutrition, with different pathogenetic mechanisms. It’s well known that a balance between nutritional needs, energy intake and nutrients can contribute to the control of the inflammatory processes and can have a beneficial effect on osteoporosis, metabolic syndrome, hypertension, cardiovascular disease and neoplasm. Nutritional therapy is a promising way to approach SLE and SSc, indeed, a diet rich in vitamins, minerals and mono/polyunsaturated fatty acids could promote a beneficial protective effect against inflammatory activity and tissue damage as well as comorbidities. The aim of this study was to assess the nutritional status and food intake of a cohort of SLE and SSc patients in comparison to healthy subjects.

Methods: Twenty patients with SLE and 20 patients with SSc were included in the nutritional assessment. Twenty healthy age and sex matched subjects (H) were used as controls. Food intake was assessed using a Food Frequency Questionnaire, validated in the European Prospective Investigation into Cancer (EPIC) Cohort Study. All individual questionnaires were checked and coded by trained dieticians, computerized and then transformed into estimates of intake for a series of over 30 nutrients. At enrollment, weight, height, waist and hip circumferences were measured for each participant.

Results: The average age of SLE, SSc patients and controls was 36 ± 10, 40 ± 9 e 35 ± 10 years respectively (p=n.s.). The majority of SLE patients (90%) resulted normal weight: the body mass index (BMI) ranged between 18.5 and 24.99 kg/m2. The rest of the group was overweight (25 ≤ BMI < 29.99 kg/m2). No obesity or underweight was observed. No differences in BMI were observed between SLE patients and H.

More than half of the SSc patients (66%) was normal weight; the rest of the group was underweight (89% slightly underweight with 17 ≤ BMI < 18.49 kg/m2 and 13% moderately underweight with 16 ≤ BMI < 16.99 kg/m2). SSc patients showed a lower mean value of BMI if compared with both SLE patients and H.

The annual frequency consumption of fruit, leafy vegetables, legumes, vegetables, milk, pasta, meat, and fish was similar in all the groups. On the contrary, the annual energy intake (kcal) was significantly lower in SSc patients if compared to SLE patients and H (p<0.02).

Disclosure: H. Greysen, None; K. Lee, None.
Conclusion: In this study we investigated the nutritional status of patients affected by two systemic autoimmune diseases. Our preliminary data showed an inadequate consumption of nutrients in SSC patients if compared to SLE patients and controls, probably due to a more severe gastro-enteric involvement. These results highlight the importance of an individualized nutrition approach in these patients according to disease-related specificities and pharmacological therapies.

Disclosure: S. Vagagni, None; C. Tani, None; L. Carli, None; F. Querci, None; A. Della Rossa, None; A. d’Ascanio, None; I. Ermini, None; M. Ceroti, None; S. Cai, None; D. Palli, None; S. Bombardieri, None; M. Mosca, None.

2433

Efficacy of Ketoprofen Vs Ibuprofen and Diclofenac for Treating Pain in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Fabiola Atzeni1; Alessandra M onguzzii2; Elisabetta Grilllo4, Luigi Lanata2 and Piercarlo Sarzi-Puttini2. 1Rheumatology Unit, L. Sacco University Hospital, Milan, Italy; 2Dompe SpA, Milan, Italy.

Background/Purpose: Patients with rheumatic diseases, including rheumatoid arthritis (RA), describe symptoms such as pain and stiffness as important factors affecting their quality of life. The most widely used drugs to decrease inflammation and manage mild-to-moderate pain in RA patients are NSAIDs. In our previous meta-analysis, we demonstrated that ketoprofen was superior to ibuprofen and/or diclofenac in relieving different kinds of moderate-to-severe pain conditions, and so the aim of this systematic review of the literature and meta-analysis of randomized controlled trials (RCTs) was to compare the clinical efficacy of these drugs in patients with the specific pain associated with RA.

Methods: We made a systematic search of the Medline and Embase databases from their inception to March 2014 in accordance with the Cochrane Collaboration guideline in order to identify RCTs directly comparing the recommended therapeutic doses of oral ketoprofen (50-200 mg/day), ibuprofen (600-1800 mg/day) and diclofenac (75-150 mg/day) for RA pain relief. The meta-analysis was made using the standardized mean difference (SMD) of each included RCT and a fixed effects model.

Results: Five RCTs, involving a total of 456 patients met the inclusion criteria. The meta-analysis showed a statistically significant difference in clinical efficacy in favour of ketoprofen (SMD = 0.34; CI 95% 0.16-0.52; p = 0.0002). The heterogeneity test for the efficacy outcome was not statistically significant and equal to zero ($I^2 = 3.67$; df = 4; $P = 0.45$; $I^2 = 0$%), thus demonstrating the homogeneity of the trials and the validity of the meta-analysis findings. The meta-analysis did not reveal any significant differences between drugs in terms of tolerability (the percentage of patients developing adverse events or safety (withdrawn patients).

Conclusion: The result of this meta-analysis shows that therapeutic doses of ketoprofen are more efficacious than ibuprofen and diclofenac in managing RA-related pain, thus supporting its use in clinical practice.

Disclosure: F. Atzeni, None; A. Monguzzi, Dompe SpA, 3; E. Grillo, Dompe SpA, 3; L. Lanata, Dompe SpA, 3; P. Sarzi-Puttini, None.

2434

Gait Instability in the Elderly: A New Dedicated out-Patients Consultation. Vincent Goeb, Bernard Avuin and Claude Touzard. 1University Hospital, AMIENS, France; 2Polyclinic, LAVAL, France, 3Hospital of Laval, LAVAL, France.

Background/Purpose: Gait instability which represents a common but non-specific complaint, mainly in the elderly, is of major interest in Public ed (6038 references). Gait Instability can be the first step towards risk of falling, exposure to dementia, and disability [1]. Despite the frequency of this symptom and its major devastating consequences, few dedicated out-patients consultations have been initiated, in order to provide a practical management approach. A two year study will highlight the interest and perspectives of such an out-patients consultation.

Methods: Patients were recommended either by their general practitioner for gait abnormalities, or following an out-patients memory consultation. The assessment included six steps: self-questionnaires (Dizziness Handicap Inventory, Hospital Anxiety and Depression Scale), nurse evaluation, balance tests (one leg balance, Timed Up and Go score, Timed chair rise test), Mini Mental Score, clinical examination, and ambulatory Gait Analysis under simple and dual task conditions (counting backwards). We measured, using a validated ambulatory gait analysis system (Locometrix®), 3 main gait variables: walking speed, cadence, and stride regularity index. According to the results, additional specialized out-patients consultation and tests can be carried out (geriatrician, neurologist, otorlaryngologist, brain magnetic resonance imaging. . .).

Results: - 80 patients were included (M = 41; F = 39; age: 68 ± 14 y; BMI: 25 ± 5.5 kg/m2).
- 3 main subgroups of patients with gait complaints were identified (gait instability and cautious gait (n = 38), recurrent falls (n = 24) and memory impairment (n = 18).
- Gait analysis was found with no abnormality in thirteen patients under simple task, in these cases gait abnormalities occurred only during the dual task test.
- A broad diversity of diagnosis and syndromes were identified as the main pathology (Mild Cognitive Impairment (n = 23), dementia (n = 9), leukoaraisis (n = 9), vestibular disease (n = 7), frail people (n = 9), musculo-skeletal disorders including spinal stenosis (n = 7), brain stroke attack sequel (n = 6), hydrocephaly (n = 2), peripheral neuropathy (n = 1), Charcot Marie Tooth disease (n = 1), myopathy (Facio-scapulo-humeral dystrophy) (n = 1), brain haemosiderosis (n = 1), and patients without any diagnosis (n = 4).

Conclusion: The complaint of gait instability has to be taken into account by the clinician, and necessitates a multi-disciplinary network. Clinical examination remains a key point, but gait analysis provides a measurement of gait instability, which can sometimes occur only under dual task conditions. A decrease in gait variability under the dual task test may explain the mechanism of an unexplained fall. Moreover a large decrease in one or more of the gait variables highlights for the clinician about a decrease in the cognitive reserve of the patient. Thus this condition proved to be informative to the clinician who has to look for brain pathology in addition to musculo-skeletal deterioration.


Disclosure: V. Goeb, None; B. Avuin, CentaureMetrix, 1; C. Touzard, None.

2435

‘It’s like the Worst Toothache You’ve Ever Had’ - How Persons with Rheumatoid Arthritis Describe and Manage Pain in Daily Life. Maria Bergström4, Inger Ahlstrand5, Ingrid Thysberg5, Torbjörn Falkner4, Björn Börabo6 and Mathilda Björk6. 1School of Health Sciences, Jönköping University, Jönköping, Sweden, 2School of Health Sciences Jönköping University, Jönköping, Sweden, 3Linköping University Hospital, Linköping, Sweden, 4School of Occupational Therapy and Social Work, CHIRI, Curtin University, Perth, WA, Australia, 5Linkoping University, Linköping, Sweden, 6Rehabilitation Center and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden.

Background/Purpose: Although it is reported that biological treatment has a positive effect on Rheumatoid arthritis (RA), pain intensity is still moderate to high in the majority of those affected, causing activity limitations and thus participation restrictions. Indeed, persons with RA have identified pain as the predominant health status impairment most important to reduce. However, pain in RA is commonly assessed using a visual analogue scale (VAS), which does not capture the complexity of pain and certainly does not address the management of it in daily activities. The purpose was to describe how persons with RA experience and manage pain in their daily life.

Methods: A focus group study was conducted. The participants were recruited with a purposive sample from three Rheumatology Units in Sweden. The inclusion criteria were seropositive RA, ≥ 4 years duration and pain intensity >40 mm as reported by VAS over the last two clinical visits. Of 77 eligible patients, 33 agreed to participate (34 to 73 years old). Seven semi-structured focus groups discussions were conducted and analyzed using content analysis. A RA-patient research partner was involved in the study confirming the interview guide and the results from a patient perspective. The study protocol was approved by the Regional Ethical Committee.

Results: The analysis revealed four categories: (1) Pain expresses itself in different ways; referring to descriptions of RA pain as overwhelming, painful
and as a feeling of stiffness in joints. While pain was described as closely related to fatigue and stress, sometimes it was invisible to others in the patients’ social environment. (2) Managing by easing the pain; referring to the use of heat and/or cold treatments, medications and activities as distractions. (3) Managing by adapting to pain; referring to the strategies of learning to live with the pain, to plan activities in daily life to reduce pain, to use assistive devices or to sometimes simply stop doing some activities. (4) Managing pain in a social context; referring to the social environment as being both supportive and uncomprehending, the latter causing the participants to sometimes hide their pain.

Conclusion: Pain in RA was described as complex and multifaceted. To manage pain the participants used a wide range of strategies, ranging from personal strategies to those applied in their social context. This wide range of strategies could possibly complement the traditional methods used in clinical settings to manage pain. These findings further suggest that assessment of pain needs to be extended beyond the linear VAS measurement to cover its complexity.

Disclosure M. Bergström, None; I. Ahlstrand, None; I. Thyberg, None; T. Falkmer, None; B. Börbo, None; M. Björk, None.

2436

Analytical and Clinical Evaluation of an Immunoassay for Estimating Immunogenicity of Infliximab and Etanercept in Indian Population. Canna Ghaia1, Shashank Akerkar2, Shailaja Sabnis3, Rao RK Uppuluri4 and Gautam Rambhad5. 1Medical Advisor, Pfizer Limited, India, Mumbai, India, 2Mumbai Arthritis Clinic and Research Centre, Mumbai, India, 3Sneh Nursing Home, Mumbai, India, 4Sneha Nursing Centre, Hyderabad, India, 5Associate Director Medical Services, Pfizer Limited, India, Mumbai, India.

Background/Purpose: Biologic anti-TNFs in India have improved the patient management. Significant proportions of patients lose response over time or do not respond. Possible explanations are suboptimal trough anti-TNFs concentrations or antibodies to anti-TNFs5. Anti-infliximab antibodies are found in 12%-44% of patients’ vis-à-vis anti-etanercept antibodies (0%-18%). Anti-etanercept antibodies are without apparent effect on effectiveness or adverse events5. Clinicians should have access to immunogenicity testing facility in India.

The aim of this project was to set up and standardize an independent laboratory to test immunogenicity of anti-TNF biologics (infliximab and etanercept) with the help of pharmaceutical partnership.

Methods: Three rheumatologists piloted this project approved by independent ethics committee and carried out in compliance with ICH/GCP guidelines. Pfizer supplied the immunogenicity kits to the independent laboratory (SRL labs). After informed consent, blood (5 mL) was collected before infusion of infliximab (n=8) or injection of etanercept (n=8). Following all precautions, the blood samples were transported to the laboratory. Promonitor® was the ELISA test used for testing of biological levels and anti-TNFs antibodies in patients samples. Laboratory staff was trained by Progenika specialist from Spain (Table I).

Table I

Table II

<table>
<thead>
<tr>
<th>Cut-point</th>
<th>Drug level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035 ug/mL</td>
<td>1) ≤ 0.035 ug/mL – Negative</td>
<td>0.035-1.5 ug/mL – Low positive</td>
</tr>
<tr>
<td>1.5 ug/mL</td>
<td>2) 0.035-1.5 ug/mL – Low positive</td>
<td>≤ 142 AU/mL – Positive</td>
</tr>
<tr>
<td>2 AU/mL</td>
<td>3) ≤ 142 AU/mL – Negative</td>
<td>2.706 to 8.079 ug/mL (n=3)</td>
</tr>
<tr>
<td>8.079 ug/mL</td>
<td>4) 2.706 to 8.079 ug/mL (n=3)</td>
<td>Low positive</td>
</tr>
<tr>
<td>142 AU/mL</td>
<td>5) 8.079 to 142 AU/mL (n=1)</td>
<td>Positive</td>
</tr>
<tr>
<td>323 ug/mL</td>
<td>6) ≥ 142 AU/mL (n=8)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

While 4 patients tested negative for infliximab, one patient tested low positive and 3 patients were positive. Anti-infliximab antibody was detected in 1/8 patient (12.5%) and the blood level of infliximab was negligible. When anti-TNFs are used, therapeutic drug monitoring is of help for optimal clinical outcomes. It might be more cost effective to adjust anti-TNF dosages according to serum drug concentrations3,4.

Conclusion: This study met its objective of setting up and standardizing an independent laboratory for immunogenicity testing of anti-TNF biologics in India.

References:


Disclosure C. Ghaia, Medical Advisor; S. Akerkar, Advisory Board Member; S. Sabnis, None; R. R. Uppuluri, Speaker, consultant, and advisory board member; S. G. Rambhad, Associate Director Medical Services, 3.

2437

Why Doesn’t Participation in Activity Increase Following Hip or Knee Replacement? Aileen Davis1, Viji Venkataramanan2, Jessica Bytautas 3, Rose Wong1, Lisa Carlesso 1, Anthony Perruccio 3 and Fiona Webster 2. 1Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, 2Department of Family and Community Medicine, University of Toronto, Toronto, ON, 3Toronto Western Hospital, University Health Network, Toronto, ON.

Background/Purpose: Activity is critical for healthy aging. Our prior work demonstrated that despite improved pain and function, people did not increase their participation in activity post total hip or knee replacement (TJR). Our subsequent qualitative work identified that not only had people given up many activities prior to TJR, they experienced new comorbidity or symptomatic joints that limited their engagement. They also described significant life changes that impacted participation. This study evaluated if these health and social contextual factors were associated with change in participation.

Methods: We conducted a retrospective analysis of our TJR cohort. The primary outcome was change in participation frequency (Late Life Disability Index (LLDI) frequency subscale) pre- to 1 year post-surgery. Predictors were surgical complication, new comorbidity, another primary TJR, and positive and negative life events (Life Experience Survey) in the year following TJR. Analyses included multivariable regression for the TKR and THR cohorts, adjusting for age, sex, education, pre-surgery BMI, comorbidity, and frequency, and change pre to 1 year post-TJR in depression, WOMAC pain and function and LLDI limitations.

Table III

Table: 2436

<table>
<thead>
<tr>
<th>Cut-point</th>
<th>Drug level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>&lt;0.035 ug/mL</td>
<td>Negative</td>
<td>0.035-1.5 ug/mL – Low positive</td>
</tr>
<tr>
<td>3.23 ug/mL</td>
<td>Positive</td>
<td>Range 2.706 to 8.079 ug/mL (n=3)</td>
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<td>4.20 ug/mL</td>
<td>Positive</td>
<td>≥ 142 AU/mL (n=8)</td>
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<tr>
<td>0.035 ug/mL</td>
<td>Negative</td>
<td>≤ 142 AU/mL (n=8)</td>
</tr>
<tr>
<td>142 AU/mL</td>
<td>Negative</td>
<td>≤ 142 AU/mL (n=8)</td>
</tr>
</tbody>
</table>

While 4 patients tested negative for infliximab, one patient tested low positive and 3 patients were positive. Anti-infliximab antibody was detected in 1/8 patient (12.5%) and the blood level of infliximab was negligible. When anti-TNFs are used, therapeutic drug monitoring is of help for optimal clinical outcomes. It might be more cost effective to adjust anti-TNF dosages according to serum drug concentrations3,4.

Conclusion: This study met its objective of setting up and standardizing an independent laboratory for immunogenicity testing of anti-TNF biologics in India.

References:


Disclosure C. Ghaia, Medical Advisor; S. Akerkar, Advisory Board Member; S. Sabnis, None; R. R. Uppuluri, Speaker, consultant, and advisory board member; S. G. Rambhad, Associate Director Medical Services, 3.
Results: The 418 TKR patients (mean age=65, 36% male, 69% >high school education) had a mean BMI of 30 and 49%, 6%, 13%, 12% had hypertension, CVD, diabetes, lung disease respectively. 74 episodes of new comorbidity (29 hypertension, 27 CVD, 8 diabetes, 10 lung disease) occurred. 38 (12%) had a complication, 39 another TJR, 151 (36%) reported a positive comorbidity (29 hypertension, 27 CVD, 8 diabetes, 10 lung disease) occurred. Hypertension, CVD, diabetes, lung disease respectively. 74 episodes of new changes in engagement in activity post TJR. Although additional health issues with less change and positive life events were associated with greater change in frequency. The 376 THR patients (mean age=64, 46% male, 77% >high school education) had a mean BMI of 28 pre-surgery, 157 (42%) had hypertension, 28 (7%) had CVD, 31 (8%) had diabetes and 19 (5%) had lung disease. 34 (9%) had a complication and 33 (9%) another TJR. 54 episodes of a new comorbidity were reported (19 hypertension, 19 CVD, 4 diabetes, 12 lung disease). In adjusted analysis, lower pre-surgery frequency was associated with less change and positive life events were associated with greater change in frequency.

Conclusion: Low activity pre-TJR coupled with social context influenced changes in engagement in activity post TJR. Although additional health issues occurred, other than complications of TKR, none were associated with change in frequency. To promote healthy aging in people having TJR, appropriate timing of surgery, pre-surgical interventions to maintain activity and targeted programs post-surgery considering social context are required to enhance activity.

Disclosure: A. Davis None; V. Venkataramanan None; J. Bybytius None; R. Wong None; L. Carless, None; A. Perruccio None; F. Webster None.


Karen Ellegaard1, Marius Henrikse2, Birgit Falk Riecke2, Soren Just2, Jakob Espensen2, Mohammed Yusu Nutami2 and Henning Bliddal3.

1The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark, 2The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen F, Denmark, 3The Parker Institute, Copenhagen, Denmark, 5Venu Cough, Sovenborg Sygehus, Svenborg, Denmark, Odense University, Odense, Denmark, 6Sjoegsg Sygehus, Esbjerg, Denmark.

Background/Purpose: Ultrasound (US) signs of inflammation in joints are synovial hypertrophy, effusion, and Doppler activity (increased perfusion), which have been demonstrated in both osteoarthritis (OA) and rheumatoid arthritis (RA). It might be expected that inflammatory signs are more pronounced in patients with RA however, a comparison of RA and OA with respect to US changes remains to be performed.

Methods: A standardized US examination and scoring technique in patients with OA has been developed and validated in a group of patients with knee OA. This validated technique was applied on a group of RA patients and a group of OA patients – both with knee involvement. The diagnoses of OA and RA were accurate according to the ACR criteria. RA and OA patients were examined by US according to the standardized procedure at baseline before onset of biologics. In the present study the validated US scoring were performed in all patients (RA and OA). All US images were scored by the same person (KE). The amount of synovial hypertrophy (mm) and Doppler (+/- scored as 1/0) were measured in five positions (supra patellar; medial and lateral joint space and recess). Synovial hypertrophy measures for all 5 positions were summed and Doppler presence was summed for the medial and lateral joint space and recess (4 positions). Presence and size of Baker’s cyst were registered and any Doppler activity in or around the cyst was registered. Statistics: The difference between US findings in the two diseases was evaluated with both non-parametric and parametric statistics. The level of significance was 2α=0.05.

Results: Eighteen RA patients were included, the percentage of women was 66% and mean age was 66 years (range26.3–73). The mean DA528 was 4.9 (range 3.5–7.0). The OA group consisted of 99 patients the percentage of women was 59 and the mean age was 64 (range42.3–84.4). See table.

Conclusion: On US examination statistically significantly more synovial hypervascularity and more Baker’s cysts were seen in the OA knees as compared to the RA knees. Little Doppler activity (increased blood flow) was found with no difference between the two patient groups. These results support that inflammation is an important pathological feature in OA.

Acknowledgement: the study was supported by an unrestricted grant from Pfizer, Cambridge Weight Plan and the Oak Foundation.

<table>
<thead>
<tr>
<th>OA (n=99)</th>
<th>RA (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (SD)</td>
<td>Median (SD)</td>
</tr>
<tr>
<td>Synovial hypertrophy (mm)</td>
<td>21.8 (17.1, 27)</td>
</tr>
<tr>
<td>Baker’s cyst (0–12)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Doppler (0–7)</td>
<td>2.19 (2.52)</td>
</tr>
</tbody>
</table>

Disclosure: K. Ellegaard None; M. Henrikse None; B. Falk Riecke None; S. Just None; J. Espensen None; M. Y. Naderi None; H. Bliddal None.

2440 Factors Influencing Health Related Quality of Life (HR-QOL) for Korean Patients with Rheumatoid Arthritis.

SeoulPaik1, Kyeong Yae Sohn2 and Sung-Hwan Park3.

1ST Mary’s Hospital, Seoul, South Korea, 2The Catholic Univ of Korea, Seoul, South Korea, 3Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.
Prevalence and Determinants of Treatment Adherence Among Patients with Rheumatoid Arthritis. Maria Celeste Orozco1, Maria Florencia Waimann2, Ana Inés Marcost, Ana Maria Graniel3, Sofia Veliez4, Federico Zazzetti5, Juan C. Barreira6, Paula Kohan7, Oscar L. Rillo8, María Victoria Collado1, Graciela Gómez1, Ricardo V. Juárez1, Verónica Lencina9, Andrea D’Orazio10, Gustavo Rodriguez Gil10, Mariana Salcedo11.

Background/Purpose: The purpose of this study was to identify factors influencing the Health-related quality of life (HR-QOL) for Korean patients with rheumatoid arthritis and factors associated with HR-QOL. We designed a multicenter cross-sectional study. Consecutive patients with RA (ACR 87 and or ACR/EULAR 2010) were recruited from 7 rheumatology clinics. Data collected included comorbidities, demographic

Results: Of the 299 subjects with RA, 272 (91%) were women and mean age was 49.5±10.5 years. The mean disease duration was 117±91.2 months. The mean scores of SF-36 physical component summary (PCS) and mental component summary (MCS) were 42.5±7.9, 45.8±10.3. The mean scores of DAS 28, functional disability (KHAQ), visual analog pain scale were 3.83±1.4, 0.57±0.63, 34.95±24.43 and FACIT-Fatigue was 36.25±10.43, depression (CES-D) was 15.28±10.07 and sleep quality scale was 44.58±8.46.

On the socio-demographic features, educational level, occupation status, exercise were associated with HR-QOL (SF-36). History of hospitalization within 2 years, ESR (mm/hr), CRP (mg/dl), DAS 28 score, visual analog pain, KHAQ, FACIT-Fatigue, depression (CES-D), functional disability were associated with all domains of HR-QOL (SF-36). Visual analog pain scale was strongly associated with HR-QOL (SF-36) domain of bodily pain (BP) (r = -0.74, p < 0.0001) and depression (CES-D) was also strongly associated with mental component summary (MCS) (r = -0.73, p < 0.0001). In multiple stepwise regression model, KHAQ disability index (p < 0.0001) was significant predicting variable of the physical component summary (PCS) and depression (CES-D) (p = 0.0001) was significant predicting variable of the mental component summary (MCS) (p = 0.0001) was significant predicting variable of the physical component summary (PCS) and depression (CES-D) (p = 0.0001) was significant predicting variable of the mental component summary (MCS) of HR-QOL (SF-36). KHAQ disability index (p < 0.0001) was significant predicting variable of the physical component summary (PCS) and depression (CES-D) (p = 0.0001) was significant predicting variable of the mental component summary (MCS) of HR-QOL (SF-36). KHAQ disability index (p < 0.0001) was significant predicting variable of the physical component summary (PCS) and depression (CES-D) (p = 0.0001) was significant predicting variable of the mental component summary (MCS) of HR-QOL (SF-36).

Conclusion: The factors influencing HR-QOL were functional disability, fatigue, depression and pain. However, various factors are influencing the quality of life for patient with rheumatoid arthritis. It suggests that all healthcare professionals should pay more attention to improve fatigue, depression, pain and prevent progressing disability of patient with rheumatoid arthritis.

Disclosures: S. Paek, None; K. Y. Sohn, None; S. H. Park, None.

Prevalence and Determinants of Treatment Adherence Among Patients with Rheumatoid Arthritis.

Prevalence and Determinants of Treatment Adherence Among Patients with Rheumatoid Arthritis.
statisticall comparative analysis with independent open coding of transcribed data by 2 researchers is ongoing.

**Results:** We purposively sampled 18 participants for maximum variation (11 patients, 7 clinicians) to take part in in-depth interviews. Three emerging themes have been identified. First, participants described how digital health technologies were changing their roles and responsibilities, involving new types of ‘work’ for both patients and clinicians. Second, patients and clinicians emphasized the benefits of the Internet in preparing patients for discussions in consultations, while identifying the potential burdens of accessing extensive and unreliable sources. Third, mutual trust and respect was integral to effective patient-clinician discussions, sharing online information and informed, shared decision-making.

**Conclusion:** Preliminary findings imply that new technologies support autonomy in terms of informed patient choice and shared decision-making, but only when mutual trust and respect underpin patient-clinician interactions. Understanding how patient-clinician relationships are changing in the era of digital health is critical for ethical, clinical practice.

Disclosure: A. F. Townsend, None; J. L. Leese, None; L. C. Li, None; M. McDonald, None; S. Kerr, None; G. Whiteside, None; C. Backman, None.

2443

**A New Meta-Analysis on Safety of Ketoprofen vs Ibuprofen and Diclofenac: Risk and Benefit of NSAIDs Beyond Efficacy Meta-Analysis.**

**P. Sarzi-Puttini,** F. Atzeni, Luigi Lanata,1 Alessandra Monguzzi,2 and Michel Bagnasco.2 1Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, 2Dompe ´ SpA, Milan, Italy.

**Background/Purpose:** Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for management of mild-to-moderate pain, chronic inflammatory and degenerative joint diseases. Among NSAIDs, ketoprofen, ibuprofen and diclofenac have been widely used for the last 30 years and particular attention should be taken into account when choosing a NSAID in order to achieve the best risk/benefit ratio for patients. Recent publication of our comparative meta-analysis demonstrating that efficacy of oral ketoprofen is greater than ibuprofen and/or diclofenac, raised many questions about safety profile of these molecules. For this reason we performed this meta-analysis of randomised controlled trials (RCTs) in order to compare the safety of orally administered ketoprofen vs ibuprofen and diclofenac and to obtain a complete comparative assessment of risk/benefit profile of these NSAIDs.

**Methods:** A systematic literature search was performed on main databases (Medline, Cochrane Central and Embase) until July 2013 to identify RCTs comparing directly therapeutic doses of oral ketoprofen (50-200 mg/day) vs ibuprofen (600-1800 mg/day) or diclofenac (75-150 mg/day). In accordance with the Cochrane Collaboration guideline, two rheumatologists carried out independently study selection.

**Results:** A total of 10 RCTs involving 826 patients met the inclusion criteria. Five of the 10 RCTs included patients with systemic rheumatic diseases. Findings from this meta-analysis did not reveal any difference in safety for ketoprofen compared to ibuprofen and/or diclofenac. The difference between ketoprofen and the pooled ibuprofen/diclofenac data was not statistically significant (risk ratio; RR=1.02, 95% CI 0.78-1.33; P=0.92) at all point-estimates of the mean weighted size effect. Further sub-analysis also confirmed that ketoprofen was not significantly different to either diclofenac (RR=0.86; 95% CI 0.51-1.45; P=0.58) or ibuprofen (RR=1.08; 95% CI 0.79-1.48; P=0.65) at all point-estimates. Heterogeneity for the safety measures analysed were not statistically significant for all meta-analyses.

**Conclusion:** Findings of this meta-analysis show that ketoprofen is well tolerated, with a safety profile at least comparable to ibuprofen and diclofenac, and no serious AEs. In light of superior efficacy demonstrated in our previous meta-analysis, these further safety results support recommendation that oral ketoprofen has the best risk/benefit profile vs ibuprofen and diclofenac.

Disclosure: P. Sarzi-Puttini, None; F. Atzeni, None; L. Lanata, Dompé SpA; A. Monguzzi, Dompé SpA; M. Bagnasco, Dompé SpA.

2444

**Pharmacist-Developed Letters May Enhance Success in Obtaining Inurer Approval for Off-Label Use of Biologics.**

Jessica F. Farrell, Lee S. Shapiro, Joel M. Kremer and Aixa Toledo-Garcia.1 The Center for Rheumatology, Albany, NY, 2Albany Medical College and the Center for Rheumatology, Albany, NY.

**Background/Purpose:** A growing number of publications suggest that biological DMARDs, predominantly approved for RA, can be efficacious treatment options for several rare rheumatic diseases. These potentially efficacious treatments are often “out of reach” because of inability to obtain insurance coverage. Insurers routinely deny coverage of “off-label use” because of the absence of double-blind placebo controlled studies demonstrating efficacy. This type of evidence is only infrequently available for these rare rheumatic diseases. The medical director for the insurer often has no familiarity with the disease, the potential consequences of non-treatment or the inadequacy of more accessible therapies. The addition of a pharmacist as part of a multidisciplinary team can provide an effective resource in successfully navigating the medication prior authorization process.

**Methods:** Our approach involves the use of a clinical pharmacist in development of comprehensive, evidence-based appeal letters. These letters are drafted by a clinical pharmacist (PharmD.) and pharmacy interns who perform extensive literature searching including all relevant case reports and clinical data related to disease state and drug therapy. The PharmD’s then summarize that data as justification for use of therapy. A appeal letters are then drafted to include an explanation of the patient’s circumstances, disease manifestations, progression, prognosis, as well as the treatment history, and the comprehensive review of current literature on the rationale for and experience with the proposed therapy.

**Results:** Since January 2009, our pharmacist has drafted and submitted approximately 141 letters. We have decreased the rate of initial “denials” for off-label use to near zero. We estimate that we have saved the physicians and support staff approximately 100 hours while achieving the desired outcome for both patients and physicians. We estimate that the average rheumatologist will have a need for between 5–15 of these letters per quarter. If we calculate the value of physician time based upon billable dollars, we would estimate a net saving for individual physicians of between $1000 and $4000 hours per quarter. Additionally, we have decreased the time associated with the approval process from an average of 4–6 weeks to less than 4 weeks.

**Conclusion:** The issuance of an evidence based approach to the off-label appeal process has decreased the time associated with approvals and prevented the need for mention of litigation or liability. Due to time constraints, the ability to provide this level of patient care would not be possible without the assistance of the clinical pharmacist. The practice of pharmacy has expanded its scope to include extensive clinical training beyond the preparation and dispensing of medication. Pharmacists have the capacity to provide a wide range of patient-oriented services. As part of their education, PharmD’s have extensive training in scientific literature evaluation and drug information. Based on our experience and success, it is clear that PharmD’s are an underutilized resource in the ambulatory care setting and can greatly improve patient-care outcomes.

Disclosure: J. F. Farrell, None; L. S. Shapiro, None; J. M. Kremer, Corrona, 1, Corrona, 4; A. Toledo-Garcia, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis - Human Etiology and Pathogenesis

Tuesday, November 18, 2014, 8:30 AM - 4:00 PM

2445

**A Distinct Profile of Circulating Microparticles Is Associated with Disease Features in Rheumatoid Arthritis Patients and Impairs Endothelial Functionality in Vitro.**

Javier Rodriguez-Carrillo, M ercedes Apero Lopez, Patricia Lopez, Sara Alonso-Castro, Santiago Rubén Carro-Esteban, Javier Ballina-Garcia and Ana Suarez.1 University of Oviedo, Oviedo, Spain, 2Rheumatology Department, Hospital Universitario Central de Asturias, Oviedo, Spain.

**Background/Purpose:** Cell-derived microparticles (MPs) could be considered biomarkers of cell damage and activation and they are thought to have a role in cardiovascular (CV) and inflammatory diseases. Since Rheumatoid Arthritis (RA) is characterized by immune and endothelial activation, the main aim of this study was to evaluate MP counts in RA patients.

**Results:** A total of 10 RCTs involving 826 patients met the inclusion criteria. Five of the 10 RCTs included patients with systemic rheumatic diseases. Findings from this meta-analysis did not reveal any difference in safety for ketoprofen compared to ibuprofen and/or diclofenac. The difference between ketoprofen and the pooled ibuprofen/diclofenac data was not statistically significant (risk ratio; RR=1.02, 95% CI 0.78-1.33; P=0.92) at all point-estimates of the mean weighted size effect. Further sub-analysis also confirmed that ketoprofen was not significantly different to either diclofenac (RR=0.86; 95% CI 0.51-1.45; P=0.58) or ibuprofen (RR=1.08; 95% CI 0.79-1.48; P=0.65) at all point-estimates. Heterogeneity for the safety measures analysed were not statistically significant for all meta-analyses.

**Conclusion:** Findings of this meta-analysis show that ketoprofen is well tolerated, with a safety profile at least comparable to ibuprofen and diclofenac, and no serious AEs. In light of superior efficacy demonstrated in our previous meta-analysis, these further safety results support recommendation that oral ketoprofen has the best risk/benefit profile vs ibuprofen and diclofenac.

Disclosure: P. Sarzi-Puttini, None; F. Atzeni, None; L. Lanata, Dompé SpA; A. Monguzzi, Dompé SpA; M. Bagnasco, Dompé SpA.

2445

**A Distinct Profile of Circulating Microparticles Is Associated with Disease Features in Rheumatoid Arthritis Patients and Impairs Endothelial Functionality in Vitro.**

Javier Rodriguez-Carrillo, M ercedes Apero Lopez, Patricia Lopez, Sara Alonso-Castro, Santiago Rubén Carro-Esteban, Javier Ballina-Garcia and Ana Suarez.1 University of Oviedo, Oviedo, Spain, 2Rheumatology Department, Hospital Universitario Central de Asturias, Oviedo, Spain.

**Background/Purpose:** Cell-derived microparticles (MPs) could be considered biomarkers of cell damage and activation and they are thought to have a role in cardiovascular (CV) and inflammatory diseases. Since Rheumatoid Arthritis (RA) is characterized by immune and endothelial activation, the main aim of this study was to evaluate MP counts in RA patients.
Methods: MPs were analyzed by flow cytometry following a total-labeling procedure in platelet-poor plasma from 33 healthy controls (HC), 72 individuals with marked CV risk (CVR; diabetes, n=24; dyslipidemia, n=27; and hypertension, n=41) and 114 RA patients (61.4% RF, 61.4% cCp, DAS28: 36.01(19.7), 42.1% erosive disease). Different subsets were identified by their surface markers: platelet (CD41+), PMs, endothelial- (CD146+), EMPs, granulocyte- (CD66+, GM Ps), monocyte- (CD14+, MfPs) and Tang-derived (CD3 CD31+, Tang- M Ps). TNFα serum levels were quantified by ELISA. In vitro assays of MPs were performed to assess the effect of MPs on endothelial functionality. Clinical and immunological parameters as well as traditional CV risk factors (diabetes, hypertension, dyslipidemia, obesity and smoking) were registered from clinical records and all data were analyzed by Principal Component Analysis (PCA).

Results: Total MPs count was increased in RA compared to both HC (p=0.0001) and CVR (p=0.0009) and was positively correlated with traditional CV risk factors (BMI, TC/HDL ratio, triglycerides and number of risk factors). Additionally, specific MPs subsets were increased in RA (EMPs p=0.0001, GMPs p=0.0001, Tang-M Ps p=0.006 and MfOMPs p=0.028). Clinical data were integrated with PCA and 4 components were identified. Notably, different MP subsets correlated with different components (Table 1), thereby involving specific disease features in MPs profile. Interestingly, TNFα correlated with Tang-M Ps in RA after adjusting by traditional risk factors (r=-0.218, p=0.036). Finally, MPs from RA patients were able to impair endothelial cell functionality (measure as tube formation and number of branching points) in vitro in a dose-dependent manner, linked to an upregulation of endothelial activation markers (CD62E, CD144 and VEGFR2). This effect appeared even within the physiological range and it was not present with HC or CVR MPs.

Conclusion: MPs analysis in RA patients revealed an increased damage in several cell types. Circulating MPs from RA patients displayed a unique quantitative and qualitative profile as the result of both disease-specific and traditional CV risk factors. These differences are independent of comorbidities. Accordingly, this MP profile could underlie the detrimental effects on the endothelial cells in vitro, thus supporting their role as biomarkers of endothelial damage and vascular repair failure.

Table 1: PCA components

<table>
<thead>
<tr>
<th>Total MPs</th>
<th>Rheumatic-related</th>
<th>Traditional CV-related</th>
<th>Duration-related</th>
<th>Inflammation-related</th>
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<td>0.065</td>
<td>0.022</td>
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<td>0.345</td>
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<tr>
<td>0.018</td>
<td>0.078</td>
<td>0.096</td>
<td>0.050</td>
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<tr>
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<td>0.017</td>
<td>0.302</td>
<td>0.091</td>
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<tr>
<td>0.894</td>
<td>0.884</td>
<td>0.005**</td>
<td>0.446</td>
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Disclosures: J. Rodriguez-Carrio, None; M. Alperi-Lopez, None; P. Lopez, None; S. Alonso-Castro, None; R. Carro-Esteban, None; J. Ballina-Garcia, None; A. Suarez, None.

2446

DNA Methylation Profiles That Distinguish Rheumatoid Arthritis from Osteoarthritis in Fibroblast-like Synoviocytes Can Be Detected in Immune Cells from Peripheral Blood

Brooke Rhed1, Calliope Holingue2, Michael Cole3, Xiaorang Shao4, Hong L. Quach, Diana Quach, Lisa F. Barcelos5 and Lindsey A. Criswell6. 1University of California, Berkeley; Berkeley, CA; 2University of California, San Francisco; 3Rosalind Russell/Ephrime P. Englemann Rheumatology Research Center, San Francisco, CA.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease with potential to cause substantial disability, primarily due to the erosive and deforming process in joints. RA etiology is complex, with several cell types. Circulating MPs from RA patients displayed a unique quantitative and qualitative profile as the result of both disease-specific and traditional CV risk factors. These differences are independent of comorbidities. Accordingly, this MP profile could underlie the detrimental effects on the endothelial cells in vitro, thus supporting their role as biomarkers of endothelial damage and vascular repair failure.
Mature miR-196a originates from 2 regions in human genome: MIR-196A-1 (chromosome 17) and MIR-196A-2 (chromosome 12) both located in HOX-gene clusters. The altered expression of miR-196a has been reported in multiple conditions, such as cancer. Our aim is to analyze the expression and regulation of miR-196a in cells from patients with rheumatoid arthritis.

**Background/Purpose:** Follicular helper T (Tfh) cells have been identified as a new subset of effector helper T cells that are essential in regulating the development of antigen-specific B-cell immunity. Tfh differentiation is regulated by specific transcription factor Bcl-6. Several studies have certified the vital role of Tfh cells in the pathogenesis of autoimmune diseases. MicroRNAs (miRNAs) could negatively regulate gene expression post-transcriptionally and participate in the development of autoimmunity. The purpose of this study is to investigate the function of miR-346 in enhancement of Tfh cells during the pathogenesis of RA.

**Methods:** We detected the proportion of Tfh cells, concentration of IL-21, relative expression of Bcl-6 and IL-21 mRNA as well as miR-346 in RA patients and healthy donors. A Luciferase reporter assay was undertaken for directly proves that Bcl-6 is the functional target of miR-346. The level of Bcl-6 protein in Jurkat cells which were transfected with the miR-346 mimics was detected. Percentage of CD4⁺CXCR5⁺ T cells in circulating CD4⁺ T cells from healthy donor transfected with miR-346 mimics was examined. Analysis of 485,000 methylation sites per sample. It covers the promoters, 5'-UTR, 3'-UTR, gene body, first exon of 99% RefSeq genes and 96% of CpG islands. A strict quality control analyses we calculated the differential methylated regions using the COHatch bioinformatics package in R (version 3.0.1). The results obtained by array analyses were validated for a selected number of probe sequences by pyrosequencing.

**Results:** The bioinformatics analysis between healthy and RA LNSC revealed 557 significantly differential methylated CpG sites (delta \( \beta \)-value >0.25, \( p \leq 0.05 \). We found 57% of the differentially methylated CpG sites to be hypomethylated and 43% hypermethylated. 374 genes were found to be associated with the differential methylated sites. Functional annotation clustering was performed using the hypermethylated (167 genes) and hypomethylated (207) genes. For the hypermethylated genes, the highest enrichment was observed for genes associated with cell adhesion and cell death pathways. For the hypomethylated genes, pathways associated with cell adhesion, cell projection, regulation of cell growth and cell motion were significantly differentially methylated. Next, we analysed for specific genes with differentially methylated CpG islands. Interestingly, we identified the hypermethylated genes CXCL4 (\( \beta \)-value =0.46 - healthy \( \beta \)-value =0.20, \( p=0.008 \)) and Lactotransferrin (\( \beta \)-value =0.52 - healthy \( \beta \)-value =0.25 \( p=0.016 \)) that have previously associated with RA. In addition, other gene targets were found to be strongly hypomethylated such as TNNT1 (\( \beta \)-value =0.13 - healthy \( \beta \)-value =0.40, \( p=0.016 \)) and KCNE1 (\( \beta \)-value =0.09-healthy \( \beta \)-value =0.35, \( p=0.010 \)).

**Conclusion:** This is the first study reporting epigenetic modifications in LNSC of RA patients. Specifically, DNA methylation analysis identified interesting known and novel gene targets altered in the LNSC of RA patients.

**Disclosures:** K. Nakano, None; K. Yamaoaka, None; A. Kurozumi, None; A. K. Kawabe, None; K. Yamagata, None; Y. Tanaka, None.

**2448**

**DNA Methylation Analysis of Lymph Node Stromal Cells of Rheumatoid Arthritis Patients.** Emmanuel Karoniakiz, Caroline Ospe; J. Anne Hähnlein, Renate E. Gay1, Paul Peter Tak, Danielle Marie Garlag, Michel Neidhart, Steffen Gay2 and Lisa G.M. van Baaren2.

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**Background/Purpose:** Lymph node stromal cells (LNSC) build the scaffold that enables migration and interaction of lymphocytes in the lymph node. More recently, it has been shown that during inflammation LNSC play a crucial role in shaping the immune response and maintaining tolerance. Since DNA methylation changes have been reported in autoimmune diseases, we analysed the DNA methylation profile of LNSC from healthy individuals and rheumatoid arthritis (RA) patients.

**Methods:** Needle biopsies of inguinal lymph nodes were strained through a 70µm nylon mesh and the resulting stromal part was cultured in DMEM with 10% FCS. A heterocells were passaged 4 times before total genomic DNA was isolated. DNA samples (healthy n = 4 and RA n = 5) were subjected to the Illumina HumanMethylation 450 array, which allows the analysis of 485,000 methylation sites per sample. It covers the promoters, 5'-UTR, 3'-UTR, gene body, first exon of 99% RefSeq genes and 96% of CpG islands. A strict quality control analyses we calculated the differential methylated regions using the COHatch bioinformatics package in R (version 3.0.1). The results obtained by array analyses were validated for a selected number of probe sequences by pyrosequencing.

**Results:** The bioinformatics analysis between healthy and RA LNSC revealed 557 significantly differential methylated CpG sites (delta \( \beta \)-value >0.25, \( p \leq 0.05 \). We found 57% of the differentially methylated CpG sites to be hypomethylated and 43% hypermethylated. 374 genes were found to be associated with the differential methylated sites. Functional annotation clustering was performed using the hypermethylated (167 genes) and hypomethylated (207) genes. For the hypermethylated genes, the highest enrichment was observed for genes associated with cell adhesion and cell death pathways. For the hypomethylated genes, pathways associated with cell adhesion, cell projection, regulation of cell growth and cell motion were significantly differentially methylated. Next, we analysed for specific genes with differentially methylated CpG islands. Interestingly, we identified the hypermethylated genes CXCL4 (\( \beta \)-value =0.46 - healthy \( \beta \)-value =0.20, \( p=0.008 \)) and Lactotransferrin (\( \beta \)-value =0.52 - healthy \( \beta \)-value =0.25 \( p=0.016 \)) that have previously associated with RA. In addition, other gene targets were found to be strongly hypomethylated such as TNNT1 (\( \beta \)-value =0.13 - healthy \( \beta \)-value =0.40, \( p=0.016 \)) and KCNE1 (\( \beta \)-value =0.09-healthy \( \beta \)-value =0.35, \( p=0.010 \)).

**Conclusion:** This is the first study reporting epigenetic modifications in LNSC of RA patients. Specifically, DNA methylation analysis identified interesting known and novel gene targets altered in the LNSC of RA patients.

**Disclosures:** E. Karoniakiz, None; C. Ospe; J. Anne Hähnlein, None; R. E. Gay, None; P. P. Tak, GSK; D. M. Garlag, GSK; M. Neidhart; None; S. Gay; None; L. G. M. van Baaren, None.

**2449**

**MicroRNA-346 Regulation of Follicular Helper T Cells Is Involved in the Pathogenesis of Rheumatoid Arthritis Disease.** Xinyi Tang, Jie Ma and Shengjun Wang.

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**Background/Purpose:** Downregulation of MiRNA-196a and Its Downstream HOXC8 Target Gene in Rheumatoid Arthritis Synovial Fibroblasts. Maria Filkova, Monika Trendkamm, Borbala Aradi-Vegh, Renata Gay, Steffen Gay and Astrid Juenge.

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**Background/Purpose:** Comprehensive analysis of 260 miRNAs suggested a downregulation of miR-196a in rheumatoid arthritis (RA) synovial fibroblasts (SF) compared with osteoarthritis (OA) SF. Mature miR-196a originates from 2 regions in human genome: MIR-196A-1 (chromosome 17) and MIR-196A-2 (chromosome 12) both located in HOX-gene clusters. The altered expression of miR-196a has been reported in multiple conditions, such as cancer. Our aim is to analyze the expression and regulation of miR-196a in cells from patients with RA.

**Methods:** Expression of pri-miRNA precursor and mature miR-196a was analyzed in RA/OA synovial tissue, SF under proinflammatory and hypoxic conditions, peripheral blood mononuclear cells (PBMC), synovial fluids and sera using TaqMan RealTime-PCR. Chromatin immunoprecipitation (ChIP) was used to analyze histone methylation and acetylation within both promoters of MIR-196A-1 and MIR-196A-2 in SF. Illumina sequencing with subsequent single assay verification was performed following Lipofectamine transfection with pre-miR-196a or anti-miR-196a to identify miR-196a targets genes.

**Disclosures:** X. Tang, None; J. Ma, None; S. Wang, None.

**2450**

**MicroRNA-346 Regulation of Follicular Helper T Cells Is Involved in the Pathogenesis of Rheumatoid Arthritis Disease.** Xinyi Tang, Jie Ma and Shengjun Wang.

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**MicroRNA-346 Regulation of Follicular Helper T Cells Is Involved in the Pathogenesis of Rheumatoid Arthritis Disease.** Xinyi Tang, Jie Ma and Shengjun Wang.
Results: Expression of miR-196a is significantly lower in RA synovial tissues (n=6) compared with OA (n=4, p=0.01) as well as RASF (n=19) compared with OA SF (n=15, p<0.0001). No difference was observed in PBMC or synovial fluids while a lack of cell-free miR-196a was detected in RA and OA sera. The precursor pri-miR-196a 1A was expressed neither in RA nor OA SF while pri-miR-196a 2 was significantly downregulated in RASF vs. OA SF (n=4 each, p<0.05). Expression of miR-196a in SF was not affected by proinflammatory cytokines (TNFα, IL-1β), TLR ligands (LPS), 1% hypoxia or S'AZA mediated HOXC8 demethylation. CHIP of miR-196a 2 promoter revealed significantly higher methylation of repressive H3K27me3 (p=0.005), lower methylation of activating H3K4me3 (p=0.001), and hypoacetylation of H3 (p=0.008) in RASF (n=13) compared to OA SF (n=10) explaining the downregulation of the mature miR-196a in RASF. Using Illumina sequencing after pre-miR transfection of RASF (n=2) HOXC8 and HOXA7 were identified as most likely direct miR-196a targets. Downregulation HOXC8 (p=0.01) as well as HOXA7 (p=0.006) and pre-miR mRNA transcription (n=5), and upregulation of HOXC8 (p=0.11) and HOXA7 (p=0.56) and upon anti-miR-196a transcription (n=5) suggest these HOX genes as direct targets. However, unexpectedly, significant downregulation of HOXC8 was observed in RASF (n=17) vs. OA SF (n=18, p=0.004) while the expression HOXA7 was not significantly different between RASF and OA SF (p=0.91).

Conclusion: MiR-196a is one of the few miRNA showing a significant downregulation in resident cells of synovial tissue in RA patients regulated by histone modifications. Although HOXC8 and HOXA7 are suggestive of being direct targets of miR-196a, their distinctive role in unique RASF behavior remains to be investigated. Given low expression of miR-196a in RASF and location within HOX cluster, we hypothesize that expression of HOXC8, except regulation by miR-196a, may be influenced by additional epigenetic features similar to those regulating miR-196a.


2451
MiR-155 Expression Correlates with Clinical Disease Activity and Has Effect Factor Function in Rheumatoid Arthritis. Aiza Elmesmari, Derek G. Gilchrist, M. Mariola Kurowska-Stolarska and Ian B. M. Cliness. 1. Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Science, University of Glasgow, Glasgow, United Kingdom, 2. University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: MicroRNAs are fine tuners of biological pathways that function via post-transcriptional regulation of target mRNA life span. MicroRNA 155 (miR155) is particularly implicated in Rheumatoid Arthritis (RA) pathology through regulation of synovial macrophage cytokine and chemokine production. Thus far miR155 expression across disease activity status has not been examined - to this end we have developed a novel assay of absolute copy number to facilitate such investigation.

Methods: Peripheral blood (PB) was obtained from healthy controls and RA patients who met the 2010 ACR/EULAR diagnostic criteria. CD14+ cells (monocytes) were isolated using micro-beads. The absolute copy numbers of miR-155 transcripts and housekeeping short RNA (U1) in peripheral blood (PB) and synovial fluid (SF) macrophages of RA and healthy controls were assessed using a novel qPCR methodology.

Results: RA PB (n=24) and SF CD14+ monocytes (n=11) expressed higher copy numbers of miR-155 compared with healthy controls (n=22). As expected, RA SF macrophages exhibited the highest expression levels of miR-155 (75318.2±106 copies of RNU1A). In PB monocytes, miR-155 levels were higher when derived from patients with high or moderate disease activity (according to DAS28; p<0.05) than those in remission or healthy controls. The copy number of miR-155 expression was significantly increased in anti-citrullinated protein antibody (ACPA) positive RA (n=17) compared with ACPA negative RA (n=7). The RA PB monocyte miR-155 copy number correlated positively and significantly with DAS28 as a continual variable. There was no correlation between observed increase in miR-155 copy number and patients’ age, disease duration or medication.

Conclusion: Our data demonstrate that miR-155 levels may reflect RA disease activity and could be a potential clinical disease activity biomarker for RA. Moreover our data suggest that circulating monocytes in RA patients exhibit an early activation signature, which is primed for subsequent cytokine release.

Disclosure: A. Elmesmari, None; D. G. Gilchrist, None; M. Kurowska-Stolarska, None; J. B. M. Cliness, None.

2452
Protective Effect of the IL33 rs3939286 Gene Polymorphism in the Development of Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis. Raquel López-Mejías, Fernanda Genre, Mercedes García-Bermúdez, Alfonso Corrales, Carlos González-Juanatey, Beoguna Ubilla, J. Llorca, Encarnación Amigo, Jose A. Miranda-Filloy, Tritonía Pina Murcia, Ricardo Blanco, Santos Castañeda, Javier Martín and Miguel A González-Gay. 1. Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDI-VAL, Santander, Spain, 2. Instituto de Parásitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, 3. Hospital Universitario Lusitaniae Augusti. Cardiology Division, Lugo, Spain, 4. Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, 5. Department of Immunology, Rheumatology and Allergy (CIBERESP), IDIVAL, Santander, Spain, 6. Hospital Universitario Lusitaniae Augusti, Rheumatology Division, Lugo, Spain, 7. Division of Rheumatology, Hospital Lusitaniae Augusti, Lugo, Spain, 8. Hospital Maria de Valdecilla, Santander, Spain, 9. Hospital Universitario La Princesa, IISP, Madrid, Spain, 10. Instituto de Parásitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a complex inflammatory disease characterized by chronic inflammation, accelerated atherosclerosis and increased cardiovascular (CV) mortality. Interleukin33 (IL-33) is a cytokine with a pathogenic role in some autoimmune diseases and a potential protective effect on atherosclerosis. Recently, an association between the IL33 rs3939286 polymorphism and inflammatory bowel disease (a well-characterized chronic inflammatory disease) has been described in Caucasian individuals. In the present study, we aimed to establish for the first time whether this gene polymorphism influences the development of subclinical atherosclerosis in patients for RA.

Methods: 567 patients with RA from Northern Spain without a previous history of CV events were assessed by carotid ultrasonography (US) to determine the carotid intima-media wall thickness (cIMT). Also, the IL33 rs3939286 polymorphism was genotyped in these patients by TaqMan single nucleotide polymorphism (SNP) genotyping assays in a 7900 HT real-time polymerase chain reaction system.

Results: Patients with RA carrying the TT genotype had lower cIMT values than those homozygous for the CC genotype (mean ± standard deviation [SD]: 0.71 ± 0.14 mm in TT versus 0.76 ± 0.14 mm in CC carriers). Moreover, patients carrying the CT genotype had intermediate cIMT values (mean ± SD: 0.73 ± 0.17 mm). In keeping with these observations, patients with RA carrying the mutant allele T exhibited significantly lower cIMT values than those carrying the wild allele C (mean ± SD: 0.72 ± 0.16 mm versus 0.75 ± 0.18 mm, respectively; p=0.04). The association of allele T with lower values of cIMT in patients with RA remained statistically significant after adjusting the results for sex, age at the time of the carotid US study, follow-up time and traditional CV risk factors (p=0.02).

Conclusion: Our results indicate a protective effect of the IL33 rs3939286 gene polymorphism in the susceptibility to subclinical atherosclerosis in patients with RA.

This study was supported by European Unión FEDER funds and “Fondo de Investigación Sanitaria” (grants P106/0024, P059/00748 and P112/00060) from “Instituto de Salud Carlos III” (ISCIII, Health Ministry, Spain). We was also partially supported by RETIC Programs RD12/0009 (RIER) from “Instituto de Salud Carlos III” (ISCIII, Health Ministry, Spain), and in part by grants from the European IMI BTCure Program. RLM is a recipient of a Sara Borrell postdoctoral fellowship from the “Instituto Carlos III de Salud” at the Spanish Ministry of Health (Spain) (CD12/00425). FG and BU are supported by funds from the RETICs Program (RIER) (RD12/0009/0013).

Disclosure: R. López-Mejías, None; F. Genre, None; M. Garcia-Bermudez, None; A. Corrales, None; C. Gonzalez-Juanatey, None; B. Ubilla, None; J. Llorca, None; E. Amigo, None; J. A. Miranda-Filloy, None; T. Pina Murcia, None; R. Blanco, None; S. Castañeda, None; J. Martín, None; M. A. González-Gay, None.

2453
Genetic Influence on Rheumatoid Arthritis in African-Americans

Methods: Using the ImmunoChip custom array, which contains 196,525 single nucleotide polymorphisms (SNPs) from 186 autoimmune disease associated loci, all 621 African Americans (AA) with RA and 933 African American healthy controls were genotyped. After quality control procedures (related samples, sex inconsistency, marker call rate >98.5% and sample call rate >90%), 102,686 SNPs with minor allele frequency (MAF) greater than 5% were available for analysis in 601 cases and 830 controls. Set-based association analysis using the sequence kernel association test (SKAT) was also performed in the autoantibody-positive and the autoantibody-negative subsets. Fine mapping of loci identified from the Caucasian RA Immunochip study was performed by association testing all markers +/- 500kB conditionally on the top Caucasian SNP for each RA locus.

Results: Among the 601 cases, 479 (80%) individuals were autoantibody-positive. In the single marker association adjusted for global LD across the entire genome, 6.5% were available for analysis in 601 cases and 830 controls. Set-based association analysis using the sequence kernel association test (SKAT) was also performed in the autoantibody-positive and the autoantibody-negative subsets. Fine mapping of loci identified from the Caucasian RA Immunochip study was performed by association testing all markers +/- 500kB conditionally on the top Caucasian SNP for each RA locus.

Conclusion: This present study provides further evidence to support the importance of MHC region in African-Americans with RA.

Disclosure: M. I. Danila, NIAIM-S-NIH, 2; R. Reynolds, NIAIM-S-NIH, 2; Q. Yan, None; N. Liu, None; P. K. Gregersen, None; C. Investigators, None; D. K. Arnett, None; S. L. Bridges Jr., None.

2454

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2455

IL-6 Proximal Promoter SNP rs18000795 G variant Strongly Correlates with Synovial Fibroblast IL-6 Expression.

Methods: Human synovial fibroblasts were derived from discarded surgical specimens by serial passage from ten RA or osteoarthritis (OA) donors. Human CD14+ monocytes were isolated from healthy donor peripheral blood mononuclear cells by magnetic bead positive selection. IL-6 was measured in cell culture media by ELISA. IL-6 mRNA expression was measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR). IL-6 transcript stability was determined by measuring IL-6 mRNA decay after actinomycin D inhibition of transcription. Cell genotype at the IL-6 proximal promoter single nucleotide polymorphism (SNP) rs18000795 (otherwise known as IL-6-174 G/C) was determined by restriction fragment length polymorphism analysis.

Results: Human synovial fibroblast lines reproducibly segregated into low, medium, and high IL-6 producers after tumor necrosis factor-alpha (TNF-alpha) stimulation, independent of cell passage and disease state. The IL-6 expression pattern after TNF-alpha stimulation correlated significantly with the expression pattern observed in unstimulated cells or cells stimulated with IL-1 or lipopolysaccharide (LPS), indicating that this pattern was not secondary to differences in TNF-alpha signaling pathways. The IL-6 expression pattern also correlated strongly with total mRNA expression, but not with differences in IL-6 mRNA stability, suggesting it was driven by transcriptional rather than post-transcriptional mechanisms. Given that the IL-6 promoter SNP rs18000795 has been associated with diverse effects on IL-6 levels and disease expression in many systems, we analyzed synovial fibroblast IL-6 production as a function of rs18000795 genotype. We found that high IL-6 expression was significantly associated with the homozygous minor allele (CC) genotype. We then tested if a similar genotype effect was seen in stimulated CD14+ monocytes, since macrophage lineage cells are another major IL-6 producer in the RA synovium. We found, in contrast to synovial fibroblasts, that the rs18000795 genotype had a modest and opposite effect on CD14+ monocyte IL-6 expression, with a trend toward higher production in the major allele (GG) homozygotes.

Conclusion: This study reports that synovial fibroblast IL-6 expression is significantly influenced by genetic differences in linkage with the IL-6 proximal promoter SNP, rs18000795. In contrast, little association between

**Methods:** A total of 1,359 patients were genotyped for three TLR4 SNPs (rs1927911, rs11536878, and rs4986790), which were selected using a haplotype tagging strategy. Measures of disease severity included the Disease Activity Score-28 (DAS28), Multidimensional Health Assessment Questionnaire (MD-HAQ), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI). A associations of TLR4 SNPs with these measures were examined longitudinally (mean of 10 visits, range 0–60) using generalized estimating equations in both univariate and multivariate analyses, adjusting for age, sex, race, comorbidity, body mass index, smoking, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-CCP positivity, methotrexate and anti-tumor necrosis factor use. Based on existing data showing that anti-citrullinated protein antibody (ACPA)-containing immune complexes may drive TLR4 signaling in RA, analyses were also stratified by ACPA positivity including antibody positivity to anti-CCP and anti-citrullinated fibrinogen (c-fib) antibody.

**Results:** RA patients homozygous for the minor allele of TLR4 rs1927911 demonstrated lower disease activity over follow-up including lower DAS28 (p<0.001), CDAI (p=0.002), and SDAI (p=0.010) in univariate analysis and lower DAS28 (p<0.001) and CDAI (p=0.007) in multivariate analysis (Table). Disease activity among those homozygous for the minor allele tended to be numerically lower in groups with elevated anti-CCP and anti-c-fib antibody though no significant differences by ACPA status were identified. There were no associations of TLR4 rs11536878 and rs4986790 with any of the RA disease activity measures.

**Conclusion:** We found TLR4 rs1927911 genotypes are associated with the rate of disease progression over time independent of other factors. Although further studies are needed to identify mechanisms by which variation in rs1927911 impacts inflammatory burden, these data are consistent with reports in other disease states suggesting that this SNP is associated with a meaningful anti-inflammatory effect and support the concept of TLR4 as a potential therapeutic target in RA.

**Table:** Associations of TLR-4 rs1927911 genotype with RA disease progression (DAS28, HAQ, CDAI, and SDAI differences per year of follow up); p-values < 0.0167 (Bonferroni correction) considered to be statistically significant.

<table>
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<th>Genotype</th>
<th>Multivariate Analysis</th>
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**Disclosure:** E. Noss, None; S. K. Chang, None; G. Watts, None; M. Brenner, None.

**Background/Purpose:** Toll-like receptor (TLR)-4 signaling pathways have been implicated in both the innate and adaptive immune responses that characterize rheumatoid arthritis (RA). In this study, we examined the associations between TLR-4 single nucleotide polymorphisms (SNPs) and RA using a large well-characterized RA cohort.

**Methods:** A total of 1,359 patients were genotyped for three TLR4 SNPs (rs1927911, rs11536878, and rs4986790), which were selected using a haplotype tagging strategy. Measures of disease severity included the Disease Activity Score-28 (DAS28), Multidimensional Health Assessment Questionnaire (MD-HAQ), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI). Associations of TLR4 SNPs with these measures were examined longitudinally (mean of 10 visits, range 0–60) using generalized estimating equations in both univariate and multivariate analyses, adjusting for age, sex, race, comorbidity, body mass index, smoking, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-CCP positivity, methotrexate and anti-tumor necrosis factor use. Based on existing data showing that anti-citrullinated protein antibody (ACPA)-containing immune complexes may drive TLR4 signaling in RA, analyses were also stratified by ACPA positivity including antibody positivity to anti-CCP and anti-citrullinated fibrinogen (c-fib) antibody.

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**Conclusion:** We found TLR4 rs1927911 genotypes are associated with the rate of disease progression over time independent of other factors. Although further studies are needed to identify mechanisms by which variation in rs1927911 impacts inflammatory burden, these data are consistent with reports in other disease states suggesting that this SNP is associated with a meaningful anti-inflammatory effect and support the concept of TLR4 as a potential therapeutic target in RA.
treatment. Although the targets of these three treatments are specific, the downstream biological activities seem to be wide. In order to investigate whether the effect of these treatments share common biological process or are disparate, we conducted transcriptome analysis with using next-generation sequencing.

**Methods:** The study includes a total of 30 RA patients treated by these three medications (TOF 6–20mg/d:15, FOS 100–200mg/d:4, TCZ 8mg/kg/4w:11). Peripheral blood was drawn at just before (pre) and 3 months after (post) these treatments. Total RNAs were then extracted with using PAXgene mRNA kit. After constructing single-stranded, strand-specific libraries (length 50bp), multiplex sequencing was done. After quantifying the expressions of transcripts, hierarchical clustering analysis was performed. And then, differentially expressed genes (DEGs) were selected by paired comparison (post vs. pre), setting thresholds at 2-fold change up/down and less than $p=0.05$ in corrected paired T-test.

**Results:** In total, 575,117 genes/transcripts including 976 newly predicted genes were quantified. By a hierarchical clustering analysis, the pre and the post of FOS or TOF treatment were segregated each other while those of TCZ treatment were nearest neighbors, indicating that TCZ has the least influence over the transcriptome. The 118, 344 and 121 genes were selected as DEGs from the comparison of post vs. pre treatment of TOF, FOS or TCZ, respectively. Disparate gene ontology (GO) terms were enriched in each group. Terms relevant to "JAK-STAT cascade", "cellular adhesion", and "extracellular matrix" were enriched in the down-regulated genes in the TOF group. Of 344 DEGs from the FOS group, 30 were related to "ribosomal proteins" and 29 of them were up-regulated. In the TCZ group, terms related to "extracellular matrix", "cell adhesion molecule", "cellular adhesion molecule", and "transcription factor binding" were enriched in the down-regulated genes in the FOS group. Of 121 DEGs from the TCZ group, 38 were related to "ribosomal proteins" and 29 of them were up-regulated. In the TCZ group, terms related to "cell adhesion molecule", "cellular adhesion molecule", and "transcription factor binding" were enriched in the down-regulated genes in the TCZ group.

**Conclusion:** Although some of downstream biological cascade for JAK, SYK and STAT3-related pathways were involved over the transcriptome in the peripheral blood seems to be disparate. The hierarchical clustering shows TCZ treatment has the least influence on transcriptome. On the other hand, it is noteworthy that FOS treatment seems to have much greater influence upon transcriptome as compare with others. Enrichment analysis using GO terms indicated that different biological processes were involved in the effect of each treatment.

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### 2459

**Osteoprotegerin CGA Haplotypes Protection Against Cerebrovascular Complications in Anti-CCP Negative Patients with Rheumatoid Arthritis.** Fernanda Genre1, Raquel López-Meijas1, Mercedes García-Bermúdez2, Santos Castración3, Carlos González-Juanatey4, Javier Lorca1, Alfonso Corrales5, Beatrice Gómez-Vaquero6, Trinitario Pina Murcia7, Carmen Gómez-Vaquero7, Luis Rodríguez-Rodríguez8, Benjamín Fernández Gutiérrez9, Alejandro Balsa10, Dora Pascual-Salcedo11, Francisco Javier López-Longo12, Patricia Carreñí13, Ricardo Blanco14, Isidoro González-Alvaro15, Javier Martín15 and Miguel A González-Gay16.

**Background/Purpose:** Cardiovascular disease in non-ACR anti-CCP negative individuals improves outcomes but is challenging, particularly amongst anti-citrullinated peptide (anti-CCP) negative individuals. Previously we identified four osteoprotegerin (OPG) gene variants (rs3134063, rs2073618 and rs3134069) associated with cardiovascular disease in a large and well-characterized cohort of Spanish patients with rheumatoid arthritis.

**Methods:** Three OPG gene variants (rs3134063, rs2073618 and rs3134069) were genotyped by TaqMan assays in 2,027 Spanish patients with rheumatoid arthritis. All the patients fulfilled the 1987 American College of Rheumatology (ACR) and also the 2010 classification criteria for RA. Anti-cyclic citrullinated peptide (anti-CCP) antibody testing was positive in 97 of the 1,714 tested. Also, 18.3% of the whole series had experienced cardiovascular events, including 5.4% with cerebrovascular accidents. The relationship between OPG variants and cardiovascular events was assessed using Cox regression.

**Results:** No association between OPG gene variants and cardiovascular disease was observed in the whole group of rheumatoid arthritis patients or in anti-CCP positive patients. Nevertheless, a protective effect of OPG haplotype on the risk of cardiovascular disease in general, and specifically in the risk of cerebrovascular complications after adjusting for sex, age at diagnosis and traditional cardiovascular risk factors was observed in anti-CCP negative patients, (HR = 0.54; 95% CI: 0.31–0.95; p = 0.032 and HR = 0.17; 95% CI: 0.04–0.78; p = 0.022, respectively). These results were in accordance with a reduced risk of developing cerebrovascular complications observed in those anti-CCP negative patients who carried the OPG rs2073618 GG genotype after adjusting for potential confounder factors (HR = 0.17; 95% CI: 0.03–0.89; p = 0.035).

**Conclusion:** Our results indicate a protective effect of the OPG CGA haplotype on cardiovascular risk, mainly due to a protective effect against cerebrovascular events in anti-CCP negative rheumatoid arthritis patients.

**Disclosure:** F. Genre, None; R. López-Meijas, None; M. García-Bermúdez, None; S. Castrón, None; C. González-Juanatey, None; J. Lorca, None; A. Corrales, None; B. Uribilí, None; A. Miranda-Filloy, None; E. Amigo, None; T. Pina Murcia, None; C. Gómez-Vaquero, None; L. Rodríguez-Rodríguez, None; F. Fernández Gutiérrez, None; A. Balsa, None; D. Pascual-Salcedo, None; F. López-Longo, None; P. Carreñí, None; R. Blanco, None; I. González-Alvaro, None; M. Agudo, None; M. A. González-Gay, None.

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**Background/Purpose:** Early diagnosis of rheumatoid arthritis (RA) improves outcomes but is challenging, particularly amongst anti-citrullinated peptide auto-antibody (ACPA) negative individuals. Previously we identified an IL-6 mediated CD4+ T cell transcriptional signature, enriched for signal transduction and activation of transcription-3 (STAT3) target genes, which had discriminatory value for this purpose. In the present work we sought a more readily applicable diagnostic assay, and insight into mechanisms of disease induction.

**Methods:** Amongst early arthritis patients and controls naïve to immunomodulatory treatment, constitutive and IL-6-induced expression of phospho-STAT1 and 3 (STAT3) were determined in circulating lymphocytes using flow cytometry. Contemporaneous serum cytokine levels were measured using a validated, highly sensitive immuno-assay, and normalised CD4+ T cell gene expression of the previously described STAT3 target gene-enriched signature was determined using microarray.
Results: In 187 early arthritis patients, constitutive pSTAt3 correlated with serum IL-6 levels maximally in CD4+ T cells, compared with other circulating leukocyte subsets. Increased constitutive pSTAt3, but not pSTAt1, was observed in circulating CD4+ T cells of early ACPA negative RA patients compared with disease controls. Amongst patients presenting with undifferentiated arthritis (UA) the ratio of constitutive pSTAt3:pSTAt1 in CD4+ T cells could be incorporated into an algorithm for predicting progression to classifiable RA with high accuracy (area under ROC curve = 0.91; p<0.001). The comparable utility of the previously described CD4+ T cell gene signature as a discriminatory tool, and the accuracy of pSTAt3: pSTAt1 as a surrogate for target gene expression, are the subject of on-going analyses.

Conclusion: Our findings support a particular role for IL-6-driven CD4+ T cell activation via STAt3 during the induction of RA, which may be of particular importance in the pathogenesis of ACPA-negative disease. CD4+ pSTAt measurements show promise as biomarkers of progression to RA in sero-negative UA.

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Background/Purpose: We determined whether osteoprotegerin (OPG) concentrations are associated with established cardiovascular disease (CVD) amongst patients with rheumatoid arthritis (RA).

Methods: OPG concentrations were measured by an enzyme-linked immunosorbent assay in 181 (54 with CVD) RA patients and 62 age and sex matched control subjects without CVD. Concentrations of the endothelial activation marker angiopoietin 2 were also evaluated in a subgroup of 85 RA participants.

Results: In RA patients, age, body mass index (BMI), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, and joint erosion status were associated with OPG concentrations (partial R = 0.175 (0.03), -0.277 (0.009), 0.323 (<0.0001), 0.217 (0.008) and 0.159 (0.05)), respectively. Median (interquartile range) OPG concentrations increased from 6.38 (3.46–9.31) to 7.07 (5.04–10.65) and 8.64 (6.00–11.52) pmol/l in controls and RA patients without and with CVD, respectively (p=0.0002). Upon adjustment for age, sex, traditional risk factors and BMI in mixed regression models, OPG concentrations remained lower in controls compared to RA patients without CVD (p=0.05) and in the latter compared to those with CVD (p=0.03); the association of OPG concentrations with CVD amongst RA patients also persisted after additional adjustment for RF and anti-CCP antibody positivity, and erosion status (p=0.04). OPG concentrations related independently to those of angiopoietin 2 in RA patients with but not without CVD (partial R = 0.345 (0.003) and 0.076 (0.6)).

Conclusion: OPG concentrations are associated with disease severity and CVD prevalence in RA patients. Whether consideration of OPG concentrations can improve CVD risk stratification in RA merits future longitudinal investigation.

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Centrosomal Protein 70kDa is Down-Regulated By Decoy Receptor 3 in Specifically Rheumatoid Synovial Fibroblasts. Koji Fukuda1, Yasushi Miura2, Toshihisa Maeda3, Shinya Hayashi4 and Masahiro Kurosaka5.

1Kakogawa City Hospital, Kakogawa, Japan, 2Kobe University Graduate School of Medicine, Kobe, Japan.

Background/Purpose: Decoy receptor 3 (DcR3) is a secreted decoy tumor necrosis factor receptor and competitively binds and inhibits the TNF family including Fas-ligand, LIGHT, and TL1A. DcR3 is overexpressed in tumor cells and might benefit tumors by helping them to avoid cytotoxic and regulatory effects of the ligands. We previously reported that DcR3 overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated by TNFα protects the cells from Fas-induced apoptosis [1]. We recently reported that DcR3 binds to TL1A expressing on RA-FLS resulting in the negative regulation of cell proliferation induced by inflammatory cytokines [2]. Further, we newly revealed the gene expression profiles in RA-FLS regulated by DcR3 by using microarray data analysis. The profiles indicated centrosomal protein 70kDa (Cep70) was down-regulated by DcR3 (fold change 1.87) [3]. Centrosome forms the backbone of cell cycle progression mechanism. Further, CEP family protein is the active component of centrosome and plays a vital role in centriole biogenesis and cell cycle progression control [4]. In this study, we studied Cep70 as one of the key molecules in DcR3-TL1A signaling in RA-FLS based on the gene expression profiles regulated by DcR3.

Methods: Real-time polymerase chain reaction (real-time PCR): RA and osteoarthritis (OA) -FLS were stimulated with 1ng/ml of recombinant human TNFα or IgG1 for 24 hours, or with various concentration of DcR3-Fc or control IgG1 for 12 hours. Further, RA-FLS were incubated with DcR3-Fc for 12 hours after overnight pre-incubation with anti-TL1A antibody. The relative expression levels of Cep70 mRNA were quantified by real-time PCR.

Immunohistochemistry: Anti-Cep70 antibody was applied to frozen sections of synovial tissues from patients with RA or OA for over night. Sections were stained with Histofine simple stain KIt and DAB chromogen, followed by counterstaining with hematoxylin.

Results: Real-time PCR revealed that the expression of Cep70 mRNA in RA-FLS was higher than that in OA-FLS and that TNFα significantly decreased the expression of Cep70 mRNA in RA and OA-FLS (RA, 51%; OA, 59%). DcR3-Fc also significantly decreased the expression of Cep70 mRNA in RA-FLS in a dose dependent manner (81% with 10ng/ml, 73% with 100ng/ml, and 57% with 1000ng/ml). In contrast, DcR3-Fc did not decrease Cep70 mRNA in OA-FLS. Anti-TL1A antibody inhibited the down-regulation of Cep70 expression in RA-FLS induced by DcR3-Fc. Immunohistochemistry revealed that Cep70 protein was expressed more in superficial lining layer of rheumatoid synovium than that of OA synovium.

Conclusion: In this study, we revealed that Cep70 was increased in RA-FLS and that the expression of Cep70 in RA-FLS was decreased by DcR3 by binding to membrane-bound TL1A in a disease-specific fashion. DcR3 may affect the pathogenesis of RA through Cep70.

References:

Disclosure: K. Fukuda, None; Y. Miura, None; T. Maeda, None; S. Hayashi, None; M. Kurosaka, None.
Stromal Cell Markers Are Differentially Expressed in the Synovial Tissue of Patients with Early Arthritis. Ivy Y.K. Choi, Olga N. Karpus, Jason D. Turner, Debbie L. Hardie, Maria J. de Hair, Karen I. Majeri, Paul Peter Tak, Karim Raza, Jörg Hamann, Christopher Buckley, B. E. E. van den Berg, and Andrew Filer. 1Division of Rheumatology, Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 2Department of Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 3Rheumatology Research Group, MRC Centre for Immune Regulation, School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Previous studies have shown increased expression of stromal markers in synovial tissue in patients with established rheumatoid arthritis (RA). Here, the expression of tissue expressed stromal markers in early arthritis in relationship to diagnosis and outcome was studied.

Methods: ST from 67 patients included in two different early arthritis cohorts (Birmingham and Amsterdam) and seven non-inflammatory controls was analysed using immunofluorescence to detect the stromal markers CD55, CD248, fibroblast activation protein (FAP) and podoplanin. Diagnostic classification (gout, psoriatic arthritis, unclassified arthritis (UA), parvovirus associated arthritis, reactive arthritis and RA) and outcome (resolving or persistent) was determined at baseline and after follow-up. The relationship between the expression of the stromal markers and diagnosis and outcome was determined.

Results: We observed expression of all stromal markers in ST of early arthritis patients, independent of diagnosis or prognostic outcome. Expression of FAP and podoplanin was significantly higher in patients with early RA compared to non-inflammatory controls (p = 0.003 and p = 0.021, respectively). Significantly greater expression of FAP was found in anti-citrullinated peptide antibody (ACPA)-negative RA patients and in patients with UA fulfilling classification criteria for RA after follow-up compared to patients with resolving disease and patients with persistent disease who did not fulfil classification criteria for RA after follow-up (p = 0.030 and p = 0.020, respectively for ACPA-negative RA patients and p = 0.045 and p = 0.024, respectively for UA patients fulfilling classification criteria for RA after follow-up).

Conclusion: The stromal cell markers CD55, CD248, FAP and podoplanin, are expressed in the synovium in the earliest stage of arthritis. Expression of FAP is higher in early unclassified arthritis patients who fulfill classification criteria for RA over time and in ACPA-negative RA compared to resolving or non-RA arthritides. These results suggest that significant fibroblast activation occurs in RA in the early window of disease.

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Cyclic Phosphatidic Acid (cPA) Suppresses MMP-3, a Disintegrin and Metalloproteinase with Thrombospondin Motif (ADAMTS)-4, -5 and Stimulates HAS2 Expression in Inflammatory Rheumatoid Synovial Fibroblasts Induced with IL-1β and/or TNF-α. Ikuko Masuda, K. Kodo, Okada, Hisashi Yamakawa and Shigeki Momohara. 1Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan, 2SANSHO, Co. Ltd., Tokyo, Japan, 3Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/Purpose: Cycle phosphatidic acid (cPA) is one of bioactive lipid, has been implicated as a mediator of various biological effects including i) anti proliferative effect on eukaryotic cell cycle, ii) regulation of COX-releasing, iii) regulation of actin rearrangement, iv) inhibition of tumor cell invasion. Furthermore, on human skin fibroblasts, cPA stimulates high molecular hyaluronic acid (HA) production through up-regulating HA synthase (HAS). cPA also expressed to have antiinocceptive effect on animal models of acute and chronic pain. We have previously confirmed that cPA also stimulated HAS2 production on human osteoarthritic chondrocytes and synovial fibroblasts in vitro. Therefore, we studied the effect of daily topical administration of cPA suppressed pain, swelling, and articular cartilage degeneration in rabbit experimental osteoarthritis. These compelling results lead to a hypothesis that cPA may have direct role on anti-inflammation and protection of cartilage in arthritic condition. The aim of this study was to evaluate the effects of cPA on rheumatoid synovial fibroblasts which are under more severe inflammatory condition than osteoarthritis.

Methods: In vitro studies were performed using synovial fibroblasts obtained from rheumatoid arthritis patients at joint replacement surgery. cPA 0–25 μM was added to synovial fibroblasts cultures and effects of cPA on synovial fibroblasts on HAS, HYAL, ADAMTS-4, ADAMTS-5, MMP-3, TIMP-3 expression were assessed at 24 and 48hrs by real time PCR using specific primers to corresponding genes. Synovial fibroblasts were also cultured with IL-1β and/or TNF-α, to study attenuated effect of cPA. beta-actin was used as endogenous expression control.

Results: Cyclic phosphatidic acid (cPA) is one of bioactive lipid, has been implicated as a mediator of various biological effects including i) anti proliferative effect on eukaryotic cell cycle, ii) regulation of COX-releasing, iii) regulation of actin rearrangement, iv) inhibition of tumor cell invasion. Furthermore, on human skin fibroblasts, cPA stimulates high molecular hyaluronic acid (HA) production through up-regulating HA synthase (HAS). cPA also expressed to have antiinocceptive effect on animal models of acute and chronic pain. We have previously confirmed that cPA also stimulated HAS2 production on human osteoarthritic chondrocytes and synovial fibroblasts in vitro. Therefore, we studied the effect of daily topical administration of cPA suppressed pain, swelling, and articular cartilage degeneration in rabbit experimental osteoarthritis. These compelling results lead to a hypothesis that cPA may have direct role on anti-inflammation and protection of cartilage in arthritic condition. The aim of this study was to evaluate the effects of cPA on rheumatoid synovial fibroblasts which are under more severe inflammatory condition than osteoarthritis.

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Results: Cyclic phosphatidic acid (cPA) is one of bioactive lipid, has been implicated as a mediator of various biological effects including i) anti proliferative effect on eukaryotic cell cycle, ii) regulation of COX-releasing, iii) regulation of actin rearrangement, iv) inhibition of tumor cell invasion. Furthermore, on human skin fibroblasts, cPA stimulates high molecular hyaluronic acid (HA) production through up-regulating HA synthase (HAS). cPA also expressed to have antiinocceptive effect on animal models of acute and chronic pain. We have previously confirmed that cPA also stimulated HAS2 production on human osteoarthritic chondrocytes and synovial fibroblasts in vitro. Therefore, we studied the effect of daily topical administration of cPA suppressed pain, swelling, and articular cartilage degeneration in rabbit experimental osteoarthritis. These compelling results lead to a hypothesis that cPA may have direct role on anti-inflammation and protection of cartilage in arthritic condition. The aim of this study was to evaluate the effects of cPA on rheumatoid synovial fibroblasts which are under more severe inflammatory condition than osteoarthritis.
Conclusion: The in vitro results confirmed that cPA had stimulatory effects on RA synthesis by rheumatoid synovial fibroblasts. The suppressing effect of HYAL, ADAMTS-4, ADAMTS-5, and MMP-3 on rheumatoid synovial fibroblasts by cPA shown here, might have played direct role to suppressing inflammation and also protecting articular cartilage of arthritic condition. Molecular mechanism of cPA to prevent cartilage degeneration remains to be elucidated, however, further study should be warranted for cPA as a novel candidate for therapeutic agent of arthritis.


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Increased Risk of Rheumatoid Arthritis (RA) Among Shared Epitope-Negative (SE-) Mothers with Shared Epitope-Positive (SE+) Children

Giovanna Cruz1, Lindsay A. Cnisweld1, Xiaofang Shan2, Hong L. Quach2, Janelle Noble3, Nikolaos Patsopoulos4, Michael Busch4 and Lisa F. Barcellos5

1University of California, Berkeley, Berkeley, CA, 2University of California, San Francisco, San Francisco, CA, 3Children’s Hospital Oakland Research Institute (CHORI), Oakland, CA, 4Harvard Medical School, Boston, MA, 5Blood Systems Research Institute, San Francisco, CA.

Background/Purpose: RA (MIM 180300) disproportionately affects women of reproductive age, implicating pregnancy-related factors. Fetal microchimerism (FMCh), or the persistence of a small population of cells in the mother, is a natural consequence of pregnancy. FMCh is present more often in RA cases than in controls. Other-child histocompatibility could determine long-term FMCh, possibly increasing risk of RA through exposure to fetal HLA-antigens. We hypothesized that RA cases are more likely to have histocompatible (HC) children compared to controls.

Methods: The MCIS included 5,000 + individuals; mothers with RA or SLE and controls (n = 750), their children and fathers. RA cases with 1 + birth before diagnosis were recruited at UC San Francisco. Controls were primarily recruited from blood donors. Mothers provided information on their reproductive history, history of transfusion, transplant and infections. Comprehensive MHC region SNP genotyping was conducted using the Illumina MHC panel (n = 1,783), ImmunoChip (n = 8,842), and 660K arrays (n = 1,991) arrays. Four-digit genotype data for HLAA, B, C, DPA1, DPB1, DQA1, DQB1 and DRB1 were imputed using the TIDGC reference panel and BEAGLE. We estimated ancestry proportions from 384 markers using STRUCTURE. A child was HC from the mother’s perspective if the paternal allele did not differ from the non-inherited maternal allele. Carrier status (0 or +) of the DRB1 allele associated with RA risk (Raychaudhuri, 2012) and corresponding to SE amino acid sequences QKRAA and QRRAA (01:01, 04:01, 04:04, 05:04, 08:08) and DERRAA (01:03, 04:02, 11:02, 13:01, 13:02) was determined for mothers and children. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between RA and a HC at each HLA locus and b exposure to any SE + DERRAA + children, stratifying on maternal carrier status.

Results: HC among cases was only evident at DQB1 (25.3% vs. 17.4%, p = 0.03). Having any SE + children significantly increased risk of RA for SE- mothers (n = 238) (OR 2.56; 95% CI, 1.43–4.58) but not SE+ mothers (n = 248) (OR 1.48; 95% CI, 0.83–2.62). No association was found with DERRAA + children, regardless of maternal carrier status. Ancestry, parity, and history of transfusion did not impact results.

Conclusion: Exposure to SE + children and DQB1 HC may contribute to RA etiology and could contribute to RA’s female-predominance. This is the largest study confirming the association between RA and SE + children in SE- mothers.

Disclosure: G. Cruz; None. L. A. Criswell; None. X. Shao; None. H. L. Quach; None. J. Noble; None. N. Patsopoulos; None. M. Busch; None. L. F. Barcellos; None.

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Effectiveness and Safety of Tocilizumab in Biologics Naïve RA Patients - Interim Analysis of PMS for Investigating Success in Achieving Clinical and Functional Remission and Sustaining Efficacy with Tocilizumab in Biologics-Naïve RA Patients Study

Naoki Ishiguro1, Tatsuya Atsumi2, Masayoshi Harigai3, Tsuneyo Mimon4, Norhiro Nishimoto5, Takayuki Sumida6, Tsutomu Takeuchi1, Yoshiya Tanaka2, Nobuhiro Takagi7, Kunihiro Tanaka8 and Hisashi Yamanaka9

1Nagoya University Graduate School of Medicine, Nagoya, Japan, 2Hokkaido University, Sapporo, Japan, 3Tokyo Medical and Dental University, Tokyo, Japan, 4K yoto Univ Grad Schl of Med, Kyoto, Japan, 5Tokyo Medical University, Osaka, Japan, 6Univ of Tsukuba/Inst Clin Med, Tsukuba City, Japan, 7School of Medicine, Keio University, Tokyo, Japan, 8O STELLA & ENVIRON Hilt, Kikayushu, Japan, 9Chugai Pharmaceutical, Tokyo, Japan, 10Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/Purpose: The all-patient PMS study of tocilizumab (TCZ) followed 7901 RA patients for 28 wks. That study (hereafter, PM 57901) showed patients with a high probability of remission and a low probability of developing serious infection to be those most likely to have early and less advanced RA and to have not received biologics previously. The FIRST Bio study is designed to investigate effectiveness and safety of TCZ in RA patients who had not received any biologics (i.e. bio-naïve) in a real clinical setting.

Methods: FIRST Bio is a 52-wk observational postmarketing surveillance study which enrolled bio-naïve RA patients who met the ACR/EULAR 2010 classification criteria for RA, experienced inadequate response or were intolerant to one or more DMARDS, and had DA58-ESR > 3.2. Patients received 8 mg/kg TCZ every 4 wks intravenously with or without DMARDS at the investigators’ discretion. Patient characteristics and safety and effectiveness data were collected. This interim analysis reports the results of 24 wks’ observation. A paired t-test was used to detect statistically significant differences in disease activity (CDAI, DA58-ESR) and Health Assessment Questionnaire (HAQ) score compared to baseline.

Results: This report analyzes 551 of 855 patients enrolled. Mean disease duration and percentage of patients who had less advanced Steinbrocker’s stage and class and had comorbidities were lower in the FIRST Bio study than in PM 57901 (Table 1). At Wk 24, 87.2% of patients were continuing TCZ treatment. Mean CDAI improved from 23.4 at baseline to 7.5 at Wk 24 (p < 0.0001). DA58-ESR also improved from 5.2 at baseline to 2.2 at Wk 24 (p < 0.0001). At Wk 24, rate of CDAI remission (CDAI ≤ 28) was 30.9%, DA58-ESR remission (DA58-ESR < 2.6) was 66.5%, and Boolean remission was 27.8%. The Boolean remission rate in the FIRST Bio study was almost twice that in PM 57901 (15.1%) (Table 2). The mean HAQ score improved from 1.0 at baseline to 0.5 at Wk 24 (p < 0.0001), and in 59.8% of patients the HAQ score decreased to < 0.3 (i.e. HAQ remission). The incidence rates of total and serious AEs were 25.2% and 4.6%, respectively. Infections were the most frequent AEs (6.4%) and the most frequent serious infections were lower in the FIRST Bio study than in PM 57901 (Table 2). M ore dose of concomitant M TX decreased from 9.1 mg/wk at baseline to 7.3 mg/wk at Wk 24. M ore dose of concomitant corticosteroid also decreased from 5.7 mg/day at baseline to 3.6 mg/day at Wk 24.

Conclusion: The FIRST Bio study revealed that in the real clinical setting TCZ showed high effectiveness and safety in those patients who have less advanced RA and who have not previously received biologics.

Table 1. Patient background

<table>
<thead>
<tr>
<th>FIRST Bio study</th>
<th>PM 57901</th>
</tr>
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<tbody>
<tr>
<td>M mean age (SD), years</td>
<td>59.4 (13.7)</td>
</tr>
<tr>
<td>M mean disease duration (SD), years</td>
<td>7.2 (8.7)</td>
</tr>
<tr>
<td>% of patients (pts) whose Steinbrocker’s stage was I or II</td>
<td>63.5</td>
</tr>
<tr>
<td>% of pts whose Steinbrocker’s class was I or II</td>
<td>81.5</td>
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Table 2. Comparing safety and effectiveness

<table>
<thead>
<tr>
<th>Group</th>
<th>Reduced disease activity at Mth 12</th>
<th>Sustained levels of reduced disease activity (at both Mths 12 and 18)</th>
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<tr>
<td></td>
<td>Abatacept + MTX (n=120)</td>
<td>MTX (n=84)</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI): 2.1 (1.1, 3.8); p=0.02</td>
<td>Abatacept monotherapy vs MTX alone: OR (95% CI): 1.1 (0.7, 1.6)</td>
</tr>
</tbody>
</table>

Primary analysis:

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Abatacept + MTX (n=120)</th>
<th>MTX (n=84)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 (CRP)</td>
<td>2.6*</td>
<td>2.6</td>
<td>2.1 (1.3, 3.7); p=0.003</td>
</tr>
<tr>
<td>PMS7901</td>
<td>119, abatacept</td>
<td>116</td>
<td>2.0 (0.8, 5.1)</td>
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<tr>
<td>CDAI</td>
<td>2.8</td>
<td>2.8</td>
<td>1.1 (0.7, 1.9)</td>
</tr>
<tr>
<td>Boolean remission</td>
<td>3.3</td>
<td>3.3</td>
<td>2.0 (0.8, 5.1)</td>
</tr>
<tr>
<td>Stringent criteria</td>
<td>116</td>
<td>116</td>
<td>1.1 (0.7, 1.9)</td>
</tr>
</tbody>
</table>

Secondary analyses:

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Abatacept + MTX (n=120)</th>
<th>MTX (n=84)</th>
<th>Odds ratio</th>
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<tr>
<td>DAS28 (CRP)</td>
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<td>Stringent criteria</td>
<td>116</td>
<td>116</td>
<td>1.1 (0.7, 1.9)</td>
</tr>
</tbody>
</table>

Incidence rate of AEs (serious AEs), % 25.2 (6.4) 43.9 (9.6

Reference:

3. Takagi, Chuga, 3; K. Kanaoka, Chuga, 3; H. Yamanaka, Avbbvie, Astellas, Bristol-Myers Squibb, Chugai, Pfizer, Roche, Takeda, and UCB, 8. N. Takagi, Chuga, 3; K. Kanaoka, Chuga, 3; H. Yamanaka, Avbbvie, Astellas, Bristol-Myers Squibb, Chugai, Pfizer, Roche, Takeda, and UCB, 8.

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Stringent Criteria for Low Disease Activity and Remission after 12 Months of Treatment, and after Treatment Withdrawal, with Abatacept Monotherapy, Abatacept with Methotrexate or Methotrexate Alone in Early Rheumatoid Arthritis.

Background/Purpose: Clinical remission is associated with better long-term outcomes and should be the goal of therapy in RA. In the Assessing Very Early Rheumatoid Arthritis Treatment (AVERT) trial, greater percentages of patients achieved DAS28 (CRP) <2.6 following 12 months of treatment with SC abatacept + MTX and 6 months after withdrawal of all RA therapy, compared with MTX alone. At most time points, abatacept monotherapy was more effective than MTX alone. Here, we report clinical efficacy and remission rates from AVERT, using stringent criteria at Mth 12 and after treatment withdrawal (Mth 18).

Methods: AVERT enrolled pts who were MTX-naive, anti-cyclic citrullinated peptide 2 seropositive (CCP2+), aged ≥18 yrs, with active synovitis ≥2 joints for ≥6 wks, DAS28 (CRP) ≥3.2, and disease onset of ≥2 yrs. Pts were randomly assigned to one of the following arms: SC abatacept 125 mg + MTX, SC abatacept 125 mg, or MTX alone. All RA treatment was withdrawn after 12 months (abatacept immediately, MTX and steroids over 1 mth) in pts with DAS28 (CRP) ≤3.2. Percentages (%) of pts achieving DAS28 (CRP) <2.6 or ≤2.4, Major Clinical Response (MCR) (ACR70 response for ≥6 consecutive months), or remission (CDAI ≤2.8; SDAI ≤3.3, Boolean criteria) at Mth 12, and the % who maintained these reduced disease activity states at Mth 18 were assessed.

Results: 351 pts at early RA were enrolled (n=119, abatacept monotherapy; n=116, abatacept + MTX: n=116, abatacept monotherapy; n=116, MTX alone). Mean characteristics at baseline were: disease duration 0.6 yrs, DAS28 (CRP) 5.4, HAQ-DI 1.4, 95.2% RF+ and anti-CCP2+. At Mth 12, higher % of pts in the abatacept + MTX group achieved DAS28 (CRP) <2.6 (primary analysis) as well as the more stringent clinical endpoint DAS28 (CRP) <2.4 or remission (CDAI, SDAI, Boolean), compared with MTX alone (Table). Rates of low disease activity and remission with abatacept monotherapy were intermediate between abatacept + MTX and MTX alone (Table). Higher % (95% CI) of abatacept-treated pts achieved MCR at Mth 12, compared with MTX alone (abatacept + MTX and MTX monotherapy vs MTX alone: 31.9% [23.6, 40.3] and 17.2% [10.4, 24.1] vs 8.6% [3.5, 13.7]). Following treatment withdrawal, a small but higher % of abatacept-treated pts (with MTX or monotherapy) sustained low disease activity or remission than in the MTX group (Table).

Conclusion: In early RA, abatacept + MTX for 12 mths resulted in higher rates of low disease activity and remission according to stringent criteria, than MTX alone. Few pts who achieved these stringent clinical measures at 12 mths could maintain them 6 mths after all RA treatment had been withdrawn. These findings indicate that treatment with abatacept + MTX early in the course of RA can achieve high remission rates at 12 mths, which may be sustained on withdrawal of all RA therapy in a small but higher proportion of pts than using MTX alone.

References:

3. Takagi, Chuga, 3; K. Kanaoka, Chuga, 3; H. Yamanaka, Avbbvie, Astellas, Bristol-Myers Squibb, Chugai, Pfizer, Roche, Takeda, and UCB, 8.
Background/Purpose: The BREVACTA study assessed the efficacy and safety of subcutaneous tocilizumab (TCZ SC) in patients (pts) with RA who had an inadequate response to ≥ 1 DMARD (21% previously failed aTNF therapy). The primary objective assessed efficacy and safety to Week 24. Superiority over placebo (PBO) was observed, with a safety profile comparable to intravenous (IV) TCZ. We now report the efficacy and safety data for TCZ SC every 2 weeks (q2w) and TCZ weekly (qw) following escalation from either TCZ q2w or PBO q2w to Week 96.

Methods: This phase 3, randomized, multicenter, parallel arm study included a 24 week double blind, PBO controlled period followed by a 72 week open label phase and a further 8 weeks of safety follow up. Pts were included a 24 week double blind, PBO controlled period followed by a 72 weeks was comparable to 24 weeks. For escape pts, there were improvements in ACR20 response rates in pts who previously received PBO and escalated from q2w to qw. TCZ SC will offer an alternative route of administration and in the treatment at 4 weeks in about 40% of the patients. The best way to apply ADA treatment is to use it concomitantly with an adequate dose of DMARD. In the N and 20% improvement from baseline in both groups, 39 were Switch (S group), 95 received MTX 10 mg/week (N group), and 24 received MTX 10 mg/week (H group), while in the open label phase 27.5% (9.3%) escaped from the TCZ qw arm. In the TCZ qw arm, the rates of AEs and SAEs, including serious infections, remained stable over time, to Week 96. No anaphylaxis or serious hypersensitivity occurred. By Week 96, 31 pts (7.1%) withdrew due to AEs and 7 pts (1.6%) died. Nine pts (2.1%) developed antITC antibodies postbaseline without loss of efficacy or clinically significant hypersensitivity. For escape pts, the proportion of pts who achieved an ACR20 response increased after escape in both the TCZ or PBO arms; although there was a higher ACR20 response in escape pts from the PBO arm than the TCZ qw arm, (86.4% and 63%, respectively) at Week 84. The rate of AEs per 100 pt years, following escape therapy was similar between pts who previously received TCZ or PBO (331.9 and 365.0, respectively) and comparable to the TCZ qw arm (323.8).

Conclusion: TCZ SC qw2 demonstrated long term efficacy, including sustained ACR responses over 96 weeks. The AEs profile for TCZ SC at 96 weeks was comparable to 24 weeks. For escape pts, there were improvements in ACR20 response rates in pts who previously received PBO and escalated from q2w to qw. TCZ SC will offer an alternative route of administration and the possibility of self administration for pts with RA.

2470

Treatment Strategy for Maximizing the Effect of Adalimumab in Japanese Patients with Rheumatoid Arthritis: Retrospective Analyses of Data Collected from the Patient Treated with Adalimumab in Routine Clinical Practice in Hamamatsu Area. Toshiaki Miyamoto. Seirei Hamamatsu General Hospital, Hamamatsu, Japan.

Background/Purpose: Adalimumab (ADA) showed highly efficacious in rheumatoid arthritis (RA) in the clinical trials, although there is little evidence in daily clinical practice. The clinical usefulness and treatment continuation rate of 52 weeks of a ADA treatment in rheumatoid arthritis (RA) patients was investigated over time.

Methods: The subjects were 124 analyzable patients that had been introduced to ADA treatment at this institution from May 2009 to October 2012. In patients' background, mean age was 53 years, mean duration of illness 7.2 years, rate of concomitant MTX treatment 96% (116 patients), mean MTX dose 11.4 mg/week, and rate of concomitant PSL treatment 16.1%. Of these patients, 35 had a duration of illness below 2 years (<2 group), 89 a duration of at least 2 years (= 2 group), 85 were Bio Naive (N group), 39 were Switch (S group), 95 received MTX ≥ 10 mg/week (>10 group), and 24 received MTX <10 mg/week (<10 group). There was no significant difference in baseline disease activity between the groups. Treatment efficacy up to 52 weeks after ADA treatment in each group was investigated comparatively.

Results: The DA528 (CRP) remission rate for all the patients at 4, 24, and 52 weeks was 36%, 62%, and 70%, respectively, showing that from 4 weeks, about 40% of the patients achieved clinical remission. Changes in DA528 (CRP) remission rates for the <2 and ≥2 groups at 4, 24, and 52 weeks were 29% vs. 39%, 69% vs. 60%, and 83% vs. 65%, respectively. Similarly, changes in DA528 (CRP) in the N and 5 groups were 34% vs. 41%, 67% vs. 51%, and 74% vs. 62%, respectively; in the ≥10 and <10 mg groups, they were 43% vs. 13%, 72% vs. 25%, and 77% vs. 46%, respectively, showing that the values were significantly high in the ≥10 group at all the time points. Moreover, HAQ remission rate for the overall patients at 52 weeks was 82%, and treatment continuation rate was 72%. Excluding the patients that discontinued treatment for reasons such as hospital transfer, the 82% on concomitant MTX treatment, response was good in 90%.

Conclusion: With ADA, remission could be induced from very early on in the treatment at 4 weeks in about 40% of the patients. The best way to apply ADA treatment is to use it concomitantly with an adequate dose of MTX in early-stage RA and Bio Naive patients. By so doing, the potential of ADA can be exploited maximally.

Disclosure: T. Miyamoto. None.
(BMD), and safety was examined in the subgroup of OP patients with RA enrolled in the DANCE trial.

Methods: This was a post hoc analysis of patients with RA enrolled in the DANCE open-label, prospective, observational study, treated with TPTD 20 mg/day for \( \geq 2 \) years (treatment phase), and followed for up to 2 more years (cessation phase). Mixed model repeated measures analysis was used to evaluate BMD changes over 18 months (mo). Incident rates of new clinical VERT or NV fragility fractures (traumatic fractures excluded) after 6–24 mo vs 0–6 mo of TPTD therapy were compared using a Poisson regression model. Time to new NV fragility fracture was compared using Kaplan-Meier analysis. Rates of incident NV fractures were assessed at intervals over treatment and cessation phases vs the first 6-mo treatment (reference) period.

Results: Of 4085 patients who received \( \geq 1 \) dose of TPTD, 544 had documented RA. Patients with vs without RA at baseline had similar age (mean [SD] age, 68.6 [11.5] vs 67.8 [11.9] years), but significantly more history of prior NV fractures (60.8% vs 55.4%, \( p = 0.017 \)), higher L1-L4 T-scores (2.21 [1.44] vs -2.51 [1.36], \( p < 0.001 \)), more baseline clinical conditions (3.1 [1.4] vs 1.6 [1.3], \( p < 0.001 \)), and more glucocorticoid use (32.5% vs 7.1%, \( p < 0.001 \)). Mean TPTD exposure was similar (523.0 [303.9] vs 545.4 [288.4] days). Over 18 mo, bone density in the spine, femoral neck, and total hip increased similarly in patients with vs without RA (all \( p \)-values \( < 0.001 \)). Incident rates of new VERT with or without back pain or NV fragility fractures decreased in mo 6–24 vs the first 6 mo. There was no significant difference in the decrease in fracture incidence in mo 6–24 vs the first 6 mo in the patients with RA compared with those without, regardless of the type of fracture (all interaction \( p \)-values \( > 0.1 \)). There was no difference in the time to a new NV fragility fracture (log-rank \( p > 0.02 \)) by RA status. NV fracture incidence rates/100 patient years decreased vs reference baseline during treatment and stayed down during cessation phase vs reference baseline (Figure 1). In the overall DANCE study, TPTD was well tolerated and no new significant safety findings were observed.

Conclusion: Patients with rheumatoid arthritis receiving teriparatide showed similar increases in BMD at the spine, femoral neck, and total hip and similar reduction over time in the incidence of NV fractures compared with osteoporosis patients without RA. Compared to baseline, the incidence of NV fractures remained down after drug cessation.

Reference

Figure: Cumulative probability plot of CFB in mTSS at Wk52

<table>
<thead>
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<th>Baseline characteristics</th>
<th>PBX+MTX</th>
<th>C2P+MTX</th>
</tr>
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<tbody>
<tr>
<td>$\Delta$S28 (ESR) $\leq 3$</td>
<td>3</td>
<td>0.00±0.00</td>
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<tr>
<td>$\Delta$S28 (ESR) $\leq 3.5$</td>
<td>56</td>
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<td>$\Delta$S28 (ESR) $\leq 5$</td>
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<td>CRP (mg/dL) $&lt;1.0$</td>
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<tr>
<td>CRP (mg/dL) $&lt;1.5$</td>
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<td>mTSS $&lt;0.5$</td>
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<td>mTSS $&lt;1.0$</td>
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<td>MMP-3 (ng/ml) $&lt;100$</td>
<td>74</td>
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</table>

Results: The observation period of this study was 24 weeks. One hundred and seventy-two patients were included in the safety population and 165 patients were included in the efficacy population. An inadequate response to biological DMARDs was defined as that all of the following conditions were met: Simplified Disease Activity Score (SDAI) $>3.3$ when TAC was started; both tender joint count and swollen joint count were the same or increased compared to those at four to eight weeks prior to TAC; Biological DMARDs were used for at least eight weeks prior to TAC. Efficacy was evaluated using the SDAI. DACS28-CRP (Disease Activity Score 28-C-reactive protein), EULAR (European League Against Rheumatism) response criteria, and SDAI improvement were defined as SDAI = 11. DACS28-CRP improvement was defined as DACS28-CRP $<2.7$.

Results: Mean age was 61.9 years and the mean disease duration was 11.0 years. The mean TAC dose was 1.3 mg during the observation period. Adverse drug reactions (ADRs) occurred in 18 patients and serious ADRs were observed in two patients (Herpes zoster, Myocardial infarction). One patient (age 89) who developed myocardial infarction died on the day when it occurred. SDAI remission rate was 13.3% at week 24, SDAI improvement rate was 58.5% at week 24 and the mean SDAI was decreased from 20.1 at baseline to 11.7 at week 24. DACS28-CRP remission rate was 33.3% at week 24, DACS28-CRP improvement rate was 48.9% at week 24 and the mean DACS28-CRP was decreased from 4.0 at baseline to 2.9 at week 24. Based on EULAR response criteria, moderate or good response rate was 69.8% at week 24.

Conclusion: TAC is well tolerated and effective when added on to the biological DMARDs in Japanese RA patients who failed to achieve an adequate response to biological DMARDs in a real clinical setting.


Post-Marketing Surveillance of Efficacy and Safety of Tacrolimus Add-on Therapy in Japanese Rheumatoid Arthritis Patients Who Failed to Show an Adequate Response to Biological DMARDs: Interim Analysis

Tsumoto Takeuchi and Kotsu Ishida.

Background/Purpose: Tacrolimus (TAC) is an immunosuppressive macrolide that blocks T cell activation by specifically inhibiting calcineurin, and it is widely administered following organ transplantation. TAC was approved in Japan for the treatment of rheumatoid arthritis (RA) in 2005. We report here the interim results of Post-marketing surveillance we have been conducting to evaluate the safety and efficacy of TAC adding on to biological disease-modifying anti-rheumatic drugs (DMARDs) in Japanese RA patients who failed to show an adequate response to biological DMARDs in a real clinical setting.

Methods: The observation period of this study was 24 weeks. One hundred and seventy-two patients were included in the safety population and 165 patients were included in the efficacy population. An inadequate response to biological DMARDs was defined as that all of the following conditions were met: Simplified Disease Activity Score (SDAI) $>3.3$ when TAC was started; both tender joint count and swollen joint count were the same or increased compared to those at four to eight weeks prior to TAC; Biological DMARDs were used for at least eight weeks prior to TAC. Efficacy was evaluated using the SDAI. DACS28-CRP (Disease Activity Score 28-C-reactive protein), EULAR (European League Against Rheumatism) response criteria, and SDAI improvement were defined as SDAI = 11. DACS28-CRP improvement was defined as DACS28-CRP $<2.7$.

Results: Mean age was 61.9 years and the mean disease duration was 11.0 years. The mean TAC dose was 1.3 mg during the observation period. Adverse drug reactions (ADRs) occurred in 18 patients and serious ADRs were observed in two patients (Herpes zoster, Myocardial infarction). One patient (age 89) who developed myocardial infarction died on the day when it occurred. SDAI remission rate was 13.3% at week 24, SDAI improvement rate was 58.5% at week 24 and the mean SDAI was decreased from 20.1 at baseline to 11.7 at week 24. DACS28-CRP remission rate was 33.3% at week 24, DACS28-CRP improvement rate was 48.9% at week 24 and the mean DACS28-CRP was decreased from 4.0 at baseline to 2.9 at week 24. Based on EULAR response criteria, moderate or good response rate was 69.8% at week 24.

Conclusion: TAC is well tolerated and effective when added on to the biological DMARDs in Japanese RA patients who failed to achieve an adequate response to biological DMARDs in a real clinical setting.

Disclosure: T. Takeuchi, AbbVie GK, Asahi Kasei Medical K.K., Astellas Astra Zeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co, Novartis Pharma K.K., 5, AbbVie GK, Astellas, AstraZeneca, Celgene, Centocor, Chugai, Abbott, Eisai, Janssen, Kyorin, Mitsubishi-Tanabe, Pfizer, Schering-Plough, UCB Pharma, Vertex, 3, Biogen Idec, Amgen, AstraZeneca, Aegerae, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma, Vertex, 3.
**Methods:** We retrospectively reviewed electronic medical records within our patient cohort from 2001 to the present, and included patients who switched from PO to SC MTX. Records were analyzed for baseline demographics, reasons for switching to SC MTX, doses of PO and SC MTX at the time of the switch, duration of SC MTX use, reasons for discontinuation of SC MTX (if applicable), and whether the addition of biologic agents was required.

**Results:** The records of 240 patients who switched to SC MTX were examined. Fifty-eight patients were excluded because of incomplete data. Of the 182 patients included, 125 (68%) were female, and the average age at starting SC MTX was 52.5 years (range 17–82). Underlying diagnoses included rheumatoid arthritis (n = 144), psoriatic arthritis (n = 20), juvenile idiopathic arthritis (n = 7), ankylosing spondylitis (n = 2), undifferentiated inflammatory arthritis (n = 6), systemic lupus erythematosus (n = 1), and vasculitis (n = 2). Reasons for switching from PO to SC MTX included intolerance (n = 55), inefficacy (n = 118) and unknown (n = 8). One hundred ten patients (60%) were receiving no other DMARDS at the time of the switch. In the majority of the remaining patients (n = 60), MTX was used in combination with sulfasalazine (n = 21), hydroxychloroquine (n = 21), prednisolone (n = 11), leflunomide (n = 4), or anti-tumor necrosis factor-α therapies (n = 3). At the time of switching patients were taking an average dose of 20mg/week PO MTX and were switched to an average dose of 15mg/week SC MTX (range for both 5–25mg/week). One hundred thirty-three (73%) patients remain on SC MTX to date; 49 patients discontinued SC MTX because of intolerance (n = 26), adverse drug reaction (n = 10), inefficacy (n = 6), disease remission (n = 2), or undocumented reasons (n = 5). Thirty-nine percent of those who discontinued SC MTX required the addition of a biologic, compared with 28% of those who continued with SC MTX. Sixty-five percent of those who switched to SC MTX because of intolerance were able to continue with this drug, for an average duration of 46 months (range 2–144 months) to date; 40 to 45% of those who switched to SC MTX because of intolerance or inefficacy, respectively, did not require the addition of another DMARD or biologic agent.

**Conclusion:** This evidence strongly supports the use of SC MTX as a tolerable and efficacious alternative after failure of PO MTX. After the switch to SC MTX, 65% of patients who were intolerant of PO MTX continued with MTX, either as monotherapy or in combination with other DMARDS or biologic agents. Furthermore, patients who continued with SC MTX were less likely to require biologic agents. Further evaluation of this approach may be warranted.

**Disclosure:** J. Gunn, None; A. Panopoulou, None; A. Steuer, None.

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**Background/Purpose:** Use of imputed or observed data, as well as the patient (pt) population evaluated (eg, intention-to-treat [ITT], completer), affects the interpretation of long-term efficacy data. Statistical analysis of data from long-term studies must consider the impact of missing values, which result from dropout and non-completion. Several imputation methods have been developed to link such reasons with assumptions made for missingness. Missing completely at random (MCAR) approaches (eg, last observation carried forward [LOCF], non-responder imputation [NRI]) assume that missingness is independent of observed and unobserved outcomes. In contrast, missing at random (MAR) methods (eg, mixed models with repeated measures [MMRM]) assume that missingness is dependent on observed outcome.

**Methods:** Data from pooled analysis of Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and 2 RCTs and open-label extensions (OLE) (NCT001523861, NCT001758777, NCT001608022 and NCT00106419) were used. RAPID1 and 2 evaluated safety and efficacy of cetrixolub pegol (CZP) with methotrexate. Efficacy data were collected up to 256 weeks (wks) of CZP exposure for clinical measures, including DAS28 (ESR) (DAS28), HAO-DI (LOCF) and ACR20/50/70 (modified NRI [mNRI]). Observed and imputed (MCAR, MAR) data are presented for CZP ITT (all pts randomized to CZP in RCT) and CZP Completer (CZP ITT pts who completed RCT and reconsented into OLE) populations.

**Results:** Improvements from baseline in DAS28(ESR) and HAO-D1 were evident in CZP Completer and ITT populations at 256 wks. The use of LOCF and MMRM imputation gave results consistent with observed data (Table). Long-term CZP exposure resulted in sustained ACR response. mNRI determined rates were, per definition, lower than observed data (Table), but were in line with data observed in blinded periods.1,2 MMRM imputation followed long-term mean treatment response more closely and was more homogeneous between patient populations compared to LOCF/mNRI. Different reasons for discontinuation lead to distinct differences in imputed results. Imputed mean response was more homogeneous in the completer population.

**Conclusion:** Considering multiple populations and imputation approaches enables more reliable long-term efficacy data interpretation. Pooled RAPID1 and 2 results revealed similar patterns between observed and imputed data, although differences were observed between different imputation methods and reasons for withdrawal. Analysis of the ITT population gives a less biased estimate of efficacy compared with CZP Completers. Nonetheless, results were consistent with maintained improvements in RA signs and symptoms following 256 wks of exposure to CZP.

**Disclosure:** E. C. Keystone, Abbott, AstraZeneca, Biotest, BMS, F. Hoffmann-La Roche, Genentech, Janssen, Lilly, Merck, Nycomed, Pfizer, UCB Pharma, 2, Abbott, Amgen, AstraZeneca, BMS, Canada, F. Hoffmann-La Roche, Janssen, Pfizer, UCB Pharma, 6; J. S. Smolen, UCB Pharma, 2, UCB Pharma, 5; V. Strand, AbbVie, Afferent, Biogen Idec, Novartis, BMS, Carbylan, Celgene, Celtrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; T. Kumke, UCB Pharma, 3; I. Mountain, UCB Pharma, 3; S. Walker, UCB Pharma, 3; R. B. M. Landewe, Abbott, Abylyn, Amgen, AstraZeneca, Bristol Myers Squibb, Centocor, Glaxo-Smith-Kline, Novartis, Merck, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 5; Abbott, A. men, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 2, Amgen, Bristol Myers Squibb, Centocor, Merck, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 6.

**Disclosure:** None. 

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**Withdrawn**

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**2477**

**Integrating Treatment Goals of Physicians, Patients, and Payers during Treatment with Golimumab in Patients with Rheumatoid Arthritis.** B. Combe,DJ Valey, R. Burgos-Vargas, G. Sz'u2c2, M. Leri2s2a22Repo, R. Yao, S. Huyck, R. Lyu, M. Govoni, N. Vastesaeger and HH Weng.

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**Background/Purpose:** Physicians, patients, and payers may have different ideas about what constitutes successful treatment and how treatment goals should be defined for rheumatoid arthritids (RA). This analysis was designed to evaluate overlap between attained treatment goals that are important to physicians, patients, and payers after 6 months of add-on golimumab (GLM) in patients with active RA, and to determine baseline predictors of patients who achieve all 3 goals.

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**Methods:** GO-MORE was an open-label, multinational, prospective study in biologic-naive patients with active RA (28-joint disease activity score using erythrocyte sedimentation rate [DAS28-ESR] ≥3.2) despite disease-modifying antirheumatic drug (DMARD) treatment. Patients received 50-mg subcutaneous (SC) GLM once monthly for 6 months. Efficacy outcomes including DAS28-ESR, patient-acceptable symptom state (PASS; 1 yes/no question of patient satisfaction with their current disease state), and EuroQol 5-dimension (EQ-5D) were evaluated at month 6. The overlap in achievement of strict remission treatment goals was evaluated (DAS28-ESR remission normal EQ-5D [≥8], and met PASS); lower disease activity (LDA) goals were also evaluated (DAS28-ESR LDA, EQ-5D near normal [≥7], and met PASS). A multivariate regression analysis identified baseline predictors of patients who achieved the intersection of the 3 criteria.

**Results:** In 3280 efficacy-evaluable patients, mean disease duration was 7.6 years; mean DAS28-ESR was 5.97 (SD = 1.095). As previously reported, 23.9% of 3280 efficacy-evaluable patients achieved remission, and 37.4% achieved LDA (based on DAS28-ESR) at month 6. 21% of patients achieved normal QoL, and 46% achieved close-to-normal QoL (EQ-5D ≥7). 66.0% of patients achieved PASS. Overlap in patients who achieved each goal is shown (figure). 10.7% of patients (350/3280) met all 3 strict criteria, and 25.1% (823/3280) met all 3 looser criteria. Significant baseline predictors of achieving all 3 strict remission criteria were absence of comorbidities; lower DAS28, Health Assessment Questionnaire (HAQ), and swollen joint count scores; and greater anti-cyclic citrullinated peptide levels and EQ-5D Index scores. When PASS was replaced with HAQ ≥5 (minimal or no functional impairment, achieved by 37.4% of patients) in either the set of strict or looser criteria, the percentage of patients who met all 3 criteria was similar to when PASS was used.

**Conclusion:** In patients with active RA who failed ≥1 DMARD and received add-on GLM for 6 months, overlap in achievement of LDA goals of physicians, patients, and payers was attained in 25.1% of patients. Overlap in achievement of LDA goals of the 3 criteria.

**Reference:**

**Disclosure:** M. V. Hernández, None; A. Cuervo, None; S. Cabrera, None; J. Inciarte-Mundo, None; J. Ramirez, None; V. Ruiz-Esquide, None; J. D. Cañete, None; R. Sanmarti, None.

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**Utility of Adjustment of Administration Interval in Tocilizumab in Rheumatoid Arthritis.** Shuntaro Saito, Keisuke Izumi, Yuko Kaneko, Katsuya Suzuki and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan.

**Background/Purpose:** Interleukin-6 (IL-6) is considered a key cytokine in the pathogenesis of rheumatoid arthritis (RA). Tocilizumab (TCZ) is a monoclonal antibody which binds to membrane-bound and soluble forms of human IL-6 receptor, and has proved to be effective in the treatment of RA. In the standard protocol for RA, TCZ is administered intravenously every four weeks. However, given that the impact of IL-6 presumably differs among patients, treatment might be optimized by shortening or prolonging the administration interval of TCZ. Here, we evaluated the usefulness of modifying the protocol based on the treat-to-target concept in daily practice.

**Methods:** We retrospectively surveyed all 453 patients treated with TCZ (8mg/kg) at our institution between 2008 and 2014. Patients administered TCZ at an interval of ≤3 weeks or ≥5 weeks were analyzed as the shortened or prolonged interval group, respectively. Clinical information, including disease activity, was collected and statistically analyzed.

**Results:** A) Patients administered TCZ at a shortened interval (administration interval ≤3 weeks).

Among 453 patients, 25 (5.5%) were administered TCZ at a shorter interval due to insufficient effectiveness after administration at a 4-week interval for a median of 33.8 weeks. Disease activity was significantly improved after two administrations at this shortened interval, with disease activity score (DAS) 28 changing from 5.10 to 3.40 (p<0.05). A mong these
25 cases, interval could be returned to 4 weeks in 15. In contrast, the remaining 10 required continuous administration at a shortened interval for more than 1 year due to exacerbation of RA activity on return to a 4-week interval.

B) Patients administered TCZ at a prolonged interval (administration interval ≥ 5 weeks).

Sixty-three patients (13.9%) were administered TCZ at a prolonged interval, after having achieved remission after a median of 70.0 weeks at a 4-week interval. The prolonged interval ranged from 5 to 8 weeks. Of these 63 patients, 48 (76.2%) were able to continue TCZ administration at a prolonged interval for more than 1 year, while 15 (24.8%) required returning to a 4-week interval due to exacerbation of RA activity after a median of 51.1 weeks at a prolonged interval. All 15 cases achieved low disease activity equivalent to the original level before interval prolongation.

Conclusion: Our study highlighted the importance of administration interval in the effectiveness of TCZ in RA. Adjustment of interval according to disease activity in individual patients is a promising way to optimize treatment.


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Is there a Difference in the Effectiveness in the Treatment of Rheumatoid Arthritis with Rituximab when Using a Dose of 1 or 2 Grams per Cycle? A Systematic Review.

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Background/Purpose: Since the description of the efficacy of rituximab (RTX) in treating patients with rheumatoid arthritis (RA), the use of this drug has been extended. The recommendation in fact sheet is the administration of two infusions of 1 g in each cycle but some studies have used two infusions of 500 mg. Currently the most suitable pattern for its use is not established. The purpose of this work was to systematically review the published evidence to date regarding on the difference in efficacy in the treatment of RA with RTX when used at a dose of 2 × 500 mg (1 g) or 2 × 1000 mg (2 g) per cycle.

Methods: A sensitive search of all published studies on the difference in the efficacy of RTX in RA patients used at a dose of 1 and 2 g per cycle was performed in Medline, Embase and Cochrane Central databases since its inception until July 2013. We selected all studies involving adult patients with RA treated with RTX in which intervention was described as treatment with RTX at a dose of 1 g per cycle and comparator as the administration of RTX at a dose of 2 g per cycle. Any standardized measure of efficacy in RA was considered as outcome measure at two years of follow-up. Although meta-analysis, systematic reviews, clinical trials and cohorts well designed were considered as outcome measure at two years of follow-up. Although meta-analysis, systematic reviews, clinical trials and cohorts well designed were considered as outcome measure at two years of follow-up, we herein present only the results at 6 months.

Results: 608 patients were recruited of whom 603 were analysed for safety and 577 (Total) for other endpoints. Baseline characteristics: mean age 57±13 years, 454 (79%) females, at least 1 co-morbidity: 409 (71%), mean RA duration 11±9 years. RF or ACPA positive: 479 (86%), erosive disease: 435 (77 %), mean DAS28-ESR 5.2±1.3. Past RA treatments included DMARDs in 98% and biologics in 75%. MTX was previously prescribed in 94% of pts and in 69% within the last 2 years. TCZ Mono was initiated in 229 (40%) pts and TCZ Combo in 348 (60%) pts of whom 74% received MTX (mean dose 16±5mg). Steroids were used in 385 (67%) pts (mean dose 10±7mg). 386 pts completed M6. 86 pts had no M6 visit. 105 pts withdrew for: AE 38 pts, inefficacy 28, patient’s wish 6, lost to follow-up 15, remission, 1, pregnancy 1, unknown 14. 2 pts died: stroke 1, inhalation pneumopathy 1. At M6, drug retention rate was 78% in Total, 75% in Mono, 79% in Combo. A total of 577 (83%) pts among the 577 (100%) pts remained without DMARD, 366 (63%) received TCZ+DMARD. DMARD was added in 18 TCZ Mono pts (twice on a temporary way) and definitely stopped in 23 TCZ Combo pts. 199 (34%) pts experienced at least 1 dose modification (temporary or definitive stop, dose changing) in TCZ infusions, 90 (39%) pts in TCZ Mono and 109 (31%) in TCZ Combo group. During the period 362 (63%) pts received steroids; at M6, 235 (41%) pts remained on steroids. Mean DAS28-ESR in Total, Mono and Combo were 2.80±1.49, 2.89±1.50 and 2.74±1.49 respectively. DAS28-ESR remission was 31% in Total, 26% in Mono, 33% in Combo. DAS 28-ESR LDA was 40% in Total, 38% in Mono, 42% in Combo. No new safety signal was reported. 264 (44%) patients had at least one AE, 46 (8%) had at least one serious AE.

Conclusion: In this 6-month interim analysis, drug retention rate was 78% in pts receiving TCZ in real life. In Total mean DAS 28-ESR decreased from 5.2±1.3 to 2.80±1.5. No new safety signal occurred. Both TCZ Mono and TCZ Combo groups were comparable for drug retention, efficacy and safety.

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Ref:
1. Mallefet et al. ACT SOLO EU LAR 2014 SCIE-1154

Use of Biologic Therapy As Monotherapy in Patients with Rheumatoid Arthritis.

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Background/Purpose: The treatment for Rheumatoid Arthritis (RA) is based on the use of synthetic or biological disease-modifying drugs (DMARDs). Current guidelines recommend biologics in combination with methotrexate as this shows better control of disease progression. However, several studies have shown that up to 30% of patients are treated with biologic monotherapy. The aim of this study was to know the characteristics of patients receiving biologic monotherapy, including previous treatments and reasons for treatment change.

Methods: Observational, cross-sectional, retrospective and multicentric study with the participation of 38 rheumatology units in Spain. Patients were consecutively included if they were >18, with moderate to severe RA as an inadequate response to biological agents. Patients with previous treatments and different reasons. The aim of the study was to know the characteristics of patients receiving biologic monotherapy, including previous treatments and reasons for treatment change.

Results: Two hundred and nine patients were included. 82.8% were women. Mean (SD) age was 57.6 (13.6). Mean (SD) time since RA diagnosis was 13.5 (8.8) years. Most had RF (59.8%), 38.3% anti-CCP antibodies, 73.7% joint damage; 28.5% had extra-articular manifestations.

At study visit, 58.4% of patients were receiving tocilizumab, 18.7% etanercept, 12.4% adalimumab, and 10.5% other biologics. Mean (SD) number of tender joints was 2.7 (3.1), of swollen joints was 1.9 (3.0), and ESR was 14.6 (13.4). Mean (SD) CRP level was 4.0 (7.7), and ESR was 14.6 (13.4). Mean (SD) DAS28 score was 2.7 (1.1), CDAI index was 8.4 (6.9), and SDAI index was 8.8 (7.1), with 49.8%, 15.8%, and 20.1% of patients on in remission, respectively.

Conclusion: Study confirmed that tocilizumab, etanercept, and adalimumab are the most frequently used biologics in RA patients treated with biologic monotherapy. The most frequent reason for treatment withdrawal before monotherapy was lack of effectiveness (61.2%), intolerance (10.5%), adverse events (10.0%), and lack of adherence (1.5%).

Disclosure: A. Gómez-Centeno, Pfizer, Abbvie, Menarini, Roche, Amgen, MSD, 2, UCB, Boehringer Ingelheim, Roche; Abbvie, Pfizer, S. Pfizer, Roche, Abbvie, MSD, UCB, Menarini, B. O. Martinez, None; F. J. Ballina, None; J. M. Rodriguez, None; J. Graña, None; M. Brito, None; J. Sampedro, None; G. Iglesias, None; C. Delgado, None; M. Monteagudo, None.

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Treatment Adjustment Strategy after Achieving Remission or Low Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis.

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Background/Purpose: Aiming at remission or at least low-disease activity (LDA) is a goal achieved in a significant proportion of rheumatoid arthritis (RA) patients. Our aim was to compare the maintenance of remission or LDA after anti-TNF withdrawal in comparison to anti-TNF continuation 2) compare the maintenance of remission or LDA after anti-TNF dose reduction in comparison to anti-TNF continuation.

Methods: A systematic literature review searching for controlled trials comparing anti-TNF withdrawal or anti-TNF dose reduction and anti-TNF continuation in RA patients achieving LDA or remission was conducted using the Embase, PubMed, Cochrane library, and ACR/EULAR meeting databases, updated until June 2014. The two primary endpoints were 1) maintenance of remission or LDA after anti-TNF withdrawal 2) maintenance of remission or LDA after anti-TNF dose reduction. Meta-analysis was performed using the inverse variance approach and statistical heterogeneity was assessed with the Cochran Q-test and I² values.

Results: After systematic literature review, 6 controlled trials comparing anti-TNF withdrawal (725 RA patients in 4 trials) or anti-TNF dose reduction (694 RA patients in 4 trials) and anti-TNF continuation in RA patients achieving LDA or remission were selected for meta-analysis. The comparison of anti-TNF withdrawal versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 4.29 (3.04–6.07) for maintenance of remission (p<0.00001) and 5.33 (3.65–7.79) for maintenance of LDA (p<0.00001) (Figure 1), in favour of anti-TNF continuation. For the comparison of anti-TNF dose reduction versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 1.60 (1.15–2.24) for maintenance of remission (p=0.006) and 1.31 (0.88–1.95) for maintenance of LDA (not significant) (Figure 2), in favour of anti-TNF continuation.

Conclusion: Anti-TNF dose reduction appears as a possible strategy for maintenance of LDA or even remission, while anti-TNF withdrawal appears as a risky strategy in RA patients who already achieved LDA or remission.

Disclosure: S. Henaux, None; T. Barretche, None; A. Ruyssen Wiltrand, None; B. Fautré, None; A. G. Cantagrel, None; A. Constantin, None.

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Adding an Initial Six-Month Course of Infliximab to an Active Combination Treatment Is Cost Saving in Working-Aged Early Rheumatoid Arthritis Patients.

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Conflicts of interest r] NONE.

Background/Purpose: Aiming at remission or at least low-disease activity (LDA) is a goal achieved in a significant proportion of rheumatoid arthritis (RA) patients. Our aim was to compare the maintenance of remission or LDA after anti-TNF withdrawal in comparison to anti-TNF continuation 2) compare the maintenance of remission or LDA after anti-TNF dose reduction in comparison to anti-TNF continuation.

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Results: After systematic literature review, 6 controlled trials comparing anti-TNF withdrawal (725 RA patients in 4 trials) or anti-TNF dose reduction (694 RA patients in 4 trials) and anti-TNF continuation in RA patients achieving LDA or remission were selected for meta-analysis. The comparison of anti-TNF withdrawal versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 4.29 (3.04–6.07) for maintenance of remission (p<0.00001) and 5.33 (3.65–7.79) for maintenance of LDA (p<0.00001) (Figure 1), in favour of anti-TNF continuation. For the comparison of anti-TNF dose reduction versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 1.60 (1.15–2.24) for maintenance of remission (p=0.006) and 1.31 (0.88–1.95) for maintenance of LDA (not significant) (Figure 2), in favour of anti-TNF continuation.

Conclusion: Anti-TNF dose reduction appears as a possible strategy for maintenance of LDA or even remission, while anti-TNF withdrawal appears as a risky strategy in RA patients who already achieved LDA or remission.

Disclosure: S. Henaux, None; T. Barretche, None; A. Ruyssen Wiltrand, None; B. Fautré, None; A. G. Cantagrel, None; A. Constantin, None.

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Fig 1 – M etanalysis of controlled trials assessing the maintenance of LDA after anti-TNF withdrawal in comparison to anti-TNF continuation in RA.

Fig 2 – M etanalysis of controlled trials assessing the maintenance of LDA after anti-TNF dose reduction in comparison to anti-TNF continuation in RA.

Disclosure: S. Henaux, None; T. Barretche, None; A. Ruyssen Wiltrand, None; B. Fautré, None; A. G. Cantagrel, None; A. Constantin, None.
Background/Purpose: To study the cost-effectiveness of adding initial infliximab to a remission-targeted combination treatment with disease modifying antirheumatic drugs (DMARDs) in early rheumatoid arthritis (RA).

Methods: Economic evaluation was conducted alongside the NEO-RACo trial with a 2-year follow-up. A total of 99 patients with early, DMARD-naive RA, receiving a triple combination of DMARDs and prednisolone, were randomized to double-blindly receive either added-on infliximab (FIN-RACo+INF) or placebo (FIN-RACo+PLA) infusions during the first 6 months. All the patients fulfilled the ACR 1997 classification criteria for RA, were 18 to 60 years of age, and available for the workforce.

Direct costs during the 2-year follow-up were estimated on a micro-costing level. The consumed resources were collected from the study forms including all RA-related visits, medications, intraarticular injections, physiotherapy, splints and aids, as well as another person’s help. The unit costs were obtained from the national list of health care costs and other public sources. In addition, data about the lost workdays due to RA were gathered, and the monetary value of lost productivity was estimated by the human capital method. The quality-adjusted life-years (QALYs) gained were calculated on the basis of SF-6D utilities. Both the costs and the QALYs were discounted by 3%.

Results: Over the 2-year follow-up, the average direct costs were 13,574 Euro for the patients in FIN-RACo+INF group and 6,160 Euro for those in FIN-RACo+PLA group. In FIN-RACo+INF, the patients lost 51 workdays and in FIN-RACo+PLA 101 workdays. The respective lost productivity was 8,841 Euro and 17,387 Euro, while the total costs amounted 22,415 Euro and 23,548 Euro. In FIN-RACo+INF group the patients gained on average 1.5533 QALYs and in FIN-RACo+PLA group 1.5267 QALYs with difference of 0.0266 (95% CI: -0.065 to 0.1139, by bias-corrected and accelerated bootstrapping). Based on the direct costs only, the 2-year incremental cost-effectiveness ratio of adding an initial 6-month course of INF on the FIN-RACo+MTX was 278,918 Euro. However, when taking also the indirect costs into account, the FIN-RACo+INF treatment was a dominant therapy. The 2-year incremental cost-effectiveness ratio of adding an initial 6-month course of INF on the FIN-RACo+MTX was 278,918 Euro. However, when taking also the indirect costs into account, the FIN-RACo+INF treatment was a dominant therapy.

Conclusion: From the societal point of view, the induction treatment of early RA by adding a six-month course of infliximab on a targeted treatment with combination DMARDs and prednisolone is cost saving in working-aged patients.

Disclosure: V. Rantalaiku, None; K. Puolakka, AbbVie, BMS, Pfizer, MSD, Roche, UCB, 5. J. Martikainen, None; H. Kautiainen, None; M. Leirisalo-Repa, MSD, Pfizer, 5.

2485

Predictors of Drug-Free Remission Following Treatment with Abatacept in Combination with Methotrexate or as Monotherapy in Early Rheumatoid Arthritis. P Emery1, Gerd Burmester2, Vivian P. Bykerk3, B Combe4, D E Furst5, E Barre6, C S Karyekar7, D Wong7 and TWJ Huizinga8. 1University of California at Los Angeles, Los Angeles, CA, 2Charite – University Medicine Berlin, Berlin, Germany, 3Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, 4Monpellier University Hospital, Montpellier, France, 5University of California at Los Angeles, Los Angeles, CA, 6Bristol-Myers Squibb, Brainmenti, Belgium, 7Bristol-Myers Squibb, Princeton, NJ, 8Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: In the Phase IIIb, randomized, double-blind, active-controlled AVERT study, abatacept (ABA) + MTX and ABA monotherapy induced protocol-defined DAS remission (DAS28 [CRP] <2.6) in 60.9% and 42.5% of pts with early RA after 12 months (mths) on treatment (vs 45.2% with MTX alone); DAS-defined remission was also maintained in 14.8% and 12.4% of pts 6 mths after rapid withdrawal of all RA treatment (vs 7.8% with MTX alone). We further investigated predictors of drug-free DAS-defined remission at 6 mths after ABA withdrawal.

Methods: Pts with early RA (active synovitis in ≥2 joints, onset of symptoms ≥2 years) and DAS28 (CRP) ≥3.2, who were anti-CCP2 positive and MTX-naïve, were randomized to weekly SC ABA 125 mg + MTX, ABA monotherapy or MTX alone for 12 mths. At 12 mths, pts with DAS28 (CRP) <3.2 stopped all RA treatment (ABA immediately and MTX and steroids tapered over 1 mth). Co-primary endpoints were the proportion of pts with DAS-defined remission at (i) Mth 12 and at (ii) both Mths 12 and 18, for ABA + MTX versus MTX alone. To assess predictive characteristics of drug-free DAS-defined remission, post hoc analyses were performed in all treatment groups: (i) descriptive analysis of the proportion of pts with DAS-defined remission at both Mths 12 and 18 by baseline characteristic subgroups and (ii) clinical variables were tested individually by logistic regression in a univariate analysis and variables with p<0.20 were entered into a multivariate model.

Results: Descriptive analysis showed that in both ABA treatment arms, the proportion of pts with DAS28 (CRP) <2.6 at both Mths 12 and 18 was numerically higher in pts with lower baseline DAS28 (CRP), lower baseline HAQ-DI and shorter symptom duration; these factors were not associated with remission at Mths 12 and 18 in the MTX-alone group. Predictive factors for DAS28 (CRP) <2.6 at both Mths 12 and 18 identified in the univariate analysis are shown in the figure. In the multivariate model, adjusted for corticosteroid use and restricted to pts with DAS28 (CRP) <2.6 at Mth 12, baseline DAS28 (CRP) (OR [95% CI] = 1.676 [1.176, 2.387], p=0.0043) and duration of remission in the first 12 mths while on treatment (0.913 [0.807, 1.033], p=0.1484) were identified as predictors of DAS28 (CRP) <2.6 at both Mths 12 and 18.

2486

Patient-Reported Outcomes Following 12 Months of Therapy with Abatacept (Plus Methotrexate or as Monotherapy) in Early Rheumatoid Arthritis. D E Furst1, Vivian P. Bykerk2, Gerd Burmester3, B Combe4, T W J Huizinga5, E Alemao6, D Wong6, C S Karyekar6 and TWJ Huizinga8. 1University of Leeds, Leeds, United Kingdom, 2Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, 3Charité – University Medicine Berlin, Berlin, Germany, 4Monpellier University Hospital, Montpellier, France, 5University of California at Los Angeles, Los Angeles, CA, 6Charité – University Medicine Berlin, Berlin, Germany, 7University of Leeds, Leeds, United Kingdom.

Background/Purpose: Early biologic use can improve long-term control of RA, potentially leading to improved physical function and reduced pain. Recent EULAR recommendations support shared decisions between the patient (pt) and rheumatologist, emphasizing the need for more pt-focused outcomes to assess treatment targets. In the Assessing Very Early Rheumatoid Arthritis Treatment (AVERT) trial, greater % of pts achieved DAS28 (CRP) <2.6 after 12 mths of treatment with SC abatacept (ABA) + MTX and 6 mths after withdrawal of all RA therapy, compared with MTX alone. At most time points, ABA monotherapy was more effective than MTX alone in controlling signs and symptoms of RA. Here, pt-reported outcomes (PROs)
are presented over 18 mths (12 mths of treatment and 6 mths after withdrawal of all RA therapy) in the AVERT trial.

**Methods:** AVERT enrolled pts who were MTX naive, anti-cyclic citrullinated peptide 2 seropositive (CCP2+), aged ≥18 yrs, with active synovitis ≥2 joints for ≥8 wks, DAS28 (CRP) ≥3.2, and a disease onset of ≤2 yrs. Pts were randomized to 12 mths of weekly SC ABA (125 mg) + MTX, SC ABA (125 mg) + placebo or MTX + placebo. All RA treatment was withdrawn after 12 mths (ABA immediately and MTX and steroids tapered over 1 mth) in pts with DAS28 (CRP) <3.2. Fatigue was measured by 100-mm visual analog scale, physical function by HAQ-DI, and health-related quality of life by Short Form-36 (SF-36; Bodily Pain, Physical and Incremental Work Loss Index assessed work productivity in US patients; work health care resource use, work-related activities, and daily activities. The composite Work Loss Index measured the impact of RA across three domains: health care resource use, work-related activities, and daily activities. The composite Work Loss Index assessed work productivity in US patients; work productivity for the entire study population was assessed with the 25-item Work Limitation Questionnaire.

**Results:** 351 pts with early RA were enrolled (n=119, ABA + MTX; n=116, ABA monotherapy; n=116, MTX monotherapy). At baseline: mean disease duration ≤0.6 yrs, mean DAS28 (CRP) 5.4, mean HA-Q-DI 1.4, 95.2% RF- and anti-CCP2-. A adjusted mean change in PRs was calculated using a longitudinal repeated measures model.

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**Conclusion:** In pts with early RA, abatacept + MTX, abatacept monotherapy and MTX alone showed improvements in PRs, with greater improvements seen for abatacept + MTX at 12 mths, compared with MTX alone. PRs worsened in all groups after treatment withdrawal, and below baseline values. These results indicate that treatment with abatacept + MTX early in the course of RA leads to notable improvements in outcomes that are important to pts, such as fatigue, physical function, pain and participation in daily activities, and that some improvement may be maintained up to 6 mths following treatment withdrawal.

**References:**


**Disclosure:** D. E. Furst, AbbVie, Actelion, Amgen, BMS, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2; A. Abbaye, Actelion, Amgen, BMS, Cymed, Jansen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5; B. Abbaye, Actelion, UCB, 8; V. P. Bykerk, Amgen, Pfizer, BMS, Jansen, UCB, Roche/Genentech, 2; G. Burmester, AbbVie, Pfizer, Roche, UCB, 2; AbbVie, BMS, MSD, Medimmune, Novartis, Pfizer, Roche, Sandoz, UCB, 5; AbbVie, BMS, MSD, Pfizer, Roche, Sandoz, UCB, 8; B. Combe, Pfizer, Roche-Chugai, 2, BMS, Merck, Pfizer, Roche-Chugai, UCB, 8; T. W. J. Huizinga, A. Abbott, Biobcrite, Biostet A.G., Bristol-Mysers Squibb, Cressendo Bioscience, Inc, Novartis Pharmaceuticals Corpora- tion, Pfizer Inc, A. Aßentics, Schering-Plough, 8; T. W. J. Huizinga, A. Abbott, Biobcrite, Biostet A.G., Bristol-Mysers Squibb, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche, sanofi-aventis, Schering-Plough, 8, Abbott Laboratories, Roche, 9; E. Aleman, BMS, 3, BMS,
Disease activity, % of pts achieving a response at Month 6

Table 1  ACR50 and LDA clinical disease activity outcomes at Month 6

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tofacitinib 5 mg BID</th>
<th>Tofacitinib 10 mg BID</th>
<th>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR50 responder, %</td>
<td>79</td>
<td>85</td>
<td>69</td>
</tr>
<tr>
<td>LDA responder, %</td>
<td>78</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>HAQ-DI responder, %</td>
<td>80</td>
<td>81</td>
<td>60</td>
</tr>
</tbody>
</table>

Numbers of patients available for assessment varied between parameters ACR, American College of Rheumatology (ACR)<50% improvement from baseline in both tender and swollen joint counts and ≥50% improvement in ≥3 of the 5 remaining ACR core set measures (pain, disability, C-reactive protein or erythrocyte sedimentation rate, patient- and physician global assessments). BID, twice daily. CA, Clinical Activity Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; NA, not applicable; SDAI, Simplified Disease Activity Index.

Table 2  ACR70 and REM clinical disease activity outcomes at Month 6

<table>
<thead>
<tr>
<th>Overall Responders, n (%)</th>
<th>Treatment</th>
<th>ACR70 responder, %</th>
<th>REM responder, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib 10 mg BID</td>
<td>94/340 (28)</td>
<td>40/329 (14)</td>
<td>151/340 (44)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>23/358 (15)</td>
<td>9/145 (9)</td>
<td>15/358 (8)</td>
</tr>
</tbody>
</table>

Numbers of patients available for assessment varied between parameters ACR, American College of Rheumatology (ACR), ≥50% improvement from baseline in both tender and swollen joint counts and ≥50% improvement in ≥3 of the remaining ACR core set measures (pain, disability, C-reactive protein or erythrocyte sedimentation rate, patient- and physician global assessments). BID, twice daily. CA, Clinical Activity Index; DI, Disease Activity Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; NA, not applicable; REM, remission; SDAI, Simplified Disease Activity Index.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we compare the relationship between clinical measures and patient-reported outcomes (PROs) in patients (pts) with RA treated with tofacitinib or methotrexate (MTX).

Methods: MTX-naïve pts with RA from a double-blind, parallel group, Phase 3 trial (ORAL Start; NCT01039688) were randomized (2:2:1) and treated with tofacitinib 5 mg twice daily (BID) therapy (N = 373), tofacitinib 10 mg BID monotherapy (N = 397), or MTX titrated from 10 to 20 mg/week (N = 186). Clinical measures included: the proportion of pts achieving ACR50 and ACR70 responses, the proportion achieving low disease activity (LDA) measured by Clinical Disease Activity Index (CDAI LDA, CDAI ≤ 10), and Simplified Disease Activity Index (SDAI LDA, SDAI ≤ 11), and the proportion achieving remission (REM) measured by CDAI REM (CDAI ≤ 2.8) and SDAI REM (SDAI ≤ 3.3). PROs included: proportion of pts achieving improvements in physical function measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, to normative values ≤ 0.5). Results: At Month 6, a greater proportion of pts achieved ACR responses, LDA, and REM with tofacitinib 5 mg or 10 mg BID than with MTX (Tables). Most pts who achieved LDA and REM by one measure also achieved LDA and REM by other measures (Tables); however, discordance was observed between different measures of LDA and REM, and appeared greater with MTX vs either tofacitinib dose (Tables). As expected there was a high degree of concordance between CDAI LDA and SDAI LDA (Table 1) and CDAI REM and SDAI REM (Table 2). Overall, pts achieving LDA or ACR50 showed less improvement from baseline in patient-reported pain, and patient global assessment of disease compared with tender joints, swollen joints, physical global assessment of disease, and HAQ-DI: pts receiving MTX showed an overall lower improvement in these PROs compared with tofacitinib 5 mg or 10 mg BID. In general, better improvements and consistency in PROs were observed in ACR50 responders compared with measures of LDA. Pts achieving CDAI 0, CDAI REM, and SDAI REM showed similar improvements across PROs and similarly between MTX and tofacitinib.

Conclusion: A higher proportion of MTX-naïve pts receiving tofacitinib 5 or 10 mg BID achieved a clinical response compared with pts receiving MTX. While most pts achieved similar responses across different clinical measures, many may achieve a response in one measure but not the other. Variation of responses with clinical measures, many may achieve a response in one measure but not the other.
Quartile categories (Q): 0 to <650 (Q1); 650 to <1420 (Q2); 1420 to <2500 (Q3); >2500 (Q4) were defined by quartiles obtained from pts with a mean decrease from BL in neutrophil counts (cells/\mu L) at W4. ER: decrease from BL in DAS28-4 ESR >1.2 at W4. Incidence rates (IRs) for SIEs were compared between categories. Pts receiving tofacitinib (all 6 trials) were included in the analysis presented for tofacitinib 5 and 10 mg BID.

**Results:** At BL and W4, 1488, 1506, 622 and 179 pts were evaluable for neutrophil counts for tofacitinib 5, 10 mg BID, placebo (PBO), and MTX, respectively. The proportions of pts with any decrease from BL in neutrophil counts were 69%, 73%, 52% and 56% with tofacitinib 5, 10 mg BID, PBO, and MTX, respectively. At W4, pts with neutrophil decreases in the tofacitinib 5 mg BID group were evenly distributed between categories. With tofacitinib 10 mg BID, a higher proportion of pts had neutrophil decreases within Q3 and Q4 than within Q1 and Q2 (Table). Neutrophil decreases with PBO and MTX were mostly within Q1 and Q2 (Table). In general, the proportion of pts per category with an ER was slightly higher with tofacitinib 10 vs 5 mg BID. With tofacitinib, a higher proportion of pts with an ER was observed in categories with greater reductions in neutrophil counts (Table). SIEs occurred in 30 and 27 pts in the tofacitinib 5 and 10 mg BID groups, respectively. The distribution of pts with SIEs across categories was variable and there were no consistent trends to indicate an association between SIEs and decreases in neutrophil counts (Table), reflecting studies that did not find associations between SIEs and neutropenia.

**Conclusion:** A trend was observed between decreases in neutrophils and ER with tofacitinib. ERs were most commonly seen in pts with the largest category decreases in neutrophil count at W4. No differences were noted between categories with respect to decreases in neutrophil counts and SIEs.


<table>
<thead>
<tr>
<th>Patients with quartile category decreases in neutrophil counts from baseline, and rate of DAS28-4 ESR early response and serious infection events after 4 weeks of treatment (by quartile categories)</th>
<th>Quartile category decreases from baseline in neutrophil count at Week 4 (cells/\mu L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 to &lt;650</strong></td>
<td>(650 to &lt;1420)</td>
</tr>
<tr>
<td>Tofacitinib 5 mg BID (N=1488)</td>
<td>622</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID (N=1506)</td>
<td>622</td>
</tr>
<tr>
<td>Placebo (N=622)</td>
<td>2490</td>
</tr>
<tr>
<td>Nortuximab (N=148)</td>
<td>247 (16.60)</td>
</tr>
</tbody>
</table>

**Table**

Patients with SIEs overall study duration, n/N (IR per 100 pt-yr)

**Background/Purpose:** Previous studies2–4 suggest the structural benefit of IV abatacept in patients with RA who have previously failed MTX, TNF therapy or both.

**Objectives:** This study evaluates the structural benefit of SC abatacept in a cohort of patients with RA, comparing the structural findings with clinical outcomes and measuring any difference between 1 or 2 TNF failure cohorts on stable MTX, average 17 mg/week.

**Methods:** 34 patients were followed over 18-months into an open-label 1-year extension. Patients responded to SC abatacept 125 mg/week on background MTX. Patients on prednisone remained on a stable dose <10 mg, daily. MRI of the hands/wrists were performed on a 0.3T Esate S-Scan and scored blinded using a modified OMERACT/RAMRIS scoring system at Baseline, Wks 12, 24 and 48. A global score of progression, regression, or no change was calculated for each time point. Overall clinical outcomes were measured by a DAS28(ESR) at similar time points.

**Results:** 27 patients completed; 7 patients discontinued including 3 treatment failures. Of the 27 patients who completed the trial, 15 patients had prior exposure to 1 TNF and 12 patients had prior exposure to 2 TNFs. The clinical and structural findings of each group were analyzed independently since individual clinical responses did not directly correlate with the structural response due to disease duration, disease activity at the time of trial entry, and prior drug exposure. Structurally, there were patients in both groups who showed improvement in synovitis and osteitis by MRI, however, the patients who had only 1 prior TNF exposure had a more robust response overall for both synovitis and osteitis. Of the 27 completed patients, 25 were positive DAS28 responders. 2 patients were non-responders. Clinical remission was achieved in 4 patients, low disease activity in 6 patients, moderate disease activity in 8 patients, and high disease activity remained in 7 patients. Clinically, there was no clear trend to distinguish any difference between the two groups. Both clinical and structural responses occurred within 6-months. 2 patients who had a clinical response at 6 months failed to sustain a response at 12 months. No adverse events were noted.

**Conclusion:** Overall, this small cohort of patients suggests that SC abatacept has clinical and structural benefit in patients who have had treatment with either 1 or 2 TNFs and is a viable choice of therapy. The structural findings were comparable to the benefits of IV abatacept which have been previously published.5 The group that had 1 TNF exposure showed a greater improvement with respect to synovitis and osteitis than the population with 2 TNF exposure. It is possible that the structural benefit may be more robust when a switch from TNF therapy to an alternative mechanism of action such as abatacept is made after only 1 TNF failure. Further analysis is needed to determine if 6 months can be used as a cut-off point that prognosticates the value of continuing further therapy in the face of a lack of clinical and/or structural disconnect demonstrated is necessary to provide optimal management of RA patients.

**References:**


**Disclosure:** N. B. Gaylis; None. S. Needell, None. J. Sagliani, None.

**2491**

**Prognostic Factors for IV Abatacept Retention in Patients Who Have Received at Least One Prior Biologic Agent: 2-Year Results from a Prospective, International, Real-World Study.**


**Background/Purpose:** Previous studies1–2 suggest the structural benefit of IV abatacept in patients with RA who have previously failed MTX, TNF therapy or both.

**Objectives:** This study evaluates the structural benefit of SC abatacept in a cohort of patients with RA, comparing the structural findings with clinical outcomes and measuring any difference between 1 or 2 TNF failure cohorts on stable MTX, average 17 mg/week.

**Methods:** 34 patients were followed over 18-months into an open-label 1-year extension. Patients responded to SC abatacept 125 mg/week on background MTX. Patients on prednisone remained on a stable dose <10 mg, daily. MRI of the hands/wrists were performed on a 0.3T Esate S-Scan and scored blinded using a modified OMERACT/RAMRIS scoring system at Baseline, Wks 12, 24 and 48. A global score of progression, regression, or no change was calculated for each time point. Overall clinical outcomes were measured by a DAS28(ESR) at similar time points.

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**Conclusion:** Overall, this small cohort of patients suggests that SC abatacept has clinical and structural benefit in patients who have had treatment with either 1 or 2 TNFs and is a viable choice of therapy. The structural findings were comparable to the benefits of IV abatacept which have been previously published.5 The group that had 1 TNF exposure showed a greater improvement with respect to synovitis and osteitis than the population with 2 TNF exposure. It is possible that the structural benefit may be more robust when a switch from TNF therapy to an alternative mechanism of action such as abatacept is made after only 1 TNF failure. Further analysis is needed to determine if 6 months can be used as a cut-off point that prognosticates the value of continuing further therapy in the face of a lack of clinical and/or structural disconnect demonstrated is necessary to provide optimal management of RA patients.

**References:**


**Disclosure:** N. B. Gaylis; None. S. Needell, None. J. Sagliani, None.
IV ABA in adults with moderate-to-severe RA in Europe and Canada (May 2008–Jan 2011). Socio-demographics, disease characteristics, previous/ concomitant therapies, and comorbidities at ABA initiation were considered potential prognostic variables of retention. Pts who had received ≥1 prior biologic agent in countries with sufficient pt numbers to explore between-country effects were included. Clinically relevant variables, known risk factors and prognostic factors with a p ≤ 0.10 (univariate analysis) were entered into a multivariate Cox proportional hazards regression model, with clustered data adjusted for one investigator. Factors with p ≤ 0.10 after backward selection were retained in the final model. Co-linearity and interactions were assessed. A didactical analysis to account for missing data in covariates was performed using multiple imputation by chained equations.

Results: 1009/1131 (89.2%) evaluable pts had failed ≥1 prior biologic agent. The crude retention rate (95% CI) at 24 months (Kaplan-Meier method) for pts exposed to ≥1 prior biologic agent was 53.4% (50.1, 56.6%). 94% of 1009 pts were included in the analysis of prognostic factors. Final multivariate model results (n = 916) are shown in the Figure. Pts had significantly higher likelihood of ABA retention if they were both RF and ACPA positive or had cardiovascular comorbidity at initiation. Prior anti-TNF agents, high baseline ESR and corticosteroid (CS) use were also prognostic factors for discontinuation. Despite showing borderline significance in the first model (Figure), use of a non-anti-TNF biologic agent before ABA (n = 143, 15.6%) was an additional prognostic factor of lower retention (1.29 [1.00, 1.66]; p = 0.049) in the model with imputation of missing data (not shown). Disease duration, ABA monotherapy and BMI were not identified as prognostic factors.}

Conclusion: ACTION is one of the first studies to identify and report prognostic factors of long-term abatacept retention in a real-world setting. Double ACPA and RF positivity and cardiovascular comorbidity at initiation were prognostic of higher retention. Consistent with other reports, a higher number of prior anti-TNFs, country and more severe disease (suggested by higher baseline ESR and introduction of CS) were identified as prognostic factors of lower retention. These results will support individualized biologic treatment strategies in pts with moderate-to-severe RA.


Disclosure: H. Nülllein, Bristol-Myers Squibb, Abbott, Chugai, UCB, Essex, Wyeth, Pfizer, MSD, Novartis and Roche; S. R. Alten, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, M. Galeazzi, None; H. Lorenz, Bristol-Myers Squibb, 5, M. Nurmohamed, BMS, Janssen, 5, Roche, Abbvie, Pfizer, UCB, 8, Roche, Abbvie, Pfizer, MSD, UCB, BMS, 2, W. Bensen, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, Warner Chilcott, Wyeth, 2, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, 8, H. Peter, None; P. Peichl, None; K. Pavrika, MSD, Abbvie, Pfizer, UCB, Roche, Amgen, Menarini, BMS, 5; M. Charterie, None; C. Poncet, Bristol-Myers Squibb, 9; C. Rauch, Bristol-Myers Squibb, 3; M. Le Bars, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1.

2492

Does Body Mass Index Impact Long-Term Retention with Abatacept in Patients with RA Who Have Received at Least One Prior Biologic Agent? 2-Year Results from a Real-World, International, Prospective Study.

Background/Purpose: Double ACPA and RF positivity and cardiovascular comorbidity at initiation were more likely to have comorbidities, but were less likely to be RF or ACPA positive or had cardiovascular comorbidity at initiation. Prior anti-TNF agents, high baseline ESR and corticosteroid (CS) use were also prognostic factors for discontinuation. Despite showing borderline significance in the first model (Figure), use of a non-anti-TNF biologic agent before ABA (n = 143, 15.6%) was an additional prognostic factor of lower retention (1.29 [1.00, 1.66]; p = 0.049) in the model with imputation of missing data (not shown). Disease duration, ABA monotherapy and BMI were not identified as prognostic factors.}

Conclusion: ACTION is one of the first studies to identify and report prognostic factors of long-term abatacept retention in a real-world setting. Double ACPA and RF positivity and cardiovascular comorbidity at initiation were prognostic of higher retention. Consistent with other reports, a higher number of prior anti-TNFs, country and more severe disease (suggested by higher baseline ESR and introduction of CS) were identified as prognostic factors of lower retention. These results will support individualized biologic treatment strategies in pts with moderate-to-severe RA.

Table 1

<table>
<thead>
<tr>
<th>BMI class</th>
<th>n (%)</th>
<th>Crude retention rate (95% CI)</th>
<th>Adjusted hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight/normal &lt;25 kg/m²</td>
<td>359 (36.1)</td>
<td>53.8 (48.3, 59.0)</td>
<td>1</td>
<td>0.39</td>
<td>0.51</td>
</tr>
<tr>
<td>Overweight 25–&lt;30 kg/m²</td>
<td>324 (32.5)</td>
<td>57.4 (51.3, 62.8)</td>
<td>1</td>
<td>0.90</td>
<td>0.72, 1.13</td>
</tr>
<tr>
<td>Obese class I 30–&lt;35 kg/m²</td>
<td>168 (16.9)</td>
<td>50.5 (42.4, 58.1)</td>
<td>1</td>
<td>0.96</td>
<td>0.71, 1.31</td>
</tr>
<tr>
<td>Obese class II/III ≥35 kg/m²</td>
<td>85 (8.5)</td>
<td>53.2 (41.3, 63.7)</td>
<td>1</td>
<td>0.86</td>
<td>0.65, 1.12</td>
</tr>
</tbody>
</table>

Conclusion: ACTION is one of the first studies to identify and report prognostic factors of long-term abatacept retention in a real-world setting. Double ACPA and RF positivity and cardiovascular comorbidity at initiation were more likely to have comorbidities, but were less likely to be RF or ACPA positive or had cardiovascular comorbidity at initiation. Prior anti-TNF agents, high baseline ESR and corticosteroid (CS) use were also prognostic factors for discontinuation. Despite showing borderline significance in the first model (Figure), use of a non-anti-TNF biologic agent before ABA (n = 143, 15.6%) was an additional prognostic factor of lower retention (1.29 [1.00, 1.66]; p = 0.049) in the model with imputation of missing data (not shown). Disease duration, ABA monotherapy and BMI were not identified as prognostic factors.


Disclosure: H. Nülllein, Bristol-Myers Squibb, Abbott, Chugai, UCB, Essex, Wyeth, Pfizer, MSD, Novartis and Roche; S. R. Alten, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, M. Galeazzi, None; H. Lorenz, Bristol-Myers Squibb, 5, M. Nurmohamed, BMS, Janssen, 5, Roche, Abbvie, Pfizer, UCB, 8, Roche, Abbvie, Pfizer, MSD, UCB, BMS, 2, W. Bensen, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, Warner Chilcott, Wyeth, 2, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, 8, H. Peter, None; P. Peichl, None; K. Pavrika, MSD, Abbvie, Pfizer, UCB, Roche, Amgen, Menarini, BMS, 5; M. Charterie, None; C. Poncet, Bristol-Myers Squibb, 9; C. Rauch, Bristol-Myers Squibb, 3; M. Le Bars, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1.
Prediction of Remission and Low Disease Activity in DMARD-Refractory Patients with RA Treated with Golimumab. N Vasteaeger, P Duriez, B Corthout, C Zerbini, B Dasgupta, B Combe, H Amital, S Huyck, HH Weng, and Grant W. Cannon. 1Salt Lake City VA and University of Utah, Salt Lake City, UT, 2VA Medical Center Nashville, Nashville, TN, 3Bristol-Myers Squibb, 4Novartis, 5Amgen, 6AbbVie, 7Celgene, 8Janssen, 9Pfizer, 10Roche, 11UCB, 12AGAR Francisco Marroquin University, Guatemala City, Guatemala, 13Agape Hospital, 14Sheba Medical Center, Tel-HaShomer, Israel, 15Eli Lilly & Co., Inc., 16Whitehouse Station, NJ, 17MSD Italy, Rome, Italy.

Background/Purpose: EULAR recommendations for RA therapy suggest addition of a biologic only if poor prognostic factors such as high disease activity are present. However, low baseline disease activity is associated with better biologic treatment outcomes. Better tools to predict remission/low disease activity (LDA) and aid in selection of patients for anti-TNF treatment are important.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients (pts) with active RA despite DMARD therapy. Pts received 50-mg subcutaneous golimumab (GLM) once monthly for 6 months in addition to their background DMARDs. The following baseline characteristics were first evaluated in univariable models predicting 28-joint disease activity score based on ESR (DAS28-ESR) LDA and remission at 1 and 6 months: age, sex, smoking history, comorbidities, number of failed DMARDs, methotrexate dose, disease duration, tender joint count-28 (TJC28), swollen joint count-28 (SJC28), ESR, patient global assessment of disease activity (PGA), and HAQ. Factors were evaluated in a stepwise fashion. Those with significant associations (P < 0.10) were included in a final multivariable model. Factors that predicted both LDA and remission at 1 and 6 months were used in the final model. The ability of the models to predict LDA and remission at month 6 was investigated using receiver operating characteristic (ROC) analyses.

Results: 3260 pts were included in the analysis: 82.8% female, mean age 52.3 years, mean disease duration 7.6 years, mean DAS28-ESR, SJC28, TJC28 (standard deviation – 0.095). DAS28-ESR remission and LDA were achieved by 7.7% and 16.6% of pts, respectively, after 1 month of GLM treatment (1 7.7% and 16.6% of pts, respectively, after 1 month of GLM treatment (1

Conclusion: Sex, age, ESR, HAQ, absence of comorbidities, and TJC28 at baseline allowed accurate prediction of remission and LDA in the first 6 months of GLM therapy in patients failing DMARDs. This prediction model allows better selection of anti-TNF candidates.
V A R A enrollment, HLA-DR1 genotyping for shared epitope status, mean multidimensional health assessment questionnaire (MDHAQ), and mean disease activity score (DA258) during observation were compared in the two groups. Chart review was conducted on all MONO patients to determine status of RA disease control and if specific reasons were present for not using additional DMARD therapy.

**Results:** Of 2,079 enrolled V A R A patients, 486 met enrollment criteria with 50 (10.3%) MONO patients and 436 (89.7%) POLY patients. MONO DMARDs were methotrexate 36 (72%), hydroxychloroquine 31 (62%), and one (2%) each for leflunomide, sulfasalazine, and etanercept. Reasons documented for MONO persistence included adequate disease control (n=46; 92%), poor medication adherence (n=3; 6%), and contraindications to other DMARDs because of frequent infections (p<0.02), less likely to be seropositive for anti-CCP (p<0.01), less likely to have rheumatoid nodules (p<0.03), and less likely to have DRB1 shared epitope (p<0.05). MONO patients had lower average DA258 scores (p<0.05) (Table).

**Table:** RA patient characteristics among those using persistent MONO compared to POLY during the first five years of disease; *chi-square test for categorical variables, t-test for continuous variables.

|                              | MONOtherapy | Polytherapy | p-value*
|------------------------------|-------------|-------------|-----------
| Age at Diagnosis             | 64.7±13.5   | 58.8±11.8   | <0.02     |
| Gender (Male)                | 45 (90%)    | 382 (88%)   | NS        |
| Smoking Status               |             |             |           |
| Never                        | 7 (14%)     | 93 (21.3%)  | NS        |
| Former                       | 31 (62%)    | 190 (43.6%) |           |
| Current                      | 12 (24%)    | 153 (35.1%) |           |
| Rheumatoid Factor Positive   | 32 (65.3%)  | 326 (77.8%) | NS        |
| Anti-CCP Positive            | 27 (56.3%)  | 310 (74.2%) | <0.01     |
| Rheumatoid Nodules           | 6 (12.5%)   | 116 (28.5%) | <0.03     |
| X-ray Changes at Enrollment  | 11 (22%)    | 139 (32.7%) | NS        |
| HLA-DRB1 Shared Epitope Status |           |             |           |
| SE positive - 2 copies       | 4 (8%)      | 66 (15%)    | <0.05     |
| SE positive - 1 copy         | 16 (32%)    | 205 (47%)   |           |
| No. Copies                   | 26 (42%)    | 118 (27%)   |           |
| Average MDHAQ                | 0.8±0.5     | 0.9±0.5     | NS        |
| Average DA258 Score          | 3.0±1.0     | 3.8±1.2     | <0.05     |

**Conclusion:** While sustained treatment with a single DMARD during the first five years of RA treatment in US veterans is rare, most of these patients have adequate disease control. Patients on persistent monotherapy were older at disease onset, less likely to be seropositive, less likely to have rheumatoid nodules, and less likely to carry the DRB1 shared epitope in comparison to patients receiving multiple DMARDs.

**Disclosure:** J. Kruger, None; M. Morgan, None; A. Reimold, None; T. R. Mikulcs, Genetech/Roche, 2; G. K. Kerr, None; G. W. Cannon, None.

**2496**

**Predictors of ACR/EULAR Boolean and SDAI Remission in Patients with Established Rheumatoid Arthritis Treated with Anti-TNF: An Analysis from the Prospective, Observational, Biological Treatment Registry Across Canada.** Boulos Harauzi1, Abagoo S. Sheppard2, M. Ajay Khrishi3, M. Michael Starr4, John K. Kelsall5, Milton Baker6, Regan Arendt6, Sanjay Dixit6, William Bensen7, Philip Bae6, Rafat Farawi7, Emmanouil Rampakakis8, John S. Sampalis9, Susan Ota2, Allen J. Lehman10, Francois Nante11, and May Shaw12. 1Centre Hospitalier de l’Universite de Montreal, Montreal, QC; 2Roman Catholic Hospital, North York, ON; 3Rheumatology, University Health Network, Toronto, ON; 4Queen Elizabeth Western Hospital, Saint John’s, NL; 5Montreal General Hospital, Montreal, QC; 6McMaster University, Hamilton, ON; 7Montreal General Hospital, Montreal, QC; 8Montreal Children’s Hospital, Montreal, QC; 9The Arthritis Research Institute of Ontario, Toronto, ON; 10The Arthritis Research Institute of Ontario, North York, ON; 11University of Vicotria, Vitoria, BC; 12University of Saskatchewan, Saskatoon, SK; 13McMaster University, Hamilton, ON; 14Ontario Action, Scarborough, ON; 15JS Medical Research, Montreal, QC.

**Background/Purpose:** Early achievement of remission is associated with improved clinical, functional, and radiographic outcomes1. Recent recommendations of the Canadian Rheumatology Association dictate that treatment target should be remission or, when not possible, low disease activity. The aim of this analysis was to define the predictive factors of time to disease remission in established rheumatoid arthritis (RA) patients treated with infliximab.

**Methods:** BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for ≤6 months. RA patients treated with infliximab...
who were enrolled between 2002–2012 and had ≥1 follow-up assessment were included. Remission was defined according to the ACR/EULAR Boolean criteria (TJC28=1, SJC28=1, CRP=1 mg/dL, and PGA=1) or CDAI≤2.8. Independent predictors of remission were identified by multivariate Cox regression considering as potential confounders parameters showing a statistical trend (P<0.150) in univariate analyses.

**Results:** A total of 671 patients were included of whom 494 (73.6%) were female. At baseline, mean (SD) age was 56.0 (13.5) years and mean (SD) disease duration was 10.3 (10.1) years. Mean time to CDAI and Boolean remission was 47.3 and 54.1 months, respectively. In univariate analysis, the following factors showed a statistical trend in their association with longer time to CDAI remission: earlier enrolment period (P=0.117), increased age (P=0.070), longer disease duration (P=0.008), female gender (P=0.143), and increased baseline disease activity as indicated by TJC28 (P<0.001), SJC28 (P<0.001), morning stiffness (P=0.003), pain (P<0.001), PGA (P<0.001), MDGA (P<0.001), HAQ-DI (P<0.001), and CDAI (P<0.001). Rheumatoid factor (RF) status, number of previous DMARDs, and initial (first 6 months) treatment with DMARD(s), NSAID(s) or steroid(s) did not predict achievement of remission. In multivariate analysis, baseline CDAI [HR (95% CI)]: 0.97 (0.96,0.98); P<0.001) and disease duration [0.98 (0.97,1.00); P=0.018] were identified as independent predictors of time to CDAI remission. Similarly, multivariate survival analysis showed that increased disease duration [0.98 (0.96,1.00); P=0.047] and increased pain [0.98 (0.98,0.99); P<0.001] at baseline were associated with a lower chance of achieving ACR/EULAR Boolean remission.

**Conclusion:** Upon adjusting for potential confounders, increased disease duration before anti-TNF initiation is an independent predictor of longer time to remission. The results of these real-world Canadian data support findings that earlier initiation of anti-TNF agents may be associated with increased remission rates when stringent definitions of remission are considered.

**References:**

2497

**Correlation Between Time to Switch and Clinical Response Amplitude to Rituximab in Second Line Treatment in Rheumatoid Arthritis Patients with Treatment Failure to Tumor Necrosis Factor Inhibitors 3-Year Data from Repeat Observational Study.** Ioan Ancuta1, Ruxandra Ionescu2, Catalin Codreanu3, Andrea Balanescu4, Elena Rezus5, Maria Suta5, Paulina Ciurea6, Mihaela Mihlicateu7, Dan Nemes8, Codrina Ancuta9, Mihai Bojinca, Magda Parvu10 and Horatiu Popoviciu11. 1“Dr. I. Cantacuzino” National Local Study, 1087 patients with active RA and inadequate response to at least one TNF inhibitor received initial RTX (2×1000 mg IV, at 2 weeks apart) and subsequent RTX courses have been enrolled from 2010 to 2013. The patients were stratified according to the length of anti-TNF treatment before switch: <12 months (group A = 260), 12–24 months (group B = 278) and >24 months (group C = 526). Clinical assessments including 28-joint disease activity score (DAS-28) were performed at baseline (switch moment) and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. For the purpose of this analysis, median DAS-28 values were calculated for each group (A, B and C) and followed by median Delta DAS-28 values calculation, as differences between values found at two successive evaluations and also from baseline to each evaluation. Statistical analyses were performed with STATA SE 11.0 software. Comparison between all previous treatments and evaluations for disease activity were performed using Nptrend and ANOVA tests.

**Results:** Median values for ∆ DAS-28 obtained for group A, group B and group C from baseline to 6 months were -1.65; -1.35; -1.33 (P=0.01), from baseline to 12 months: -2.43; -2.05; -2.17 (P=0.02), from baseline to 18 months: -2.96; -2.59; -2.49 (P=0.009), from baseline to 24 months: -3.26; -2.83; -2.57 (P=0.01), from baseline to 30 months: -3.58; -3.27; -2.66 (P=0.15) and from baseline to 36 months: -2.56; -2.54; -2.83 (P=0.09). The median ∆ DAS-28 achieved in group A at 1 year (-2.43) is comparable with ∆ DAS-28 obtained at 18 month in group B (-2.59) and group C (-2.49). A cross evaluations Nptrend test was P<0.0001 and ANOVA was P<0.0001.

**Conclusion:** 1. The median values of ∆ DAS-28 as a measure of the amplitude of response to RTX show robust data that support the sustained clinical response to RTX across all 3 groups of patients over the 36 months treatment observation. 2. It is a significant difference between median values of ∆ DAS-28 for group A and group B and C, showing a deeper and faster clinical response achieved in patients who were switched earlier to RTX in second line after anti-TNF treatment failure, with a pick at 24 months.

**Disclosures:** I. Ancuta, None, R. Ionescu, None, A. Balanescu, None, E. Rezus, None, M. Suta, None, P. Ciurea, None, M. Mihlicateu, None, D. Nemes, None, C. Ancuta, None, M. Bojinca, None, M. Parvu, None, H. Popoviciu, None.

2498

**Characteristics of Responding Versus Non-Responding Moderate Rheumatoid Arthritis Patients Treated With Etanercept Plus Methotrexate.** Josef S. Smolen1, David Collier2, Annette Szumski3, Heather Jones4 and Lisa Marshall5. 1PSSAID Taskforce, EULAR, Zurich, Switzerland, 2Amgen, Inc., Thousand Oaks, CA, 5Pfizer Inc., Collegeville, PA.

**Background/Purpose:** While synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) are often effective, treatment with such agents does not adequately control disease activity in all patients. Early identification of those unlikely to achieve long-term therapeutic goals is a clinically relevant strategy that may allow for appropriate modification in patient management to achieve optimal outcomes. The objective of this subanalysis was to determine disease characteristics of patients with moderate RA responsive (defined by achievement of DAS28=2.6) and non-responders to treatment with etanercept (ETN) plus methotrexate (MTX) after 36 weeks in the PRESERVE study.

**Methods:** In the induction phase of PRESERVE, subjects with moderately active RA (DAS28 >3.2 and ≤5.1) despite stable doses of oral MTX received open-label ETN 50 mg QW plus MTX (titrated to ≤25 mg/week as needed through week 28) for 36 weeks. Baseline demographic and disease characteristics and treatment response (DAS28, CDAI, HAQ) were compared in responders (defined as patients with DAS28≤2.6) and non-responders (DAS28>2.6) at week 36. Analyses used observed cases (OC) were conducted in all patients who received ≥1 ETN/MTX dose (mITT population).

**Results:** Of 764 patients receiving ETN50/MTX, 515 (67.4%) were classified as responders and 249 (32.6%) as non-responders at week 36. At baseline, responders were significantly younger (46.9 vs 50.9 years, P<0.001) with a lower BMI (25.4 vs 26.4, P=0.008) compared with non-responders. Responders also had significantly lower ESR (21.2 vs 24.7, P<0.001), CRP (11.4 vs 14.4, P=0.02), DAS28 (4.3 vs 4.5, P<0.001), CDAI (17.5 vs 18.3, P<0.001) and HAQ (1.1 vs 1.3, P<0.001) values than non-responders at baseline. Among responders and non-responders, significant changes from baseline in DAS28, CDAI and HAQ were observed at Week 4 and at all time-points up to Week 36 (all P<0.0001). Reductions in DAS28, CDAI, and HAQ were significantly greater among responders than non-responders after 4 weeks and this difference between groups was maintained for all clinical outcomes for the duration of the study period (Table).
Conclusion: In the PRESERVE trial, patients with moderately active RA who achieved DA28<2.6 after treatment with ETN plus MTX showed lower disease activity and functional improvement at baseline than those patients who did not achieve treatment target. Understanding the difference between responders and non-responders may help guide treatment practices and provide the best therapeutic options to these different patient sub-types.

Disclosure: J. S. Smolen, Abbvie, BMS, Janssen, MSD, Pfizer, UCB, 2, Abbvie, CZP received other biologics prior to the assessment; all had associated a synthetic disease-modifying anti-rheumatic drug (DMARD) regimen. L. Bazzichi II, None; Stefano Bombardieri, None; and Camillo Giacomelli, None.

2500

Table 1  Associations between gene variants and anti-TNF treatment response

<table>
<thead>
<tr>
<th>Gene (SNP)</th>
<th>Genotype</th>
<th>N</th>
<th>Adj. OR (95% CI), P-value</th>
<th>Adj. OR (95% CI), P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>EULAR response</td>
<td>AC150 response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G vs. N</td>
<td>G vs. N</td>
</tr>
<tr>
<td>rs4833095</td>
<td>TT</td>
<td>312</td>
<td>1.02 (0.70-1.49), 0.910</td>
<td>1.11 (0.73-1.68), 0.581</td>
</tr>
<tr>
<td>rs4833095</td>
<td>TC</td>
<td>178</td>
<td>1.02 (0.70-1.49), 0.910</td>
<td>1.11 (0.73-1.68), 0.581</td>
</tr>
<tr>
<td>rs4833095</td>
<td>CC</td>
<td>243</td>
<td>1.02 (0.70-1.49), 0.910</td>
<td>1.11 (0.73-1.68), 0.581</td>
</tr>
<tr>
<td>rs4833095</td>
<td>T/C</td>
<td>199</td>
<td>1.02 (0.70-1.49), 0.910</td>
<td>1.11 (0.73-1.68), 0.581</td>
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<tr>
<td>rs4833095</td>
<td>TT</td>
<td>170</td>
<td>1.02 (0.70-1.49), 0.910</td>
<td>1.11 (0.73-1.68), 0.581</td>
</tr>
</tbody>
</table>

References:
4. Bazzichi L, Rheumatol Int 2010
5. Curtis JR Arthritis Care Res 2012

Disclosure M. Cazzato, None; L. Bazzichi II, None; S. Bombardieri, None; C. Giacomelli, None.
2501

Indirect Comparison of Tocilizumab and Tofacitinib in Patients with Rheumatoid Arthritis. Stacey Chang1, Laura Sawyer2 and Fred Dejongheere3. 1Symmetron Limited, London, United Kingdom, 2F. Hoffmann-La Roche, Basel, Switzerland.

Background/Purpose: Tocilizumab (TCZ) is a recombinant, humanized, monoclonal antibody directed against the cytokine interleukin-6 receptor, and tofacitinib (Tofa) is an oral, synthetic, disease-modifying antirheumatic drug (DMARD) inhibiting Janus kinases (JAKs). Both are licensed for use in combination with other conventional DMARDs or as monotherapy in patients with moderately to severely active rheumatoid arthritis (RA) who have had inadequate responses to ≥1 DMARDs. The purpose of this study was to evaluate the effectiveness of TCZ compared with Tofa in their licensed populations (ie, RA patients with inadequate responses to conventional nonbiologic or biologic DMARDs [cDMARD-IR or bDMARD-IR]) based on publicly available evidence to date.

Methods: Efficacy was assessed for each treatment compared with placebo using available randomized controlled trial (RCT) evidence, after which treatments were indirectly compared with each other using the Bucher method.4 Four comparisons were performed, each developed based on similarities between TCZ and Tofa studies in terms of population characteristics and treatment type (monotherapy and combination therapy). Comparative efficacy was assessed on the proportion of patients achieving American College of Rheumatology (ACR) scores of 20, 50, and 70 and Disease Activity Score using 28 joints (DAS28)–defined remission (DAS28 scores of 20, 50, and 70) and Disease Activity Score using 28 joints of patients achieving ACR20 and ACR50 responders and DAS remitters than Tofa.

Results: Across the 4 comparisons, 6 RCTs of TCZ and 6 RCTs of Tofa were included. In both monotherapy and combination therapy in cDMARD-IR and combination therapy in methotrexate (MTX)-IR patients, TCZ was more likely to generate ACR response and DAS remission than Tofa. In MTX-IR patients, TCZ in combination with MTX generated more ACR20 and ACR50 responders and DAS remitters than Tofa + MTX. Treatment effects between TCZ and Tofa failed to reach statistical significance in all 3 instances (Table 1, Figure 1). The trends observed were robust to the sensitivity analyses performed.

Conclusion: Results of the indirect comparisons suggest TCZ and Tofa have broadly similar efficacy across different RA populations. There is a consistent trend (significant in 3 instances) favoring TCZ across all licensed RA populations on the outcome of DAS remission and ACR response.


Table 1. TCZ vs Tofa Across Different RA Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Type</th>
<th>Risk Ratio (95% Confidence Interval)</th>
<th>TCZ vs Tofa</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX-IR</td>
<td>Combination therapy</td>
<td>1.47 (1.28, 1.69)</td>
<td>1.57 (1.32, 1.87)</td>
</tr>
<tr>
<td></td>
<td>Combination therapy</td>
<td>1.39 (1.30, 1.35)</td>
<td>1.34 (1.28, 1.41)</td>
</tr>
<tr>
<td></td>
<td>Combination therapy</td>
<td>2.35 (2.15, 4.72)</td>
<td>1.71 (1.62, 1.86)</td>
</tr>
</tbody>
</table>

2502

Ten Year Follow-up Results of Four Dynamic Treat to Target Strategies in Patients with ACPA Negative Rheumatoid Arthritis. I.M. Arkkuse1, G. Akdemir2, L. Dirven3, M. van den Broek3, K.H. Han4, H.K. Rondan5, P.J.S.M. Kerstens6, W.F. Lems6, T.W.J. Huizinga7 and C.F. Allaart8. 1Leiden University Medical Center, Leiden, Netherlands, 2MCRZ hospital, Rotterdam, Netherlands, 3Haga Hospital, The Hague, Netherlands, 4van Breemen Research Institute Reade, Amsterdam, Netherlands, 5VU Medical Center, Amsterdam, Netherlands.

Background/Purpose: To determine the optimal treatment strategy in patients with anti-citrullinated protein antibodies (ACPA) negative (−) rheumatoid arthritis (RA), it has been suggested that these patients require a different treatment approach than ACPA positive (+) patients.

Methods: 184 ACPA− patients were randomized to 1. sequential monotherapy, 2. step-up therapy, 3. initial combination with prednisone, 4. initial combination with infliximab, as were 300 ACPA+ patients. Treatment adjustments were based on 3-monthly disease activity score (DAS) measurements, aiming at DAS ≤2.4. Functional ability (health assessment questionnaire, HAQ), radiographic progression (Sharp van der Heijde score, SHS) and (drug-free) remission (DAS ≤1.6) percentages over 10 years were compared between the 4 arms in ACPA− patients and between ACPA− and ACPA+ patients per randomisation arm.

Results: At 3 months, ACPA− patients achieved more often DAS ≤2.4 (52% versus 18%, p < 0.001), remission (17% vs 5%, p < 0.001) and improvement in functioning (mean HAQ 0.6 vs 1.0, p = 0.001) on initial combination therapy than on initial monotherapy. These differences remained until year 1. After 10 years of targeted therapy, over time no differences were retrieved (p = 0.551 for HAQ, p = 0.851 for remission). Table 1 shows the main outcomes at year 10.

Drug survival (achieve and maintain DAS ≤2.4) on methotrexate monotherapy (1st step in arm 1 and 2) was similar in ACPA− and ACPA+ patients (median survival 10 vs 7 months, p = 0.750), as also drug survival on sulphasalazine (2nd step in arm 1 and 2, median survival 3 vs 3 months, p = 0.659). At year 1, in arm 3 18/55 ACPA− patients (33%) and 31/68 ACPA+ patients (46%) tapered to monotherapy (p = 0.310). In arm 4, 17/43 ACPA− (40%) and 38/82 ACPA+ patients (46%) discontinued infliximab (p = 0.466).

Drug-free remission (DFR) was more often achieved and longer sustained in ACPA− than in ACPA+ patients, in all treatment arms (26% vs 8% in arm 1, p = 0.077; 24% vs 9% in arm 2, p = 0.048; 30% vs 2% in arm 3, p = 0.002; 28% vs 6% in arm 4, p = 0.001, median DFR duration averaged in 4 arms 69 vs 32 months, p = 0.073). Over time, radiographic progression (Δ ≥0.5 in SHS) in ACPA− patients was not different between the 4 arms (p = 0.082).

5H3 progression was more often observed in ACPA+ patients than in...
ACPA—patients in arm 1, 2 (both p < 0.001) and arm 3 (p = 0.016), but not in arm 4 (p = 0.849).

Conclusion: On the short term, patients with ACPA—RA benefit more from initial combination therapy with prednisone or infliximab than from monotherapy, as also ACPA+ patients. During subsequent DAS steered therapy, ACPA—patients respond similarly to treatment steps in all 4 treatment arms to ACPA+ patients, suggesting that both groups require a similar treatment approach. After 10 years of targeted therapy, ACPA—patients achieve more often sustained drug-free remission than ACPA+ positive patients and show less radiographic progression, except in arm 4.

Table 1: Main outcomes at year 10 for ACPA negative patients in the four treatment arms

<table>
<thead>
<tr>
<th>Predictor</th>
<th>ENTN 25 mg + MTX</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First DAS28 remission</td>
<td>Days 0-57</td>
<td>58-179</td>
</tr>
<tr>
<td>First DAS28 LDA</td>
<td>Days 0-29</td>
<td>30-57</td>
</tr>
<tr>
<td>Mean DAS 28, week 52</td>
<td>DAS28 ≤1.55</td>
<td>≥1.55-1.91</td>
</tr>
<tr>
<td>CRP level, week 52</td>
<td>0.05 mg/L</td>
<td>&gt;0.5-1.09 mg/L</td>
</tr>
<tr>
<td>*Mantel-Haenszel chi-square correlation (trend) test.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Early onset of response to induction therapy with etanercept plus MTX predicted sustained remission with the reduced-dose combination maintenance regimen. These results are clinically important as critical identification of patients unlikely to reach target responses may promote more timely adjustments in therapy and ultimately improved long-term outcomes.

References:
2. Disclosure: P. Emery, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma. 2, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma. 3. R. Pedersen, Pfizer Inc, 1, Pfizer Inc, 3, J. Bukowski, Pfizer Inc, 1, Pfizer Inc, 5, L. Marshall, Pfizer Inc, 1.

2504

Impact of Concomitant Methotrexate on the Enhanced Clinical Efficacy of Bataccept after 24 Weeks in Rheumatoid Arthritis Patients. Nobunori Takahashi1, Toshitaka Kojima1, Yuki Hirano, Yasuhide Kanyama2, Koji Funahashi1 and Naoki Ishiguro1. 1Nagoya University Graduate School of Medicine, Nagoya, Japan, 2Toyohashi Municipal Hospital, Toyohashi, Japan, 3Toyota Kosei Hospital, Toyota, Japan.

Background/Purpose: A bataccept (ABT) is the first in a new class of biological agents for the treatment of rheumatoid arthritis (RA) that inhibits T cell activation by binding to CD80/86, and modulating its interaction with CD28. Although some reports demonstrated that concomitant methotrexate (MTX) had little enhancing effect on short-term clinical efficacy of ABT, there have been only few long-term studies. We studied whether background MTX treatment enhanced the ABT efficacy after 24 weeks, by using data from Japanese multicenter registry system for RA patients using biological DMARDs.

Methods: All RA patients who underwent ABT treatment for at least 52 weeks (n = 254) in Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Registry Study Group) were enrolled in this study. Demographic data and the following parameters of disease activity were collected; tender joint count (TJC) and swollen joint count (SJC) on 28 joints, patient global assessment (VAS), ESR, and serum CRP and MMP-3 levels at baseline, 24 weeks, and 52 weeks. We compared these clinical data between the patients treated with concomitant MTX (ABT-MTX, n = 130) and those treated with concomitant MTX (ABT-MTX, n = 124, mean MTX dose of 7.4 mg/week). The last observation carried forward (LOCF) method was used in each analysis.

Results: In the baseline characteristic data, the ABT-Mono group had higher pulmonary comorbidty rate (21.5 vs 6.5%, p = 0.001) compared to the ABT-MTX group while no other clinical parameters showed significant difference including the presence of patients with previous biological DMARDs history (47.7 vs 47.6, p = 0.986) or the all disease activity indices such as DAS28 (4.48 and 4.54). As shown in Figure Left and Middle panel,
the ABT-MTX group demonstrated statistically significant decreasing of DA528 from 24 to 52 weeks while no difference in the ABT-mono group. We next studied the patients that still adhered on ABT therapy in spite of their poor clinical efficacy (moderate or high disease activity, DA528-CRP > 2.7) at 24 weeks. Logistic regression analysis identified the concomitant MTX therapy and female as independent predictors of DA528 category improvement (e.g. high to moderate disease activity) from 24 to 52 weeks (Figure Right panel).

**Conclusion:** Concomitant MTX therapy significantly decreased the disease activity after 24 weeks, while it seemed to not have enhancing effect on short-term clinical efficacy of ABT. It is true that the ABT efficacy is still significant even in the patients without MTX usage. However, it would be beneficial to use concomitant MTX in most of RA patients without serious comorbidity for MTX usage.


2505

**Long-term Treatment with Tocilizumab (TCZ) Strongly Suppresses Joint Destruction in Biologic-naive Patients with Rheumatoid Arthritis (RA) Regardless of Inflammation Status.** Akira Sagawa. Sagawa Akira Rheumatology Clinic, Sapporo, 060-0001, Japan.

**Background/Purpose:** It is still difficult to completely prevent the progression of joint destruction with any of the currently available biologics. It has been reported that baseline CRP may predict early improvement of synovitis and bone erosion by TCZ therapy1). However, only a few reports have described whether TCZ may prevent joint destruction for a long period of time in clinical settings.

TCZ was administered for 3 years to identify risk factors for the progression of joint destruction in clinical settings and utilize the data to build treatment plans in RA patients.

**Methods:** TCZ was administered at a dose of 8 mg/kg every 4 weeks in combination with DMARDs including methotrexate. The effect on joint destruction was assessed on the basis of X-ray findings at baseline and year 3 of treatment using the modified total Sharp score (mTSS). Statistical analysis was performed using chi-square tests and Wilcoxon tests.

**Results:** Among 57 patients registered, 51 patients evaluable with X-ray were assessed. At baseline, patients were 53.5 years in average, had suffered from RA for 10.9 years, and had a DAS28-ESR of 5.31 and an mTSS of 100.6. Biologic-experienced patients at baseline accounted for 66%, and PSL users 68.6%. One patient received TCZ as monotherapy. The mean DmTCC at year 3 was 1.0, and the structural remission rate (i.e., DmTSS of 100.6). Biologic-experienced patients, the mean DmTSS was 0.2 for those with CRP < 2.8, and 8.0 for those with CRP ≥ 2.8, with a significant difference between the two subgroups (p = 0.011). This significantly higher score in the latter subgroup may be explained by the presence of severe inflammation not controlled with previous treatment as well as the higher DA528-ESR, swollen joint count and ESR at baseline (p < 0.05).

Long-term treatment with TCZ prevented joint destruction of RA patients, and a high structural remission rate was observed. Our findings suggest that TCZ, if given to biologic-naive patients, may strongly prevent the progression of joint destruction regardless of inflammation status.

**Reference**

1) **ARTHRITIS AND RHEUMATOLOGY** Vol.62 No.10 Sup. P.S49–S50 (2010.10)

Disclosure: A. Sagawa. None.

2506

Decrease in the Number of Peripheral Leukocytes and Neutrophils and Increase of the Percentage of Eosinophils at 4 Week Predict the DA528-ESR Remission at 24 Weeks After Administration of Tocilizumab. Tamao Nakashita, Shinji Motojima and Akihira Jibatake. 1) Kameda Medical Center, Kamogawa-city, Japan. 2) Kameda Medical Center, Kamogawa City, Japan.

**Background/ Purpose:** Tocilizumab (TCZ) is a monoclonal anti-IL-6 receptor antibody, and it is very effective in controlling RA activity. However, we have noticed that the change in leucocyte number after the administration of TCZ is different from that of TNF-inhibitor, and the change in leucocyte number by TCZ is rapid occurring within few days of administration. We analyzed retrospectively the relationship between the change in leucocyte number at week 4 and disease activity evaluated by DA528-ESR at 24 weeks.

**Methods:** Subjects were 50 patients with RA (male/ female = 10/40, mean age 56.7 +/- 12.7 years-old). The mean doses +/- SD of PSL (n = 35), M TX-ER = 14.5 mg/week, SSZ (n = 7), and bucillamine (n = 4) were 4.5 +/- 1.9 mg/day, 7.4 +/- 2.4 mg/week, 1000 +/- 0 mg/day, and 163 +/- 48 mg/day, respectively, at the introduction of TCZ. Patients were administered with 8 mg/kg of TCZ every 4 weeks, and blood test and physical examination were done at the time of TCZ administration. Of the 50 patients, 19 were biologics naive.

**Results:** The mean DA528-ESR at week 0 and 24 were 4.72 and 2.22, respectively, and the difference was statistically significant. Thirty-one out of 50 patients reached DA528-ESR remission at 24 weeks. The changes of leucocyte number after administration of TCZ are summarized as follows: total leucocyte number: decrease, neutrophil number: decrease, % of neutrophil: decrease, eosinophil number: no changes, % of eosinophil: increase as a result of the decrease in total leucocyte number. The changes of leucocyte number occurred at 4 weeks and did not change thereafter until 24 weeks. The change of DA528-ESR, on the other hand, occurred gradually and reached plateau at 16 weeks. The decrease of the number of total leucocyte and neutrophil at 4 weeks significantly correlated with the decrease of DA528-ESR at 24 weeks. The increase of % of eosinophil at the sum of 4 and 8 weeks significantly correlated with the decrease of DA528-ESR at 24 weeks.

**Conclusion:** The administration of TCZ induced significant changes of leucocyte count at 4 weeks, which is a good predictor of reaching DA528-ESR remission at 24 weeks.

Authors have no COI.

Disclosure: T. Nakashita. None; S. Motojima, None; A. J. Jibatake. None.

2507

**Is There an Autoinflammatory Component in Rheumatoid Arthritis Associated with Better Response to Anakinra (Kinera)?** Barbara M. Niesser-Karger, Hans-Eckhard Langer, M. Leinenon and Bjorn Pilestrom.

Rheumatology consultant, Cologne, Germany, 2) Rheumatology Institute, Düsseldorf, Germany, 3) Pharmacia AB, Stockholm, Sweden, and 4) Swedish Orphan Biovitrum AB, Stockholm, Sweden.

**Background/ Purpose:** 458 patients with rheumatoid arthritis (RA) and inadequate response to traditional DMARDs alone and/or TNFα blocking agents were treated with the IL-1 receptor antagonist anakinra. The initial analysis showed no difference between TNFα blocker non-responders and
TNFα blocker naïve RA patients (1). In order to identify factors that could predict response to anakinra treatment we performed a post hoc analysis of the original study data.

**Methods:** Original study data including demographic parameters, concomitant diseases and other anti-rheumatic treatment were subject to multivariate statistical analysis to identify independent factors that impact on the DAS score difference and EULAR response after one year of anakinra treatment. Cohort analyses of patients leaving the study were performed to identify characteristics predictive for study dropout. Data from patients leaving the study prematurely were imputed based on the LOCF (last observation carried forward) methodology.

**Results:** Patients leaving the study prematurely (non-completers) were characterised by less DAS improvement and higher age than completers. A diverse events did not increase the risk of dropout. 79% of patients had high disease activity at baseline which was reduced to 48% after one month’s treatment. Over the 12-month study most patients obtained moderate disease activity or better and 15–19% reached low disease activity or remission. A multivariate analysis of DAS score reduction over time concluded that the most predictive factors were disease severity (DA28) at baseline (p<0.001), previous use of biologics (p<0.05), no or low dose steroids (<7.5 mg prednisolone/day, p=0.06) and the prevalence of diabetes (p=0.14).

**Conclusion:** In a study with 458 RA patients treated with anakinra, further post hoc analysis of the raw data suggests that higher disease severity, no or low dose steroid use or concomitant diabetes are predictive of a better response to anakinra treatment. We speculate that there may be two distinct cohorts of RA patients, one with a more autoimmune, steroid responsive disease, the other with a more autoinflammatory, steroid non-responsive disease.

**References:**

**Disclosure:** B. Missler-Karger, Swedish Orphan Biovitrum AB, 5; H. E. Langer, Swedish Orphan Biovitrum AB, 5; M. Leinonen, Swedish Orphan Biovitrum AB, 5; B. Pilström, Swedish Orphan Biovitrum AB, 1, Swedish Orphan Biovitrum AB, 3.

**2508**

Tocilizumab Serum Trough Levels and Its Relationship with Disease Activity and Drug Dosage in Rheumatoid Arthritis Patients. Virginia Ruiz-Esquivel1, Azucena Gonzalez-Navarro2, Jordi Yague3, Jose Inciarte-Mundo4, M. Victoria Hernandez5, Julio Ramirez5, Sonia Cabrera-Villalba5, Juan D. Canete6 and Ramon Sanmarti7. 1Hospital Clinic of Barcelona, Barcelona, Spain, 2Hospital Clinic of Barcelona, Barcelona, Spain, 3Hospital Clinic Barcelona, Barcelona, Spain.

**Background/Purpose:** Tocilizumab (TCZ) is a humanized monoclonal antibody against interleukin-6 receptor used for the treatment of active rheumatoid arthritis (RA). The response to this treatment may depend on the serum levels achieved, which depends on the interval and the total dose administered.

**Purpose:** To analyze TCZ serum trough levels and antidrug antibodies (ADA) in a cohort of RA patients in chronic treatment with TCZ; and to evaluate its relationship with disease activity, serum levels of IL6 and CRP and drug levels.

**Methods:** Cross-section study including all RA patients attended in our Arthritis Unit undergoing chronic treatment with TCZ. Analysis of demographic data, disease activity IL6 and CRP serum levels together with TCZ serum levels and ADA (LISA TRACKER Tocilizumab LTT005 DuoDrug™-ADA) was done. All drug levels were measured before treatment infusion. Drug levels were correlated with different clinical and serological parameters.

**Results:** 33 RA patients were included (91% women, age 53 ± 12 years, disease duration 15.3 ± 9.7 years, anti-CCP = 66.7%, monotherapy 22.2%, DAS28 2.9 ± 1.1). No patient showed presence of ADA. In 14 patients (42%) serum levels of TCZ were non-detectable (<1 ug/ml). Patients with detectable levels of TCZ showed higher levels of IL6 and lower levels of CRP than those with non-detectable levels (Table 1). 15 patients received reduced dose of TCZ (4-6 mg/kg) due to persistent remission or low disease activity. In these patients serum levels of TCZ were lower than in those with standard dose, without differences on disease activity or CRP between groups. A significant positive correlation was found between IL6 levels and TCZ serum levels (R2=0.268, p=0.005), but not with DAS28 or CRP. In 3 patients, all of them with low disease activity, a curve of TCZ serum levels was done by TCZ dosage at baseline (before drug infusion) and 10, 20 and 28 days thereafter. In two patients, TCZ serum levels were not detectable by day 20. The third patient showed adequate levels through the entire period.

**Conclusion:** In a clinical setting of RA patients in treatment with TCZ no ADA were found. An important proportion of RA patients treated with TCZ had undetectable serum trough levels (42%), showing higher CRP levels, and lower IL-6, but no differences were found in disease activity measured by DAS28-ESR.

**Distribution of patients according to TCZ serum trough levels**

<table>
<thead>
<tr>
<th>Non detectable drug levels (&lt; 1 ug/ml)</th>
<th>Detectable drug levels (&gt; = 1 ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=14</td>
<td>n=19</td>
</tr>
<tr>
<td>Dose interval (days – mean)</td>
<td></td>
</tr>
<tr>
<td>31.9 ± 3</td>
<td>29.9 ± 3</td>
</tr>
<tr>
<td>Serum IL6 levels (ug/ml)</td>
<td>2.8 ± 2.3</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3.1 ± 1.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5 ± 15</td>
</tr>
<tr>
<td>Reduced dose of TCZ (%)</td>
<td>79%</td>
</tr>
<tr>
<td>DAS28-ESR</td>
<td>3.1 ± 1</td>
</tr>
<tr>
<td>Remission (DAS28-ESR&lt;2.6) (%)</td>
<td>29%</td>
</tr>
</tbody>
</table>

**Disclosure:** V. Ruiz-Esquide, None; A. Gonzalez-Navarro, None; J. Yague, None; J. Inciarte-Mundo, None; M. V. Hernandez, None; J. Ramirez, None; S. Cabrera-Villalba, None; J. D. Canete, None; R. Sanmarti, None.

**2509**

ADAM-10 As a Tocilizumab Treatment Predictive Factor in Rheumatoid Arthritis. Takeo Isosaki, Sakiko Isojima, Takahiro Tokunaga, Masayu Umemura, Hidekazu Furuya, Ryo Yana, Ryo Takahashi, Kuninobu Wakahayashi, Nobuyuki Yajima, Ysusuke M Iwa and Tsyoshi Kasa. Showa University School of Med, Shinagawa-ku Tokyo, Japan.

**Background/Purpose:** A disintegrin and metalloproteinases (ADAMs) are a family of transmembrane and secreted proteins. ADAM-10 has been reported to be the enzyme responsible for the release of a number of chemokines and cytokine receptors. We have shown that ADAM-10 is overexpressed on rheumatoid arthritis (RA) synovial tissue endothelial cells (ECs) and lining cells compared with osteoarthritids and normal tissues. We also demonstrated that ADAM-10 mediates EC migration and tube formed. In this study, we examined ADAM-10 as a predictive treatment factor in RA.

**Methods:** The serum was collected from patients before the initial treatment with biological therapies. Fifteen patients were treated with adalimumab (ADA), and 20 patients were treated with tocilizumab (TCZ). ADA-10 and fractalkine/CX3CL1 were measured by enzyme-linked immunosorbent assay at 0, 12, 24 and 54 weeks. Clinical disease activity was evaluated by disease activity score 28 (DAS28). Following biological therapies, we defined biologic-responders as patients whose DAS28 scores decreased by more than 1.2 at 24 weeks. ADAM-10 baseline was compared between responders and nonresponders.

**Results:** There were no significant differences were observed in the mean age, gender ratio, doses of prednisolone and methotrexate between ADA and TCZ groups. In ADA group, baseline DAS28 for the 15 patients was 4.8 ± 0.3 (2.5–7.2). On the other hand, baseline DAS28 for the 20 patients was 4.8 ± 0.3 (2.5–6.8) in TCZ group. There were no differences between ADA and TCZ groups. RA patients with an insufficient response to ADA or TCZ showed highly significant improvement of DAS28 after 12 weeks (2.9±0.3 and 2.2±0.4, respectively), and 24 weeks (2.5±0.4 to 2.2±0.2, respectively). ADAM-10 highly correlates with fractalkine/CX3CL1. Serum ADAM-10 levels were no remarkable change after treatment with ADA despite decrease of disease activity of RA. On the other hand, serum ADAM-10 levels in patients who were treated with TCZ were significantly diminished following successful treatment and clinical improvement (baseline 408±88 pg/ml and 54 weeks 138±51 pg/ml, p<0.05). ADAM-10 baseline in TCZ responder was significantly higher than TCZ nonresponders at 24 weeks (620±134 pg/ml and 109±25 pg/ml, respectively, p<0.05).

**Conclusion:** This study indicates that ADAM-10 is correlated with RA disease activity, and is higher in TCZ responders. These results suggest that ADAM-10 may be a predictor of treatment effectiveness for RA with TCZ.

**Disclosure:** T. Isosaki, None; S. Isojima, None; T. Tokunaga, None; M. Umemura, None; H. Furuya, None; R. Yana, None; R. Takahashi, None; K. Wakahayashi, None; N. Yajima, None; Y. Miwa, Tanabe-Mitsubishi, 2, Wyeth Pharmaceuticals, 2, Chugai, 2; Abbott Immunology Pharmaceuticals, 2, Astellas, 2, Ono, 2, Bristol-Myers Squibb, 2; T. Kasa, None.
Good Response to Methotrexate (MTX) and/or MTX Plus Adalimumab (ADA): 3 Yrs Study Results in Patients with Rheumatoid Arthritis (RA). Kazuko Shiozawa, Takashi Yamanaka, Miki Murata, Chihiro Tanaka, Noriaki Yoo, Ryo Suke Yoshiba, Yasuhi Tanka, Ken Tsumiyama, and Shinunchi Shiozawa.

Background/Purpose: To achieve comprehensive disease control (CDC; defined as simultaneous achievement of DAS28 < 3.2, HAQ-DI < 0.5 and ΔmTSS ≤ 0.5) or comprehensive disease remission (CDR; defined as simultaneous achievement of DAS28 ≤ 2.6, HAQ-DI ≤ 0.5 and ΔmTSS ≤ 0.5) is our therapeutic goal of treating RA. According to 2010 ACR/ARHP recommendation for early treatment of RA (Aletha D et al, Arthritis Care Res 69:1598, 2010), we found, in line with the finding of O’Dell et al. (Arthritis Care Res 65:1985, 2013), that 96/137 (50.4%) of RA patients given low-dose methotrexate (MTX) monotherapy showed no radiographic progression over 3 years when the patients were treated continuously with MTX monotherapy until significant adverse events or radiographic progressions were suspected. However, it remains unclear if the CDC and/or CDR are comparable between the patients treated with MTX monotherapy and those with MTX plus biologics. We here compared the clinical efficacy of MTX monotherapy and adalimumab (ADA) + MTX: 161 patients who showed adequate responses to methotrexate (MTX) (MTX group) were compared with 96 patients treated with ADA + MTX for inadequate response to MTX (MTX-IR) (ADA group) as to the effects on functional and structural outcomes for 3 years.

Methods: Grip strength, CDR and CDC rates and patients’ proportions with structural remission (ΔmTSS ≤ 0.5), clinical relevant radiographic progression (CRP; ΔmTSS > 3) and rapid radiographic progression (RRP; ΔmTSS = 5) were measured in MTX group (n=161, mean disease duration: 4.4 years) or ADA group (n=96, mean disease duration: 8.5 years) every year for 3 years.

Results: There was no significant difference in clinical remission rates (DAS28-ESR<2.6) between MTX and ADA groups at 3 years (LOCF). While, CDR rates for 3 years were much higher in ADA group (43.2%) than those of CDC (45.9% vs. 24.0%, respectively). However, it remains unclear if the CDC and/or CDR are comparable between the patients treated with MTX monotherapy and those with MTX plus biologics. We here compared the clinical efficacy of MTX monotherapy and adalimumab (ADA) + MTX: 161 patients who showed adequate responses to methotrexate (MTX) (MTX group) were compared with 96 patients treated with ADA + MTX for inadequate response to MTX (MTX-IR) (ADA group) as to the effects on functional and structural outcomes for 3 years.

Conclusion: It was demonstrated that grip strength gradually decreased from 1 year after the initiating of MTX treatment in the patients with MTX monotherapy, while ADA treatment to MTX-IR patients improved grip strength in a time dependent manner, which was supported by significantly better CDC and CDR rates over 3 years in the ADA group than those in the MTX group. Thus, the treatment in combination with biologics seems preferable for the patients with increased disease activity in face of MTX monotherapy.

Disclosure: K. Shiozawa, None; T. Yamanaka, None; M. Murata, None; C. Tanaka, None; N. Yoo, None; R. Yoshiba, None; Y. Tanaka, None; K. Tsumiyama, None; S. Shiozawa, None.

Predictors of Discontinuation of Biologic DMARD Therapy Due to Remission in Patients with Rheumatoid Arthritis in a National Registry. Jose A. Gomez-Puerta, M. Victoria Hernandez, Fernando Sanchez-Alonso, Kazuki Yoshida, Raimon Sammarti, Daniel H Solomon, Juan J. Gomez-Reino, and On behalf of BIOBADASER 2.0 study group.

Background/Purpose: Remission is considered an achievable goal for many patients under biologic therapies. However, currently there is limited information about predictors of discontinuation of biologic therapy in patients with RA. Our aim was to conduct a cohort study of patients enrolled in a National Registry of Biologic therapies to clarify how often biologic DMARD are discontinued due to remission and to identify predictors of discontinuation according to baseline characteristics at the time of initiation of biologic treatment.

Methods: We conducted a retrospective, observational cohort study of previously collected data from one national registry. We included RA patients who had at least 3 consecutive months on the same first biologic DMARD. Patients receiving rituximab were excluded. The index date was defined as visit when biologic therapy was started. The study period included patients recorded in the registry from April 1998 until December 2013. The endpoint of interest was defined as discontinuation of biologic DMARD due to remission defined by treating physician. Censoring occurred administratively (end of registry data), when patients stopped the treatment for other causes (side effects, lack of efficacy or pregnancy among others) or by loss to follow up. We used multivariable proportional sub-distribution hazards (SHR) models to examine the association between several predictors with discontinuation due to remission with loss to follow-up, discontinuation due to lack of efficacy, side effects or other causes as competing events.

Results: The study included 3,516 patients with diagnosis of RA and of these 3,161 patients having received at least 3 months of biological DMARD. 753 patients stopped treatment due to side effects, 867 patients discontinued treatment due to lack of efficacy, 101 were loss of follow-up, 143 for other reasons, 48 patients for pregnancy. In 15 cases the cause of discontinuation was not established. 1175 patients still receiving biological DMARD until the end of the study. Only 59 (1.8%) patients were able to discontinue biologic therapy due to remission. Baseline characteristics of patients at the moment of starting biologic DMARDs are in Table. A tier multivariate SHR analysis, sex (female) (SHR 2.81 95% CI 1.01–7.83), age at onset (SHR 1.04 95% CI 1.01–1.07) and disease duration (HR 0.94, CI 0.95–0.99) were significant predictors of discontinuation due to remission adjusting by methotrexate and biologics use.

Conclusion: A small proportion (<2%) of patients with RA were able to discontinue biologic DMARD therapy due to disease remission. Sex, age at onset and disease duration were predictors of such discontinuation. The prognosis of biologic-free patients after remission is still unknown and further studies are needed to elucidate their clinical course.

Table. Baseline characteristics at the moment of starting biologic DMARDs.

<table>
<thead>
<tr>
<th>No remission</th>
<th>Discontinuation due to remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female %)</td>
<td>79.9 88.1 0.11</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>9.3 (8.7) 7.0 (6.0) 0.04</td>
</tr>
<tr>
<td>Seropositive RA (%)</td>
<td>89.3 89.8 0.89</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12.2 6.8 0.20</td>
</tr>
<tr>
<td>Extra-articular disease (%)</td>
<td>20.1 15.3 0.35</td>
</tr>
<tr>
<td>Nodular disease (%)</td>
<td>7.4 5.1 0.25</td>
</tr>
<tr>
<td>Mean DAS-28 (SD)</td>
<td>3.75 (2.85) 4.22 (2.47) 0.21</td>
</tr>
<tr>
<td>Methotrexate (ever, %)</td>
<td>56.7 62.7 0.35</td>
</tr>
<tr>
<td>Steroids use (at index date, %)</td>
<td>53.4 59.3 0.37</td>
</tr>
<tr>
<td>DMARDs use (at index date, %)</td>
<td>71.2 71.2 0.99</td>
</tr>
<tr>
<td>Anti-TNF (ever, %)</td>
<td>93.9 96.3 0.15</td>
</tr>
</tbody>
</table>

Disclosure: J. A. Gomez-Puerta, None; M. V. Hernandez, None; F. Sanchez-Alonso, None; K. Yoshida, None; R. Sammarti, None; D. H. Solomon, None; J. J. Gomez-Reino, None; O. B. O. BIOBADASER 2.0 study group, None.
Golimumab therapy retention rates in patients with rheumatoid arthritis and seronegative spondyloarthritis: data from the Italian LORHEN registry.

**Background/Purpose:** The efficacy of Golimumab (GLM) treatment in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) has been widely documented. In everyday clinical practice, however, many patients discontinue therapy due to adverse events (AE), lack of efficacy or other reasons. [1] We compared first year retention rates of GLM treatment among RA, PsA and AS, using the first one as reference standard, in a multicentric observational cohort (the LORHEN Registry).

**Methods:** All patients in the LORHEN database who started GLM were included. All patients were treated according to current EULAR recommendations for the management of RA and spondyloarthritis. Drug survival during the first year of treatment was measured, along with specific reasons for discontinuation (inefficacy or adverse events). We compared drug retention rates using the Kaplan-Meier method. Cox regression analyses, using RA as reference category, were used to adjust for age, sex, disease duration, number of previous csDMARDs and treatment with low dose prednisone.

**Results:** 134 RA patients, 84 PsA patients and 108 AS patients were included. 49 (37%) RA patients, 29 (35%) PsA patients and 22 (20%) AS patients discontinued treatment during the first year. Thirty-six (27%) and 12 (9%) RA patients, 17 (20%) and 11 (13%) PsA patients, 14 (13%) and 7 (6%) AS patients discontinued GLM due to lack of efficacy or AE, respectively. Patients with a diagnosis of AS showed a lower, but not significant, risk of discontinuation, with an adjHR (95%CI) of 0.35 (0.10 - 1.17).

Patients treated with low dose prednisone showed a reduced risk of discontinuation with an adjHR (95%CI) of 0.35 (0.14 - 0.86). Age, sex, disease duration and number of previous csDMARDs did not significantly influence the risk of discontinuation.

**Conclusion:** AS patients seem to have better GLM retention rates with respect to RA and PsA patients; however this difference is significantly reduced after adjusting for confounders. The significantly lower adjHR observed for low dose prednisone therapy might reflect a beneficial effect even in patients treated with biDMARDs.

**References**


**Table 1.** Patients at baseline. IQR: interquartile range

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>PsA</th>
<th>AS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>134</td>
<td>84</td>
<td>108</td>
<td>326</td>
</tr>
<tr>
<td>Male (%)</td>
<td>104 (78)</td>
<td>60 (72)</td>
<td>77 (71)</td>
<td>241 (74)</td>
</tr>
<tr>
<td>Age (years), mean (IQR)</td>
<td>53.4 (34-71)</td>
<td>55.3 (42-72)</td>
<td>55.4 (42-78)</td>
<td>55.7 (42-78)</td>
</tr>
<tr>
<td>Disease duration (mean (IQR))</td>
<td>8.4 (3-14)</td>
<td>10.6 (5-16)</td>
<td>9.6 (3-14)</td>
<td>9.6 (3-14)</td>
</tr>
<tr>
<td>Active smokers, num (%)</td>
<td>20 (15%)</td>
<td>13 (15%)</td>
<td>21 (19%)</td>
<td>54 (17%)</td>
</tr>
<tr>
<td>Previous csDMARDs, num (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (0-1)</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>Treatment with prednisone, num (%)</td>
<td>117 (87%)</td>
<td>71 (85%)</td>
<td>68 (63%)</td>
<td>256 (78%)</td>
</tr>
</tbody>
</table>

---

**2513**


**Background/Purpose:** There is a close association between serum Infliximab (Ifx) levels and the Antibodies To Infliximab (ATI) with the clinical activity in rheumatoid arthritis (RA) patients. Several markers have been described to predict the response to biological therapy but for now no evidence of serological markers during the TNFi therapy is available. Our aim was to analyze whether Ifx drug levels at 2, 6 and 14 weeks after starting Ifx can predict the disappearance of serum Ifx levels and ATI detection at 6 months and 1 year in a cohort of RA patients treated with Ifx.

**Methods:** 85 RA patients were included in this study. The clinical activity was measured by DAS28 at baseline, 6 months and 1 year. The serum samples were obtained before each infusion at baseline, 2, 6, 14 months after starting Ifx, 6 months and 1 year. Ifx and ATI levels were measured by ELISA. Receiver-operator characteristics (ROC) analysis was used to establish a cut-off value for Ifx levels (2, 6 and 14 w) between patients with or without detectable Ifx levels at 6 months and 1 year. A cut-off value to discriminate which RA patients will have a faster Ifx clearance with the subsequent ATI detection and poor clinical outcomes. Patients with Ifx trough levels lower than 21.2 g/ml at 2, 6 and 14 weeks were predictive to Ifx disappearance at 6 months (2 weeks: AUC 0.708, SP 67%, SP 87%, LR +5.1; 6 weeks: AUC 0.810, S 70%, SP 88%, LR +6.0: 14 weeks: AUC 0.923, S 83%, SP 92%, LR +10.4) and 1 year (2 weeks: AUC 0.708, S 64%, SP 89%, LR 5.8; 6 weeks: AUC 0.800, S 63%, SP 90%, LR 6.3; 14 weeks: AUC 0.923, S 75%, SP 94%, LR +13.1).

**Conclusion:** The monitoring of Ifx levels at early stages of therapy has a high value to discriminate which RA patients will have a faster Ifx clearance with the subsequent ATI detection and poor clinical outcomes. Patients with Ifx trough levels lower than 21.2, 4.4 and 0.4 g/ml at 2, 6 and 14 weeks, respectively, have a high probability to develop ATI in the 12th year under the therapy.

**Disclosure:** C. Plasencia-Rodrigue, Pfizer Inc; D. Pascual-Salcedo, Pfizer Inc; M. G. Bonilla, None; A. Villalba, None; D. Peiteado, None; L. Nuño, None; P. Aguado, None; T. Jurado, None; E. Martin-Mola, None; A. Balsa, Pfizer Inc.

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**2514**

Results: A total of 2373 RA patients from eight different rheumatologic centers were included. Patients treated in the [11–14] time group had a statistically significant lower baseline DAS28 and HAQ compared with previous time group. DAS28 at first switch was significantly lower in [11–14] patients, shrinking to mean values of 5.59 (1.27) in the previous csDMARDs, with an established disease, in conflict with the principles of treat-to-target. The incomplete availability of biological drugs over territory and economical concerns, in addition to incomplete adherence to international recommendations, might at least in part explain this occurrence. The observation that real life population treated with biological drugs significantly differs for duration of disease from those selected in the majority of clinical trials should be taken into account when applying inferences from randomized controlled trials to everyday clinical practice.

Table 1. Patients at baseline. IQR: interquartile range. *Student’s T test. Wilcoxon-Mann-Whitney test

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, num</td>
<td>2373</td>
<td>837</td>
<td>3210</td>
<td>837</td>
<td>3210</td>
<td>837</td>
<td>3210</td>
<td>837</td>
<td>3210</td>
<td>837</td>
<td>3210</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean</td>
<td>54.32 (13.54)</td>
<td>54.81 (13.48)</td>
<td>54.16 (13.70)</td>
<td>ns</td>
<td>55.48 (13.10)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration in year, median</td>
<td>5.06 (1.74 – 11.85)</td>
<td>5.83 (12.26 – 16.51)</td>
<td>5.13 (13.83 – 15.14)</td>
<td>ns</td>
<td>4.74 (1.96 – 10.05)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Previous csDMARDs, median (IQR)</td>
<td>2 (2 – 3)</td>
<td>3 (2 – 4)</td>
<td>2 (2 – 3)</td>
<td>ns</td>
<td>0.05</td>
<td>2 (2 – 3)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>DAS28, mean (sd)</td>
<td>5.93 (±1.25)</td>
<td>5.93 (±1.44)</td>
<td>5.26 (±1.27)</td>
<td>ns</td>
<td>5.07 (±1.28)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>HAQ, median (IQR)</td>
<td>1.35 (1.05 – 1.70)</td>
<td>1.39 (1.01 – 1.88)</td>
<td>1.29 (1.07 – 1.60)</td>
<td>ns</td>
<td>1.25 (1.05 – 1.70)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 2. Disease variables at first switch. IQR: interquartile range. *Student’s T test. Wilcoxon-Mann-Whitney test

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, num</td>
<td>626</td>
<td>394</td>
<td>122</td>
<td>ns</td>
</tr>
<tr>
<td>Months before first bDMARD discontinuation, mean (sd)</td>
<td>28.77 (±28.69)</td>
<td>26.90 (±24.70)</td>
<td>31.94 (±34.25)</td>
<td>ns</td>
</tr>
<tr>
<td>DAS28, mean (sd)</td>
<td>4.97 (±0.70)</td>
<td>5.15 (±1.30)</td>
<td>4.68 (±1.34)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HAQ, median (IQR)</td>
<td>1.125 (0.625 – 1.625)</td>
<td>1.250 (0.750 – 1.750)</td>
<td>1.125 (0.625 – 1.500)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Disclosures: V. Grosso, None; R. Goria, None; P. Sarzi-Puttini, None; F. Atzeni, None; R. Pellerito, None; E. Fusaro, None; G. Paolazzi, None; P. A. Rocchetta, None; E. G. Favaelli, None; A. Marchesoni, None; R. Caporalis, None.
over switching to the next one at failing their biologic agent. On the other hand, there are some patients who discontinue any biologic agent treatment due to various reasons such as tolerability concern, complications, economic issue, remission and so on. The impact of this concern has been less studied.

The objective of this study was to investigate the reasons and the risk factors for discontinuation any biologic agent in RA patients.

**Methods:** In total patients (n=2179) who underwent biologic agent treatment between 2003 and 2011 at Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Study Group), 1966 patients who were confirmed continuation or discontinuation of biologic agent treatment were enrolled. We analyzed the retention rate of biologic agent treatment and the reasons for discontinuation. To identify the risks for discontinuation, baseline demographics were compared between the continuing group and the discontinuing group using Cox hazard regression analysis.

**Results:** In total 1966 patients, 1479 patients were administered biologics continuously, 487 patients were withdraw. Table 1 showed the demographic date in total patients. The retention rate was 72% (n=1563) at least 1 year from starting biologics treatment, 68.7% (n=866) at 3 years, 65.6% (n=360) at 5 years. In 327 patients who were confirmed the reasons of discontinuation, the reasons were adverse events in 191 patients, lack of effectiveness in 66 patients, others in 70 patients. Comparison of incidence for discontinuation using cumulative hazard function, the reason of adverse events was significantly higher than others reasons (Figure 1). To identify the risks of discontinuation, we used cox hazard model regression in patients who discontinued treatment due to adverse events and lack of effectiveness, the risk factors were over 70 years of age (OR 1.80 [1.31-2.46]), male (OR 1.79 [1.27-2.52]), over 3 of steinblocker class (OR 1.51 [1.12-2.04]). Non concomitant with methotrexate (OR 1.47 [1.06-2.04]).

**Conclusion:** The most common reason for discontinuation was adverse events. In a numerically greater proportion of patients who discontinued any biologic agent treatment, timing of discontinuation was within a first year from starting treatment. In addition, the risk factors for discontinuation were similar with those of adverse events.

**Table 1.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Disease duration (years)</th>
<th>stage</th>
<th>class</th>
<th>Methotrexate use, no (%)</th>
<th>Corticosteroid use, no (%)</th>
<th>DAS-ESR at starting</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-18</td>
<td>n (%)</td>
<td>60 (17%)</td>
<td>326 (17%)</td>
<td>1.6 ± 10.3</td>
<td>29%</td>
<td>62%</td>
<td>1018 (75%)</td>
</tr>
<tr>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
<td>3.2 after 26 wks</td>
</tr>
</tbody>
</table>


**2517**


**Background/Purpose:** Methotrexate (MTX) is used as first line therapy for treatment of rheumatoid arthritis (RA). Current recommendations state that therapy should be adjusted if patients (pts) fail to attain remission or low disease activity (LDA) after 6 mo of MTX, and TNF inhibitors could be considered for pts with high risk of aggressive disease. The objective of this post hoc analysis was to identify the benefits of treatment adjustment vs no treatment adjustment in pts who did not achieve a stable LDA after 6 mo of MTX.

**Methods:** A post hoc analysis from OPTIMA, and PREMIER was conducted in MTX-naive, early RA pts. In OPTIMA, non-achievers (NAs) were defined as pts failing to achieve a stable LDA target of DAS28(CRP) <3.2 at 2 weeks (wks) 22 and 26 following placebo (PBO)+MTX for 26 wks. Pts who were NAs to MTX switched to open-label (OL) ADA +MTX for an additional 52 wks. In PREMIE, following MTX monotherapy, NAs were defined as pts failing to achieve a stable LDA target at wks 20 and 24; however, these pts continued MTX monotherapy up to 104 wks. Clinical and functional outcomes were evaluated at wk 78 and 76 for OPTIMA and PREMIE, respectively, while radiographic outcomes were evaluated at wk 78 for OPTIMA and both wks 52 and 104 for PREMIE. Additionally, ANOVA and logistic regression analysis was conducted on continuous and dichotomized endpoints, respectively, with the following baseline characteristics as variables: age, sex, RA duration, RF status, previous DMARD use, tender joint count, swollen joint count, C-reactive protein, DAS28 score, HAQ-DI, mTSS, erosion score, and estimated annual TSS progression.

**Results:** 348 out of 517 total pts in OPTIMA and 172 out of 257 total pts in PREMIE did not achieve a stable LDA target of DAS28(CRP) <3.2 after 26 and 24 wks of MTX monotherapy. In those NAs, mean disease duration at baseline was 0.3 and 0.8 for OPTIMA and PREMIE, respectively. In OPTIMA, NAs to MTX, mean DAS28(CRP), HAQ-DI, and mTSS at baseline for NAs were 6.1, 1.7, and 11.7, respectively. In comparison, the mean DAS28(CRP) at baseline from the NAs in the PREMIE trial was 6.4, while the HAQ-DI and mTSS were 1.6 and 23.4, respectively. There was a significant decrease compared to baseline in the clinical and functional outcomes for both pts who were given OL ADA +MTX as well as pts who remained on MTX monotherapy; however, compared with pts who continued MTX, there was a significant increase in the percentage of pts achieving LDA and remission, according to all scores used, for those who switched to combination therapy with ADA +MTX in the OPTIMA trial, where pts were switched to OL ADA +MTX after 26 wks.

**Table.** Clinical, Functional, and Radiographic Outcomes at Week 78 and 76 for Patients who were Non-Achievers to MTX Monotherapy in OPTIMA and PREMIER.
Conclusions: Not adjusting treatment in pts who did not receive a stable LDA after 6 mo of initial MTX appears to result in worse long-term clinical, functional, and structural outcomes compared to pts whose treatment was adjusted by adding ADA.

Disclosure: J. S. Smolen, AbbVie Inc, Amgen, AstraZeneca, BMS, Celgene, Jansen, Glaxo, Lilly, Pfizer, MSD, Novo-Nordisk, Roche, Sandoglobulins, and UCB, 2; AbbVie Inc., Amgen, AstraZeneca, BMS, Celgene, Jansen, Glaxo, Lilly, Pfizer, MSD, Novo-Nordisk, Roche, Sandoglobulins, and UCB, 2; R. F. van Vollenhoven, AbbVie Inc., BMS, Glaxo, HGS, MSD, Pfizer, Roche, and UCB, 2; AbbVie Inc., BMS, Glaxo, HGS, MSD, Pfizer, Roche, and UCB, 2; S. Fiorentinis, AbbVie Inc., 1; Y. Zhou, AbbVie Inc., 1; A. Kavanagh, AbbVie Inc., Amgen, AstraZeneca, BMS, Celgene, Centocor-Jansen, Pfizer, Roche, and UCB, 2; AbbVie Inc., Amgen, AstraZeneca, BMS, Celgene, Centocor-Jansen, Pfizer, Roche, and UCB, 5.

Table 1: Percent agreement of response criteria

<table>
<thead>
<tr>
<th>Disease Parameter</th>
<th>DSAS28 LDA</th>
<th>SDAI LDA</th>
<th>CDAI LDA Remission</th>
<th>CDAI 28 Remission</th>
<th>SDAI Remission</th>
<th>CDAI Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 70</td>
<td>71.4</td>
<td>71.4</td>
<td>52.0</td>
<td>72.4</td>
<td>84.8</td>
<td>48.4</td>
</tr>
<tr>
<td>ACR 20</td>
<td>61.7</td>
<td>72.1</td>
<td>71.4</td>
<td>52.0</td>
<td>72.4</td>
<td>48.4</td>
</tr>
<tr>
<td>ACR 50</td>
<td>70.4</td>
<td>76.3</td>
<td>75.1</td>
<td>67.1</td>
<td>68.6</td>
<td>68.9</td>
</tr>
<tr>
<td>HAQ 0.22</td>
<td>56.1</td>
<td>63.1</td>
<td>62.0</td>
<td>47.2</td>
<td>44.1</td>
<td>44.3</td>
</tr>
<tr>
<td>HOQ 0.5</td>
<td>59.6</td>
<td>64.2</td>
<td>63.0</td>
<td>55.8</td>
<td>55.6</td>
<td>56.2</td>
</tr>
<tr>
<td>SDAI Major</td>
<td>54.8</td>
<td>62.3</td>
<td>61.4</td>
<td>49.3</td>
<td>52.5</td>
<td>52.3</td>
</tr>
<tr>
<td>SDAI Minor</td>
<td>52.9</td>
<td>64.9</td>
<td>63.9</td>
<td>39.7</td>
<td>37.2</td>
<td>36.6</td>
</tr>
</tbody>
</table>

2518

What Is the Level of Agreement Between Disease Activity Indices and Response Criteria Among Rheumatoid Arthritis Patients Treated with TNF Inhibitors?

Objective: To compare the level of agreement between the three measures: ACR, SDAI, and HAQ.

Methods: The study includes 2,759 patients with RA, treated with TNF inhibitors. The primary outcome is the level of agreement between the three measures. The study was conducted from 2002 to 2014.

Results: A total of 2,759 patients were included. The level of agreement between the three measures was measured using the Cohen's kappa statistic. The results showed that the level of agreement is lowest for HAQ and SDAI, with a kappa statistic of 0.001 and 0.006, respectively.

Conclusion: The level of agreement between the three measures is low, and further research is needed to improve the measurement of disease activity in RA.


2519

Are Patients with Rheumatoid Arthritis Initiating a TNF Biologic Comparative to Patients Initiating a Non-TNF Biologic? A Matched Cohort Study

Objective: To compare the level of agreement between the three measures: ACR, SDAI, and HAQ.

Methods: The study includes 2,759 patients with RA, treated with TNF inhibitors. The primary outcome is the level of agreement between the three measures. The study was conducted from 2002 to 2014.

Results: A total of 2,759 patients were included. The level of agreement between the three measures was measured using the Cohen's kappa statistic. The results showed that the level of agreement is lowest for HAQ and SDAI, with a kappa statistic of 0.001 and 0.006, respectively.

Conclusion: The level of agreement between the three measures is low, and further research is needed to improve the measurement of disease activity in RA.
Conclusion: RA patients who receive a NTNFi as their first biologic differ from those initiating TNFi. Proper application of statistical methods and careful evaluation of baseline conditions, prior/concomitant medications and biologic use is critical when performing comparative effectiveness analyses. Line of therapy should also be considered in future comparative research analyses.

Disclosure: K. Michaud, None; K. Gandhi, Bristol-Myers Squibb; T. Simon, Bristol-Myers Squibb; S. Pedro, None.

2520

Patient, Genetic and Disease Factors Influence the Response to the Drug Modifying Anti-Rheumatic Drug Leflunomide. Michael D. Wiese1, Ashley Hopkins1, Llew Spargo1, Leah McWilliams2, Catherine O’Doherty3, Leslie G. Cleland4, and Susanna Proudman5, 1University of South Australia, Adelaide, Australia; 2Royal Adelaide Hospital, Adelaide, Australia; 3Royal Adelaide Hospital, SA, Australia.

Background/Purpose: Leflunomide is a disease modifying anti-rheumatic drug that is used in the treatment of rheumatoid arthritis (RA). Leflunomide is converted to teriflunomide by the Cytochrome P450 enzymes 1A2, 2C19 and 3A4, which is cleared via secretion into the gastrointestinal tract. The primary metabolite action is inhibition of di-hydrorote dehydrogenase (DHODH) by teriflunomide. It is very effective in some patients, but treatment can be limited by intolerance and/or lack of efficacy. This study aimed to determine steady state teriflunomide concentration in a group of patients with RA and correlate steady state concentrations with response to leflunomide.

Methods: Patients with RA taking a stable dose of leflunomide according to the treat-to-target strategy were recruited from the Royal Adelaide Hospital Early Arthritis Clinic. Blood samples were taken for determination of free teriflunomide concentration and genetic differences in CYP1A2, CYP2C19, ABCG2 and DHODH. Disease activity was assessed by the 28-joint disease activity scores (DAS28). Factors associated with teriflunomide concentration and DAS28 were assessed by multivariate linear regression.

Results: 55 patients were included. The average leflunomide dose was 16.1mg/day, and the free teriflunomide concentration was 0.062mg/L - there was a 150-fold difference between maximum and minimum concentration. Leflunomide dose accounted for 10% of the variability in free teriflunomide concentration, and this increased to 38% when CYP1A2 and ABCG2 genotype were considered. 25 patients took leflunomide for at least 9 months (no other agents were added for treatment failure) and 76% of the variability in DAS28 was accounted for by considering baseline DAS28, shared epitope carriage, DHODH haplotype and free teriflunomide concentration.

Conclusion: Pharmacokinetic and pharmacogenomic variables appear to be associated with response to leflunomide in a group of RA patients treated according to a treat-to-target strategy, but this should be assessed in a prospectively recruited cohort.

Disclosure: M. D. Wiese, None; A. Hopkins, None; L. Spargo, None; L. McWilliam, None; C. O’Doherty, None; L. G. Cleland, None; S. Proudman, None.

2521

Analysis on Predictors for Long-Term Clinical Efficacies of Golimumab in Patients with Rheumatoid Arthritis. Tsutomu Takeuchi1, Yutaka Ishii2, Kimie Tanaka1, Yoshihumi Ukyo3 and Hiroshi Sekine1. 1Keio University School of Medicine, Tokyo, Japan; 2Janssen Pharmaceutical K.K., Tokyo, Japan; 3Janssen Pharmaceutical K.K., Tokyo, Japan; 4Janssen Pharmaceutical K.K., Tokyo, Japan.

Background/Purpose: The GO-FORTH, phase 2/3 clinical trial was conducted to examine the efficacy and safety of Golimumab (GLM) plus MTX in Japanese patients (pts) with active RA despite MTX therapy (NCT02779687). In treatment for RA, it has been recommended to assess the clinical disease activity at least every 3 months according to the treat to target (T2T) recommendation. Therefore, predictors of long-term efficacy with GLM treatment using clinical data at baseline and 3 months would seem to be extremely important.

Objective: To assess the predictability of using clinical data at baseline and week 12 (W12) after GLM treatment in GO-FORTH study, for achievement of each remission criteria after 1 year.

Methods: GO-FORTH was a multicenter, randomized, double-blind, placebo-controlled study in pts with active RA despite MTX therapy. Pts were randomized to Placebo (PBO), GLM 50 mg or GLM 100 mg q4 wks combined with MTX (6–8 mg/ week). Data of all pts who were randomized to GLM 50 mg or GLM 100 mg as active treatment were used for analysis. Several definitions of remission at week 52 (W52) were used and defined as: DAS remission (DAS28ESR <2.6), HAQ remission (HAQ <0.5) and radiographic remission (CT Score <<0). Akaikes Information Criteria (AIC) were calculated to assess predictability with all possible predictors using univariate logistic regression model. Area under the curves (AUC) were calculated to assess the performance of possible predictors using receiver operating characteristics (ROC) curves. Cutoff values were also calculated using Euclidean method. The correlations between possible predictors were carefully considered to determine predictor.

Results: DAS28ESR score at W12 was chosen based on the values of AUC as a possible predictor of DAS remission at W52. HAQ score at W12 was also chosen as a possible predictor of HAQ remission at W52. Similar trends were observed in the both scores at baseline. The cutoff point (AUC) of DAS28ESR for DAS remission with GLM 50 mg and GLM 100 mg at W12 were 3.0 (0.876) and 3.5 (0.863), then cutoff point of HAQ score for HAQ remission with them were 0.625 (0.880) and 0.500 (0.958), respectively (see table). The results of baseline and PPVs/ NPVs for each determined predictors were also calculated as table shown. Both potential predictors showed larger AUC and smaller cutoff values at W12 than those at the baseline. There were no noticeable differences between GLM 50mg and GLM 100mg in the potential predictors. Predictors for radiographic remission were not specified by this analysis.

Conclusion: These analyses suggest that DAS28ESR and HAQ score at baseline and W12 can be predictors for DAS remission and HAQ remission at W52 in Japanese pts treated with GLM combined with MTX individually. In particular in terms of DAS remission, it seems to be important to achieve LDA within 3 months to maintain long term clinical remission.

Table.  AUC and PPV/NPV for each possible predictor calculated with GLM pts data

<table>
<thead>
<tr>
<th>Predictor (1-year) Group</th>
<th>Baseline</th>
<th>Possible Predictors</th>
<th>AUC (PPV, NPV)</th>
<th>Cutoff Value</th>
<th>Prediction (1-year) Group</th>
<th>Baseline</th>
<th>Possible Predictors</th>
<th>AUC (PPV, NPV)</th>
<th>Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS remission</td>
<td>GLM 50 mg</td>
<td>DAS (ESR)</td>
<td>0.706 (55.0%, 13.0%)</td>
<td>0.60</td>
<td>GLM 100 mg</td>
<td>DAS (ESR)</td>
<td>0.706 (55.0%, 13.0%)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>HAQ remission</td>
<td>GLM 50 mg</td>
<td>HAQ</td>
<td>0.745 (75.0%, 70.0%)</td>
<td>0.80</td>
<td>GLM 100 mg</td>
<td>HAQ</td>
<td>0.80</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

Effect of Infliximab Dose Increase in Rheumatoid Arthritis at Different Trough Concentrations. Alejandro Balsa, Chaimada Plasencia-Rodriguez, María Gema Bonilla, Alejandro Villalba, Diana Peiteado, Sara García-Carazo, Laura Nuño, Teresa Jurado, Emilio Martín-Mola, and Dora Pascual-Salcedo. Hospital La Paz IdiPaz, Madrid, Spain. 1Hospital La Paz - IdiPaz, Madrid, Spain. 2Hospital La Paz - IdiPaz, Madrid, Spain. 3La Paz University Hospital, Madrid, Spain. 4Hospital La Paz - IdiPaz, Madrid, Spain. 5La Paz University Hospital-IdiPaz, Madrid, Spain. 6Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: To evaluate the effects of infliximab (Ifx) dose increase in active rheumatoid arthritis (RA) patients, presenting different serum infliximab concentrations.

Methods: Retrospective study including 42 RA patients treated with increased Ifx following insufficient response (DA528 > 3.2). Serum concentrations of Ifx and antibodies to Ifx (ATI) were recorded together with DAS28 from baseline (deltaDAS28) followed a similar pattern (p = 0.05 after Bonferroni correction), but the improvement did not persist at 1 year (3.98 vs 3.95, p = 0.075 after Bonferroni correction). The change in deltaDAS28 from baseline (deltaDA528) followed a similar pattern (−0.63 ± 1.18 at T2 to 1.17 ± 1.45 at T4 (p = 0.001)(Figure 1). Overall, 5 (13.2%) patients achieved a good response by EULAR response after the first dose increase, whereas 18 (47.4%) patients had no response. At T4, 3 (10.7%) patients achieved a good response by EULAR response after the first dose increase, independently of pre increase/H11006

Disclosures: A. Balsa, Pfizer Inc; 9. C. Plasencia-Rodriguez, Pfizer Inc; 2. M. G. Bonilla, None; A. Villalba, None; D. Peiteado, None; S. García-Carazo, None; L. Nuño, None; T. Jurado, None; E. Martín-Mola, None; D. Pascual-Salcedo, Pfizer Inc; 2.

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cıkşahin, Ahmet M. Esen Onat, Ayşegül Ates, and Veli Cobancak.

Background/Purpose: Biologic drugs including anti-TNF agents have been used in the treatment of secondary amyloidosis, however, there is no controlled study concerning the efficacy of therapy. In this study, we retrospectively analyzed the clinical features and outcome of RA and AS patients with clinically symptomatic secondary amyloidosis who were treated with any of the biologic agents in various rheumatology centers in Turkey.

Methods: The hospital files in 10 university hospitals were examined to determine the presence of clinically apparent amyloidosis in RA and AS. Data concerning the clinical features, extraarticular involvement and biologic and other treatment response were obtained from hospital records.

Results: 27 RA (17F, 10M, mean age: 52.2), 42 AS (11F, 31M, mean age: 45.6) patients were included. Rheumatoid factor (RF) was positive in 24 (88.9%) RA patients. In 25 RA patients, the initial presentation of amyloidosis was with proteinuria; one had hematuria; and one patient presented with renal dysfunction. Eight patients with proteinuria also had renal dysfunction.

The disease duration of RA patients before amyloidosis was 127.9 months; the duration of biologic therapy was 47.9 months. The first-line therapy was TNF-blockers in 21 RA patients; rituximab and abatacept in 2; and tocilizumab in one. Second-line biologicals were used because of side effects in 1 patient; and because of inefficacy in 8 (2 TNP blocker, 4 rituximab, 1 tocilizumab). The median tocilizumab therapy was 7 months; the duration of biologic therapy was 47.9 months. The first-line therapy was needed in 5 RA patients. 28 AS patients presented with proteinuria, 2 with hematuria, and 4 with isolated renal dysfunction. At the time of diagnosis for amyloidosis, 13 patients had also renal dysfunction. The disease duration of RA patients before amyloidosis was 101.2 months. All had been given anti-TNF agents as first-line therapy (infliximab in 13; etanercept in 19; adalimumab in 7; golimumab in 3 patients). 10 patients were switched to a second anti-TNF (because of serious side effects in 2 and inefficacy in 8). Proteinuria and/or renal functions improved in 7 cases; however, they got worse in 7; and remained stable in 13. When patients who improved were compared to others, it was seen that there were more females (100% vs. 50%, p = 0.026); and significantly longer duration of biologic therapy in this group. 2 patients using biologics developed tuberculosis; 3 patients died during follow-up because of nondrug-related causes. Renal replacement therapy was needed in 5 RA patients. 28 AS patients presented with proteinuria, 2 with hematuria, and 4 with isolated renal dysfunction. At the time of diagnosis for amyloidosis, 13 patients had also renal dysfunction. The disease duration of RA patients before amyloidosis was 101.2 months. All had been given anti-TNF agents as first-line therapy (infliximab in 13; etanercept in 19; adalimumab in 7; golimumab in 3 patients). 10 patients were switched to a second anti-TNF (because of serious side effects in 2 and inefficacy in 8). Proteinuria and/or renal functions improved in 7 cases; however, they got worse in 7; and remained stable in 9 after anti-TNF therapy. The results could not be evaluated in 8 patients. Initial CRP levels of patients who had any kind of improvement with anti-TNF therapy were significantly higher than others (p = 0.007). There was need for renal replacement therapy in 12 AS patients.

Conclusion: Amyloidosis develops in RA and AS nearly 10 years after diagnosis; and it generally presents with proteinuria and/or renal dysfunction. In RA, the response to biologics was associated with a longer response to biologics and female sex. In AS patients, having a high CRP at the time of diagnosis of amyloidosis was associated with response to anti-TNF agents.

Table 1: Demographic and clinical characteristics of patients

<table>
<thead>
<tr>
<th>Overall population (n = 42)</th>
<th>Die-tectable infliximab levels (n = 20)</th>
<th>Sub-therapeutic infliximab levels (n = 13)</th>
<th>High infliximab levels (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years), mean ± SD</td>
<td>57.1 ± 14.0</td>
<td>49.6 ± 14.5</td>
<td>61.6 ± 10.8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>37 (88.1%)</td>
<td>19 (95%)</td>
<td>9 (69.2%)</td>
</tr>
<tr>
<td>Disease duration (years), mean ± SD</td>
<td>19.4 ± 10.4</td>
<td>14.6 ± 6.3</td>
<td>17.9 ± 10.1</td>
</tr>
<tr>
<td>Duration of treatment (years), median (IQR)</td>
<td>62 (11-93)</td>
<td>42 (23.6-84.3)</td>
<td>6.25 (4.38-10.75)</td>
</tr>
<tr>
<td>ACPA-positive, n (%)</td>
<td>36 (85.7%)</td>
<td>19 (95%)</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>RF-positive, n (%)</td>
<td>35 (83.3%)</td>
<td>18 (90%)</td>
<td>10 (76.9%)</td>
</tr>
<tr>
<td>Concomitant methotrexate before dose increase, n (%)</td>
<td>30 (71.4%)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Methotrexate dose mg/week, median (IQR)</td>
<td>12.5 (0-25)</td>
<td>15.0 (0-35)</td>
<td>7.5 (0-20)</td>
</tr>
<tr>
<td>Other DMARD*, n (%)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concentration of glucocorticoids, n (%)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DA528 at the start infliximab treatment, mean ± SD</td>
<td>5.50 ± 1.20</td>
<td>5.68 ± 1.29</td>
<td>5.03 ± 1.04</td>
</tr>
<tr>
<td>Baseline DA528 before infliximab increase, mean ± SD</td>
<td>4.55 ± 1.01</td>
<td>4.81 ± 0.73</td>
<td>3.72 ± 0.94*</td>
</tr>
<tr>
<td>Trough infliximab levels before dose increase (µg/ml), median (IQR)</td>
<td>94.5 (10-105)</td>
<td>N.D.</td>
<td>574 (16-1024)</td>
</tr>
<tr>
<td>ATI levels before infliximab increase, (AU/ml), median (IQR)</td>
<td>0 (0-6000)</td>
<td>1086 (173-1228)</td>
<td>0 (0-15)</td>
</tr>
<tr>
<td>Treatment withdrawal, n (%)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: INF: Infliximab; SD: standard deviation; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DAS28: disease activity score in 28 joints; IQR: interquartile range; AU/ml: arbitrary units per ml; ND: not detectable.
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Smoking and Response to Rituximab in Anti-CCP Positive and Negative Rheumatoid Arthritis - Results from an International European Collaboration. Katerina Chatzidionysiou1, Elisabeth Lie2, Evgeny Nasonov3, Galina Lukina4, M erete Lund Hel tland5, Ellen Hauge6, Karel Pavelka7, Cem Gabay8, Dan Nordström9, Helena Canhão10, Matjaž Tomsič11, Piet van Riel12, Jonas K. Eriksson13, Pierre Geborek3, Ronald F. van Vollenhoven14 and Saedis Saevardsdottir15. 1Unit for Clinical Research Therapy, Inflammatory Diseases (ClinTrid), Karolinska Institutet, Stockholm, Sweden, 2Diakonhjemmet Hospital, Oslo, Norway, 3ABTHER, Institute of Rheumatology, Moscow, Russia, 4DANBIO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, 5Glostrup University Hospital, Glostrup, Denmark, 6Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, 7Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 8SCOM registry, University Hospitals of Geneva, Geneva, Switzerland, 9ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, 10Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa María, Lisbon, Portugal, 11University Medical Centre Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal, 12Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 13Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Smoking has been identified as an important negative predictor of response to antirheumatic therapy. The aim of this study was to assess whether smoking status influenced the clinical response to rituximab (RTX) in an observational patient cohort with rheumatoid arthritis (RA).

Methods: Pooled data from the Collaborating European Registries for RTX in RA (CERERRA) project were used. Patients with RA who received at least 1 cycle with RTX and at least 2 follow-up visits were included in the analyses. Smoking status was defined as smokers (current smokers) and non-smokers (never and ex-smokers). Baseline characteristics were compared by means of descriptive statistics. Analysis of co-variance (ANCOVA) was performed with DeltaDAS28 as the dependent variable and smoking status as well as other baseline variables (age, sex, disease duration, number of prior biologic DMARDs) as covariates. Separate analyses were made for anti-CCP positive and negative patients.

Results: A total of 2431 patients with available smoking information were included. 1916 (79%) were non-smokers and 515 (21%) were smokers. 81% were female and 80% (out of 1199 patients with available anti-CCP status) were anti-CCP positive. Smokers had shorter disease duration than non-smokers (mean ± SD = 9.5 ± 7.9 vs. 11.9 ± 8.7, p < 0.0001), higher number of prior biologic DMARDs (1.3 ± 1.2 vs. 1.0 ± 1.0, p < 0.0001), lower DAS28 at baseline (5.1 ± 1.7 vs. 5.7 ± 1.5, p < 0.0001), 16% of females and 42% of males were smokers (p < 0.0001). 84% of smokers and 78% of non-smokers were anti-CCP positive (p = 0.04).

Smokers had less improvement in disease activity than non-smokers at 6 months follow-up (mean ± SD: DeltaDAS28 = -1.5 ± 1.7 vs. -1.8 ± 1.7, respectively, p < 0.01). However, the difference was no longer significant after adjustment for baseline differences (age, sex, disease duration, number of prior biologic DMARDs, concomitant corticosteroids and DMARDs: p = 0.40). When the analysis was stratified by anti-CCP status, smoking did not influence the response to therapy in the anti-CCP negative subset (p = 0.39) but there was a trend in the anti-CCP positive subset (p = 0.06, see figure 1). Similar trends were observed for EULAR good/moderate response rates. For the anti-CCP negative RA patients, 63% of non-smokers and 60% of smokers achieved EULAR response (p = 0.51), while in the anti-CCP positive subgroup the respective response rates were 73% among non-smokers and 67% among smokers (p = 0.07).

Conclusion: Smoking was negatively associated with the clinical response to rituximab therapy in RA patients who were anti-CCP positive.

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Infliximab Versus Conventional Combination Treatment and Work Loss in Early RA over 7 Years: A Randomized Trial. Jonas K Eriksson1, Heather Miller2, Johan A K arlsson3, Ingermar F Petersson4, Sofia Ernsten5, Pierre Geborek6, Ronald F van Vollenhoven7 and Martin Neovius2. 1Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 2ClinTrid, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, 3Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, 4Section of Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, 5Department of Learning, Informatics and Medical Education (LIME), Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: The introduction of TNF inhibitors has improved the treatment of RA, but at a substantial cost. The randomized Swefot trial compared the addition of infliximab vs conventional disease-modifying anti-rheumatic drugs in patients with early RA who had failed initial MTX monotherapy. From the Swefot trial we previously reported superior 2-year radiographic outcomes in the infliximab group, while disease activity, quality of life and work loss improved similarly. Here we report work loss over 7 years after randomization.

Methods: In this multicenter, two-arm, parallel, randomized, active-controlled, open label trial RA patients with <1 year symptom duration were recruited from 15 rheumatology clinics in Sweden between October 2002 and December 2005. After 3–4 months of MTX monotherapy, patients not achieving low disease activity were randomized to addition of biologic treatment with infliximab or further conventional treatment with sulfasalazine + hydroxychloroquine. Register-based follow-up continued despite protocol breach, and treatment was thereafter decided by the responsible rheumatologist.

The main outcome measure in this study was yearly sick leave and disability pension days at 7 years after randomization, retrieved from the nationwide Swedish Social Insurance Office register. The analysis were by intention to treat, including all working age patients (<65y), and adjusted for work loss 1 year before randomization. Patients were followed for a maximum of 7 years and were excluded from the yearly average calculations if they (in the current year) had emigrated, died, or turned 65y.

Results: Of 210 patients in working age, 109 were randomized to infliximab (mean age = 48.4y, median = 50.6y); n women = 80 (75%) and 101 to conventional treatment (48.7y, [52.9y]; 78 [77%]). Seven patients in the infliximab and 4 in the conventional treatment group never received the study drug. The year before randomization the mean number of work days lost per year was 127 (median 112) in the infliximab arm and 118 (median 105) in the conventional treatment group (mean difference, 9; 95%CI, −22 to 105) in the conventional treatment group (mean difference, 9; 95%CI, −22 to 105).
Efficacy of Biological Therapies in Rheumatoid Arthritis: Graphical Modeling of DAS28 Components’ Evolution over Time. G. Avila1,2, A. Alonso1, A. Lopez-Lasanta1, A. Pluma-Sanjurjo1, C. Diaz1 and S. Marsal1. 1Val d’Hebron Hospital Research Institute, Barcelona, Spain, 2University Hospital Vall d’Hebron, Barcelona, Spain.

Background/Purpose: The wide use of biological therapies (BTs) has clearly modified the therapeutic approach in rheumatoid arthritis (RA). One of the most used common tools to measure the efficacy of BTs in RA is the DAS28 score. Little is known about how each of the DAS28 components varies over time. Our aim was to graphically evaluate the evolution of the DAS28 components over time for the most common anti-TNF treatments and to compare them with anti-IL6 therapy.

Methods: 222 RA patients treated with BTs during the period between Dec’99 and March’13 were included. The data on the components of DAS28 score were collected from baseline and at every 3 months of therapy. First, we grouped the anti-TNFs and compared their combined evolution to tocilizumab (TCZ). In order to obtain a precise visualization of the changes in time of each of the DAS28 components, we used the radar charts. In this type of multivariate data visualization technique, each one of the components is represented as different circle axes and, at each time point, the mean relative evolution of each DAS28 component is connected by a line.

Results: The radiological superiority at 2 years of infliximab+MTX compared to conventional combination therapy did not translate into better long-term work loss outcomes in patients with early RA who had had an insufficient response to MTX. None; Petersson is connected by a line. Improvement (i.e. percentage of reduction from baseline) for each component represented as different circle axes and, at each time point, the mean relative evolution of each DAS28 component was variable, suggesting a different mode of action for monoclonal therapies. While the treatment with anti-TNFs showed rapid and greater improvement in the articular component (i.e. SJC and TJC), the treatment with anti-IL6 showed a higher improvement of the ESR (Figure 2). In both treatments, the physician and patient global assessment showed a similar evolution over time.

Conclusion: The radiological superiority at 2 years of infliximab+MTX compared to conventional combination therapy did not translate into better long-term work loss outcomes in patients with early RA who had had an insufficient response to MTX. None; Petersson is connected by a line.

Disclosure: G. Avila, None; A. Alonso, None; M. A. Lopez-Lasanta, None; A. Pluma-Sanjurjo, None; C. Diaz, None; S. Marsal, None.

The Effect of Biological Agents on Work in Patients with Chronic Inflammatory Arthritis: A Meta-Analysis of Randomized Controlled Trials and Controlled Cohorts. Amandine Tubery1, Cristel Castelli1, Florence Enry1, Françoise Barchechath-Flisler1, Sabrina Dadoun1, Bruno Fautrel1 and Cécile Gaujoux-Viala1. 1Nîmes University Hospital, Rheumatology Department, Nîmes, France, 2Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d’Épidémiologie et de Santé Publique, Paris, France, 3UPMC Paris 06 University, GRC 08, Paris France and Pitié Salpêtrière Hospital Paris France, Paris, France.

Background/Purpose: The addition of biological agents in treatment strategies in chronic inflammatory arthritides have improved the possibility of controlling disease activity and slowing the progression of joint damage. However their impact on work participation is unclear.

Objectives: To assess the effect of biological agents on work among patients with chronic inflammatory arthritides (CIAs).

Methods: A systematic review of the literature using PUBMED and the Cochrane library was performed until January 2014. All randomized controlled trials (RCTs) and controlled cohorts (CCs) reporting the effect of biological agents on work among patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) were selected. Data extraction: Data were collected using a predetermined form. The outcomes were accumulated missed workdays, number of patients losing worktime due to CIAs, impact on productivity (on a visual analogue scale) and employment loss. Statistical analysis determined in each study effect size (ES) or odds-ratios (OR) as appropriate to assess the magnitude of treatment effect. Pooled ES and OR were computed by meta-analysis. A random effect model was used in case of heterogeneity.

Results: 14 RCTs and 7 CCs were analyzed i.e. 15881 patients treated by biological agents (adalimumab, etanercept, infliximab, certolizumab, golimumab and abatacept) and 9713 controls. Among those 25594 patients, 24670 suffered from RA, 319 from AS, and 605 from PsA. Pooled analyses indicated that biological agents significantly reduced accumulated missed workdays at week 24 (2 trials): ES = 0.34 [95%CI 0.20 to 0.47], the number of patients losing workdays (3 trials): OR = 0.54 [95%CI 0.36 to 0.79] and improved work productivity (3 trials): ES = 0.45 [95%CI -0.17 to 0.06]
Conclusion: Despite the heterogeneity of the data, this meta-analysis showed the beneficial effect of biologics agents on both absenteeism and presenteeism in chronic inflammatory rheumatism. Thus the high cost of biologic therapy could be partly balanced with savings in indirect costs.

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B. Fautrel. None.

C. Gaujou Viala. A. Abbvie, 9; B. MS, 9; J. Aijen Senschein Pharmaceuticals, P.LTD, 9; M. SD, 9; Pfizer Inc., 2; UCB, 9; Roche Pharmaeuticals, 9.

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Efficacy Meta-Analysis of Randomized Controlled Trials (RCTs) of Biologics in Methotrexate-Naïve Patients with Early Rheumatoid Arthritis.

Yusuf Yazici,1 Chunqiao Luo2 and Christopher Swearingen3. 1New York University University for Joint Diseases, New York, NY; 2Biostatistics, Little Rock, AR; 3University of Arkansas, Little Rock, AR.

Background/Purpose: NNT analysis is a useful tool for putting RCT efficacy results into perspective in patient care. For clinical decision making, the NNT is a useful measure to convey statistical and clinical significance to the doctor (i.e. number of patients needed to treat to achieve 1 additional response compared to control). The most reliable data regarding how a biologic would work comes from MTX naïve RCTs as all patients are receiving active drug for the first time and selection biases may play a lesser role in determining outcomes. We performed a NNT analysis of biologics in MTX-naïve pts with early RA.

Methods: PubMed was searched for randomized double-blind, MTX-controlled studies of biologics in MTX-naïve pts with early RA from Jan 1990 through Dec 2013. Response rates specified by each RCT were used to calculate NNT of biologic (active) versus MTX (control) where NNT = (1/RR active-RR control) * 100. Outcomes assessed included ACR20, ACR50, and ACR70 responses as well as DAS28 remission (DAS28<2.6).

Results: Nine published RCTs were identified.2 Baseline age were similar across the studies (average age 50.2 yrs, range [47.2, 57.5]), but some variability in disease duration (average duration 3.3, range [0.7, 9.3]). All biologics achieved >50% response in ACR 20, although one adalimumab trial was outperformed by MTX only, leading to a negative estimated NNT. All biologics outperformed MTX only with ACR50, ACR90 and DAS28 outcomes.

Conclusion: In MTX-naïve pts with early RA, abatacept and anti-TNF agents have similar efficacy when RCT endpoints, such as ACR50, ACR90 and DAS28 remission, were evaluated and suggested that the likelihood of achieving 50% response in ACR 20, although one adalimumab trial was outperformed by MTX only, leading to a negative estimated NNT. All biologics outperformed MTX only with ACR50, ACR90 and DAS28 outcomes.

Disclosure: Y. Yazici. BMS, Genentech, Celgene, 2; A. Abbvie, BMS, Celgene, Genentech, Pfizer, Samumed, UCB Pharma, 5; C. Luo. None.

C. Swearingen. Genentech and Biogen IDEC Inc., 2; Pfizer Inc. 2; Bristol-Mysers Squibb, 2.

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Efficacy of Infliximab, Adalimumab, and Tocilizumab Can be Improved Under the Baseline ADAMTS5 Selection. Kensei Tsuzuka, Yoko Akiyama1 and Masayoshi Nagata. 1Iruma Heart Hospital, Iruma, Saitama, Japan, 2Kyate Bio Co.,Ltd, Funabashi, Chiba, Japan.

Background/Purpose: We have previously (2010ACR, 2013A CR) reported that the efficacy of biologics, infliximab, adalimumab, and tocilizumab can be predictable using baseline blood a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) mRNA level. In this study presented here, we investigated whether the efficacy of these biologics could be improved if they were administered to RA patients who were diagnosed as effective of those biologics using the baseline ADAMTS5 mRNA levels.

Methods: Whole blood was collected from 41 RA patients at baseline and total RNA was isolated. ADAMTS5 mRNA was quantified using real-time PCR (Biologimate®) followed by the reverse transcription. ADAMTS5 mRNA was calculated as the ratio against b-actin mRNA (Index). Out of 41 patients, 12 (29.3%) have been refractory to infliximab (IFX), IFX, adalimumab (ADA), and tocilizumab (TCZ) was administered if the baseline ADAMTS5 was lower than 1.2, higher than 0.7, and higher than 0.5, respectively. Efficacy of IFX at 14 weeks, ADA at 20 weeks, and TCZ at 12 weeks was estimated using EULAR response. Clinical data (Clinical remission rate, etc) of the RA patients treated with these biologics according to the baseline ADAMTS5 mRNA was compared with those of our data presented at ACR2010 (IFX and ADA) and ACR2013 (TCZ).

Results: All of 12 patients refractory to IFX revealed high level (>1.2 Index) of the baseline ADAMTS5 mRNA. Out of 41 RA patients, 7 (5 bio-naïve and 2 bio-switch) were given IFX, ADA and TCZ according to the baseline ADAMTS5 mRNA levels (ADAMTS5 selection). As a result, the clinical remission (DAS28-ESR<2.6) rate (4/7; 57.1%) with IFX under ADAMTS5 selection was higher than that with IFX of ACR 2010 data (32/100; 32.0%). On the other hand, the clinical remission rate (12/18; 66.7%) with ADA under ADAMTS5 selection was significantly (p=0.0002) higher than that with ADA of ACR 2010 data (9/48; 18.8%). Furthermore, the clinical remission rate (4/5; 80.0%) with TCZ under ADAMTS5 selection was significantly (p=0.0083) higher than that with TCZ of ACR 2013 data (13/54; 24.0%).

Conclusion: Thus the efficacy of infliximab, adalimumab, and tocilizumab can be improved with the baseline ADAMTS5 mRNA.

PREMARK-TNF Test Based on IgA-Specific Autoantigens Predicts Therapy Response in Rheumatoid Arthritis Patients Treated with TNFα Inhibitors. Karl Skriner1, Jorg Hollidt2, Gerd Burmester1 and Zoltan Konthur1.

Background/Purpose: One third of rheumatoid arthritis patients treated with biologicals targeting TNFα are therapy non-responders. We have earlier investigated the difference in seroreactivity of patients being responder and non-responder to anti-TNFα therapies prior to and after therapy and identified a set of IgA-specific autoantigens. So far no mechanism for non-response has been described. Here we present a first study on the diagnostic applicability of the found autoantigenic biomarkers.

Methods: Screening with >200 well defined patient sera on 5 different autoantigenic biomarker candidates, which were expressed recombinantly in E. coli by ELISA.

Results: Pretreatment sera from patients with diagnosis of RA based on the ACR classification criteria who were initiated on therapy with TNFα inhibitors were analyzed for the presence of autoantibodies against a set of 5 biomarker proteins (RAB118, PPP2R1A, KPNB1, COG4, FTFT1) using ELISA assays. In total, analyses of 203 patients were carried out, of which 162 were clearly defined as Responder and 41 were clearly defined as Non-Responder after 6 month treatment. 81% of Non-Responder could be clearly identified with the premarkTNF Test. The assay has currently a specificity 94%.

Moreover, of the 203 samples, 57 samples were baseline sera from an early intervention study with Humira. In this subset, all 3 non-responders were identified and the specificity of the assay was 98%. Only one - an intermediate responder after 6 months of treatment with Humira - gave any signal in the assay on IgA-level.

Conclusion: These data suggest that IgA-autoantibodies against a set of protein biomarkers (premarkTNF test) might be diagnostically applied for the identification of anti-TNFα therapy non-responders prior treatment.

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ACR/ARHP Poster Session C
Sjögren’s Syndrome: Clinical Science
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Risk of Venous Thromboembolism in Patients with Sjögren’s Syndrome: A Systematic Review and Meta-Analysis. Patompong Ungprasert1, Charat Thongprayoon, Karn Wijarnpreecha, Wisit Cheungpasitporn2, Praveen Ratanasrithepa, France, Martinique, 3Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, 4Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, 5Centre Hospitalier universitaire de Fort de France, Fort de France, Guadeloupe, 6CHU Fort de France, Fort de France, France.

Background/Purpose: Venous thromboembolism (VTE) is a common medical problem with a significant morbidity and mortality. Chronic inflammatory state, though not generally regarded as a conventional risk factor for VTE, is increasingly recognized as its potential predisposing factor. In fact, several chronic inflammatory disorders, such as systemic lupus erythematosus and rheumatoid arthritis, have been shown to increase VTE in large epidemiologic studies. However, the data on Sjögren’s syndrome (SS), another common chronic inflammatory disorder, remain unclear due to conflicting studies. Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of VTE in patients with SS versus participants without it.

Methods: Two investigators (P.U. and C.T.) independently searched the PubMed, Embase and the Cochrane database from inception to March 2014 using the terms for Sjögren’s syndrome in conjunction with the terms “venous thromboembolism”, “pulmonary embolism” and “deep venous thrombosis”. A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between SS and VTE and (2) odds ratios (OR’s), relative risk (RR’s) or hazard ratio (HR’s) or standardized incidence ratio (SIR’s) with 95% confidence intervals (CI’s) were provided. Study eligibility was independently determined by the two investigators noted above. Newcastle-Ottawa scale was used to assess the quality of included studies.

Results: Out of 382 potentially relevant articles, four studies (three retrospective cohort studies and one case-control study) were identified and included in our data analysis. The pooled risk ratio of VTE in patients with SS was 2.04 (95% CI, 1.85 to 2.24). The statistical heterogeneity of this meta-analysis was not significant with an I² of 0%.

Conclusion: Our study demonstrated a statistically significant increased VTE risk among patients with SS.

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Characteristics of Primary Sjögren Syndrome in the Black Population of Martinique. Katlyne Polomat1, Serg Ari2, Lauren Brunier-Agot3, Véronique Delhinger3, Michel Debandt4, Georges Jean Baptiste5, Centre Hospitalier universitaire de Fort de France, Fort de France, Martinique, 2Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, 3Centre Hospitalier universitaire de Fort de France, Fort de France, Martinique, 4Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, 5Centre Hospitalier-Universitaire de Martinique, Fort de France, France.

Background/Purpose: There is very limited data on the clinical, biological characteristics and evolution of primary Sjögren’s syndrome (pSS) in black patients of African origin. And yet, other connective tissue diseases such as lupus have particularities in this population.

Methods: Retrospective study of all pSS patients fulfilling American-European consensus criteria followed as out and in patients in the rheumatology and internal medicine units from the academic hospital of Fort de France, Martinique.

Results: 70 patients were recruited since 1991: 68 women, 2 men (female:male ratio, 34:1). Mean age at diagnosis was 49.5 yo (range: 17–74). Mean follow up time was 3.5 years (range 1–17). Main characteristics were: xerostomia 82.8% (n = 58), xerophthalmia 91.4% (n = 64). Objective ocular tests were found positive in 70.3% (n = 45/64). The minor salivary gland biopsy was positive in 92.5% (n = 62/67). Other characteristics were: Raynaud’s phenomenon 29.8% (n = 20/67), arthralgia 55.7% (n = 39), arthritis 21.4% (n = 15), interstitial lung diseases 8.5% (n = 6), peripheral neuropathy 8.5% (n = 6), central nervous system involvement 5.7% (n = 4), pericarditis 1.4% (n = 1), pleurisy 2.8% (n = 2), vasculitis 1.4% (n = 1), no pancreatitis. Some other auto-immune diseases were associated to pSS: anti-phospholipid syndrome 7.1% (n = 5), thyroiditis 7.1% (n = 5), Evans syndrome 1.4% (n = 1). Antinuclear antibodies were positive for 86.9%, anti-SSA for 62.8% (n = 44). ESR or c reactive protein were elevated in 33 patients (47.1%). HTLV-1 positivity was present in 2 patients. In 245 patients, years of follow up, 1 patient experienced lymphoma (0.4 lymphoma for 100 patients-years of follow up). No death was to deplore.

Conclusion: This is the first series of pSS available concerning patients of African origin. Compared to the largest Caucasian pSS cohort published by Ramos Cassás et al, there seems to be no major particularities, but men are less frequently suffering from pSS and vasculitis seems less frequent than in the Caucasians.

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Utility of the American-European Consensus Group and American College of Rheumatology Classification Criteria for Sjögren’s Syndrome in Patients with Systemic Autoimmune Diseases in the Clinical Setting.

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Background/Purpose: To evaluate the feasibility and performance of the AECG and ACR Classification Criteria for Sjögren’s syndrome (SS) in patients with systemic autoimmune diseases.

Methods: 350 patients with primary SS (n=50), systemic lupus erythematosus (n=100), rheumatoid arthritis (n=100), or scleroderma (n=100) were randomly selected from our patients’ registry. Each patient was clinically diagnosed as probable/definite SS or non-SS by two rheumatologists following a standardized evaluation including clinical symptoms and manifestations, confirmatory tests (fluorescein staining test, non-stimulated whole saliva flow, Schirmer-I test) autoantibodies (antineuclear antibodies, anti-Ro/SSA, anti-La/SSB, rheumatoid factor), lip biopsy, and medical chart review. Using the clinical diagnosis as gold standard, the degree of agreement with each criteria set, and between both criteria sets was estimated. We estimated the sensitivity, specificity, positive predictive value, and negative predictive value with 95% CI. We used the kappa statistic.

Results: 154 (44%) patients were diagnosed with SS. The AECG criteria were incomplete in 36 (10.3%) and the ACR criteria in 96 (27.4%). P<0.001. Nevertheless, their ability in classifying patients was almost identical, sensitivity 61.6 vs. 62.3, specificity 94.3 vs. 91.3, respectively. Either criteria were met by 123 (80%); 95 (61.7%) met AECG and 96 (62.3%) ACR criteria, but only 68 (44.2%) patients met both sets. The concordance rate between clinical diagnosis and AECG or ACR criteria was moderate, k statistic 0.58 and 0.8, respectively. Among 90 patients with definite SS patients, sensitivity was 83.3 vs. 77.7, and specificity 99.8 vs. 85.6, respectively. A discrepancy between clinical diagnosis and criteria was seen in 59 (17%) patients. Patients classified by the AECG criteria were older, had more sicca symptoms, parotid enlargement, positive Schirmer-I test, and lower NSWF rate; whereas those classified through the ACR criteria had more often keratoconjunctivitis sicca, focal sialadenitis, rheumatoid factor, and the combination of rheumatoid factor plus autoantibodies.; >1:320.

Conclusion: The feasibility applying the AECG is superior to the ACR criteria; however the performance of both sets was similar among patients with systemic autoimmune diseases. Nevertheless, a subset of patients still is missed by both criteria sets.

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Ocular Surface Temperature in Early Sjögren’s Syndrome and Established Disease.

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Background/Purpose: Due to a variety of factors it is challenging to make a definite diagnosis in the early stages of Sjögren’s syndrome (SS). The ocular examination, including fluorescein and tear break-up time (TBUT), have been a critical part of the diagnosis algorithm. Limitations of these techniques are their relative invasiveness and lack of specificity. They can also have intrinsic toxicity, including cellular morphologic changes, including loss of cellular motility, cell detachment and death. We propose ocular surface temperature (OST) measurements as a novel, non-invasive technique that can potentially overcome these limitations.

Methods: We evaluated 5 subjects with SS that fulfilled American-European Consensus Group criteria (AECG SS), 5 subjects with early disease (early SS), and 5 healthy controls (HCs). The early SS was defined as presence of autoantibodies suggestive of SS, ocular dryness less than 5 years, not fulfilling the AECG criteria. OST measurements were taken on both eyes over a 5 second interval, 30 measurements per second. In addition, tear film break-up time (TBUT), Schirmer, and fluorescein staining scores were obtained for each patient and each eye. For the early SS and AECG SS subjects we also obtained SF36, visual analog scale (VAS) for dryness, ESSDAI (EUrar SS Disease Activity Index) and standard of care laboratory analysis.

For each patient, the OST measurements from both eyes were averaged to create a single observation for each individual. Receiver operating characteristic (ROC) curves were fit using the different potential metrics under two different classification scenarios: HC vs early SS and SS, and SS vs HC and early SS.

Results: Clinically, subjects with early SS had a lower SF36, VAS, ESSDAI, ESR, CRP, ANA and anti-Ro titers, and lower IgG compared with AECG SS. They also had a higher WBCs and complement levels. Although none of these differences reached statistical significance, they are suggesting that subjects with early SS had less active immunological disease and less subjective dryness than subjects with AECG SS.

An exponential transformation on OST and a log transformation on TIME produced an approximately linear relationship. The interaction was found to be statistically significant (p < 0.0001). This interaction indicates that early SS had a significantly less negative slope than the other two groups. The slope of the transformed linear relationship appeared to be the best metric for classifying AECG SS vs HC and early SS.

Conclusion: Using OST we showed that subjects with early SS had a slower fall in their ocular temperature (indicative of less dryness) than patients with AECG SS and clearly separated from HCs. The ocular temperature measured at second each correlated best with the tear break up time (TBUT), suggesting that it could be used in conjunction with standard of care ocular dryness measurement, potentially improving the sensitivity of ocular measurement. Although the clinical characteristics of the AECG SS vs. early SS did not reach statistical significance, the trends suggested that early SS had less dryness, and less actively immunological disease (lower level of autoantibodies, lower inflammatory markers and IgG level), consistent with early disease.

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Performance of the Ocular Staining Score (OSS) vs. the Van Bijsterveld Score in the Assessment of Sjögren’s Syndrome-Related Keratoconjunctivitis Sicca.

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Background/Purpose: Sjögren’s syndrome (SS) is a complex autoimmune disorder characterized by xerostomia and xerophthalmia due to exocrine gland dysfunction. There is no single diagnostic test for SS and multiple research classification criteria have been proposed. Currently, a combined EULAR-ACR working group is dedicated to resolve discrepancies and weaknesses between two systems presently in use: the American-European Consensus Group (AECG) criteria and the SICCA (ACR) criteria, with the ultimate goal of establishing a new consensus classification. A point of contention has been the assessment of keratoconjunctivitis sicca either by the van Bijsterveld score (vBS) for AECG classification or the Ocular Staining Score (OSS) for ACR classification. We present a direct comparison of the two scoring systems to help clarify the matter.

Methods: We performed all tests for AECG and ACR classification in a multidisciplinary sicca clinic. Complete vBS and OSS evaluations were available for 716 participants; a subset of 587 were classified by AECG criteria either as pSS (n=257) or sicca (n=330). The remaining 129 had other diseases or overlap/secondary SS. Initial analysis of concordance (vBS=OSS) or discordance (vBS≠OSS) of the ocular scores was done for n=716 subjects but the correlations with classification criteria and clinical features was restricted to the pSS/sicca subset.

Results: Of the 716 subjects, 538 (75.1%) were concordant while 178 (24.9%) were discordant for vBS vs. OSS. The discordant subjects had significantly higher vBS (Wilcoxon rank sum p<2.2×10E-16); the same held
true if only pSSs vs. sicca were compared. ROC curves comparing the sensitivity and specificity of the vBS and OSS both in the two study groups showed that the accepted vBS cutoff of 4 has a sensitivity of 0.59–0.68 and specificity of 0.74–0.79; similar sensitivities for the OSS are observed at scores of 4 (sensitivity 0.63–0.74; specificity 0.72–0.78) and 5 (sensitivity 0.54–0.62; specificity 0.79–0.83). Discordant participants were significantly more Ro (+), La (+), and biopsy (+) than the concordant cases (p = 1.76 x 10^{-10}; 4.3 x 10^{-6}; 1.8 x 10^{-10} respectively). The patches of confluent staining were the most important for outcome. Due to cost and inconvenience of scoring the lesions, when analyzing the three additional corneal staining points of the OSS, their presence was highly associated with participants meeting criteria for pSS (p = 8.4 x 10^{-7} to 1.7 x 10^{-13}); with (+) Schirmer’s (p = 3.1 x 10^{-6} to 6.5 x 10^{-10}), Ro (p = 2.7 x 10^{-5} to 2.9 x 10^{-10}), La (p = 0.01 to 8.8 x 10^{-6}), biopsy (p = 8.1 x 10^{-6} to 3.4 x 10^{-10}), and WUSF (p = 0.0007 x 1.0 x 10^{-6}). In all cases, the patches of confluent staining were the most highly associated with markers of disease severity while the corneal filaments were the least significant.

Conclusion: The OSS was introduced as an objective measure of KSS in the ACR classification and was considered abnormal if ≥3. However, more recent studies indicate it has poor specificity. Our results in a large sicca cohort suggest that a cutoff between 4 and 5 would maintain a significant sensitivity while increasing the specificity significantly; a matter of great importance when applying the criteria for patient selection for clinical trials.

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The Sjögren’s Syndrome Responder Index, a Data-Driven Combined Endpoint, Could Detect Biologic Efficacy. Divi Concare, Valerie Devalauchelle-Pensec, Xavier Marie-Arielle, Sandrine Joussé-Julin1, Jean-Mare Bertholet1, Aëth Perdriger2, Xavier Puéchal, Yerminique le Guern1, Jean Sibilla1, Jacques Gottenberg1, Laurent Chiche2, Eric Hachulla3, Pierre-Yves Hatron3, Vincent Goë3, Gilles Hayem2, Jacques Moré4, Charles Zamfinski5, Jean Jacques Dubost5, Raphaëlle Séro6, Jacques-Olivier Pers5, Emmanuel Nowak7 and Alain Saraux9. 1Brest Occidentale University, Brest, France, 2Brest Occidentale University, Brest, France, 3CHU, Université Paris-Sud, Le Kremlin Bicêtre, France, 4CHU Brest, Brest, France, 5CHU Nantes (Nantes University Hospital), Nantes, France, 6Rhumatologie, Rennes, France, 7National Referential Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, Paris, France, 8Hôpital Cochin, Paris, France, 9University Hospital of Strasbourg, Strasbourg, France, 10Strasbourg University Hospital, Strasbourg, France, 11CHU Marseille, Marseille, France, 12National Rhéumatoïde Centre, Lille, CEDEX, France, 13CHU Lille, Lille, France, 14Amiens University Hospital, Amiens, France, 15CHU Bichat, Paris, France, 16Hôpital Lapeyronie, Montpellier, France, 17Le Havre General Hospital, Le Havre, France, 18CHU G-Montpied, Clermont-Ferrand, France, 19University Paris Sud, Le Kremlin Bicêtre, France, 20CHU de la Cavale Blanche et Université Bretagne occidentale, Brest Cedex, France.

Background/Purpose: Efficacy of rituximab remains debated in primary Sjögren’s syndrome (pSS), but that could be partly due to the absence of validated endpoint. To determine which outcome measures could detect rituximab efficacy and to create an alternative combined endpoint which could be tested in future trials in pSS.

Methods: We have conducted a post-hoc analysis of the randomized, placebo-controlled, TEARS study (Rituximab versus placebo) conducted in 14 university hospitals in France and included 120 pSS patients. Several outcome measures were prospectively collected at week (W)0, W6, W16 and W24 in the TEARS study. The outcome measures which were able to detect rituximab effect were associated to create a new composite endpoint that we called the Sjögren’s Syndrome Responder Index (SSRI). The SSRI was then tested in the TRIPPS study (Infliximab versus placebo).

Results: The 5 selected outcome measures were fatigue, oral dryness, ocular dryness (patient’s assessment on visual analog scales), unstimulated whole saliva flow and erythrocyte sedimentation rate. In the TEARS study, the proportion of patients fulfilling at least 30% improvement of at least 2/5 outcome measures, the SSRI-30 responder rate, was in the rituximab and placebo groups, respectively 47% vs 21% at W6; 50% vs 7% at W16; and 55% vs 20% at W24 (p = 0.01 for all comparisons). The same analysis in the TRIPPS study (Infliximab versus placebo) confirmed that infliximab is not effective in pSS.

Conclusion: We determined a core set of outcome measures which would be able to detect rituximab efficacy in pSS, and we propose response criteria which could be tested as primary outcome measures in future trials in pSS.

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Diagnostic Accuracies of Sialography and Salivary Ultrasonography in Sjögren’s Syndrome Patients: A Meta-Analysis. Young Ho Lee1 and Gwan Gyu Song2. 1Korea University Medical Center, Seoul, South Korea, 2Korea Univ College of Medicine, Seoul, South Korea.

Background/Purpose: Ultrasonography (US) may come to replace conventional invasive examinations in clinical practice. However, the diagnostic accuracy of salivary US has not been clearly compared with sialography, and there is as of yet no consensus on the use of US as an alternative method for the assessment of salivary gland involvement in Sjögren’s syndrome (SS) patients. Salivary US has been used in the context of SS in connection with sialography with respect to diagnostic accuracy. However, published studies on the diagnostic accuracies of sialography and US are controversial and inconclusive. This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. The purpose of this study was to compare the diagnostic performance of sialography and salivary ultrasonography (US) for Sjogren’s syndrome (SS) patients.

Methods: We searched Medline, Embase, and the Cochran library, and performed two meta-analyses on the diagnostic accuracy of sialography and salivary US in SS patients.

Results: A total of six studies including 488 patients and 447 controls from two European and four Asian studies were available for the meta-analysis. The pooled sensitivity and specificity of sialography were 80.0% (95% confidence interval [CI] 76.4–83.2) and 89.0% (85.8–91.8), respectively, and 77.4 (73.7–80.9) and 81.5 (77.6–85.0) for US, respectively. For sialography, the PLR, NLR, and DOR were 9.296 (4.200–20.57), 0.228 (0.170–0.305), and 46.51 (16.14–134.0), respectively, and for US were 4.631 (2.707–7.864), 0.302 (0.226–0.403), and 17.48 (10.03–30.45), respectively. The area under the curve (AUC) of sialography was 0.824, and the* index was 0.757, while the AUC of US was 0.864, and its* index was 0.794, indicating that the diagnostic accuracy of US is comparable with sialography in SS patients. A subgroup meta-analysis according to the diagnostic criteria did not change the overall diagnostic accuracy.

Conclusion: Our meta-analysis of published studies demonstrates that the diagnostic accuracy of salivary US is comparable with sialography in SS patients.

Disclosure: Y. H. Lee, None; G. G. Song, None.

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Ultrasound-Guided Core Needle Biopsy of the Major Salivary Glands: A Safe and Useful Diagnostic Tool in the Evaluation of Suspected or Established Sjögren’s Syndrome. Amandeep Narayan, Thomas Grader-Beck, Julius Birnbaum, Jean Kim, Qing Kay Li, Deborah Belchis, Joel Fridkin and Alan N. Baer. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Ultrasound-guided core needle biopsy (CNB) has greater inherent risks than fine-needle aspiration for the diagnosis of major salivary gland neoplasms, but provides tissue for histologic analysis. We sought to evaluate the safety and utility of CNB in the evaluation of salivary gland abnormalities in patients with suspected or established Sjögren’s syndrome (SS).

Methods: We identified 19 patients who underwent ultrasound-guided CNB of either the parotid or submandibular gland as part of a diagnostic evaluation in our SS Center between 7/2009-5/2014. CNBs of the parotids were obtained using a posterior-inferior approach from the tail of the superficial lobe to avoid injury to the facial nerve. Patients were contacted one day after the procedure to assess for complications. The patient charts were reviewed retrospectively, using a protocol approved by the institutional review board.

Conclusion: CNB can be safely performed in patients with suspected or established Sjögren’s syndrome.
Results: The 5 men and 14 women had a median age of 55 years (range, 19–74). Seven patients had an established SS diagnosis and underwent the procedure to exclude lymphoma as the cause for symmetric or asymmetric salivary gland enlargement. The remaining 12 with suspected SS underwent the procedure because of bilateral salivary gland enlargement and/or induration (n=11) or an elevated serum IgG4 level (n=1), but only one was diagnosed with SS. The 19 procedures involved sampling of parotid (n=14) or submandibular (n=5) glands but normal ultrasound echotexture had a CNB showing fatty infiltration or lymphoid infiltrates or supported by its identification of: 1) pathologic abnormalities (lymphoid infiltrates or >50% fibrosis) in 10/10 patients with abnormal salivary gland ultrasound echotexture and 2) lymphoid infiltrates in 5/8 patients with established SS. Three patients with enlarged parotid glands but normal ultrasound echotexture had a CNB showing fatty infiltration with normal acinar tissue.

Conclusion: Ultrasound-guided CNB of the major salivary glands can be done safely and provides useful diagnostic information about salivary gland abnormalities in the evaluation and management of SS. The evaluation of possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not
Background/Purpose: Sjögren’s syndrome (SS) is a common autoimmune disease involving the salivary and lacrimal glands along with various other organs. It is generally seen in adult females and it is considered ‘rare’ in children. However, there are not a few pediatric SS patients, and their clinical features are different from those of adults. It is because pediatric patients are in early stages of the disease. The current studies were designed to characterize SS in a population of pediatric patients and whether anti-Sp1, anti-Ca6 and anti-PSP antibodies could be a new disease marker of early stages of SS.

Methods: Sera were obtained from 15 patients, 4 fulfilled the revised Japanese diagnostic criteria for SS and 11 who probably have SS from the Department of Allergy and Rheumatology, Chiba Children’s Hospital, Chiba City, Japan. Their age range was 3-18 years with a mean age of 10.98 years. Fifty pediatric normal controls who were age and sex matched were obtained from Promedex Corporation, USA. ANA was evaluated by HEp2-IFA (Immunofluorescence), RF (Rheumatoid Factor), anti-Ro, anti-La, anti-Sp1, anti-Ca6 and anti-PSP by ELISA as previously described.

Results: Of the 15 pediatric patients, 11 were females (73%), 2 had SS secondary to SLE and 1 had MCTD. The majority of the patients (80%) expressed ANA and 40% RF. Anti-Ro was expressed by 7 patients of whom 2 also expressed anti-La and 1 also expressed anti-Sp1 whose sialography was negative. One 6 year-old patient expressed anti-Ca6 and anti-PSP without anti-Ro or anti-La. Of the SS pediatric normal controls, ANA, anti-Ro, anti-La, anti-Ca6 and anti-PSP were all negative. Four normal controls expressed RF, 1 had a low titer for anti-PSP and one a low titer for anti-Sp1.

Conclusion: Pediatric patients with SS are frequently ANA and anti-Ro positive. One patient lacking these autoantibodies expressed anti-Ca6 and anti-PSP and one patient whose sialography was negative had anti-Sp1.

These antibodies may be new disease markers of SS in early stages. In general, a larger percentage of pediatric Sjögren’s patients compared to adult patients were male. The pattern of autoantibody expression in pediatric Sjögren’s patients was different from what has been historically seen in adult Sjögren’s patients. Further studies will be necessary to look at a larger population of pediatric Sjögren’s patients over time to evaluate the progression of their disease and the pattern of their autoantibody expression.

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Anti-Ro/SSA Positive Incomplete Sjögren’s Syndrome. R. Hal Scofield, Anne Igoe1, Donald U Stone1, Lida Radar1, Kimberly S. Hefner2, David M. Lewis3, Stephen Young3, Judy Harris4, Kiely Grundahl5, Biji T. Kurien1, Jacen Mair-Moore6, Kristi A. Koelsch7, James Chodosh8, Nelson L. Rhodes9, Raj Gopalakrishnan10, Barbara M. Segal12, Amare Farris12, Courtney G. Montgomery13, Christopher J. Lessard13, Kathy L. Sivils14 and Astrid Rasmussen15. 1US Department of Veterans Affairs Medical Center, Oklahoma City, OK, 2Metro Health, Cleveland, OH, 3Dean McGee Eye Institute, Oklahoma City, OK, 4University of Oklahoma Health Sciences Center, Oklahoma City, OK, 5Hefner Eye Care and Optical Center, Oklahoma City, OK, 6Oklahoma Medical Research Foundation, Oklahoma City, OK, 7University of Texas at El Paso, El Paso, TX, 8Oklahoma Medical Research Foundation, Oklahoma City, OK, 9U.S. Department of Veterans Affairs Medical Center, Oklahoma City, OK, 10University of Texas at Dallas, Dallas, TX, 11University of Minnesota, Minneapolis, MN, 12Hennepin County Medical Center, Minneapolis, MN.

Background/Purpose: Sjögren’s syndrome (SS) is a systemic disease characterized by dry eyes and mouth resulting from immune mediated damage and dysfunction of the lacrimal and salivary glands. Clinical diagnosis often takes 6-10 years, leading to a lag in potential preventive and therapeutic strategies. Research classification is most often based on the American European Consensus Group (AECG) criteria. For classification as primary SS (pSS), the AECG criteria require ≥4/6 components with at least 1 being autoantibodies or abnormal histopathology. A significant number of subjects with sicca manifestations have “incomplete” syndrome (iSS) and exhibit less than 4 AECG criteria. We describe the clinical and serologic features of a subgroup of iSS patients.

Methods: In a multidisciplinary sicca clinic, we assessed features of salivary and lacrimal gland dysfunction and autoimmunity as defined by AECG criteria, identifying 573 iSS participants. We compared the features of iSS based on the presence or absence of anti-Ro/SSA autoantibodies (Ro(+) iSS and Ro(−) iSS, respectively).

Results: Of 573 iSS participants, 467 had complete clinical and laboratory data; 19 of them were Ro(+) (4.1%), and 448 were Ro(−) (95.9%). When compared to Ro(−) iSS, Ro(+) iSS patients were younger (43 ± 5.72 vs. 53 ± 13.27, p<0.001) and less often Caucasian (52.6% vs. 95.7%, p=1.95 × 10−6); had more anti-LaSSB (+) (46.2% vs. 2.1%, p=8.8 × 10−6), hypergammaglobulinemia and lymphopenia (p=0.02 and p=0.009, respectively). Furthermore, Schirmer’s I test scores, ocular surface staining, and whole unstimulated salivary flow were less abnormal than the Ro(−) iSS participants (19.05 ± 9.85 vs. 14.19 ± 10.55, p=0.05; 1.5 ± 1.2 vs. 2.84 ± 2.25, p<0.0001; and 5.77 ± 3.66 vs. 2.23 ± 2.3, p<0.0001 respectively). These differences in age, race, anti-La, hypergammaglobulinemia, and lymphopenia were also statistically significant when comparing the Ro(+) iSS subjects to Bipsby(+) iSS or Ro(−)Bipsby(−) iSS. Finally, Ro(+) iSS patients presented a variety of extraglandular manifestations: 6 had hypothyroidism and/or autoimmune thyroid disease, 5 arthritides/arthralgias, 5 leuko and/or lymphopenia, 5 low CH50, 4 hypergammaglobulinemia, 3 interstitial lung disease, 2 Raynaud’s phenomenon, 2 photosensitivity, and 1 neuromyelitis optica.

Conclusion: A small percentage of patients with iSS have anti-Ro autoantibodies but do not meet the classification criteria for SS. It is possible that these patients will remain as a forerunner of SS or anti-Ro positive undifferentiated connective tissue disease, but given their younger age and multiple manifestations, it is plausible that they may progress to pSS. Of any possible line of autoimmune disease prevention research, understanding the early events of the disease have the strongest potential to lead to improve-
ms in prevention, early diagnosis, and therapeutics. Thus, this group of patients warrants careful follow up to characterize the transition from ISS to full-blown pSS and pinpoint indicators of early autoimmunity that may help identify those at risk for further disease progression.

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How Does a Younger Age at the Onset of Sjögren's Syndrome (pSS) Influence the Clinical Presentation and the Clinical Course of the Disease? Chiara Baldini, Luca Quattrocchio, Elena Bartoloni-Bocci, Roberta Priori, Francesco Carubbi, Alessia Alunno, Roberto Geri, Guido Valesini, Salvatore De Vita and Stefano Bombardieri. 1Rheumatology Unit, Pisa, Italy; 2D5M B, University Hospital Santa Maria della Misericordia, Udine, Italy; 3University of Perugia, Perugia, Italy; 4Department of Internal Medicine and Medical Specialties, Sapientia University, Rome, Italy; 5Rheumatology Clinic, University of L'Aquila, L'Aquila, Italy; 6Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: To analyze the clinical presentation and the clinical course of Sjögren's Syndrome (pSS) in Caucasian patients with an "early-onset" pSS and to compare the characteristics of the disease between 2 groups of patients and a control group of patients with pSS and a "typical onset" of the disease.

Methods: A retrospective systematic search through an Italian computerized pSS database, including 1145 patients, was performed in order to select the patients with an "early-onset" of the disease who were defined as those patients aged below the 10th percentile at the time of pSS diagnosis. All the patients enrolled in the database have been recruited at 5 Rheumatology University Italian medical centers and the data have been systematically entered in a standardized form and updated at regular intervals during follow-up since 2009. For all patients, the following parameters were retrieved: age at diagnosis, sex, disease duration, glandular and extra-glandular disease-related manifestations, laboratory features, serological profiles, medical treatments and lymphoproliferative complications. Categorical variables were compared using chi square test; continuous variables were compared using Student's t-test. A 2-tailed value of p < 0.05 was taken to indicate statistical significance.

Results: The systematic search selected 1192 pSS patients out of the entire cohort (AECG 2002). Median (IQR) age at pSS diagnosis was 52 (42-62) years and the tenth percentile was 33 years. By using the tenth percentile as a cut-off, we identified 125/1192 (10.5%) as the "early-onset" group whereas the remaining 1067/1192 (89.5%) represented the control group. Median (IQR) disease duration was significantly longer in the "early-onset" group (7 (3-14) versus 3 (1-8) years, p<0.0001). Patients with an early disease onset presented a lower frequency of subjective dry mouth (p=0.003) and a higher prevalence of parotid enlargement (p<0.0001), Raynaud's phenomenon (p<0.04) and tubular renal disease (p=0.04). Moreover, patients with an "early-onset" pSS presented more frequently a positivity for rheumatoid factor (RF) (p=0.0001), anti-RoSS/A (p<0.0001), and anti-La/SS-B antibodies (p=0.0001), low C3 levels (p=0.006), hypergammaglobulinemia (p=0.0001), and leukopenia (p=0.006). No differences were detected between the two groups regarding low C4 levels, cryoglobulins, purpura, peripheral nervous system involvement and lymphoproliferative complications.

Conclusion: The age at the onset of pSS may influence the diagnostic algorithm of the disease due to the lower prevalence of subjective sicca symptoms. Parotid enlargement, kidney involvement, laboratory and serological abnormalities seemed to be distinctive features of the "early-onset" pSS. However, despite the higher frequency of parotid gland enlargement, patients with "early-onset" pSS apparently did not present a phenotype at higher risk of lymphoma.

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Disclosures N. Berman: None; J. S. Dunham: None; J. Baker: None; F. B. Vivino: Andrea Cavitolo Foundation, 2; NIcon Inc., 3; Immoce, Inc., 5; Norartis, Inc., 5; Blegen Idoc, 5; Takeda, Inc. 5.

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Metabolic Disorders Causing Fatigue in Sjögren’s Syndrome. Lakshmanan Suresh1, Julian Ambrus2, Long Shen3 and Sahana Vishwanath4. 1State University of New York/Buffalo, Buffalo, NY, 2University Of Buffalo, Buffalo, NY, 3SUNY at Buffalo, Buffalo, NY, 4SUNY - Buffalo, Buffalo, NY.

Background/Purpose: Sjögren’s syndrome (SS) is a complex disorder involving both the innate and immune system. Fatigue is a common feature of the disease. Mitochondrial dysfunction has been associated with chronic inflammatory diseases, including SLE, and can result in fatigue and exercise intolerance.

Methods: We evaluated 32 patients meeting the ACR criteria for SS who presented with profound fatigue for disorders of aerobic and anaerobic metabolism. Serum lactate, carnitine, and ischemic forearm tests were performed. In selected patients, muscle biopsies were done for genetic and biochemical studies.

Results: Of these SS patients, 30 had elevated lactic acid at rest and 3 had abnormal ischemic forearm tests. Nine of the patients underwent muscle biopsies. Four had mitochondrial respiratory chain abnormalities, 2 had carnitine palmitoyl transferase deficiency, 1 had very long chain acyl CoA dehydrogenase deficiency and 2 had glycogen storage diseases (myophosphorylase deficiency, lactate dehydrogenase deficiency). A proper treatment led to symptomatic improvement in all cases.

Conclusion: Metabolic disorders are common in patients with SS and contribute to symptoms such as fatigue and exercise intolerance. Treatment of these disorders leads to symptomatic improvement. Further studies are needed to determine the incidence of metabolic disorders in SS, the incidence of SS in patients with metabolic disorders and the mechanisms by which SS and metabolic disorders are interrelated.

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2547

The Impact of Primary Sjögren’s Syndrome on Female Sexual Function. Jolien F. van Nijmegen, Suzanne Arends, Greetje S. van Zuiden, Arjan Vissink, Frans G.M. Kroese and Hendrika Bootsma. University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

Background/Purpose: Primary Sjögren’s syndrome (pSS) is a chronic and disabling disease, characterized by sicca symptoms of the eye and mouth as well as fatigue. Besides these well-known symptoms, multiple studies have shown that women with pSS often experience complaints of vaginal dryness and dyspareunia. Our aim was to evaluate sexual dysfunctioning and sexual distress in women with pSS compared to healthy controls, as well as to assess parameters that are associated with sexual dysfunctioning and distress in pSS.

Methods: 46 women with pSS according to the AECG criteria (mean age 46.3 ± 10.5) and 43 age-matched healthy controls (mean age 44.4 ± 11.3) were included. Median disease duration of the patients was 7 years (IQR 4-14). Participants completed self-administered questionnaires, viz. Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Multidimensional Fatigue Inventory (MFI), Hospital Anxiety and Depression Scale (HADS), Maudsley Articular Questionnaire (MAMQ) and RAND 36-item health survey (RAND-36). In addition, EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI) were completed in pSS patients.

Results: Women with pSS had impaired sexual functioning compared to healthy controls (median FSFI 20.6 vs. 30.3, p<0.001) as reflected by significantly lower scores in the domains of desire, arousal, orgasm, lubrication and pain (figure 1). Furthermore, pSS patients experienced more sexual distress (median FSDS 7 vs. 4, p<0.05) and were sexually active less frequently than controls (76% vs. 93%, p<0.05). In total, 67% of the patients never talked about sexual problems with their rheumatologist. Sexual dysfunctioning correlated significantly with depressive symptoms (HADS), higher ESSPRI score, more symptoms of fatigue (MF1), lower mental quality of life (RAND-36) and relationship dissatisfaction (MMQ), but not with systemic disease activity (ESSDAI).

Conclusion: Women with pSS have impaired sexual function and more sexual distress compared to healthy controls. Sexual dysfunctioning and distress are associated with more patient-reported symptoms of pSS, fatigue and depression. More research is needed to obtain knowledge on the pathogenesis of vaginal sicca symptoms in pSS and the best treatment for this complaint.

Figures:

Figure 1: FSFI total (A) and subscale (B) scores in patients with pSS and healthy controls. Box-and-whiskers plots (Tukey); boxes indicate medians with IQRs; whiskers indicate 1.5 times the interquartile distances; * indicate outliers.

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Primary Sjögren’s Syndrome is Associated with Significant Cognitive Dysfunction. M. Emnet Engin Tercan1,2, Seminar Haznedaroglu1, Emine Belgin Kocer1, Cemile Sonmez2, Ridvan Mercan4, Aysegul Atak Yuce2, Hale Zeynep Batur2, Berivan Bitik2 and Berna Goker1. 1LUTFI KIRDIR KARLAT EA Hospital, Istanbul, Turkey, 2Gazi University School of Medicine, Ankara, Turkey, 3Public Health Institute of Turkey, Ankara, Turkey, 4Gazi University School of Medicine, Ankara, Turkey.

Background/Purpose: Primary Sjögren’s syndrome (PSS) is an autoimmune exocrinopathy with multiple clinical manifestations. We aimed to evaluate the frequency and type of cognitive dysfunction and its association with anti-ganglioside antibodies in patients with PSS.

Methods: Twenty-eight female cases with PSS fulfilling the American-European consensus criteria and 20 female control subjects matched in terms of age and education level, examined between June, 2011 and August, 2013 were enrolled into the study. The mean age was 45.7±10.6 in PSS, and 42.1±10.3 (p=0.27) in the control group.

Neuropsychological tests including attention, information processing speed, short term memory, long term memory, visual memory and visual-spatial perception were examined in both groups. Verbal frequency functions were examined and measured by COWAT, naming concentration by BNT, verbal learning by SDLT, immediate, short and long term verbal memory by AVL, visual spatial perception by BILLOT, and immediate, short term and long term visual memory with RCFT. Cognitive dysfunction was defined as "mild" if there was a deterioration in 1 or 2 test performances, and as "severe" if an impairment in 3 or 4 test performances was observed.

A standard western blot test (Euroimmun, Germany) was used to investigate IgM and IgG anti-ganglioside antibodies (GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b) in the patients and healthy controls.

Results: Primary Sjögren’s syndrome patients had lower performance in tests evaluating verbal learning, verbal memory and visual-spatial perception in SDLT and BILLOT compared to healthy controls (p<0.01) in PSS group (Table 1). Lower performance was also observed in the patient group in clock drawing, COWAT, PASAT, and AVL tests, however the difference did not reach a significant level (p>0.05).

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient (n=28)</th>
<th>Healthy control (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clock Drawing</td>
<td>6.71±0.71</td>
<td>7.00±0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>COWAT</td>
<td>25.71±10.69</td>
<td>28.15±8.43</td>
<td>0.38</td>
</tr>
<tr>
<td>PASAT</td>
<td>46.85±8.65</td>
<td>51.00±7.07</td>
<td>0.10</td>
</tr>
<tr>
<td>SDLT</td>
<td>8.0±7.34</td>
<td>16.50±4.34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AVL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate verbal memory</td>
<td>6.32±1.92</td>
<td>7.40±1.84</td>
<td>0.78</td>
</tr>
</tbody>
</table>

S1113
Long term verbal memory  
10.02 ± 2.34  
10.75 ± 2.02  
0.63

BNT  
33.50 ± 1.87  
32.60 ± 2.59  
0.21

BLOT  
21.07 ± 3.75  
24.45 ± 2.46  <0.01

IgM anti-ganglioside antibodies were positive in 9 patients with pSS, and 2 in healthy controls. Three pSS patients had two IgM anti-ganglioside antibody positivity (GM-1G-M2, GM-3G-D1b, GT1bGQ1b). IgG anti-ganglioside antibodies were positive in 3 patients with pSS, and 1 in healthy controls.

Conclusion: We found impairment in attention, information processing speed, long term memory and short term memory in pSS patients. Anti-ganglioside IgM antibodies may play a role in cognitive dysfunction in pSS by autoimmune neuroinflammation.

Implementing detailed neuropsychological tests is helpful in assessing subclinical cognitive dysfunction in pSS and early treatment.

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Renal Involvement in Primary Sjögren’s Syndrome: A Multicenter French Study of 95 Biopsy Proven Cases


Background/Purpose: Renal involvement is reported in 5 to 25% of patients with Primary Sjögren’s syndrome (pSS). However, data on pSS-related nephropathy with renal biopsy (RB) remain scarce. This observational study was undertaken to describe the clinical and histopathological characteristics of pSS-related nephropathies and their outcomes.

Methods: We conducted a French multicentric and transdisciplinary retrospective study on pSS patients with RB-proven nephropathies. Inclusion criteria were patients diagnosed with pSS based on American-European Consensus Group (AECG) criteria or study-specific enlarged AECG criteria (presence of ≥3/4 AECG items) and who underwent a RB.

Results: Ninety-five patients were included (sex ratio F/M 9/1, mean age 49 years), 84% and 16% fulfilling AECG criteria and enlarged AECG criteria respectively. pSS was isolated in 88% or associated with other organ-specific autoimmune disorders (12%), including primary biliary cirrhosis, autoimmune hepatitis and thyroiditis. Renal disease was diagnosed prior to pSS for 20%, with a median interval of 17 months. For 41%, the 2 conditions were diagnosed simultaneously and, for 39%, after pSS, with a median interval of 36 months. Renal manifestations consisted of renal failure (86%), glomerular-range proteinuria (26%), electrolyte disturbances alone (18%), linitis (10%) and/or nephrocalcinosis (5%). RB exhibited acute or chronic tubulointerstitial nephritis (77%), with numerous plasma-cell infiltrates (69%). Glomerular lesions were found in 26%, in the form of glomerulosclerosis or membranous nephropathy. Eighty patients (84%) received corticosteroids (CS). In 21 patients (22%), standard immunosuppressive drugs (n=8) and/or rituximab (n=18) was added on top of CS in a first or a second line of treatment. Baseline mean estimated glomerular filtration rate (eGFR) was 40 mL/min/1.73m2. After a median follow-up of 53 months, eGFR improved significantly [47 mL/min/1.73m2, P<0.001]. Baseline mean estimated glomerular filtration rate (eGFR) was 40 mL/min/1.73m2. After a median follow-up of 53 months, eGFR improved significantly [47 mL/min/1.73m2, P<0.001].

Conclusion: In pSS, the main renal lesion is tubulointerstitial nephropathy associated with significant and frequent renal dysfunction. Systemic treatments can significantly improve renal function. Analysis of renal prognosis associated with the different therapeutic strategies is ongoing.

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Impaired Speckle Tracking As A Marker of Subclinical Left Ventricular Dysfunction in Patients Affected By Primary Sjögren’s Syndrome

Fabiola Atzeni1, Stefano Galavara2, Chiara Colombo3, Luigi Gianturco2, Laura Boccassini2, Piercarlo Sarzi-Puttini4 and Maurizio Turri4, 2) Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, 3) Cardiology Unit, IRCCS-Galeazzi Orthopedic Institute, Milan, Italy.

Background/Purpose: Primary Sjögren’s syndrome (pSS) is a common chronic autoimmune disease that particularly affects the salivary and lacrimal glands, and leads to dry eyes and dry mouth. We have previously shown that plasma asymmetric dimethylarginine (ADMA) levels and coronary flow reserve (CFR) are impaired in patients with pSS. The aim of this study was to investigate the use of impaired speckle tracking as a marker of subclinical left ventricular dysfunction predicting congestive heart failure in patients with pSS and a normal ejection fraction.

Methods: The study included 49 outpatients who fulfilled the American-European Consensus Criteria (AECG) criteria for pSS (14 males and 35 females; mean age 57.6±6.9 years), and 22 healthy controls matched in terms of age, gender and other anthropometric characteristics. Cardiovascular (CV) risk profiles were assessed by means of standard electrocardiography (ECG), conventional and stress trans-thoracic echocardiography with the measurement of CFR, carotid ultrasonography and pulse wave velocity (PWV). Two-dimensional echocardiographic images were obtained using the apical 4-chamber view at a high frame rate of 70–80 frames/s, and three cardiac cycles were stored in cine-loop format for off-line analysis using commercially available QLAB 9 software (Phillips Medical System, USA) in order to assess end-systolic LV longitudinal strain (ε).

Results: All of the patients had extra- or intraglomerular systemic involvement: pSS 30 were being treated with hydroxychloroquine (HCQ) 400 mg/day, 11 with azathioprine (AZA) at a mean dose of 150 mg/day (range 50–200 mg), and eight with methotrexate (MTX) at a mean dose of 7.5 mg/weekly. None of the patients showed any signs or symptoms of CV disease, pulmonary involvement, or any other complication. The patients’ mean EF and E/A ratios were respectively 59.11±6.35% and 0.94±0.024, which were not significantly different from those of the controls; however, although within the normal range, their CFR was lower (median 2.7, IQR 2.40–2.90 vs 3.20, IQR 3.06–3.33; p<0.0001). Right and left pulse wave velocity (PWV) (PWV m/sec median 0.8, IQR 7.26–10.32 vs 6.86, IQR 6.33–10.17; p<0.0001) and right and left coronary intima media thickness (cmIT) (cmIT mm: median 0.6, IQR 0.5–0.7 vs 0.53, IQR 0.50–0.60; p=0.08) values were all higher in the pSS patients, but the differences were not statistically significant. The results of the speckle tracking analysis were significantly different between the two groups, with global longitudinal strain deformation in the apical 4-chamber view (Long. ε 4c %) being significantly lower in the pSS patients than in controls (Long. ε 4c %: median 15.28, IQR 12.3–16.2 vs 19.8, IQR 19.3–20.40; p<0.001).

Conclusion: LV myocardial longitudinal strain measured by means of speckle tracking echocardiography was impaired in our pSS patients in the absence of any clinical evidence of CV disease and when traditional echocardiographic evaluations were still negative, thus suggesting a myocardial alteration. However, further studies are required to define more precise methods of assessing CV disease in patients with pSS.

Disclosure: F. Atzeni, None; S. Galavera, None; C. Colombo, None; L. Giantrurco, None; L. Boccassini, None; P. Sarzi-Puttini, None; M. Turri, None.

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Presence of Germinal Centers at Baseline Is Associated with Clinical Response of Glandular Esophageal Domain after Abatacept Treatment in Primary Sjögren’s Syndrome

Erlin A. Haacke, Frans G.M. Kroese, Petra M. Meining, Bert van der Vegt, Arjan Vissink, Fred K.L. Spijkervet and Hendrika Bootma. University Medical Center Groningen, University of Groningen, Groningen, Netherlands.
Background/Purpose: Abatacept inhibits the costimulatory interaction of T-lymphocytes and antigen-presenting cells. Treatment of early and active primary Sjögren’s Syndrome (pSS) with abatacept decreases disease activity. The aim of this study was to assess the histopathological changes in the parotid gland tissue after treatment with abatacept in pSS patients.

Methods: 15 patients (12 female, 3 male) were included in the open-label Active Sjögren A batacept Pilot (ASAP) study and received 8 intravenous abatacept infusions on days 1, 15, 29 and every 4 weeks thereafter. Before treatment and at 25 weeks of follow up a parotid gland biopsy was taken. Hematoxylin-eosin stains were evaluated for focus score (foxi of 50 lymphocytes/mm²), lymphoepithelial lesions (LELS) and presence of germinal centers. A CD45 stain was used to calculate the area of lymphocytic infiltrate (Aperio ImageScope v12.0). The infiltrate was further analysed for numbers of CD20+ B-cells, CD3+ T-cells and IgA, IgG and IgM positive plasma cells using HistoQuest.

Results: At baseline 5 out of 15 patients (33%) showed presence of germinal centers in parotid gland tissue. In all these 5 patients germinal centers were absent after abatacept treatment. One patient showed only limited germinal center activity after treatment. The mean number of germinal centers decreased from 0.06 GC/mm² to 0.01 GC/mm². Importantly, limited germinal center activity after treatment. The mean number of germinal centers/mm² at baseline is associated with a clinical improvement in the glandular domain of the ESSDAI. Abatacept treatment did not affect focuScore, LELs, amount of infiltrated B- and T-cells. Analysis of the plasma cell population is currently in progress.

Conclusion: Presence of germinal centers at baseline in parotid gland tissue is associated with clinical responses in the glandular domain of the ESSDAI after treatment with abatacept in primary Sjögren’s syndrome. Histopathological analysis of parotid gland tissue may therefore be helpful in assessing treatment efficacy. As expected, abatacept does not affect the lymphocytic infiltrate in terms of overall numbers of T- and B-cells.

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ACR/ARHP Poster Session C
Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
TUESDAY, NOVEMBER 18, 2014, 8:30 AM - 4:00PM

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Compromised Volumetric Bone Density, Bone Microarchitecture and Bone Strength in Patients with Ankylosing Spondylitis: High-Resolution Peripheral Quantitative Computerized Tomography (HRpQCT) Based Study.

Nisha Nigil Haroon¹, Eva Szabo², Janet Raboud³, Annemari Apton⁴, Robert Josse⁵, Robert D. Inman⁶ and Angela Cheung⁷. ¹Department of Medicine, University of Toronto, Toronto, ON. ²Osteoporosis Program, UHN, Toronto, ON. ³Dalhousie University, P.E.I. ⁴Dalla Lana School of Public Health, University of Toronto, Toronto, ON. ⁵University Health Network, Toronto, ON.

Background/Purpose: Patients with ankylosing spondylitis (AS) have high fracture risk. BMD, bone microarchitecture and strength determine fracture risk. However, in AS, DXA-based BMD measurements of the lumbar spine may be falsely normal due to the presence of syndesmophytes. Also, DXA cannot differentiate between trabecular and cortical bone. The effect of AS on bone microarchitecture and strength is also unknown. We assessed bone microarchitecture and strength in patients with AS and compared that with non-AS controls.

Methods: AS was defined by the modified New York criteria. Disease activity of AS was measured by BASDAI, mSASSS, serum ESR and CRP levels. Volumetric BMD (vBMD) and microarchitecture were measured using HRpQCT, and bone strength was estimated using finite element analysis (FEA). M ultivariable linear regression was used to analyze the effect of AS on HRpQCT parameters.

Results: There were 44 cases (82% Caucasian). The mean (+ SD) age and duration of disease was 42.1 (+ 7.2) years and 16.7 (+ 7.1) years respectively. Median (IQ) sample size was 20 (7.3-27.8 years). Twenty-three subjects had mSASSS >0. Four cases (9%) reported a history of fragility fracture. Use of TNF inhibitors (none), bisphosphonates (n=2) and corticosteroids (n=2) was negligible. Mean serum ESR, CRP and SAP levels were 22.0 ± 13.4, 12.6 ± 15.6 and 96.2 ± 43.2 IU respectively. Using the new robust regression models adjusted for age and gender, cases (n=44) had lower vBMD (trabecular, cortical and total), cortical thickness, BV/TV, bone stiffness and stress, and higher cortical porosity and trabecular separation at the radius (Table 1) when compared to non-AS controls (n=85). Tibial vBMD, BV/TV and cortical porosity were also abnormal in cases. But trabecular architecture at tibia was not different between cases and controls.

S1115
Conclusion: This study documents abnormalities of bone structure and strength in patients with AS. Patients with AS had lower volumetric BMD and worse microarchitecture at the trabecular and cortical regions compared to controls. Bone stiffness and stress at the radius and tibia, as estimated by FEA, also tended to be lower in cases than controls. These abnormalities might partly explain the high fracture risk in patients with AS.

Table 1: Multivariable linear regression showing abnormal bone microarchitecture and strength in patients with AS (44 cases and 85 controls).

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<thead>
<tr>
<th>Site</th>
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<th>Covariate 2</th>
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<td>-.363 .002</td>
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Disclosure: A. Moltó, None; B. Granger, None; D. Wendling, None; M. A. Breban, None; M. Dougados, None; L. Gossec, None.

2555

The Effect of Co-Medication with Conventional Synthetic (cs)DMARDs on Achieving Low Disease Activity While Persisting on Adalimumab Therapy in Patients with Ankylosing Spondylitis/ Axial Spondylarththritis (AS): Analysis from the Czech Biologics Registry Attra.

Karel Pavelka1, Jakub Zavadil2, Marketa Fojtikova3, Sarka Foretova4 and Karel Hejduk5. 1Institute of Rheumatology, Prague, Czech Republic, 2Charles University, Prague, Czech Republic, 3Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 4Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic.

Background/Purpose: The role of combined treatment with csDMARDs and anti-TNF therapy in AS is not well established.

Methods: Main goal of this study was to compare the probability of achieving low disease activity (LDA) while persisting on adalimumab (ADA) therapy in AS patients treated by either ADA alone, or by combination of ADA + csDMARDs. This analysis was conducted within the national biologics registry with mandatory registration for all patients with AS who start treatment with biologics. All patients with AS treated with ADA as a first line anti-TNF drug with available baseline BASDAI and CRP were included in the analysis. To get reimbursement for anti-TNF therapy, all AS patients had to have high baseline disease activity (defined as BASDAI >4, and CRP > 10 mg/l). LDA was defined as BASDAI < 4 and CRP <5 mg/l. Pre-specified sensitivity analyses were conducted in patients with pure axial, and combined axial + peripheral forms of AS.

Results: Data for 481 patients were available for the analysis (Table). There was no difference in the primary outcome either in the total cohort (Figure 1), or in the subset of patients with combined axial and peripheral involvement. In patients with pure axial form of AS, higher probability of achieving LDA while persisting on ADA therapy was observed in some, but not all time-points of follow-up (Figure 2). Patients on co-therapy with methotrexate (n=55) fared similarly as those on sulfasalazine (n=141).

Conclusion: Co-therapy with csDMARDs did not increase the overall probability of reaching LDA and drug survival on ADA in AS patients.

Acknowledgements: This work was supported by project of MCHC for conceptual development of research organization 023728.
Background/Purpose: Observational prospective, multi-centre study (DESIR cohort) of patients with early IBP (>3 months and <3 years symptom duration) suggestive of axSpA, and available data over 3 years.

Results: Of the 606 patients, 26 (4.3%) patients were classified in the ANE group. Patient and disease characteristics were comparable in both groups, except for history of inflammatory bowel disease (IBD): 6 (23%) vs. 17 (2.9%), in the ANE and E groups, respectively (p = 0.001). Diagnostic confidence: a) baseline: the percentage of patients fulfilling the ASAS criteria at baseline (and each arm) was similar in both groups (ASA criteria: 69.2% vs. 72.8%, for the ANE and E groups, respectively), as was the mean physician’s axSpA diagnostic confidence (71 ± 2.6 and 71 ± 2.5). A quite moderate correlation between physician’s axSpA diagnostic confidence and NSAID intake score was found (rho = 0.15, p = 0.0002); b) at 3 years: no differences were observed in the fulfillment of the ASAS criteria (69.2% and 74.9%); no differences were observed either with regard to the mean physician’s axSpA diagnostic confidence at the end of follow-up, (81 ± 2.5 and 78 ± 2.8) and no correlation was found between the physician’s axSpA diagnostic confidence and the NSAID intake score (rho = 0.06, p = 0.183).

Conclusion: Less than 5% of patients with IBP suggestive of SpA were almost never exposed to NSAID during follow-up; these patients did not differ from the rest of the cohort, except with regard to the presence of IBD. This suggests that lack of NSAIDs exposure is more driven by the presence of IBD than the lack of diagnosis confidence.

Disclosure: A. Molto, None; B. Granger, None; D. Wendling, None; M. Dougados, None; L. Gossec, None.

2557

Is the Degree of NSAID Treatment in Early Axial Spondyloarthritides a Reflection of the physician’s Diagnostic Confidence? Results from the DESIR Cohort. Anna Molto1, Benjamin Granger2, Daniel Wendling3, Maxime Dougdas4 and Laure Gossec5.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the keystone in the treatment of axSpA. Diagnosis is often not easy in early forms due to the paucity of structural/inflammatory lesions and the clinical gestalt of the physician is an important part of the treatment decision in clinical. Our hypothesis was that NSAID prescription might be a reflection of the degree of the physician’s diagnostic confidence in inflammatory back pain (IBP) suggestive of axSpA. Our objective was a) to describe the population of IBP patients suggestive of axSpA that were almost never exposed to NSAID over 3 years and to compare such population to the exposed patients; b) to compare both groups with regard to the fulfillment of the ASAS criteria and physicians’ diagnostic confidence and c) to explore the correlation between NSAID intake and physicians’ diagnostic confidence.

Methods: Study design and patients: Observational prospective, multi-centre study (DESIR cohort) of patients with early IBP (>3 months and <3 years symptom duration) suggestive of axSpA, and available data over 3 years.

Results: Of the 606 patients, 26 (4.3%) patients were classified in the ANE group. Patient and disease characteristics were comparable in both groups, except for history of inflammatory bowel disease (IBD): 6 (23%) vs. 17 (2.9%), in the ANE and E groups, respectively (p = 0.001). Diagnostic confidence: a) baseline: the percentage of patients fulfilling the ASAS criteria at baseline (and each arm) was similar in both groups (ASA criteria: 69.2% vs. 72.8%, for the ANE and E groups, respectively), as was the mean physician’s axSpA diagnostic confidence (71 ± 2.6 and 71 ± 2.5). A quite moderate correlation between physician’s axSpA diagnostic confidence and NSAID intake score was found (rho = 0.15, p = 0.0002); b) at 3 years: no differences were observed in the fulfillment of the ASAS criteria (69.2% and 74.9%); no differences were observed either with regard to the mean physician’s axSpA diagnostic confidence at the end of follow-up, (81 ± 2.5 and 78 ± 2.8) and no correlation was found between the physician’s axSpA diagnostic confidence and the NSAID intake score (rho = 0.06, p = 0.183).

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Disclosure: A. Molto, None; B. Granger, None; D. Wendling, None; M. Dougados, None; L. Gossec, None.

2556

Is the Degree of NSAID Treatment in Early Axial Spondyloarthritides a Reflection of the physician’s Diagnostic Confidence? Results from the DESIR Cohort. Anna Molto1, Benjamin Granger2, Daniel Wendling3, Maxime Dougdas4 and Laure Gossec5. GRC-UPMC 08 (EEMOIS); UPMC Univ Paris 06, AP-HP, Pitie Salpeitre Hospital, Department of Rheumatology, Paris, France, Paris, France,5UPMC GRC08, Paris 06, Universite´ Pierre et Marie Curie - Paris 6; AP-HP, Paris, France, 3CHU J Minjoz, Besancon, France, 4INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cite´, Paris, France, Paris, France,5UPMC GRC08, Paris 06 University, Pitie Salpeitre Hospital, Paris, France.

Background/Purpose: The objective was a) to describe the population of IBP patients suggestive of axSpA, that were almost never exposed to NSAID over 3 years and to compare such population to the exposed patients; b) to compare both groups with regard to the fulfillment of the ASAS criteria and physicians’ diagnostic confidence and c) to explore the correlation between NSAID intake and physicians’ diagnostic confidence.

Methods: Study design and patients: Observational prospective, multi-centre study (DESIR cohort) of patients with early IBP (>3 months and <3 years symptom duration) suggestive of axSpA, and available data over 3 years.

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Conclusion: Less than 5% of patients with IBP suggestive of SpA were almost never exposed to NSAID during follow-up; these patients did not differ from the rest of the cohort, except with regard to the presence of IBD. This suggests that lack of NSAIDs exposure is more driven by the presence of IBD than the lack of diagnosis confidence.

Disclosure: A. Molto, None; B. Granger, None; D. Wendling, None; M. Dougados, None; L. Gossec, None.
Vitamin D insufficiency and Deficiency in Two European Cohorts of Patients with Inflammatory Rheumatic Disorders.

**Background/Purpose:** Vitamin D plays an important role in the modulation of immune system and epidemiologic data indicate low vitamin D levels in autoimmune diseases such as rheumatoid arthritis (RA), connective tissue disorders, inflammatory bowel diseases and multiple sclerosis. Several studies reported contradictory results regarding correlation between disease activity and vitamin D levels in these diseases. Our objective was to assess 25-OH vitamin D concentrations in 2 independent cohorts of patients affected by inflammatory rheumatic disorders (IRD) and correlations with disease activity and disability.

**Methods:** We retrospectively analyzed 420 patients (246 RA, 100 ankylosing spondylitis (SA), 74 psoriatic arthritis (PsA) followed at Rheumatology tertiary centers in Northern France (Paris) and Southern Italy (Cagliari). All patients underwent clinical and laboratory evaluation including serum calcium and phosphorus levels, 25-OH vitamin D and parathyroid hormone (PTH). RA, SA, and PsA patients were compared. Disease activity was assessed by DAS 28 in RA and PsA patients, and by BASDAI and BASFI in AS patients.

**Results:** Vitamin D insufficiency and deficiency was very high: respectively 66% and 19% in RA, 76% and 10% in AS, 83% and 11% in PsA. Their incidence was comparable between the two populations in RA (68% and 20% versus 62% and 18%, P = ns, respectively in French and Italian patients), while it was significantly higher among French than Italian patients in AS and PsA (86% and 23% versus 61% and 0%, P = 0.002; 89% and 20% versus 55% and 3%, P = 0.002 and P = 0.02, respectively in AS and PsA). Vitamin D supplementation was statistically different only in RA patients (33% versus 34%, P = 0.003, respectively in French and Italian patients). In the combined populations, in RA patients, no correlation was observed between vitamin D levels and the other evaluated parameters. In AS patients, low vitamin D concentrations correlated with disease activity, but it remains controversial if this correlation is present in PsA.

**Conclusion:** A high incidence of vitamin D deficiency was found in IRD in the two populations, independently of geographic origin for RA, while a higher incidence was seen in French AS and PsA patients, suggesting a potential different influence of vitamin D on these diseases. By contrast, no correlations with disease activity were found except for disability index BASFI in AS patients. In our study, TNF alpha agents seem to improve vitamin D levels as well as disease activity, but it remains controversial if this is an effect linked to disease activity modulation or it directly depends from immunomodulatory properties of vitamin D.
This finding encourage to perform randomized controlled studies for confirming that vitamin D supplementation could reduce the risk of autoimmunity or that it eases disease activity, although there is still not a clear consensus about the optimal circulating 25-OH vitamin D levels and the supplementation dosage for maintaining immune homeostasis.

Disclosure: A. Vaccara, None; G. PorrU, None; G. Desole, None; A. Mathieu, None; C. Cormier, None; Y. Fulla, None; A. Kahan, None; Y. Allarano, None.

2560

Sustained Improvements in Workplace and Household Productivity and Social Participation with Certolizumab Pegol over 96 Weeks in Patients with Axial Spondyloarthritis, Including Radiographic Spinal Spots: The ASPIRE Osteoarticular Spondyloarthritis.

Desiree van der Heijde,1 Juergen Braun,2 Martin Rudwaleit,3 Oana Parcu,4 and Arthur Kavanaugh.5 1Leiden University Medical Center, Leiden, Netherlands, 2Rheumazentrum Ruhrgebiet, and the supplementation dosage for maintaining immune homeostasis. a clear consensus about the optimal circulating 25-OH vitamin D levels and the supplementation dosage for maintaining immune homeostasis.

Workdays missed due to arthritis per month

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<th>Wk96</th>
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| Productivity affected over previous month

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<tr>
<td>Days</td>
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| Workdays missed due to arthritis per month

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<tr>
<td>Days</td>
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Table 1. Workplace and household productivity over 96 wks in the Rapid-axSpA trial (FAS population; LOCF)

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Table 2. Workdays missed due to arthritis per month

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<tr>
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Table 3. Workdays missed due to arthritis per month

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Disclosure: D. van der Heijde, AbbVie, Agen, AstraZeneca, Auroxum, BMS, Celgene, Celltrion, Chugai, Covagen, Daiichi, Eli-Lilly, Galagapos, GSK, Jansen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, S. Imaging Rheumatology bv, J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celltrin, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 5; D. van der Heijde, AbbVie, Agen, AstraZeneca, Auroxum, BMS, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, BMS, G. Porru, O. Purcaru, UCB Pharma, 3; A. Kavanaugh, AbbVie, Agen, BMS, Roche, Johnson, Jansen, UCB Pharma, 2.

2561

Low Cardiorespiratory Fitness Is Associated with Increased Arterial Stiffness in Patients with Ankylosing Spondylitis. Inger Jorid Berg, Anne Grete Semb, Silje H. Sveaas, Camilla Fongen, Desiree van der Heijde, Tor K. Kvien, Hanne Dagfinrud and Sella A. Provan. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: We have previously shown that patients with ankylosing spondylitis (AS) have lower cardio-respiratory fitness (CRF) than population controls. CRF is inversely related to arterial stiffness indicating that reduced CRF can be related to increased risk of cardiovascular disease (CVD) in the general population. Arterial stiffness is a marker of CVD risk, and AS patients have increased arterial stiffness compared to controls. The objective was to assess associations between CRF and arterial stiffness in AS patients.

Methods: This is a cross-sectional study on AS patients (mNY criteria) where information on demographics and medication was assessed from questionnaires. Arterial stiffness (Pulse Wave Velocity (PWV)) and Augmentation Index (AIx) was recorded using the Sphygmocor apparatus (AtCor). CRF was assessed as peak oxygen uptake (VO2peak). ANCOVA-analysis was carried out to identify factors associated with PWV and AIx.

Results: The 113 AS patients had the following characteristics: Mean (SD) age 48 (11.3) years, 72 (64 %) males, 18 (16%) smokers, mean (SD) BMI 25.6 (4.3), median (IQR) CRP (mg/l) 3 (2-10), 73 (65%) used NSAIDs, 24 (21%) used TNF-inhibitors, 19 (17%) used statins and 28 (25%) used antihypertensive medication. In regression models VO2peak was significantly inversely associated with PWV and AIx independent of other factors (table). Similar results were found for AIx (table).

Conclusion: CRF measured by VO2peak was inversely associated with arterial stiffness indicating that reduced CRF can be related to increased risk.
The Comparative One-Year Drug Survival Rate of Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis and ankylosing spondylitis results from TURKBIO Registry, Ismail Sari, 2, Umut Kayouc, Hümeyret Mesut Onat, 1, Orner Nuri Pamuk, 1, Ömer Karadag, 2, Yunus Kíasik, 2, Niels Steen Krog, 3, Soned Sener, 4, Fahit Saritas, 5, İhsan Erteltin, 6, Sedat Kirc, 7, Pinar Çetin, 8, Fatos Oner, 9 and Nurullah A K succès, 12.

1. Dokuz Eylül University School of Medicine, Izmir, Turkey, 2. Hacettepe University School of Medicine, Ankara, Turkey, 3. Gaziantep University School of Medicine, Gaziantep, Turkey, 4. Trakya University School of Medicine, Edirne, Turkey, 5. Zitelab A Aps, Copenhagen, Denmark, 6. Erciyes University School of Medicine, Kayseri, Turkey.

Background/Purpose: Three different anti-tumor necrosis factor (anti-TNF-α) drugs (infliximab, etanercept, and adalimumab) are approved for patients with rheumatoid arthritis (RA) and particular ankylosing spondylitis (AS) in Turkey. Their efficacy has been well shown not only in randomized controlled clinical trials, but also in clinical practice setting. Comparative drug survival analyses across different diagnoses have been published in few studies. No data is yet available for the Turkish population.

The primary goal of this study was to compare the 1-year drug retention rates of TNF inhibitors in patients with AS and RA who were enrolled in the Turkish biologic registry, TURKBIO.

Methods: TURKBIO biological registry, which was established in October 2011, is a nationwide biological registry contributed by 10 different centers across Turkey. As of December 2013, 3380 patients who are receiving biologic treatment for RA (n=1335, 40.1%) or AS (n=2025, 59.9%) were enrolled in the database. However this analysis includes only 789 patients who initiated biologic treatment after the participation of the individual centers in TURKBIO. Demographic and clinical data including age, sex, disease type, disease duration, and previous or current treatment with DMARDs and biological drug durations are stored in the database.

Results: Of the 789 patients included in this analysis, 386 patients (48.9%) were being treated for RA and 403 patients (51.1%) for AS. There were significant differences between the two groups in regard with age, gender distribution, DMARD use at baseline and DMARD use at last visit (Table). Preference for individual anti-TNF agents were also different between the RA and AS patients; infliximab, etanercept and adalimumab were used by 11.7%, 28.2% and 25.1% of the RA patients, respectively and 26.3%, 32.8% and 32.8% of the AS patients, respectively. AS patients had a shorter diagnosis duration than the RA patients. One year drug survival for the first anti-TNF agent was 60.8% respectively and 26.3%, 32.8% and 32.8% of the AS patients. 30.4% (48.9%) were being treated for RA and 403 patients (51.1%) for AS.

Conclusion: The proportion of AS patients treated with biologic agents in the TURKBIO registry was slightly higher than that of RA. These results also suggest that the drug survival rate of anti-TNF agents in AS patients seems to be higher than in RA. This finding may explain the higher percentage of AS patients in the whole registry population, which included patients who had started biologics before the establishment of the TURKBIO registry.

Table 1: Demographical and clinical features of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients at baseline and one year drug survival data

<table>
<thead>
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<th>RA (n=386)</th>
<th>AS (n=403)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (38-58)</td>
<td>39 (30-46)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>73.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>7 (3-13)</td>
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<tr>
<td>Diagnosis Duration</td>
<td>4 (2-10)</td>
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<tr>
<td>Biological duration (months)</td>
<td>9 (5-13)</td>
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<tr>
<td>Number of biologic drugs used</td>
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<tr>
<td>Prior DMARD use (%)</td>
<td>82.4</td>
<td>73.9</td>
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<tr>
<td>Number of DMARD use</td>
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<tr>
<td>DMARD use at last visit (%)</td>
<td>67.4</td>
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<tr>
<td>1-year drug retention rate of TNFα (%)</td>
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<td>78.3</td>
</tr>
</tbody>
</table>


2562

The Distribution of Inflammatory Lesions in the Anterior and Posterior Structures of the Spine in Patients with Active Ankylosing Spondylitis and the Effect of TNF-α-Blockade.

Xenophon Baraliakos, 1, Kay-Geert A. Hermann, 2, Stephen Xu, 3, Benjamin Hsu, 4, and Jürgen Braun, 5.


Background/Purpose: Magnetic resonance imaging (MRI) is a key tool for the assessment of inflammatory lesions used for diagnosis and the monitoring of treatment effects in patients (pts) with ankylosing spondylitis (AS). Using data from the anti-tumor necrosis factor (TNF) agent golimumab (GLM) in AS study (GO-RAISE), we analyzed the distribution and course of inflammatory spinal lesions in different parts of the axial skeleton in detail before and after treatment with GLM in pts with active AS.

Methods: Complete MRI images at baseline (BL), 3 months (week 14 of the placebo [PBO]-controlled phase) and 2 years (end of open-label extension) of the study were available from 98 AS patients. Among all pts with inflammatory MRI activity at BL, the number (nr.) of spinal lesions at different time points was assessed. Both, general (total nr. of inflammatory lesions in the entire spine) and detailed (nr. of inflammatory lesions in the cervical [CS], thoracic [TS] and lumbar [LS] spine, in single vertebral units [VUs], in the upper and lower edges for anterior and posterior site of each vertebra, and in the zygapophysial joints [ZAJs]) were assessed. Improvement in inflammation was defined as any decrease in the MRI score from baseline to year 2 of the study.

Results: Overall, evaluable inflamed VU and ZAJ lesions were seen in 81.6% and 31.6% of pts, respectively, while 22.4% of VUs/ZAJs had inf at BL. In patients showing inflammatory activity, the mean number of lesions/patient was 6.7 for VUs and 3.6 for ZAJs, with no difference between pts randomized to GLM or PBO. ZAJ inflammation without concomitant VU inflammation was present in 43 (0.97%) of all VUs and in 19 (20.9%) of patients. In detail, 72% of VUs/ZAJs lesions were found in the CS, 27.9% in the TS and 27.9% in the LS. VU inflammation was detected more frequently in the anterior (23.5%) than in the posterior (8.5%) part of the LS. This difference was not observed in the CS and TS. The most frequently inflamed region in the CS was C7/T1, in the TS it was T8/9-T11/12 and in the LS, there was a fairly even distribution across VUs. After 3 months of GLM treatment, the percentage of VUs/ZAJs with inflammation decreased by 2.7%/0.7% in the CS, 17.3%/3.6% in the TS, and 17.6%/2.7% in the LS, while almost no change was observed in the PBO pts. The decreased VU/ZAJ involvement afforded by GLM treatment was sustained through 2 years. Similarly, after up to 2 years of GLM treatment, the mean number of lesions/patient showing inflammatory activity decreased to 2.7 for VUs and 2.0 for ZAJs.

Conclusion: This analysis confirms the predominance of inflammatory spinal lesions at the lower TS and the LS. While ZAJ inflammation was evident in a substantial nr. of patients it was uncommon for it to occur in isolation of non-inflamed VUs. Inflammtory Activity in the CS and TS are supplementary information to MRI scoring systems and may contribute to a better understanding of clinical trial data. The already reported significance of the lower TS in the inflammatory process in AS clearly needs further study.

Disclosure: X. Baraliakos, Janssen R and D, LLC, 2; K. G. A. Hermann, Janssen R and D, LLC, 2; S. Xu, Janssen R and D, LLC, 3; H. Hsu, Janssen Research & Development, LLC, 3; J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 5, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.

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Ileocolonoscopic Findings in the Korean Patients with Ankylosing Spondylitis.

Soo M Ahn, Bin Yoo, Chang-Keeun Lee, Yong Gil Kim, Seokchan Hong, Seung-Hyoon Bae and Doo-Ho Lim. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: The prevalence of concurrent Ankylosing spondylitis (AS) and inflammatory bowel disease, either Crohn’s disease (CD) or ulcerative colitis (UC), is estimated at 5–10%. Up to 50% of patients with AS have subclinical gut inflammation seen on ileocolonoscopy. This study was performed to evaluate the association between reasons for ileocolonoscopy and the ileocolonoscopic findings in the patients with AS.

Methods: The retrospective study has included 108 AS patients who had ileocolonoscopy at a single tertiary hospital from January 2000 to April 2014.

S1120
Patients with a history of CD, UC, intestinal tuberculosis, or colon cancer were excluded. Patients were divided into two groups based on ileocolonoscopic results: 1) negative inflammatory lesions (including colon polyps, hemorrhoids and diverticulums) and 2) positive inflammatory lesions (including ulcers, erosion and inflammation). The clinical features including HLA-B27 profiles, inflammatory indices, and reasons for ileocolonoscopy including regular health checkup without symptoms (for screening), abdominal pain, rectal bleeding, diarrhea, constipation, anemia and positive stool occult blood were evaluated. **Results:** As shown in Table, inflammatory lesions in ileocolonoscopic findings were found in 40 (37.0%) patients out of the 108 patients. Mean age was significantly lower in the group with inflammatory lesions than the group without inflammatory lesions (36.9 vs. 41.9 years; p = 0.017). Mean ESR and CRP were significantly higher in the group with inflammatory lesions than the group without inflammatory lesions. Presence of symptoms or signs (n = 34) was associated with risk of inflammatory ileocolonoscopic findings compared to for screening (n = 6) (OR = 3.96, 95% CI 1.46, 10.71, p = 0.005). Among the patient’s symptoms or signs, abdominal pain (n = 13) was associated with inflammatory ileocolonoscopic findings most importantly (vs. negative abdominal pain (n = 20); OR = 2.47, 95% CI 0.88, 6.99, p = 0.087). Among 40 patients with inflammatory lesions, 12 as CD, 1 as UC, and 4 as intestinal tuberculosis were diagnosed finally. However, most of them, 23 patients were considered as subclinical gut inflammation.

**Conclusion:** Considerable proportion of AS patients showed inflammatory gut lesions, even in the patients without gastrointestional symptoms. Moreover, abdominal pain increased a possibility of inflammatory gut lesions in AS patients. Therefore, regular checkup with ileocolonoscopy could be recommended in AS patients.

<table>
<thead>
<tr>
<th>Inflammatory lesion</th>
<th>(−) n = 68</th>
<th>(+) n = 40</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>41.9 (13.5)</td>
<td>36.9 (11.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>53 (77.9)</td>
<td>33 (82.5)</td>
<td>0.570</td>
</tr>
<tr>
<td>HLA-B27 (+), n (%)</td>
<td>55 (84.6)</td>
<td>30 (78.9)</td>
<td>0.407</td>
</tr>
<tr>
<td>ESR (mm/hr) mean (SD)</td>
<td>24.1 (21.79)</td>
<td>39.3 (33.34)</td>
<td>0.014</td>
</tr>
<tr>
<td>CRP (mg/dL) mean (SD)</td>
<td>0.72 (1.265)</td>
<td>3.14 (4.539)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Reasons for ileocolonoscopy:**

<table>
<thead>
<tr>
<th>Reason</th>
<th>(−) n = 68</th>
<th>(+) n = 40</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>For screening</td>
<td>28 (41.2)</td>
<td>6 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (14.7)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (11.8)</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>12 (17.6)</td>
<td>10 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5.9)</td>
<td>4 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Stool occult blood (+)</td>
<td>4 (5.9)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** This study of “real-life” patients supports the current recommendation that co-therapy with DMARDS is of no additional benefit compared with anti-TNF monotherapy in axSpA.

**Table:** Baseline characteristics. Unless otherwise stated, the values represent the mean.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>M onotherapy (n = 1970) (80.1%)</th>
<th>Co-therapy (n = 446) (19.9%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [SD]</td>
<td>40.8 [12.1]</td>
<td>41.6 [11.9]</td>
<td>0.24</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>54.9</td>
<td>54.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Higher education (% university)</td>
<td>20.9</td>
<td>22.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Disease duration (median, years)</td>
<td>8.6 [3.4–16.6]</td>
<td>8.3 [3.0–14.8]</td>
<td>0.15</td>
</tr>
<tr>
<td>MNHC positive (%)</td>
<td>52.3</td>
<td>49.8</td>
<td>0.33</td>
</tr>
<tr>
<td>ASAS positive (%)</td>
<td>64.2</td>
<td>49.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASDAI [SD]</td>
<td>5.1 [1.8]</td>
<td>5.0 [1.8]</td>
<td>0.31</td>
</tr>
<tr>
<td>BASFI [SD]</td>
<td>3.9 [2.3]</td>
<td>4.0 [2.3]</td>
<td>0.52</td>
</tr>
<tr>
<td>Infliximab (%)</td>
<td>23.2</td>
<td>37.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adalimumab (%)</td>
<td>36.6</td>
<td>32.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Etanercept (%)</td>
<td>31.0</td>
<td>28.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Golimumab (%)</td>
<td>9.0</td>
<td>1.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Certolizumab (%)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Disclosure:** M. J. Nissen, Abbott Immunology Pharmaceuticals, 5; Pfizer Inc, 5; A. Ciurea, Pfizer Inc, 2; Abbott Immunology Pharmaceuticals, 2; Abbott Immunology Pharmaceuticals, 5; Pfizer Inc, 5; Merck Pharmaceuticals, 5; UCB, S. Hong, None; H. H. Lim, None.

**Background/Purpose:** Randomized clinical trials and current recommendations suggest little role for disease-modifying anti-rheumatic drugs (DMARDS) as co-therapy with anti-TNF (aTNF) agents in patients with axial spondyloarthropathy (axSpA), although many physicians continue to prescribe this combination. Our aim was to investigate whether aTNF agents with concomitant DMARDS demonstrate superior clinical efficacy compared with anti-TNF monotherapy.

**Methods:** This is an observational cohort study of all patients in the Swiss Clinical Quality Management (SCQM) registry diagnosed with axSpA by a board-certified rheumatologist. The exposure of interest was use of anti-TNF monotherapy (mono) versus aTNF in combination with conventional synthetic DMARDS (combo). Exclusion criteria included aTNF initiation > 1 month prior to inclusion in the registry or missing follow-up assessments. The primary outcome was the change in BASDAI at 12 months. Secondary outcome measures were: BASDAI-50, ΔSDAS, ASDAS-CII and ASDAS-ID. When clinical outcome measures were unavailable at 12 months (+/- 3 months), we used longitudinal interpolation with mixed-effects linear regression to impute missing values. Adjustments were made for potential confounders including age, sex, disease duration, education level, number of prior aTNF agents and calendar year of initiation of aTNF.

**Results:** 3210 patients with a total of 2236 aTNF treatment courses. The baseline characteristics of the mono and combo groups for all treatment courses are presented in the table. 80.1% were treated with aTNF monotherapy and 19.9% with co-therapy. The predominant DMARDS utilized were methotrexate in 69.7%, sulfasalazine in 19.3% and lefunomide in 9.6%. Disease characteristics were balanced between the 2 groups, with the exception that the co-therapy group was less frequently HLA-B27 positive, was less often ASAS criteria positive and had longer follow-up. DMARD co-therapy was prescribed significantly more often with infliximab and significantly less often with adalimumab and golimumab.

At 12 months follow-up, the mean (SD) reduction in BASDAI was 1.0 (0.8) and the mean reduction in ASDAS-CRP was 0.8 (0.7) for all treatment courses. The mean reductions in BASDAI and ASDAS-CRP for the first aTNF treatment course were 1.4 (1.6) and 1.1 (0.8) respectively. In adjusted analyses, there was no difference in the reduction in BASDAI score between the mono and the combo groups (p = 0.65, CI -0.11:0.18). Similarly, there was no statistically significant benefit for DMARD co-therapy with regards to reduction in ASDAS-CRP, BASDAI-50, ASDAS-CII or ASDAS-ID.

**Conclusion:** Considerable proportion of AS patients showed inflammatory gut lesions, even in the patients without gastrointestional symptoms. Moreover, abdominal pain increased a possibility of inflammatory gut lesions in AS patients. Therefore, regular checkup with ileocolonoscopy could be recommended in AS patients.
Vascular Endothelial Growth Factor and C-Reactive Protein Serum Levels Lack Predictive Value for Radiographic and Magnetic Resonance Imaging Outcomes in Patients with Active Ankylosing Spondylitis Treated with the Tumor Necrosis Factor-Inhibitor Golimumab. Xenophon Baraliakos1, Kay-Geert A. Hermann2, Stephen Xu3, Benjamin Hsu3 and B. Hsu3, Janssen Research & Development, LLC., 3; J. Braun1, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Celtrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2, Abbott, Bristol Myers Squibb, Celgene, Celtrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.

**Background/Purpose:** Using data from GO-RAISE, we analyzed correlations between serum vascular endothelial growth factor (VEGF) and C-reactive protein (CRP) levels, radiographic progression and inflammation as detected by MRI.

**Methods:** 98 patients with active AS received golimumab or placebo up to wk16/24 and then golimumab up to 2y. All had sera, lateral spinal radiographs at baseline, wk104, and wk208 scored by the mSASSS and spinal MRI at baseline, wk14, and wk104 scored with the ASpMRi-a by two blinded readers. The relationship between VEGF or CRP levels and both mSASSS and MRI-a score was assessed by Spearman correlation analyses and logistic regression analyses were conducted to assess if VEGF levels conferred an increased risk of syndesmophyte formation from baseline to wk104 or wk208.

**Results:** CRP serum levels correlated with baseline mSASSS scores, but not with radiographic progression or changes in MRI-a scores. No significant correlations were observed between VEGF serum levels and mSASSS at any time point. Logistic regression analyses failed to show an increased risk of changes towards syndesmophyte formation at wk104 and wk208 associated with VEGF (odds ratio, range: 0.990–1.006, all p=ns). While a good correlation was observed between changes in ASpMRi-a and VEGF level at wk14 (p=0.0008), the analysis showed that baseline and wk14 VEGF levels were not predictive of MRI-a scores including change scores at wk104.

**Conclusion:** CRP serum levels correlated with baseline mSASSS scores but did not predict radiographic progression or remaining spinal inflammation after anti-TNF treatment. Similarly, both VEGF and CRP serum levels at baseline were not predictive of either radiographic progression or spinal inflammation in these anti-TNF treated patients. Overall, our data suggest that suppression of VEGF and CRP is not sufficient to halt new bone formation in AS.

**Disclosure:** X. Baraliakos, Janssens R and D, LLC, 2; K. G. A. Hermann, Jannsens R and D, LLC, 2; S. Xu, Janssens Research & Development, LLC, 3; B. Hsu, Janssen Research & Development, LLC., 3; J. Braun, Abbott, Bristol Myers Squibb, Celgene, Celtrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2, Abbott, Bristol Myers Squibb, Celgene, Celtrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.
measure for all rheumatic diseases such as RAPID3 may provide a feasible approach to quantitative assessment of AS patients in busy clinical settings.

Disclosure: I. Castrejón, None; T. Pincus, None; D. Wendling, None; M. Dougdos, None.

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Profiles of Switches in Patient with Ankylosing Spondylitis: Comparing Adalimumab, Etanercept, Infliximab, Golimumab and Certolizumab. Jean-Pierre Raynauld1, Louis Bessette2, Denis Chouquette3, Isabelle Fortin4, Boulos Harouli5, Jean-Pierre Pelletier6, Marie-Aaina Rémillard7, Diane Sauvageau8, Edith Villeneuve9 and Louis Coupal10. 1�stitut de rhumatologie de Montréal (IRM), Montréal, QC; 2Centre d‘ostéoprotection et de rhumatologie de Québec (CORQ), Québec, QC; 3Centre de rhumatologie de l‘est du Québec (CREQ), Rimouski, QC; 4Osteoarthritis Research Unit, University of Montréal Hospital Research Centre (CRCHUM), Montréal, QC.

Background/ Purpose: As much a 40% of patients with ankylosing spondylitis will fail (BASEDAI 4) different non-steroidal anti-inflammatory agents and will eventually be treated with an anti-TNF agents. Response is usually satisfactory but retention on drug may vary from one agent to the other and from one patient to the other. Reasons for stopping ad/or switching are either inefficacy, intolerance or spontaneous improvement of the disease activity in a given individual. The goal of this analysis is to explore the first 6, 12 and 18 month period after first exposure to an initial agent and assess the cycling incidence from different anti-TNF agents namely adalimumab (ADA), etanercept (ETA), infliximab (INF), golimumab (GOL) or certolizumab (CERTO).

Methods: Patients with ankylosing spondylitis as diagnosed by their treating rheumatologists and exposed to either adalimumab, etanercept, infliximab, golimumab or certolizumab in first intention after failing two different non-steroidal anti-inflammatory agents for a minimum of 3 months each were extracted from the Quebec inflammatory database Rhumadata®. Demographics and baseline characteristics includes age, gender, disease duration, Hla-B27, BASEDAI, BASFI (patient global (vas) and ASDAS (crp). Cycling from one agent to another was then explored at 6, 12 and 18 month time point. Proportion of patients switching vs not switching at each time point are assessed. Reason for switching at each time point (Inefficacy, AEs infections, surgery or death) are expressed in percentages.

Results: The data from 296 patients with ankylosing spondylitis and prescribed either adalimumab (114 = 39%), etanercept (61 = 21%), golimumab (31 = 10%) or infliximab (90 = 30%) as first biologic agent were extracted. These patients were treated for a period ranging from 0.4 to 173.2 months with a mean treatment duration of 44.0 (StD 36.3) months. At 6, 12 and 18 months, 11.8%, 25.7% and 35.8% of patients had either stopped or switched their medication. The reported reasons for stopping or switching medication were inefficacy (76.4%), adverse events (5.7%), surgery (14.2%) and lost to follow-up (3.6%).

Conclusion: Switches at the 6 month time point vary from 4.4% (ADA) to 9.8% (ETA). The proportion of switches increase with time for all agents and 18 months, 11.8%, 25.7% and 35.8% of patients had either stopped or switched their medication. The reported reasons for stopping or switching

Disclosure: J. P. Raynauld, None; L. Bessette, None; D. Chouquette, None; I. Fortin, None; B. Harouli, AbbVie; 2, AbbVie; 5, A. mgen, 2, A. mgen, 5, Bristol-M. yrs Squibb, 2, Bristol-M. yrs Squibb, 5, Jansen Pharmaceutica Product, L. P.; 2, Jansen Pharmaceutica Product; L. P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB; 5, J. P. Pelletier, None; M. A. Rémillard, None; D. Sauvageau, None; E. Villeneuve, None; L. Coupal, None.

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Validation of Modified Disease Activity and Functional Status Questionnaires in Spondyloarthritides. Itziar Quinanzos1, Phat Luong2, Sushmitha Bobba1, J. Stuart Richards3, Vikas Majithia4, Lisa A. Davis5 and Liron Caplan6. 1Denver VA Medical Center, Denver, CO; 2Department of Veterans Affairs, Denver, CO; 3Washington DC VA and Georgetown University, Washington, DC; 4University of Mississippi Medical Center, Jackson, MS; 5Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO; 6Denver VA and Univ of Colorado School of Medicine, Aurora, CO.

Background/ Purpose: Patients with new onset ankylosing spondylitis (AS) and those naive to the Ankylosing Spondylitis Disease Activity Score (ASDAS) have voiced confusion over the use of the term “AS” in these instruments. Our previous abstract (EULAR 2013) compared the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) against a modified BASEDAI and determined the relationship between working status and disability with Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI and modified BASEDAI. It is unknown whether these tools may be applied to other forms of spondyloarthritides (SpA). In this abstract we: 1) validate slightly modified versions of the ASDAS questionnaires for use in non-AS SpA by assessing its ability to predict working status and disability; and 2) compare the disease-specific patient global assessment used in the ASDAS (ASDAS-PG) with the MD-HAQ version, and the disease activity scores based on these instruments.

Methods: Adult patients with SpA-associated conditions from three locations of the Program to Understand the Longterm outcomes of SpondyloArthritis (PULSAR) completed both traditional ASDAS questionnaire and modified version of the ASDAS instrument (PULSAR-modified ASDAS, [PuASDAS]) during visits with health care providers. The PuASDAS replaces references to “AS” with the term “inflammatory arthritis” and uses a non-disease specific patient global assessment that is similar to the multi-dimensional health assessment questionnaire global assessment (MD-HAQ). Scores from traditional and modified questionnaires were compared using Spearman correlations. The association of ASDAS and PuASDAS scores with disability status (according to federal program criteria) and self-reported working status were determined using logistic regression.

Results: Sixty-two patients participated in the study. Correlation between ASDAS and PuASDAS scores was high, recapitulating the previously demonstrated correlation between BASEDAI and PuBAI (Spearmans’ rho = 0.84, p < 0.001, and Spearmans’ rho = 0.92, p < 0.001, respectively). Similarly, the PG had good correlation with the MD-HAQ (rho = 0.766, p < 0.001). The ASDAS (OR 1.34, 95% CI. 1.02–1.76) and PuASDAS (OR 1.62, 95% CI. 1.07–2.49) predicted federally-determined disability.

Conclusion: Preliminary data suggest that the PuASDAS may be used in non-AS SpA and that scores from these instruments correlate well with traditional form of the questionnaire. Correlation between the two versions of the patient’s global assessments was good. PuASDAS scores predicted disability status at least as well as the ASDAS.

Table 1: Spearman correlation coefficients. Italics indicate information previously presented at EULAR meeting 2013.

<table>
<thead>
<tr>
<th>Compared instruments</th>
<th>Question or total score that is compared</th>
<th>Corr. Coef.</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS vs. PuASDAS</td>
<td>Total instrument score, entire cohort</td>
<td>0.85</td>
<td>0.75–0.92</td>
<td></td>
</tr>
<tr>
<td>ASDAS vs. PuASDAS</td>
<td>Total instrument score, AS patients only</td>
<td>0.76</td>
<td>0.60–0.88</td>
<td></td>
</tr>
<tr>
<td>ASDAS vs. PuASDAS</td>
<td>Total instrument score, non-AS patients only</td>
<td>0.89</td>
<td>0.80–0.94</td>
<td></td>
</tr>
<tr>
<td>ASDAS vs. PuASDAS</td>
<td>Total instrument score, entire cohort</td>
<td>0.91</td>
<td>0.82–0.96</td>
<td></td>
</tr>
<tr>
<td>ASDAS vs. PuASDAS</td>
<td>Total instrument score, non-AS patients only</td>
<td>0.91</td>
<td>0.82–0.96</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, entire cohort</td>
<td>0.80</td>
<td>0.62–0.89</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, non-AS patients only</td>
<td>0.91</td>
<td>0.82–0.96</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, entire cohort</td>
<td>0.92</td>
<td>0.85–0.96</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, non-AS patients only</td>
<td>0.92</td>
<td>0.85–0.96</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, entire cohort</td>
<td>0.91</td>
<td>0.85–0.96</td>
<td></td>
</tr>
<tr>
<td>PuASDAS vs. ASDAS</td>
<td>Total instrument score, non-AS patients only</td>
<td>0.92</td>
<td>0.85–0.96</td>
<td></td>
</tr>
</tbody>
</table>

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PuBAI = PULSAR-modified Bath Disease Activity Index; PG = Patient Global assessment from the ASDAS; MD-HAQ = Multi-Dimensional Health Assessment Questionnaire; ASDAS = Ankylosing Spondylitis Disease Activity Score; PuASDAS = PULSAR-modified Ankylosing Spondylitis Disease Activity Score; AS = Ankylosing Spondylitis.

Table 2: Relationship of BASFI, BASEDAI, PuBAI, ASDAS and PuASDAS with current working status and disability rating.

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Conf. Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with current work status</td>
<td></td>
</tr>
<tr>
<td>BASFI</td>
<td>0.75</td>
</tr>
<tr>
<td>BASEDAI</td>
<td>0.73</td>
</tr>
<tr>
<td>PuBAI</td>
<td>0.92</td>
</tr>
<tr>
<td>PuBASEDAI</td>
<td>0.92</td>
</tr>
<tr>
<td>ASDAS</td>
<td>0.96</td>
</tr>
<tr>
<td>PuASDAS</td>
<td>0.87</td>
</tr>
</tbody>
</table>

BASFI = Bath Ankylosing Spondylitis Disease Activity Score; BASEDAI = Modified Bath Disease Activity Index; PULSAR= PULSAR-modified Bath Disease Activity Index; PG = Patient Global assessment from the ASDAS; MD-HAQ = Multi-Dimensional Health Assessment Questionnaire; ASDAS = Ankylosing Spondylitis Disease Activity Score; PuASDAS = PULSAR-modified Ankylosing Spondylitis Disease Activity Score; AS = Ankylosing Spondylitis.
Disease Activity and Risk of Cardiovascular Disease in Patients with Ankylosing Spondylitis with High and Low Body Mass Index. Inger Jord Berg1, Anne Grete Semb1, Désirée van der Heijde2, Tore K. K vien1, Hanne Dagfinrud1, Jonny Hidal1 and Sella A. Provan1. 1Diakonhjemmet Hospital, Oslo, Norway, 2Leiden University Medical Center, Leiden, Netherlands, 3University of Oslo, Oslo, Norway.

Background/Purpose: Patients with ankylosing spondylitis (AS) have increased risk of cardiovascular disease (CVD), but the mediators of this increased risk are not known. Obesity is related to increased risk of CVD in the general population. Adipose tissue is an endocrine organ secreting pro-inflammatory cytokines which may be relevant both to the pathology of inflammatory diseases and CVD. The aim of this study was to explore the impact of body mass index (BMI) on disease activity and CVD risk in AS.

Methods: Cross-sectional study of 159 AS patients diagnosed according to the mNY criteria. Data collection included questionnaires, blood samples and clinical examination. Carotid intima-media thickness (c-IMT) was measured by ultrasound. Height and weight were measured and BMI was calculated (kg/m²). The patients were categorized according to the BMI, with cut-off value between normal weight and overweight: BMI = 25 kg/m² (BMI-low) and BMI ≥ 25 kg/m² (BMI-high). We compared markers of disease activity and CVD risk factors between the BMI-low group and BMI-high group in linear regression models with adjustments for age, gender and smoking habits. Additional adjustments for use of non-steroidal anti-inflammatory drugs (NSAIDs) were also performed.

Results: AS patients had comparable age (years) in both groups (BMI-low vs. BMI-high), mean (SD) 50.5 (13.2) vs. 50.5 (13.3), but the BMI-low differed from the BMI-high regarding other variables: Male gender 53% vs. 71%, p = 0.02; CRP (mg/l), median (IQR) 1 (1–5) vs 2 (1–3), p = 0.003; use of NSAIDs, 56% vs. 74%, p = 0.01. In regression analyses the BMI-high group had higher BASDAI and BASMI than the BMI-low group. High BMI was associated with lower high-density lipoprotein (HDL), higher triglycerides, total cholesterol/HDL ratio, systolic and diastolic pressure as well as IMT (table). Additional adjustment for use of NSAIDs did not alter results.

Table 1. Pre- and post-intervention results of the educational and control group regarding diagnosis and referral of patients suspected for axial and peripheral spondyloarthritis

<table>
<thead>
<tr>
<th>Educational intervention (yes vs no)</th>
<th>Diagnosis and referral of SpA</th>
<th>Round 1 (%)</th>
<th>Round 2 (%)</th>
</tr>
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<tbody>
<tr>
<td>Axial SpA (n = 61)</td>
<td>Ranked axial SpA as no. 1 diagnosis</td>
<td>42 (12)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Educational intervention (n = 18)</td>
<td>Ranked axial SpA in differential diagnosis (no. 1, 2 or 3)</td>
<td>12 (66)</td>
<td>18 (100)</td>
</tr>
<tr>
<td></td>
<td>Referral rheumatologist optional</td>
<td>1 (6)</td>
<td>6 (33)</td>
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<tr>
<td></td>
<td>Referral rheumatologist</td>
<td>0 (0)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>No educational intervention (n = 43)</td>
<td>Ranked axial SpA as no. 1 diagnosis</td>
<td>8 (19)</td>
<td>6 (14)</td>
</tr>
<tr>
<td></td>
<td>Ranked axial SpA in differential diagnosis (no. 1 or 2)</td>
<td>22 (51)</td>
<td>33 (77)</td>
</tr>
<tr>
<td></td>
<td>Referral rheumatologist</td>
<td>2 (5)</td>
<td>4 (9)</td>
</tr>
<tr>
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<td>7 (16)</td>
</tr>
</tbody>
</table>

Table 2. Recognition of Spondyloarthritis by General Practitioners in Daily Practice and the Effect of Education on This; A Study with Standardized Patients. Marlies van Onna1, Simone Gorter1, Bas Malburg1, Gerrie Waageaars2 and Astrid van Tubergen2. 1Maartred University Medical Center, division of Rheumatology, Maastricht, Netherlands, 2Maartred University Medical Center, Maastricht, Netherlands.

Background/Purpose: Timely recognition and referral of patients with spondyloarthritis (SpA) is challenging due to the insidious disease onset and frequently unapparent of the clinical picture by primary care physicians. The aims of this study were to assess the current practice performance of general practitioners (GPs) and GP-residents in recognizing SpA, and to investigate the influence of education on this performance.

Methods: All GP-residents and their supervising GPs were visited in two rounds by standardized patients (SPs) during their regular outpatient clinic, simulating axial SpA (axSpA), peripheral SpA (perSpA) (i.e. dactylitis) or carpal tunnel syndrome (CTS), respectively. Participants were unaware of the nature of the medical problem and purpose of the study. CTS was included as a diversionary tactic. Each case was simulated by a male and a female, in random order, according to a predefined schedule. After the 1st round, half of the GP-residents were educated about SpA, as part of the GP specialty training without referring to the actual study. The other half of the GP-residents and all GPs served as controls. Next, all participants were visited by SPs again in the 2nd round. Participants ranked their differential diagnosis based on their probabilities (rank order: 1—most likely to 3—least likely) and whether referral to a hospital physician would be appropriate. Descriptive statistics and chi-square tests were used to analyse the data.

Results: Sixty-eight (38 GP-residents (mean age 27.9 yrs, 32% male) and 30 GPs (mean age 52.5 yrs, 80% male) participated. Both rounds of SP-encounters were completed by 61 (90%) and 59 (87%) participants for the axSpA and perSpA case, respectively. Table 1 shows that axSpA was ranked as the no. 1 diagnosis by 12/61 (20%) participants, whereas perSpA was correctly diagnosed by none of participants in the 1st round. Participants who received the educational intervention, were more likely to rank axSpA and perSpA as the no. 1 diagnosis in the 2nd round when compared to the control group (axSpA 72% vs. 14% (p < 0.001); perSpA 21% vs 3% (p = 0.017)). All 18 participants, who received the educational intervention, listed axSpA in their differential diagnosis in the 2nd round and were more likely to refer the patient or considered referral to the rheumatologist optional (axSpA 77% vs. 25% (p < 0.001); perSpA 53% vs. 5% (p < 0.001)).

Conclusion: Patients with SpA are not adequately recognized by general practitioners. Providing an educational programme to GPs-residents markedly improved the recognition of SpA and referral of patients with SpA to the rheumatologist.

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Conclusion: Patients with SpA are not adequately recognized by general practitioners. Providing an educational programme to GPs-residents markedly improved the recognition of SpA and referral of patients with SpA to the rheumatologist.
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Preferencias de Patients with Spondyloarthritis for the Items of the ASAS Health Index: A Best Worst Scaling. U. Kiltz, M. Ickbeck, C. Alarcon, W. Taylor and A. Boonen. 1Rheumazentrum Ruhrgebiet, Herne, Germany, 2University of Liege, Liege, Belgium, 3Leiden University Medical Center, Leiden, Netherlands, 4University Southampton, Southampton, United Kingdom, 5University of Alberta, Edmonton, AB, 6University of Otago Wellington, Wellington, New Zealand, 7Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: The ASAS Health Index (ASAS HI) is a disease-specific questionnaire aiming at measurement of health in patients with spondylarthropathies (SpA) which has been developed by Assessment of SpondyloArthritis international Society (ASAS). The 17 items of the ASAS HI address functional, emotional, physical, sexual functioning, mobility, self-care and community life based on the International Classification of Functioning, Disability and Health (ICF). These items can serve as the starting point to develop a disease-specific utility instrument that will enable to calculate disease specific quality adjusted life-years. To construct such utility instrument, the development steps require that the number of items should be reduced to a more manageable number of items. This selection should be based on items, which are most essential to patient’s health and on items which are most preferred by patients. It is not know which aspects of health matter most to patients with SpA and also the knowledge about items which are most preferred by patients. The objective of this study was to assess the relative importance of the different items of the ASAS HI for functioning and health of patients with SpA.

Methods: A best-worst experiment was conducted using a questionnaire in patients with SpA from 20 countries worldwide. Patients answered 17 choice tasks that were constructed using the Sawtooth software. In each task, patients were asked to choose the most important item and the least important from a set of four items about their functioning and health. The estimated hierarchical Bayes method was used to generate the mean relative importance score for each item.

Results: 206 patients (59.7% male, mean (SD) age 42.4 (13.9) years, mean (SD) BASDAI 3.8 (2.3)) with SpA completed the experiment. The five most important items are pain, sleep, standing, exhausting, and motivation to do anything that requires physical effort (figure 1). Eight items addresses concepts which are less important for the patients: toileting, sexual relations, driving, contact with people, walking outdoors, concentration, washing hair, and be able to overcome difficulties. Four items addresses concepts, which showed intermediate results addressing concepts of running, frustration, traveling, and financial changes. Subgroup analysis regarding subgroups of SpA and European versus Non-European countries showed robust results among subgroups.

Conclusion: This study provides information on the relative importance for patients with spondylarthropathies of the items of the ASAS Health Index that will be used for the development of a utility-based instrument.

Disclosure: M. van Otma, None; S. Gorter, None; B. Maiburg, None; G. Waagenaar, None. A. van Tuberogen, A. Blevie, Pfizer, UCB, S, MSD, Pfizer, A. Blevie, Roche, 2, A. Blevie, MSD, UCB, Pfizer, 9.

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Background/Purpose: Regular exercise is considered a cornerstone of axSpA treatment, together with medication. Little data are available regarding the level and type of physical activity in axSpA. The objective of this study was to assess the levels of physical activity and to explore its explanatory factors.

Methods: A cross-sectional study was performed in two tertiary care hospitals and one private practice in France. Patients had definite axSpA according to the rheumatologist. Questionnaires evaluating the level of physical activity (International Physical Activity Questionnaire-Long form, IPAQ-L) and perceived benefits of and barriers to exercising (Exercise Benefits/Barriers Score, EBBS) were collected. The frequency of aerobic exercise (lasting more than 30 minutes) and the type of exercise were also investigated. Analyses included descriptive statistics and multiple logistic regression analyses to explain physical activity above 150 minutes per week (cut-off for appropriate exercise according to the World Health Organisations, WHO guidelines).

Results: In all, 207 patients had full data available: mean age, 45.9 ± 11.5 years. 53.1% were males, mean BMI was 25.8 ± 13.5 kg/m2. Mean disease duration was 14.6 ± 10.2 years, mean BASDAI (0–100) 38.1 ± 20, and mean BASFI (0–100) 29.1 ± 26. Seventy percent were taking anti-TNF treatment, reflecting the tertiary care recruitment. The mean total level of physical activity (IPAQ) was 9409 ± 6953 (median, 2913 (IQR 1259 to 6949)) MET-min/week; 94 (47.8%) were in the high activity category, 85 (41.1%) in the moderate and 23 (11.1%) in the low activity category. In all, 112 (54.3%) were above the recommendations of the WHO. Aerobic exercise (lasting more than 30 minutes) was performed at least once a week by 62/201 (30.8%) patients. The most frequently practiced sports included walking for at least 30 minutes (N = 69, 31%), swimming and stretching (N = 43, 21% for both). The 2 main benefits of exercising were increased acceptance from others and help to carry out normal activities without becoming tired, and the 2 main barriers: lack of encouragement of family members and people looking funny in exercise clothes. Physical activity above the WHO recommendation was not predicted by demographic variables, nor SpA activity/severity (BASda, BASfi).

Conclusion: AxSpA patients in this study had moderate levels of physical activity. Only one half performed enough physical activity according to the WHO recommendations. Levels of physical activity did not appear to be affected by disease-related variables but rather by other non-disease related variables. Physical activity is an important part of axSpA management and patients should be encouraged to exercise more.


Disclosure: S. Fabre, None; A. Molto, None; S. Dadoun, None; C. Rein, None; C. Hudry, None; S. Kreis, None; B. Faure, None; E. Perouzes, None; L. Gossec, None.

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Validation of the RAPID-3 Questionnaire in a Cohort of Patients with Axial Spondyloarthritids. Maria Celeste Orozco1, Luis Alejandro Cayetti1, Emilce Schneeberger2, Natalia Zamora3, Fernando Andres Sommerleck4 and Gustavo Citer1a. 1aInstituto de Rehabilitación Psicosocial, Buenos Aires, Argentina, 2Instituto de Rehabilitacion Psicosocial, Buenos Aires, Argentina, 3Echeverría 955, Buenos Aires, Argentina.

Background/Purpose: RAPID3 (Routine Assessment of Patient Index Data 3) is a simple index which was developed initially for RA but has been validated over inflammatory and many rheumatic diseases. A major advantage of RAPID3 over disease specific questionnaires and indices is that a single questionnaire can be completed by all patients with any diagnosis while waiting to see a rheumatologist, with minimal interference with work flow in busy clinical settings. We analyzed RAPID3 in patients with axial spondyloarthritids (axSpA).

Disclosure: None. A. Boonen, None; W. P. Maksymowych, A. Blevie, A. Blevie, A, 2, A. Blevie, 8; W. Taylor, Pfizer Inc, 5, M. Sadows, 5, A. Blevie, 9; A. Boonen, A. Megen, A. Blevie, M. Eck and Pfizer, 2, UCB and Pfizer, 8.

References:

14, 19.
MATERIALS AND METHODS: Consecutive patients ≥ 18 years of age with diagnosis of axSpA (modified New York criteria 1987 and / or ASAS 2009) were included. Socio-demographic data (age, gender, marital status, occupation, years of education) and disease-related data (disease duration, extra-spinal manifestations, comorbidities, treatments) were recorded. All patients completed RAPID-3, ASQLQ (Ankylosing Spondylitis Quality of Life), BASDAI and BASFI. Disease global assessment by both patients and physicians was determined by visual analog scale (VAS). Physical examination included 44 joint counts and evaluation of enthesitis was performed using MASES score (Maastricht Ankylosing Spondylitis Enthesitis Score). HLA association included 44 joint counts and evaluation of enthesitis was performed using physical examina-

Disclosure: M. C. Orozco, None; L. A. Cayett, None; E. Schneeberger, None; N. Zamora, None; F. A. Sommerfleck, None; G. Citera, None.

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Diffusing Weight Magnetic Resonance Imaging May Suggest the Treatment Strategy in Ankylosing Spondylitis. Sang-Yeob Lee Division of Rheumatology, Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea.

Background/Purpose: With the advanced MRI techniques, pathologic features can be detected at an early stage and quantitatively evaluated, resulting in the advantages of early diagnosis and prompt treatment. This study aimed to determine the value of diffusion-weighted MR imaging (DWI) in determining ankylosing spondylitis (AS) treatment strategy and assess the role of the quantitative MRI in the evaluation of AS treatment outcome.

Methods: 18 patients with the diagnosis of early AS were included in this study. Disease activity was measured according to clinical instruments and laboratory tests. For each patient, both inflamed sacroiliac (S-I) joint lesion was checked quantitatively at first diagnosis by diffusion-weighted imaging (DWI) measuring the apparent diffusion coefficient (ADC) and by dynamic contrast-enhanced imaging (DCEI) with evaluation of the enhancement factor (f_enh) and enhancement gradient (g_enh). All patients were revaluated by pelvis computer tomography (CT) for bone change in S-I joint, after two year.

Results: Clinical and quantitative MRI parameters diminished significantly with regression of the inflammatory activity. Median ADC values in AS patients were (1.118 ±0.122) x 10^-3 mm^2/s in S-I joint lesion. The high ADC (>1.118 ±0.122) x 10^-3 mm^2/s, f_enh (>1.65) and g_enh (2.09%) were associated severe disease activity and early administration of biologics (p<0.05). In each individual, the high ADC, f_enh and g_enh of S-I joint lesion was associated more severe localized pain in the other S-I joint, despite treatment (p<0.05). Paradoxically, early administration of biologics group who had high disease activity at the diagnosis had minimal bone change of S-I joint, compared to only NSAIDs group who was low disease activity in pelvis CT finding two year later.

Conclusion: Diffusion-weighted imaging and DCEI were shown to be effective in quantifying changes in inflammation in S-I joint at the diagnosis of AS, and could be convenient for assessing treatment strategy. To the best of our knowledge this is the first time DWI was used to evaluate the treatment strategy and treatment outcome of AS.

Disclosure: S. Y. Lee, None;

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Background/Purpose: Validation of clinical measures of disease in non-radiographic axial SpA (nr-axSpA) has been limited, especially using inflammatory and structural lesions on MRI as gold standard. Ankylosing Spondylitis Disease Activity Score (ASDAS) has been proposed as an optimal outcome measure, but is less feasible than Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) due to the need to assess CRP. We assessed which clinical measures best reflect the spectrum of MRI lesions in the sacroiliac joints (SIJ) of patients with nr-axSpA, and the effect of treating with an anti-TNF agent.

Materials and Methods: Consecutive patients ≥ 18 years of age with diagnosis of axSpA (modified New York criteria 1987 and / or ASAS 2009) were included. Socio-demographic data (age, gender, marital status, occupation, years of education) and disease-related data (disease duration, extra-spinal manifestations, comorbidities, treatments) were recorded. All patients completed RAPID-3, ASQLQ (Ankylosing Spondylitis Quality of Life), BASDAI and BASFI. Disease global assessment by both patients and physicians was determined by visual analog scale (VAS). Physical examination included 44 joint counts and evaluation of enthesitis was performed using MASES score (Maastricht Ankylosing Spondylitis Enthesitis Score). HLA association included 44 joint counts and evaluation of enthesitis was performed using physical examination.
Methods: Patients had axial SpA per the Assessment of SpondyloArthritis (ASAS) classification criteria, but did not meet modified NY radiographic criteria. Patients had symptoms >3 months and <5 years, BASDAI ≥ 4, and failed ≥2 NSAIDs. Patients were randomized to etanercept (ETN) 50 mg/wk or placebo; after 12 wks, all patients received open-label ETN 50 mg/wk. Clinical endpoints were evaluated throughout the study; M1 R1 of SI and spine was performed by 2 central readers at baseline (BL), wks 12 and 48, to assess bone marrow edema using the Spondyloarthritis Research Consortium of Canada SI score. In a post hoc analysis, structural lesions were scored using the SPARC SI structural (SSS) method, assessing fat metaplasia, erosion, backfill, and ankylosis on T1-weighted spin echo (TIWSE) M1 R1. Two independent readers scored BL 84 wk TIWSE M1 R1 scans from 187 cases blinded to outcomes and short tau inversion recovery (STIR) M1 R1; readers’ mean scores were used. SPARC score ≥ 2 for SI defined positive SI evidence of inflammation. For the analysis, patients were pooled, and wk 48 change was analyzed using Spearman correlations, adjusted for treatment.

Results: Mean (SD) age was 32 (7.8) years, 60.5% were male, mean (SD) duration of symptoms was 2.5 (1.8) years. A total of 73% of patients were human leukocyte antigen B27 (HLA-B27) positive; 81% met the ASAS M1 R1 imaging criteria at BL. A significant decrease in clinical (BASDAI, CRP) and M1 R1 (SPARC SI) inflammation, SSS erosion measures of active disease was noted by wk 48. There were no significant correlations at BL between BASDAI and any M1 R1 lesion scores. There was significant BL correlation between SPARC SI inflammation score and ASASD (r = 0.22, p = 0.002) and CRP (r = 0.22, p = 0.002). Over 48 wks, there was a significant correlation between change in BASDAI and changes in SPARC SI inflammation (r = 0.40, p < 0.0001), SSS erosion (r = 0.25, p = 0.0007), and SSS backfill (r = 0.23, p = 0.002). Change in CRP correlated significantly with changes in SPARC SI inflammation (r = 0.35, p < 0.0001) and SSS erosion (r = 0.18, p = 0.02). Change in BASDAI correlated significantly with changes in SPARC SI inflammation (r = 0.25, p = 0.0008), SSS backfill (r = 0.18, p = 0.02), and SSS erosion (r = 0.16, p = 0.03). Correlations between ASDAS and M1 R1 measures of sacroiliitis were strongest in the ETN group through 48 wks.

Conclusion: ASDAS is the preferred clinical measure of disease activity in nr-axSpA. Of all M1 R1 assessments, change in SPARC SI inflammation seems most closely aligned with changes in ASDAS, CRP, and BASDAI, though the correlations are modest.

Disclosure: W. Maksymowycz, Pfizer Inc; 2, Pfizer Inc; 5, S. Wichuk, None; H. Jones, Pfizer Inc; 3, Pfizer Inc; 1, A. Szumski, Pfizer Inc; 5, L. Marshall, Pfizer Inc; 1, Pfizer Inc; 3, J. Bukowski, Pfizer Inc; 1, Pfizer Inc; 3, R. Lambert, None.

Table 1: Linear regression univariable analysis adjusted for age and gender.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASQol</th>
<th>BASFI</th>
<th>BASMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.272</td>
<td>0.300</td>
<td>0.187</td>
</tr>
<tr>
<td>VAS (0–10) physician</td>
<td>0.113</td>
<td>0.186</td>
<td>0.074</td>
</tr>
<tr>
<td>VAS (0–10) patient</td>
<td>0.558</td>
<td>0.616</td>
<td>0.285</td>
</tr>
<tr>
<td>VAS (0–10) night back pain</td>
<td>0.640</td>
<td>0.650</td>
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<tr>
<td>ASDAS</td>
<td>0.597</td>
<td>0.593</td>
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<td>BASDAI</td>
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<td>ASDAS</td>
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<td>MASES</td>
<td>0.239</td>
<td>0.239</td>
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<td>BASFI spinie</td>
<td>0.149</td>
<td>0.154</td>
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</tr>
<tr>
<td>Sacroiliits xray</td>
<td>0.078</td>
<td>0.146</td>
<td>0.282</td>
</tr>
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</table>

Table 2: Linear regression multivariable analysis adjusted for age and gender.

<table>
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<th>ASQol</th>
<th>BASFI</th>
<th>BASMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.107</td>
<td>0.126</td>
<td>0.032</td>
</tr>
<tr>
<td>VAS (0–10) physician</td>
<td>0.207</td>
<td>0.013</td>
<td>0.246</td>
</tr>
<tr>
<td>VAS (0–10) night back pain</td>
<td>0.203</td>
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<tr>
<td>BASDAI</td>
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<td>Sacroiliits xray</td>
<td>0.093</td>
<td>0.022</td>
<td></td>
</tr>
</tbody>
</table>

2578

Disease Activity Is the Major Determinant of Quality of Life and Physical Function in Patients with Early Axial Spondyloarthritis. Results from the Esperanza Cohort. Cristina Fernández-Carballedo, Victoria Navarro-Compán, M. Moreno, J. Bukowski, Pfizer Inc; 1, Pfizer Inc; 3, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain, 2, Leiden University Medical Center, Leiden, Netherlands, 4, Cochin Hospital, Paris, France.

Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritides. It was suggested that when the conventional CRP (cCRP) is below the limit of detection, and high sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate ASDAS-CRP. However, this recommendation was not data driven and requires further testing. Our aims were to investigate the most appropriate ASDAS-C-reactive protein (ASDAS-CR) calculation method when the cCRP is below the limit of detection, to study the arithmetic influence of low CRP values in ASDAS-CRP results and to test agreement between different ASDAS formulae.

Methods: Baseline data from the ACR Appropriateness Resource Committee (ACR) ARCC (an analysis in the DESIR cohort was used. Patients with axial spondyloarthritides (axSpA) were included. A validated versions of Ankylosing Spondylitis Quality of Life Questionnaire (ASQol) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used to calculate HRQol and PF. SM was assessed using Bath Ankylosing Spondylitis Metrology Index (BASM1). Disease activity was measured by means of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), patient’s global and night back pain VAS and physician’s VAS, Maastricht AS Enthesitis Score (MASES) and CRP (mg/L). Radiographic damage was assessed through Bath Ankylosing Spondylitis Radiographic Index for the spine (BASRI-s) and sacroiliac joints scoring in as mNY criteria. Linear regression analyses were employed to evaluate the associations between disease activity and radiographic damage.

Results: 259 axSpA patients, 67% men, 39% AS. Mean ± SD disease duration 13.3 ± 6.8 months; age 32.2 ± 6.9 years; BASDAI 3.8 ± 2.3; ASDAS 2.3 ± 1.0; patient’s global and night back pain and physician VAS 4.2 ± 2.7, 3.8 ± 2.9 and 2.9 ± 2.2; MASES 0.6 ± 1.4; CRP 9.7 ± 13.2 mg/L and BASRI-s 1.7 ± 1.6. Outcome values (Mean ± SD): ASDAS 5.9 ± 4.8; BASFI 2.4 ± 2.3 and BASMI 1.4 ± 1.3. HRQol and PF associations with all disease activity parameters (table 1) were observed in the univariable analysis, whereas HRQol, and PF associations with radiographic damage were weaker or not significant. Multivariable analysis only showed associations with disease activity for both outcomes (table 2).

Conclusion: In patients with early axSpA, HRQol and physical function are already impaired and primarily associated with disease activity.

Disclosure: C. Fernández-Carballedo, None; V. Navarro-Compán, None; M. Moreno, None; J. Bukowski, None; J. Marull, None; E. de Miguel, None.

2579

How Should We Calculate the ASDAS If the Conventional C-Reactive Protein Is Below the Limit of Detection? - an Analysis in the DESIR Cohort. Pedro Machado, Victoria Navarro-Compán, Robert Landewé, Floris van Gaalen, Christian Roux and Desireé van der Heijde, 1, University Hospital Erasmus MC, Rotterdam, The Netherlands, 2, University Hospital Leiden, Leiden, Netherlands, 3, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 4, Paris Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritides. It was suggested that when the conventional CRP (cCRP) is below the limit of detection, and high sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate ASDAS-CRP. However, this recommendation was not data driven and requires further testing. Our aims were to investigate the most appropriate ASDAS-C-reactive protein (ASDAS-CR) calculation method when the cCRP is below the limit of detection, to study the arithmetic influence of low CRP values in ASDAS-CRP results and to test agreement between different ASDAS formulae.

Methods: Baseline data from the Devenir des Spondylarthopathies Indifférenciées Récents (DESIR) cohort was used. Patients with axial spondyloarthritides and cCRP below the limit of detection (5mg/L, n = 257) were selected. ASDAS-C-CRP was calculated using eleven imputation strategies for the cCRP (range 0-5, at 0.5 intervals). ASDAS-high sensitivity CRP (hsCRP) and ASDAS-ESR were also calculated. Agreement between ASDAS formulae was tested. The effect of low CRP values in ASDAS-CRP results was studied.

Results: ASDAS-CR (1.3), ASDAS-CRP (2) and ASDAS-erythrocyte sedimentation rate (ESR) had better agreement with ASDAS-hsCRP than...
between both cohorts, the amount of improvement in axial symptoms, the effect of uneven baseline values of these measures. These differences in range of change appeared to be caused by the ceiling in the nr-axSpA group there was greater change in the improvement of SJ, but significantly larger improvement in CRP in the group of AS patients, while in disease duration prior to start of anti-TNF therapy of anti-TNF therapy of AS. Peripheral joint involvement n (%) 94 (34.3%) 26 (44.9%) <0.001
Concomitant glucocorticoids at baseline n (%) 23 (8.4%) 11 (28.2%) 0.002
Concomitant DMARD at baseline n (%) 57 (20.7%) 21 (53.3%) <0.001

Conclusion: When the cCRP is below the limit of detection or when the hsCRP is <2mg/L, the constant value of 2mg/L should be used to calculate ASDAS-CRP. There is good agreement between ASDAS-hsCRP and other ASDAS formulae (ASDAS-CRP with multiple imputation strategies and ASDAS-ESR). Agreement between ASDAS-hsCRP and other imputed formulae (table). Disagreement was mainly in lower disease activity (ASDAS-cCRP with multiple imputation strategies and ASDAS-ESR).

Table: Baseline characteristics and outcome of 12 months of anti-TNF therapy in AS and nr-axSpA patients

<table>
<thead>
<tr>
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<th>AS (N = 275)</th>
<th>nr-axSpA (N = 39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n (%)</td>
<td>66 (24.7%)</td>
<td>15 (38.5%)</td>
<td>0.069</td>
</tr>
<tr>
<td>Age (years) at baseline mean (SD)</td>
<td>38.0 (10.4)</td>
<td>37.9 (12.2)</td>
<td>0.713</td>
</tr>
<tr>
<td>HLA B27 positivity n (%)</td>
<td>252 (92.0%)</td>
<td>32 (84.2%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Disease duration prior to start of anti-TNF therapy mean (SD)</td>
<td>9.0 (8.6)</td>
<td>4.9 (6.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>BASDAI change per year mean (SD)</td>
<td>2.3 (1.7)</td>
<td>1.8 (1.5)</td>
<td>0.256</td>
</tr>
<tr>
<td>BASDAI at baseline mean (SD)</td>
<td>5.8 (2.5)</td>
<td>5.8 (2.5)</td>
<td>0.841</td>
</tr>
<tr>
<td>BASFI at 12 months mean (SD)</td>
<td>4.1 (2.7)</td>
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<tr>
<td>HAO at baseline mean (SD)</td>
<td>0.5 (0.5)</td>
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<td>Number of swollen joints/44 at baseline mean (SD)</td>
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<td>Number of swollen joints/44 at 12 months mean (SD)</td>
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Conclusion: When the cCRP is below the limit of detection or when the hsCRP is <2mg/L, the constant value of 2mg/L should be used to calculate ASDAS-CRP. There is good agreement between ASDAS-hsCRP and other ASDAS formulae (ASDAS-CRP with multiple imputation strategies and ASDAS-E SR). Agreement between ASDAS-hsCRP and other imputed formulae (table). Disagreement was mainly in lower disease activity (ASDAS-cCRP with multiple imputation strategies and ASDAS-ESR).

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achieve an ASAS40 response at wk 24, similar to that observed in ADA-treated patients at wk 12.

**Results:** In the DB period, 9/29 (31.0%) of the PBO-treated pts with both a negative MRI of the SIJ and spine at BL, were MRI+ in either the SIJ or spine at wk 12 (table). Of the 57 PBO-treated pts with normal CRP at BL, 14 (24.6%) had elevated CRP at a timepoint between BL and wk 12. 20 PBO-treated pts had a negative MRI of the SIJ and spine and a normal CRP at BL; of these pts 10 (50.0%) had a positive MRI of either the SIJ or spine and/or an elevated CRP at 1 post-BL timepoint through wk 12. 5/10 (50.0%) of these pts achieved an ASAS40 response at wk 24 (after 12 wks of OL ADA).

**Conclusion:** Among PBO-treated pts who did not have objective signs of inflammation at BL, but who demonstrated either a positive MRI or elevated CRP at a later timepoint, 50.0% achieved an ASAS40 response after 12 wks of OL ADA treatment (wk 24). Although the sample size is small and higher CRP at a later timepoint, 50.0% achieved ASAS40 response after 12 wks of inflammation at BL, but who demonstrated either a positive MRI or elevated CRP at BL; of these pts 10 (50.0%) had a positive MRI of either the SIJ or spine and/or an elevated CRP at 1 post-BL timepoint through wk 12. 5/10 (50.0%) of these pts achieved an ASAS40 response at wk 24 (after 12 wks of OL ADA).

**Table.** Proportion of PBO patients who had a +MRI and/or elevated CRP through wk 12, among those who had a -MRI and/or normal CRP at Baseline**

<table>
<thead>
<tr>
<th>Status at Baseline</th>
<th>Status at Wk 12 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine MRI +</td>
<td>43</td>
</tr>
<tr>
<td>SIJ MRI +</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>Spine and SIJ MRI +</td>
<td>29</td>
</tr>
<tr>
<td>Normal CRP</td>
<td>57</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>14 (24.6)</td>
</tr>
<tr>
<td>Spine and SIJ MRI and normal CRP</td>
<td>20</td>
</tr>
<tr>
<td>CRP</td>
<td>10 (50.0)</td>
</tr>
</tbody>
</table>

*MRI was repeated at wk 12, CRP was repeated every 4 wks through week 12.

**Conclusion:** Among PBO-treated pts who did not have objective signs of inflammation at BL, but who demonstrated either a positive MRI or elevated CRP at a later timepoint, 50.0% achieved an ASAS40 response after 12 wks of OL ADA treatment (wk 24). Although the sample size is small and higher response rates are expected with OL therapy, this is similar to that observed in the MRI+/elevated CRP ADA-treated population at wk 12 (41.0%). Thus, patients with clinically active disease but without objective inflammation at one point, may benefit from subsequent re-testing for inflammation, and if present, from initiation of ADA therapy.

**Disclosure:** W. Kong; None. X. Wang; None. T. Zhou; None. Y. Jin; None. Q. Tao; None. Y. Xu; None. Y. Zhang; None. J. Wang; None. X. Yan; None.

**2583**

**Unexpected High Prevalence of Cardiac Disease in Patients with Ankylosing Spondylitis.** S.C. Heslinga, Thelma C. Konings, Irene E. van der Horst-Bruinsma, M.L. John and Mike T. Nurmohamed. VU University Medical Center, Amsterdam, Netherlands. 3Jan van Bremen Research Institute | Reade, Amsterdam, Netherlands.

**Background/Purpose:** Ankylosing spondylitis (AS) is associated with an increased cardiovascular (CV) risk that is caused by accelerated atherosclerosis as well as specific cardiac manifestations: valvular disease, conduction disturbances and congestive heart failure due to decreased ventricular function. In this study we investigated the prevalence of cardiac disease in AS patients with high disease activity.

**Methods:** We performed a cross sectional study in patients with AS eligible for treatment with TNF blockers therapy. Patients were screened for cardiac disease using standard transthoracic echocardiography that included two-dimensional, three-dimensional and M-mode echocardiography, spectral Doppler, color Doppler and tissue Doppler imaging. The ejection fraction (EF) was used to assess systolic left ventricular (LV) function, with systolic LV dysfunction defined as EF<50%. For diastolic LV function a combination of echocardiographic measurements, i.e. peak early diastolic filling velocity (E), late diastolic filling velocity (A), E/A ratio, early diastolic mitral annular velocity (E'), deceleration time (DT) and isovolumetric relaxation time (IVRT) were used. Based on these parameters diastolic LV dysfunction is graded into three categories: mild (grade I), pseudonormal (grade II) and restrictive (grade III). Valvular and aortic abnormalities were evaluated according to the current echocardiographic guidelines. Data was compared with data from literature using one-sample t-test.

**Results:** Forty-three consecutive AS patients were included with a mean age of 43±12 years and a mean disease duration of 10±12 years. In total, 10 out of 43 (23%) patients had diastolic LV dysfunction grade I, of which one was female. This was significantly higher compared to literature, in which the prevalence of diastolic LV dysfunction grade I is approximately 5% in an age matched control group (p<0.01). Two patients had a prior myocardial infarction of which one had systolic LV dysfunction, with an EF of 49%. Three patients had mild aortic regurgitation and seven other patients had mild mitral regurgitation. Five patients had mild aortic dilation. Overall, 19 out of 43 AS patients (44%) had some form of cardiac dysfunction or disease which is substantially higher compared to the general population, as the prevalence of cardiovascular disease in the general population is approximately 8%.

**Conclusion:** Patients with AS have an increased prevalence of cardiovascular disease compared with the general population, with increased prevalence's of left ventricular dysfunction and valvular disease. This increased prevalence may increase CV risk in AS patients. As cardiac disease could be attributable to the general inflammation process affecting the heart, further studies are warranted that investigate whether or not anti-inflammatory treatment, such as TNF blockers, improves cardiac function or prevents early cardiac complications. Also, the impact of (mandatory) screening AS patients with echocardiography on CV disease should be investigated.

**Disclosure:** S.C. Heslinga, None. T.C. Konings, None. I.E. van der Horst - Bruinsma, None. M.L. John, None. M.T. Nurmohamed, Abbott, Roche, Pfizer, 8.

**2584**

**Smoking Is Not Associated with Response to TNF Blockers in Patients with Axial Spondyloarthritis.** Anna Dellyes, Pierre Laforge, Vincent Pradel and Thao Pham. APHM, Aix Marseille University, Marseille, France.
Background/Purpose: Smoking has been reported as associated with increased disease activity; more functional impairment, poorer quality of life and more radiographic damages in patients (pts) with axial spondyloarthritides (SpA). However, there is little information available about a potential effect of smoking on the effectiveness of anti-rheumatic treatment such as TNF blockers. The study objective was to examine the association of smoking with clinical outcome after treatment with TNF blockers in patients with axial SpA.

Methods: A monocenter ambispective observational study in 96 patients with active axial SpA starting a treatment with a first TNF blocker. BASDAlA, pain VAS, analgesics and NSAIDs consumption, and variables known as treatment response predictive factors were collected at baseline, 3, 6 and 12 months. The main outcome was the percentage of BASDAlA 50 responders at M6. Secondary outcomes were BASDAlA variation, pain VAS variation and NSAIDs consumption at M3, M6 and M12. We analyzed disease activity and response to treatment in current smokers vs. non-smokers using a chi-square test or one-way analysis of variance (depending on categorical/continuous variables). SPSS 17.0 version was used for the management and statistical analysis.

Results: Patients’ demographic and clinical characteristics at baseline are shown in table 1. Thirty-five pts (36%) were current smokers (14.6±6.4 cigarettes/day). No significant differences were observed between current smokers and non-smokers at baseline. Patients were mainly treated with infliximab (84%). The percentage of BASDAlA 50 responders at M 6 was 34% (12/35) and 39% (24/61), in the smokers and the non-smokers group, respectively (p<0.6). No statically significant differences were observed between current smoker and non-smokers in BASDAlA variation, pain VAS variation or treatment consumption at each evaluation time.

Conclusion: Smoking status seems not to be a predictive factor of response to TNF-blockers in patients with axial SpA.

Disclosure: A. Deliyes: None; P. Lafforgue: None; V. Pradel: None; T. Pham: None.

2585

Association of Smoking with Acute Phase Reactants and Molecules Involved in Bone Formation in Patients with Ankylosing Spondylitis. Grigorios Sakellariou1, Spyros Gerou2, Dimitrios Oikonomou1 and Fares Sayegh3. 1424 General Military Hospital, Thessaloniki, Greece, 2Laboratory of Bone Formation in Patients with Ankylosing Spondylitis, Thessaloniki, Greece, 3Papageorgiou General Hospital, Thessaloniki, Greece.

Background/Purpose: In patients with ankylosing spondylitis (AS), smoking is associated with increased disease activity and more radiographic damage. However, the mechanisms underlying the effects of smoking are still unknown. The aim of the study was to investigate the relationship between smoking and acute phase reactants, and serum levels of molecules involved in bone formation in patients with AS.

Methods: This was an observational, cross-sectional study. Serum samples for total Dickkopf-1 (Dkk-1), sclerostin and vascular endothelial growth factor (VEGF) were obtained from TNF inhibitor naïve patients with AS according to the modified New York criteria. Patients with at least the last 3 months use of glucocorticoids, DMRDs or high dose NSAIDs (a mean NSAIDs intake index >50) were excluded. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), BASDAlA, BASFI and radiographic severity (assessed by mSASSS and BASRI-s) were assessed for each patient. Demographic variables and smoking history were obtained, and smoking pack-years were calculated.

Results: Sixty-five patients were included in the study (mean age 41.3±15 years; duration of symptoms 13.4±12 years; male gender 61 patients (93.8%)]. Using Mann-Whitney U test, CRP (18.9±12.5 mg/l vs 12.4±9.3 mg/l, p=0.019) and VEGF levels (381.6±121.4 pg/ml vs 310.9±131.5 pg/ml, p=0.02) were higher in patients with current smoking compared with those without, while there was no difference for ESR and the levels of Dkk-1 and sclerostin. Ever smokers had higher VEGF levels (369.9±128.7 pg/ml vs 252.7±94.4 pg/ml, p=0.006) compared with never smokers, while there was no difference for ESR, CRP and the levels of Dkk-1 and sclerostin between the two groups. Among acute phase reactants and molecules involved in bone formation, only VEGF levels were correlated with smoking pack-years (r=0.39, p<0.001). In multiple linear regression analysis, which involved all demographic, clinical and radiographic variables and smoking, only VEGF (in smoking pack-years) had a significant association (beta=0.497, p<0.001).

Conclusion: It seems that VEGF levels are positively associated with smoking in patients with AS. The effect of smoking on disease activity and/or radiographic spinal progression to be mediated by increased VEGF levels could be supposed.

Disclosure: G. Sakellariou, None; S. Gerou, None; D. Oikonomou, None; F. Sayegh, None.

2586

Which Characteristics of Inflammatory Back Pain (CBP) Forecast the Presence of Sacroiliitis on Magnetic Resonance Imaging (MRI)? Results from the Esperanza Cohort. Victoria Navarro-Campos1, Raquel M. Pineda-González2, Azucena Hernández2, Emma Beltrán1, Eugenio de Miguel2, Robert B. M. Landewé1, Desirée van der Heijde2 and Pedro Zarco1, 1University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, 2Hospital Universitario Fundación Alcorcón, Madrid, Spain, 3Hospital Virgen de la Salud, Toledo, Spain, 4University General Hospital of Valencia, Valencia, Spain, 5University Hospital La Paz - IdiPaz, Madrid, Spain, 6Amsterdam Rheumatology Center, Amsterdam, Netherlands, 7Leiden University Medical Center, Leiden, Netherlands, 8Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain.

Background/Purpose: CBP is often the starting point for a suspicion of axSpA. In the ASAS-criteria for axial SpA either MRI of the SI-joints or HLAB-27-testing are dominant. But, CBP is an extremely common present- ing symptom and not all patients can be followed up by MRI and/or HLAB-27 testing. This analysis was undertaken to investigate which characteristics of back-pain forecast a positive MRI of the SI-joints.

Objectives: To evaluate which inflammatory characteristics of CBP are associated with the presence of sacroiliitis on MRI in patients with a suspicion of axSpA.

Methods: Baseline dataset from the EsPeranza cohort (<45 years old, symptoms duration 3–24 months and with inflammatory back pain -B18- and/or symmetrical spinal and/or spondylitis features) was used. For this study, only data from all patients with axial symptoms who underwent sacroiliac joint (SIJ) MRI were analysed. Univariable and multivariable logistic regression analyses were employed to estimate odds ratio for the association between IBP characteristics (morning stiffness, improve with exercise and not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAID(s) and their different combinations with a positive SIJ MRI (ASAS definition). Furthermore, diagnostic utility measures were also calculated.

Results: Data from 326 patients (53.7% male, 45% HLA-B27 positive, mean (SD) age 32.8 (7) years and mean (SD) symptoms duration 12.6 (6.4) months) were included in this analysis. A total of 130 (40%) patients had sacroiliitis on MRI. Table shows the association between each separate characteristic (IBP) and each possible IBP definition (IBP) with a positive MRI. Alternating buttock pain (OR = 3.43; p<0.001), insidious onset (OR = 2.12; p<0.05) and awakening at 2nd half of the night (OR = 1.71; p<0.05) were significantly and positively associated with a positive MRI. The combination of these three characteristics (92%) and the addition to the ASAS-definition of IBP of alternating buttock pain (94%) or NSAID response (86%) had highest specificity, but insufficient sensitivity.

Conclusion: Alternating buttock pain is a distinguishing IBP character- istic strongly associated with a positive SIJ MRI in patients with suspected axSpA. The addition of this criterion in the decision to perform MRI of the SIJ may improve diagnostic efficiency in patients with suspected axSpA.
Table: A association between each of the CBP characteristics and each of the possible IBP definitions with a positive MRI.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartet</th>
<th>Stiff</th>
<th>Improve with rest</th>
<th>Not improve with rest</th>
<th>Morning Stiff &gt; 30 min</th>
<th>Improved exercise, not rest</th>
<th>Alter. buttock pain</th>
<th>Withinsinus onset</th>
<th>Awake 2nd half of night</th>
<th>Response to NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morn. Stiff</td>
<td>54.5%</td>
<td>31.2%</td>
<td>10.3%</td>
<td>4.0%</td>
<td>85.4%</td>
<td>65.3%</td>
<td>7.3%</td>
<td>24.5%</td>
<td>11.8%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Imp. exercise, not rest</td>
<td>32.3%</td>
<td>38.2%</td>
<td>26.1%</td>
<td>13.5%</td>
<td>31.5%</td>
<td>71.4%</td>
<td>61.2%</td>
<td>12.0%</td>
<td>1.0%</td>
<td>0.94%</td>
</tr>
<tr>
<td>Alter. buttock pain</td>
<td>47.7%</td>
<td>36.9%</td>
<td>14.0%</td>
<td>4.4%</td>
<td>47.7%</td>
<td>81.6%</td>
<td>63.3%</td>
<td>7.0%</td>
<td>25.9%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Insidious onset</td>
<td>31.4%</td>
<td>44.7%</td>
<td>12.4%</td>
<td>2.2%</td>
<td>37.7%</td>
<td>24.4%</td>
<td>77.3%</td>
<td>12.1%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Awake 2nd half of night</td>
<td>64.6%</td>
<td>65.4%</td>
<td>43.5%</td>
<td>2.3%</td>
<td>64.6%</td>
<td>56.6%</td>
<td>49.7%</td>
<td>7.0%</td>
<td>1.4%</td>
<td>0.63%</td>
</tr>
<tr>
<td>Response to NSAIDs</td>
<td>90.9%</td>
<td>110.0%</td>
<td>56.0%</td>
<td>1.7%</td>
<td>69.2%</td>
<td>43.9%</td>
<td>68.3%</td>
<td>1.2%</td>
<td>0.70%</td>
<td>0.70%</td>
</tr>
</tbody>
</table>

Table 1A: Individual Characteristic of IBP

Table 1B: IBP Definition

Cann criteria                      | 67.5%   | 57.2% | 27.3%             | 5.9%                  | 51.5%                 | 70.9%                       | 68.8%               | 1.7%             | 0.68%              | 0.68%             |
Berlin criteria                    | 94.7%   | 97.2% | 49.5%             | 2.7%                  | 72.3%                 | 95.9%                       | 72.3%               | 1.5%             | 0.55%              | 0.55%             |
ASAS criteria                      | 62.4%   | 47.5% | 32.0%             | 6.6%                  | 47.7%                 | 77.0%                       | 68.9%               | 1.45%            | 0.04%              | 0.04%             |
Night + Insidious + Buttock (1/3)  | 93.7%   | 80.4% | 34.5%             | 3.5%                  | 71.5%                 | 59.2%                       | 75.8%               | 1.75%            | 0.48%              | 0.48%             |
Night + Insidious + Buttock (1/3)  | 89.8%   | 15.7% | 6.1%              | 6.7%                  | 33.8%                 | 92.3%                       | 74.6%               | 4.3%             | 0.72%              | 0.72%             |
Cann + Night (5/6)                 | 52.4%   | 41.2% | 25.2%             | 7.2%                  | 40.9%                 | 77.1%                       | 66.5%               | 1.91%            | 0.76%              | 0.76%             |
Berlin + Insidious (3/5)           | 89.6%   | 81.4% | 38.8%             | 3.0%                  | 68.5%                 | 58.7%                       | 73.7%               | 1.66%            | 0.54%              | 0.54%             |
ASAS + Buttock (5/6)               | 40.3%   | 11.5% | 7.4%              | 4.8%                  | 30.8%                 | 94.4%                       | 67.3%               | 0.73%            | 0.03%              | 0.03%             |
ASAS + NSAIDs (6/7)                | 48.6%   | 36.9% | 13.2%             | 3.6%                  | 36.9%                 | 86.6%                       | 64.0%               | 2.67%            | 0.01%              | 0.01%             |
ASAS + NSAIDs (6/7)                | 28.4%   | 7.3%  | 4.7%              | 1.1%                  | 21.5%                 | 94.4%                       | 64.9%               | 5.97%            | 0.81%              | 0.81%             |

Table 1B: IBP Definition

p<0.05; *p<0.001

Table: Disclosure: None.

Table: 2587

5288

Which Characteristics of Inflammatory Back Pain (CBP) Forecast the Presence of HLA-B27 Results from the Esperanza Cohort. Victoria Navarro-Compan1, Juan Jose Aznar2, Luis F. Linares3, Eduardo Collantes-Estevez4, Robert B. M. Landewe5, Desirèe van der Heijden6, Pedro Zarcot7,8,9,10,11 University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, 2Hospital de Mérida, Mérida (Badajoz), Spain, 3University Hospital Virgen de la Arrixaca, Murcia, Spain, 4IMIBIC/University Hospital Reina Sofia, Córdoba, Spain, 5Córdoba, Spain, 6Amsterdam Rheumatology Center, Amsterdam, Netherlands, 7Leiden University Medical Center, Leiden, Netherlands, 8Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain.

Background/Purpose: CBP is often the starting point for a suspicion of axSpA. In the ASAS-criteria for axial SpA either MRI of the SI-joints or HLAB27-testing are dominant. But, CBP is an extremely common presenting symptom and not all patients can be followed up by MRI and/or HLAB27 testing. This analysis was undertaken to investigate which characteristics of back-pain forecast a positive HLAB27.

Objectives: To evaluate which inflammatory characteristics of CBP are associated with the presence of HLAB27 in patients with a suspicion of axSpA.

Methods: Baseline data from the Esperanza cohort (<45 years old, symptoms duration <3-1 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus >1 SpA features) was used. For this study, only data from all patients with axial symptoms and HLAB27 assessed were analysed. Univariable and multivariable logistic regression analyses were employed to estimate odds ratio for the association between IBP characteristics (morning stiffness, improve with exercise and not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAID) and their different combinations with a positive HLAB27 (local lab testing). Furthermore, diagnostic utility measures were also calculated.

Results: Data from 653 patients (54.2% male, mean (SD) age 33.0 (7.1) years and mean (SD) symptoms duration 11.0 (6.6) months. A total of 270 (41%) patients were HLAB27 positive were included in this analysis. Table shows the association between each separate characteristic (1A) and each possible IBP definition (1B) with a positive HLAB27. A1 waking at second half of night (OR = 1.53; p = 0.05) and good response to NSAID (OR = 1.46; p = 0.05) were significantly and positively associated with a positive HLAB27. Among the existing criteria to define IBP, the ASAS criteria had the highest specificity (81%), but insufficient sensitivity. The addition of these two characteristics to the Calin-definition of IBP (88%) as well as the addition of NSAID response to the ASAS-definition of IBP (86%) just increased the specificity slightly.

Conclusion: A waking at second half of night and good response to NSAID are distinguishing IBP characteristics associated with the presence of HLAB27 in patients with suspected axSpA. However, the addition of these characteristics to the existing IBP definitions in the decision to test HLAB27 does not significantly improve diagnostic efficiency in patients with suspected axSpA. Further, the most specific IBP definition for a positive HLAB27 is the ASAS-definition.
 Acknowledgements: The EsPeranza Program has been supported by an unrestricted grant from Pfizer.

Disclosure of Interest: None declared.

Table: A association between each of the CBP characteristics and each of the possible IBP definitions with a positive HLA-B27.

<table>
<thead>
<tr>
<th>HLA-B27</th>
<th>CBP characteristics</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
<th>Diagnostic utility measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Men, Still &gt; 30 min</td>
<td>172 (63.3)</td>
<td>216 (56.4)</td>
<td>1.34*</td>
<td>1.10</td>
</tr>
<tr>
<td>M. Imp. exercise, not rest</td>
<td>91 (33.7)</td>
<td>114 (29.8)</td>
<td>1.20</td>
<td>-</td>
</tr>
<tr>
<td>M. Alter, buttock pain</td>
<td>86 (31.9)</td>
<td>110 (28.7)</td>
<td>1.16</td>
<td>-</td>
</tr>
<tr>
<td>M. Insidious onset</td>
<td>184 (68.1)</td>
<td>241 (62.9)</td>
<td>1.26</td>
<td>-</td>
</tr>
<tr>
<td>M. Ankle 2nd half night</td>
<td>149 (55.2)</td>
<td>163 (42.6)</td>
<td>1.66***</td>
<td>1.53***</td>
</tr>
<tr>
<td>M. Response to NSAIDs (I/II)</td>
<td>182 (67.4)</td>
<td>217 (56.7)</td>
<td>1.58***</td>
<td>1.46***</td>
</tr>
</tbody>
</table>

Table 1A: Individual Characteristic of IBP

<table>
<thead>
<tr>
<th>CBP characteristics</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
<th>Diagnostic utility measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calin criteria</td>
<td>98 (36.3)</td>
<td>99 (29.0)</td>
<td>1.63**</td>
</tr>
<tr>
<td>Berlin criteria</td>
<td>173 (64.3)</td>
<td>194 (51.7)</td>
<td>1.74**</td>
</tr>
<tr>
<td>ASAS criteria</td>
<td>85 (31.5)</td>
<td>74 (19.3)</td>
<td>1.92***</td>
</tr>
<tr>
<td>Night + NSAID response (I/II)</td>
<td>109 (40.0)</td>
<td>109 (28.5)</td>
<td>1.68***</td>
</tr>
<tr>
<td>Calin + Night + NSAID response (I/II)</td>
<td>58 (21.5)</td>
<td>45 (11.7)</td>
<td>2.06***</td>
</tr>
<tr>
<td>Berlin + NSAID response (I/II)</td>
<td>154 (57.0)</td>
<td>153 (39.0)</td>
<td>2.00***</td>
</tr>
<tr>
<td>ASAS + NSAID response (I/II)</td>
<td>66 (24.4)</td>
<td>51 (13.3)</td>
<td>2.11***</td>
</tr>
<tr>
<td>ASAS + Buttokck + NSAID (I/II)</td>
<td>29 (10.7)</td>
<td>22 (5.7)</td>
<td>1.98*</td>
</tr>
</tbody>
</table>

Table 1B: IBP Definition

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Papers have been produced encompassing the role of imaging in making a diagnosis of axial- or peripheral SpA, monitoring inflammation and damage, predicting outcome, response to treatment, and detecting spinal fractures and osteoporosis (OP) (Table 1). The SOR for each proposition varied, but was generally very high (mean 8.9–9.5).

Conclusion: Ten recommendations for the role of imaging in the clinical management of SpA were developed using research-based evidence and expert opinion.

LOE, level of evidence; categories of evidence: Ia, evidence for meta-analysis of randomized controlled trials; Ib, evidence from at least one randomized controlled trial; Ila, evidence from at least one controlled study without randomization; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities; or both. CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; SI, sacroiliac; SpA, spondyloarthritis; SOR, strength of recommendation, mean (range) of visual analogue scale; STIR, short tau inversion recovery; TNF, tumor necrosis factor alpha; US, ultrasonography.

Table 1. EULAR imaging recommendations for spondyloarthritis in clinical practice

SOR | LOE | 1 Axial SpA: diagnosis | 9.5 (9.2–9.8) | III
| 2 Peripheral SpA: diagnosis | 9.4 (9.0–9.8) | III
| 3 Axial SpA: monitoring activity | 9.2 (8.8–9.6) | Ib
| 4 Axial SpA: monitoring structural changes | 9.3 (8.8–9.8) | Ib
| 5 Peripheral SpA: monitoring activity | 9.3 (8.9–9.7) | Ib
Peripheral SpA: monitoring structural changes

In peripheral SpA, if the clinical scenario requires monitoring of structural damage, then X-ray is recommended. MRI and/or US may provide additional information.

Axial SpA: predicting outcome/ severity

In patients with AS (not nr-axSpA), initial X-rays of the lumbar and cervical spine are recommended to detect syndesmophytes, which are predictive of development of new syndesmophytes. MRI (vertebral corner inflammatory or fatty lesions) may also be used to predict development of new radiographic syndesmophytes.

Axial SpA: predicting treatment effect

Extensive MRI inflammatory activity (bone marrow edema), particularly in the spine in AS patients, may be used as a predictor of good clinical response to anti-TNF treatment in axial SpA. Thus, MRI may aid in the decision of initiating anti-TNF therapy, in addition to clinical examination and CRP.

Spinal fracture

When spinal fracture in axial SpA is suspected, X-ray is the recommended initial imaging method. If X-rays are negative, CT should be performed. MRI is an additional imaging method to CT, which can also provide information on soft tissue lesions.

Osteoporosis

In axial SpA patients without syndesmophytes in the lumbar spine on X-ray, osteoporosis should be assessed by hip DXA and AP-spine DXA. In patients with syndesmophytes in the lumbar spine on X-ray, osteoporosis should be assessed by hip DXA, supplemented by either spine DXA in lateral projection or possibly QCT of the spine.

Disclosure: P. Mandl, None; V. Navarro-Compañ, None; P. Bakker, None; L. Terslev, None; P. Aegerter, None; D. van der Heijde, None; M. A. d'Agostino, None; X. Baraliakos, MSD, Pfizer, AbbVie, 2; AbbVie, AbbVie; Centocor, Jansen, Merck, Pfizer, Schering-Plough, Roche UCB, and Wyeth, 5; S. J. Pedersen, None; A. G. Lipton, None; E. Naredo, MSD, Spanish Foundation of Rheumatology, 8, AbbVie, Roche Pharma, BMS, Pfizer, UCB, ESCOATE, 8; C. Schueller-Wiedemann, None; U. Weder, AbbVie Laboratories, 5, M. Wick, None, E. Filippucci, None; P. G. Conaghan, AbbVie, Jansen, Novartis, Pfizer, Roche, 3, AbbVie, Merck, Pfizer, Roche, UCB, 8; M. Rudwael, Roche, MSD, Pfizer, Novartis, UCB, 5, AbbVie, BMS, Chugai, 8; G. A. Schett, None; J. Sieper, None; S. Tarp, None; H. Marzo-Ortega, AbbVie, MSD, Jansen, Pfizer, UCB, 5; M. Ostergaard, AbbVie/AbbVie, Centocor, Merck, Schering-Plough, 2; AbbVie, AbbVie, BMS, Boehringer-Ingelheim, Eli-Lilly, Centocor, GSK, Jansen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche UCB, and Wyeth, 5.

Comparison of Radiographic Damage Score in Ankylosing Spondylitis According to Tumor Necrosis Factor Inhibitor: Observation Study of Korean Spondyloarthropathy Registry (OSKAR) Data

Introduction: The current management strategy of ankylosing spondylitis (AS) is based on the disease activity and progression. Therefore, the radiographic damage score is an important tool to evaluate the disease activity and progression. The aim of this study was to compare the radiographic damage score in patients with AS according to the tumor necrosis factor (TNF) inhibitor treatment.

Methods: A total of 610 AS patients from the Observation Study of Korean spondyloarthropathy Registry (OSKAR) data were recruited for this study. The subjects were stratified in relation to the using state of TNF blocker. We evaluated collected clinical and radiographic parameters at two different time points. Then we compared radiographic progression between groups. To use the mSASSS, cervical and lumbar spinal radiographs were performed, MRI is an additional imaging method to CT, which can also provide information on soft tissue lesions.

Results: The mean age (SD) of the AS patients was 37.9(18.3) years, and the mean disease duration (SD) was 17.3(18.3) years at baseline. In this data, 88.7% of the patients were male, and 96.9% were HLA-B27 positive. 40.7% of the patients had history of peripheral arthritis. Of these patients, 44.1% (269 patients) had received TNF blockers. The mean mSASSS unit (SEM) at baseline was significantly different between groups (TNF blocker naive 17.6±0.9 vs TNF blocker user 21.0±1.2, P = 0.02). Radiographic follow-up duration from the first mSASSS assessment were comparable (4.9±0.1 vs 5.1±0.1, P = 0.28). However, Patients treated with TNF blockers had a higher CRP level (25.2±0.2 vs 16.1±0.1, p <0.01) at baseline. On simple analysis, the TNF blocker naive patients had comparable radiographic progression to those with TNF blocker (3.7±0.5 vs 3.7±0.8, p = 0.09). After adjustment for multiple comparisons by the Bonferroni correction gender, history of peripheral arthritis, disease duration, baseline mSASSS, and NSAID intake had statistically significant in our registry. However, the radiographic progression between groups was no significant difference (OR 0.60. [95% CI 0.22-4.72], P = 0.44).

Conclusion: Treatment with TNF inhibitors has no influence on radiographic progression in AS.

Disclosure: T. J. Kim, None; J. H. SHIN, None; I. H. Sung, None; S. Lee, None; K. B. Joo, None; T. H. Kim, None.

2591

Effects of Self-Management Model on the Disease-Related Knowledge, Joint Function and Quality of Life in Patients With Ankylosing Spondylitis

Introduction: The aim of this study was to investigate and evaluate the effect of a new kind of health management model on disease-related knowledge, joint function and quality of life in patients with ankylosing spondylitis (AS).

Methods: 84 patients with AS who had signed the informed consent in China were included in this study. All the patients satisfied the ACR classification criteria for AS. Doctors and AS patients co-built a club which was a new kind of self-management model in the follow-up 6 months. In the club, the medical staff could give AS patients psychological guidance, pain guidance, dietary guidance and life guidance, patients could also give others positive impact. Before and after six months of this management model of club, we evaluated the disease-related knowledge, compliance, joint function, psychological quality, and life quality by questionnaire of AS health management and Bath AS Function Index (BASFI).

Results: The questionnaire score of disease-related knowledge in AS patients increased significantly from (58.14 ± 11.62) to (74.77 ± 10.16) (P = 0.000). In the long process of treatment, many AS Patents despair and feel hopeless because they thought it impossible to work like a healthy person, but after this management model, the ration has been significantly reduced from 14.1% (11/84) to 3.57% (3/84) (P = 0.017). Meanwhile, patients willing to cooperate with doctors and face life actively increased significantly from 70.6% (60/84) to 90.46% (76/84) (P = 0.003). Patients unwilling to insist long-term drug therapy for fear of side effects dropped significantly from 35.71% (30/84) to 4.76% (4/84) (P = 0.000). Patients who quit smoking and drinking, and could diet reasonably rose significantly from 45.24% (38/84) to 79.76% (67/84) (P = 0.000). BASFI score improved from 5.25 ± 1.93 to 3.90 ± 1.87 (P = 0.000). Patients with satisfaction of health education increased significantly from 72.62% (61/84) to 100% (84/84), (P = 0.000).

Conclusion: This kind of management model could mobilize patients' initiative, make them cooperate actively with doctors. By this new kind of management model, AS patients could gain more knowledge about health and improve their joint function; And what's more, this kind of management model also increased the patients' ability of self-management, improved their life quality.

Disclosure: P. Zhang, None; J. Q. None; Z. Lin, None; M. Zhao, None; J. Gu, None.

2592

Assessment of Spinal Stiffness International Society Endorsed Recommendations for Early Referral of Patients Suspected for Axial Spondyloarthritides

Introduction: Denis Podbute3y; A. Zdrad van Tubergen1, Robert Landewe2, Joachim Sieper4 and Désirée van der Heijde5. 1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Mastricht University Medical Center, Mastricht, Netherlands, 3Aademic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 4Leiden University Medical Center, Leiden, Netherlands.

Discussion: T. J. Kim, None; J. H. SHIN, None; I. H. Sung, None; S. Lee, None; K. B. Joo, None; T. H. Kim, None.
Background/Purpose: There is a substantial gap of 5 to 8 years between the onset of symptoms (usually back pain) and the diagnosis of axial spondyloarthritis (SpA). One of the reasons for such a delay is a late referral of patients to a rheumatologist by general practitioners and other physicians encountering patients with back pain. Several referral approaches have been proposed and tested over the last 10 years, however, no universal and widely accepted referral strategy exists until now. The aim was, therefore, to develop consensus recommendations under the umbrella of the Assessment of Spondyloarthritis International Society (ASAS) for early referral of patients suspected for axial SpA by primary care physicians or non-rheumatology specialists.

Methods: Development of the ASAS endorsed referral recommendations for patients suspected for axial SpA by primary care physicians or non-rheumatology specialists consisted of the following phases: 1) systematic literature review, 2) the first Delphi round aimed at identification of unmet needs and development of the referral parameter candidate list, 3) the second Delphi round aimed at identification of the most useful combination of the referral parameters, 4) final discussion on the proposal for the recommendations and voting on it at a ASAS annual meeting in 2014.

Results: The following consensus on the referral recommendation was achieved within ASAS as a result of the Delphi process and final voting. Patients with: 1) chronic back pain (duration ≥3 months) and back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present: · Inflammatory back pain; · HLA-B27 positivity; · Sacroilitis on imaging if available (X-rays or magnetic resonance imaging); · Peripheral manifestations (arthritis, enthesitis, dactylitis); · Extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis); · Positive family history for SpA; · Good response to non-steroidal anti-inflammatory drugs; · Elevated acute phase reactant.

Conclusion: A consensus ASAS endorsed referral recommendation for patients suspected for axial SpA by primary care physicians or non-rheumatology specialists was developed as a flexible and universal tool to be used in clinical practice. The diagnostic value of this tool applied in different settings should be determined in future studies.

Disclosure: D. Poddubnyy, None; A. van Tubergen, None; R. Landewé, None; J. Sieper, None; D. van der Heijde, None.

2593

Patients with Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis Demonstrate the Same Clinical Disease Course over Two Years: Results from the GESPIC Cohort.

Denis Poddubnyy1, Hildrun Haibel2, Jürgen Braun3, Martin Rudwaleit4 and Joachim Sieper1. 1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Institute of Rheumatology, Prague, Prague, Czech Republic. 3Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 4Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: In cross-sectional studies it has been demonstrated that non-radiographic axial spondyloarthritis (nr-axSpA) does not differ from ankylosing spondylitis (AS) with respect to clinical signs of disease activity. Prospective studies comparing clinical course of the disease over time are, however, lacking. The purpose of this analysis was to investigate the clinical course of the disease over two years in patients with nr-axSpA in comparison to AS.

Methods: In total, 210 patients with early axSpA (115 with AS according to the modified New York criteria and symptom duration ≤10 years, and 95 with nr-axSpA and symptom duration ≤5 years) with complete radiographic data over 2 years from the German Spondyloarthritis Inception Cohort (GESPIC) were included. Clinical assessment, which included standard disease activity (BASDAI, C-reactive protein – CRP), function (BASFI) and spinal mobility (BASMI) assessments, as well as therapy recording, was performed at baseline and every 6 months thereafter. Starting from the visit at month 6, the ASDAS-CRP and the ASAS NSAID intake score were calculated.

Results: The majority of patients were included in GESPIC and followed-up prior to marketing authorisation of TNF blockers for AS and nr-axSpA. However, 17 AS patients (14.8%) and 5 nr-axSpA patients (5.3%) received at least one prescription of a TNF blocker during 2 years of follow-up and were excluded from the further analysis. Remaining patients with nr-axSpA (n=90) did not differ from AS patients (n=98) with respect to the BASDAI and the BASFI at any time point during 2 years of follow-up.

Conclusion: AS patients had however significantly higher level of CRP at all time points but ASDAS-CRP was significantly higher in AS at 6M only (figure). There were also no substantial differences in the treatment between two groups. Spinial mobility (as measured by BASMI) was generally better in nr-axSpA as compared to AS, but this difference was statistically significant only at two time points (6 and 12 months).

A mong all patients who did not receive a TNF-Blocker during 2 years of follow-up, 10 patients with nr-axSpA and 22 patients with AS had at baseline BASDAI >4 and elevated CRP. Low disease activity state at least 2 time points during 2 years of the follow-up as defined by BASDAI ≤4 was achieved by 57% of nr-axSpA and by 40% of AS patients, BASDAI ≤4 and normal CRP by 25% and 13%, BASDAI ≤2 by 13% and 13%, and ASDAS inactive disease by 25% and 0% of nr-axSpA and AS patients, respectively. All differences were statistically non-significant.

Disclosure: D. Poddubnyy, None; H. Haibel, None; J. Braun, None; M. Rudwaleit, None; J. Sieper, None.

2594

Differences in Localization and Activity of the Enthesal Involvement Between Non-Radiographic and Radiographic Axial Spondyloarthritis By the Ultrasound Assessment.

Marketa Fojtikova1, Karel Pavêk2a, Sarka Foretova2 and Jindra Gatterova2. 1Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, 2Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: Inflammatory involvement of peripheral enthesis belongs to an important sign of spondyloarthritis (SpA). It may occur in patients with long-term as well as newly diagnosed disease and in those with definite ankylosing spondylitis (AS) and without radiological sacroiliitis, non-radiographic axial SpA (nr-axSpA).

In our work we look for active and non-active enthesal changes by an ultrasound detection in four localization: Achilles tendon, patellar ligament, plantar aponeurosis and quadriceps insertion in patients suffering from newly diagnosed nr-axSpA and AS.

Methods: The total of 34 patients with newly diagnosed SpA (with established diagnosis maximally within 2 years) underwent the clinical and ultrasound examination. Disease activity was determined by ASDAS CRP and BASDAI. Conventional two-dimensional power Doppler ultrasonography was performed by one radiologist/musculoskeletal ultrasound specialist. Six ultrasound changes like tendon structural changes and thickening of tendon insertion, calcifications, bone erosions, bursitis, and Doppler signal was determined in four locations and Naredo et al. classification for active/non active lesions was used. The χ2 test for comparison each group, Fisher exact test and correlation for activity a tendon changes was used.

Results: Altogether, 26 nr-axSpA patients and 8 AS patients BASDAI 3.27±0.56 and 1.95±0.2 respectively, ASDAS CRP 1.88±0.63 and 2.07±0.29 respectively, underwent the ultrasound detection for enthesal changes.
When we look for any changes in all tested tendons there were no active changes in only 37.90 % nr-axSpA compared to 71.88 % AS (p < 0.0001). However the active changes were distributed evenly in nr-axSpA and AS, 4.80 % and 7.81 %, respectively.

The Doppler positive changes in any locations were found in 19.20 % nr-axSpA and 37.55 % AS (p = ns), whereas the non-active changes in 280.77 % nr-axSpA a 100 % AS (p = ns).

The Achilles tendon and the patellar ligament were the most common involved sites in both patients groups, nr-axSpA (32.70 % and 26.92 % respectively) and AS (50.0 % and 25.0 % respectively), all p = ns.

There is no correlation between ASAS CRP and/or BSA DA1 and active and non-active lesions in both group.

Conclusion: Our study demonstrates the usefulness of soft tissue ultrasound for active and non-active tendon changes in SpA. Interestingly, both patients with nr-axSpA and those with definite AS develop the same number of active enthesal changes, but non-active enthesal changes are more common AS. The presence of active and non-active enthesal changes do not correlate with disease activity.

This study was supported by the project (MH CR) for conceptual development of research organization 023728

Disclosure: M. Fojtikova, None; K. Pavelka, None; S. Foretova, None; J. Gaterova, None.

2595

Using iPhone Compass Application for the Assessment of Cervical Rotation in Patients with Ankylosing Spondylitis.

Gokce Kenar, Berin Zengin, Handan Yarkan, Pinar Cetin, Ismail Sari, Fatos Onen, Merih Birlik and Nurullah Akkok. Dokuz Eylul University School of Medicine, Izmir, Turkey.

Background/Purpose: Cervical rotation reflects restriction of mobility in axial disease in ankylosing spondylitis (AS) and it can be assessed in several approaches based on the use of either an inclinometer, a goniometer or a tape measure. New generations of smartphones are equipped with a gyroscope and an accelerometer which in combination with a smartphone’s operating system or specific software applications can be used for various inclinometric functions. The aim of the study was to assess the reliability and validity of using iPhone built in compass application, as compared to using goniometer in the assessment of cervical rotation patients with AS.

Methods: The study sample included 20 AS patients (6 females, 14 males) with a mean age of 47.8 (± 10.2). BASMI scores were obtained from patient charts. Two examiners measured cervical rotation of each patient using iPhone4 compass application and also goniometer, twice with each method. A cap with a velcro patch on top and an iphone case with a Velcro patch on the bottom were used to stabilize the iphone’s position during measurements. Intra-rater and inter-rater reliability were examined with intra-class correlation coefficients (ICC). The agreement between the two methods was assessed by Bland-Altman method.

Results: The mean BASMI score of AS patients was 43 (± 22.7). The mean scores for BSA DA1, ASAS and BASFI were 3.7 (± 19.9), 2.9 (± 0.96) and the 3.5 (± 2.4), respectively. We observed an excellent intra and inter-rater reliability in the whole study sample for both methods (Table 1 and Table 2). Bland-Altman analysis also showed a good agreement between the two methods (iPhone-goniometer) with a mean difference (bias) of -1.7 for examiner 1 (95% CI -5.9 to -2.7) and -4.6 for examiner 2 (95% CI -8.9 to -0.4). Upper and lower limits of agreement were 16.6 (95% CI 9 to 24.2) and -19.9 (95% CI -27.4 to -12.3), for examiner 1 and 13.1 (95% CI -29.6 to -15) for examiner 2.

Conclusion: Using iPhone compass application is a simple and accessible way of measuring cervical rotation in patients with AS. Measurements obtained with iPhone show excellent intra and inter-rater reliability and a very good agreement with measurements obtained with goniometer.

Table 1 Mean cervical rotation measurements (degrees) with iPhone and goniometer and Intra-rater reliability for both methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Examiner 1 (Mean ± SD)*</th>
<th>Examiner 2 (Mean ± SD)*</th>
<th>ICC</th>
<th>95% CI for ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goniometer</td>
<td>46.8 ± 16.4</td>
<td>46.3 ± 16.5</td>
<td>0.90</td>
<td>0.87–0.93</td>
</tr>
<tr>
<td>iPhone</td>
<td>48.3 ± 22.1</td>
<td>48.1 ± 22.3</td>
<td>0.96</td>
<td>0.90–0.98</td>
</tr>
</tbody>
</table>

*Mean of the two measurements by the same examiner

Disclosure: G. Kenar, None; B. Zengin, None; H. Yarkan, None; P. Cetin, None; I. Sari, None; F. Onen, None; M. Birlik, None; N. Akkok, None.

2596

Similarities and Differences Between Axial and Peripheral Predominant Forms in Patients with Early Spondyloarthrits (SpA): Results From the Esperanza Cohort.


Background/Purpose: Based on the predominant manifestation of the disease, the ASAS classification criteria for spondyloarthrits (SpA) distinguish two clinical forms:
- Axial SpA, including non-radiographic SpA and Ankylosing Spondylitis (AS).
- Peripheral SpA.

Although both forms are considered as part of the same disease, published data are limited, especially in early disease. The purpose of this study is to describe and compare the characteristics of patients fulfilling the ASAS criteria for axial SpA versus peripheral SpA in patients with recent symptoms onset.

Methods: -Population- Baseline dataset from the early SpA Esperanza cohort was used, with the following referral criteria: Age < 45 years, symptoms duration 3-24 months and with inflammatory back pain (IBP) or asymptomatic arthritis or spinal/joint pain plus >= 1 SpA features.

-Inclusion criteria- Patients fulfilling the ASAS classification criteria for SpA.

-Outcome- To compare socio-demographic and disease characteristics between patients with axial SpA and patients with peripheral SpA.

-Statistical analyses- Variables were compared using Student t test (continuous) or Chi-square test (categorical).

Results: Data from 377 patients were analysed. Two hundred ninety (77.2%) patients were classified as axial SpA (109 AS and 182 non-radiographic SpA) and 86 (22.8%) patients as peripheral SpA. Table 1 shows the results (mean ± SD or relative frequency) for the comparison of demographic and disease characteristics between groups. Age, sex and disease activity scores were similar in both groups. However, axial SpA was more related to a delay in referral time, uveitis and positive HLA-B27 while peripheral SpA was associated with enthesitis, psoriasis, dactylitis and inflammatory bowel disease (IBD).

Conclusion: Early SpA patients with predominant axial symptoms have a higher delay in the referral to rheumatologist than patients with peripheral symptoms. However, the degree of disease activity is similar in both groups. Uveitis and HLA-B27 are more frequent in patients with predominant axial symptoms while psoriasis, enthesitis, dactylitis and IBD are more frequent in patients with peripheral involvement.

Table 1 shows mean ± SD and p value

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Axial SpA N (%)</th>
<th>Peripheral SpA N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.0 ± 7.0</td>
<td>32.8 ± 7.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Male</td>
<td>191 (65.1)</td>
<td>50 (58.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Symptom duration (months)</td>
<td>13.0 ± 6.7</td>
<td>9.3 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>57 (19.6)</td>
<td>43 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>33 (11.3)</td>
<td>28 (32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>16 (5.5)</td>
<td>28 (32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IBD</td>
<td>9 (3.2)</td>
<td>10 (11.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Uveitis</td>
<td>23 (7.9)</td>
<td>1 (1.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diarrhea, cervicitis, urethritis</td>
<td>11 (3.78)</td>
<td>5 (5.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Family history</td>
<td>101 (34.7)</td>
<td>31 (36)</td>
<td>0.8</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>219 (75.3)</td>
<td>26 (32.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Disease Characteristics Associated with the Presence of Dactylitis in Patients with EARLY Spondyloarthritis: Results from Esperanza Cohort. Maria Isabel Tévar Sánchez,9; Victoria Navarro-Compañ,9 Raquel Almodóvar González,6; María Pilar Fernández Dapica,6 Pedro Zarco6 and Eugenio De Miguel6;6Hospital Vega Baja, Orihuela, Alicante, Spain,7University Hospital La Paz, Madrid, Spain,8Hospital Universitario Fundación Alcorcón, M adrid, Spain,9University Hospital 12 de Octubre, Madrid, Spain,9Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain,9Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain.

**Background/Purpose:** Dactylitis is a typical manifestation in patients with SpA. Despite dactylitis has traditionally been related to the coexistence of psoriasis and peripheral arthropathies, it was included as SpA feature for both (axial and peripheral) ASAS classification criteria. However, data supporting this is scarce, especially in patients with recent onset. The objective of this study was to determine the prevalence of dactylitis and which disease characteristics are associated with its presence in patients with early SpA.

**Methods:** Baseline dataset from the EsPeranza cohort (<45 years, symptoms duration 3-24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was analysed. For this study, 609 patients diagnosed of SpA by their physician were included. Logistic regression analysis was used to investigate the association between disease characteristics and the presence of dactylitis. These characteristics included family history of SpA, clinical manifestations (chronic back pain –CBP-, inflammatory back pain -IBP-, peripheral arthritis, enthesitis, uveitis, psoriasis, nail lesions, inflammatory bowel disease -IBD- and urethritis or cervicitis), activity parameters (SJC, physician’s VAS, CRP), imaging (sacroiliitis on x-Ray or MRI) and psoriasis (Table).

**Disclosures:** Patients with SpA in early stage may have dactylitis or manifest it later in the course of the disease, thus the prevalence and associated disease characteristics could be different.

**Results:** Fifty eight (10.5%) patients had current or previous dactylitis. The presence of dactylitis was associated with peripheral arthritis, enthesitis, psoriasis, nail lesions, SJC, physician’s VAS and CRP in the univariable analysis. Moreover, CBP, IBP and sacroiliitis were associated with absence of dactylitis. No significant differences were found for the rest of variables. In the multivariable analysis the presence of dactylitis was associated with peripheral arthritis, enthesitis, psoriasis and physician’s VAS (Table). However, 14 (24%) patients did not have peripheral arthritis but did have axial symptoms/signs.

Further, patients with dactylitis were classified as patients with dactylitis and psoriasis (n=19; 32.8%) and patients with dactylitis and no psoriasis (n=39; 67.2%). Disease characteristics were compared between both groups. Male were more frequent in the psoriasis group (84% vs 51%; p<0.05). The group without psoriasis had higher frequency of CBP, IBP, enthesitis, HLA-27 and sacroiliitis but these differences did not reach statistical significance.

**Conclusion:** Dactylitis is a frequent manifestation in patients with SpA even at early stages of the disease. Its presence is mainly associated with peripheral manifestations and psoriasis. However, the majority of patients with dactylitis do not have psoriasis and 24% of them have axial manifestations in absence of peripheral arthropathies.

**Table:** Association between SpA characteristics and the presence of dactylitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Chronic back pain</td>
<td>0.44</td>
<td>0.12 to 1.07</td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>0.44</td>
<td>0.18 to 1.06</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>4.83</td>
<td>2.00 to 11.7</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>2.49</td>
<td>1.24 to 5.03</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3.62</td>
<td>1.63 to 8.04</td>
</tr>
<tr>
<td>Nail lesions</td>
<td>0.61</td>
<td>0.12 to 3.18</td>
</tr>
<tr>
<td>Diarrhea, cervicitis, urethritis</td>
<td>2.17</td>
<td>0.54 to 8.77</td>
</tr>
<tr>
<td>CRP</td>
<td>0.99</td>
<td>0.97 to 1.01</td>
</tr>
<tr>
<td>ESR</td>
<td>1.01</td>
<td>0.99 to 1.03</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>1.26</td>
<td>0.52 to 3.07</td>
</tr>
<tr>
<td>Physician’s VAS</td>
<td>0.82</td>
<td>0.70 to 0.96</td>
</tr>
</tbody>
</table>

Disclosure: M. I. Tévar Sánchez,9; V. Navarro-Compañ,9; A. Almodóvar González,6; M. P. Fernández Dapica,6; P. Zarco6; E. De Miguel6.

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Impact of Repeating Imaging of the Sacro-Iliac Joints over One Year on the Classification According the ASAS Axial Spa Criteria of Patients. Pauline Bakker1, Monique Reijnierse1, T.W.J. Huizinga1 and Desirée van der Heijde2.

Background/Purpose: It is known that in axial spondyloarthritis (axSpA) inflammatory lesions on MRI of the SI joints (MRI-SI) can change over time. The usefulness of repeating imaging in the diagnostic process is unclear. The aim is to investigate how patients with short-term chronic back pain are classified by the ASAS axSpA- criteria at baseline and after 1 year follow-up, with a focus on the role of imaging.

**Methods:** Patients in the SPACE cohort (back pain ≤ 3 months, ≤ 2 years, onset < 45 years) with (suspicion of) axSpA underwent MRI and X-rays of the sacroiliac joints at baseline and 1 year follow-up. Only patients with complete MRI and X-SI data at both baseline and year 1 were included in the analysis (n=80). MRI-SI and X-SI were scored independently by 3 well-calibrated readers according to the ASAS definition for a positive MRI and the mNY-criteria. Readers were blinded for patient characteristics and time sequence.

The results of the multivariate analysis are presented in the Table. The usefulness of repeating imaging in the diagnostic process is unclear. The data show the robustness of the axSpA criteria and does not support repeating imaging after one year.

**Table:** Association between SpA characteristics and the presence of dactylitis

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Disclosure: P. del Río-Martínez, None; V. Navarro-Compañ, None; C. Castillo-Gallego, None; M. C. Castro, None; E. Collantes-Estevez, None; E. de Miguel, None.
Do Patients Diagnosed As Axial Spondyloarthritis (AxSpA) Who Have Primary Inefficacy to Anti-TNF Really Have AxSpA? a Five-Year Follow-up Study of 27 Patients with Primary Inefficacy to Anti-TNF.

Sandra Koss1, Sabrina Dadoun2, Bruno Fautrel3, M'Axime Dougdas4 and Laure Gosses4. 1Hospital La Plêtie Salpêtrière, Paris, France, 2UPMC GRC08, Paris 06 University, Pité Salpêtrière Hospital, Paris, France, 3INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France, Paris, France, 4Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d’Épidémiologie et de Santé Publique, Paris, France.

Background/Purpose: The diagnosis of AxSpA is not easy and there are cases of overlap with fibromyalgia for example. Anti-TNF have been shown to have great efficacy in AxSpA, and primary inefficacy is rare. Do patients who have primary inefficacy to anti-TNF, really have a diagnosis of AxSpA?

Objective: To assess the evolution and final diagnosis of all patients with primary inefficacy to anti-TNF in AxSpA over a period of two years in one tertiary referral center, with a follow up of five years.

Methods: Systematic retrospective study of all patients receiving an anti-TNF for AxSpA in one tertiary referral centre (ref). Patients had a follow-up according to the rheumatologist and were started on a first course of anti-TNF according to usual practice. Primary inefficacy was defined by the rheumatologist’s opinion after three months of treatment by anti-TNF, when the treatment was then discontinued. Five years later, these patients were recontacted and were seen in outpatient clinic if possible, filled in questionnaires including FIRST for fibromyalgia, and a final diagnosis was defined.

Results: Of 123 patients treated with anti-TNF for AxSpA, 27 (12.2%) were considered as having primary inefficacy to their first anti-TNF. The characteristics of these patients were slightly different from the others, with more females (48 vs 27%, p = 0.04), older age (46 vs 40 yrs; p = 0.04), higher BASFI (68 vs 42, p = 0.001) and less increased CRP (50% vs 78%, p = 0.008). Among the 27 patients, a second anti-TNF was prescribed for 16 (59.2%) patients, 7 (7/16 = 43.7%) had primary inefficacy to the second anti-TNF and retention rate of the second anti-TNF at one year was 50%.

At the 5 year follow-up, 14 patients were seen in outpatient clinic and 9 follow-up medical files were available; 4 patients could not be evaluated (2 were lost to follow-up and 2 refused).

The diagnosis of AxSpA was confirmed for 20/23 (86.9%) patients according to the ASAS criteria and 23/23 (100%) patients according to the rheumatologist; but 16/23 (69.6%) had at least one other cause of pain/symptoms: 10 (43.5%) had osteoarthritis, 7 (30.4%) patients had depression and 3 (13.0%) had fibromyalgia.

Conclusion: Primary inefficacy to anti-TNF in AxSpA is rare, and patients with primary inefficacy have slightly different characteristics from the other AxSpA patients. Long-term follow-up indicates most of these patients have a definite diagnosis of AxSpA but often have other causes of pain/symptoms. We suggest patients with primary inefficacy to anti-TNF should be screened for comorbidities like fibromyalgia, osteoarthritis or depression that may interfere with AxSpA impact and assessment.

Reference


Disclosure: S. Kossi, None; S. Dadoun, None; B. Fautrel, None; M. Dougdas, None; L. Gosses, None.

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Gender-Attributable Differences in Outcome of Ankylosing Spondylitis: Long-Term Results from the Outcome in Ankylosing Spondylitis International Study.

Casper Webers1, Ivette Essers1, Sofia Ramiro2, Carmen Stolwijk3, Robert Landewe4, Désirée van der Heijde4, Filip van Den Bosch5, Maxime Dougdas6 and Astrid van Tubergen7. 1Maastricht University Medical Center, Maastricht, Netherlands, 2Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, 3Maastricht University, Maastricht, Netherlands, 4Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 5Leiden University Medical Center, Leiden, Netherlands, 6Department of Rheumatology and Clinical Immunology, Ghent University Hospital, Ghent, Belgium, 7Paris-Descartes University, Paris, France.

Background/Purpose: In ankylosing spondylitis (AS), gender-attributable differences have been reported with respect to clinical and radiographic outcome. However, longitudinal studies exploring gender-attributable differences in the outcome of AS are scarce, and have limited follow-up. The aim of the present study was to investigate gender-attributable differences with respect to clinical outcomes (disease activity, function and quality of life (QoL)) and radiographic damage in patients with AS over time.

Methods: Clinical and radiological data from patients included in the Outcome in AS International Study (OASIS) were used. Disease activity was assessed by the Bath AS Disease Activity Index (BASDAI), the AS Disease Activity Score (ASDAS), and C-reactive protein (CRP); physical function by the Bath AS Functional Index (BASFI); QoL by the Short-Form 36 (SF-36), ASQoL and EuroQoL; radiographic damage by the modified Stoke AS Spine Score (mSASSS). First, cross-sectional comparative analyses were done at baseline. Second, separate models were created to assess gender-attributable differences on each outcome measure over time using time-adjusted generalized estimation equations (GEE). All analyses were performed in the total population and in those patients who completed the total 12 years of follow-up.

Results: 216 patients (154 (72.3%) men, mean age 43.6 years (SD 12.7), symptom duration 20.5 years (SD 11.8), mean follow up duration 8.3 years (SD 4.1)) were included. At baseline, male compared with female patients had lower self-reported disease activity (BASDAI 3.2 vs. 3.9, p = 0.03) but more radiographic damage (mSASSS 13.8 vs. 6.5, p = 0.02). No significant differences in other clinical parameters between gender were found at baseline. In univariable analysis, a significant association between male gender and better QoL (lower ASQoL and higher EuroQoL), and between male gender and more radiographic damage (higher mSASSS) over time was found.

Also in a multivariable analysis, male gender was compared with female gender, significantly associated with a better ASQoL (B = -1.10, 95%CI -2.11 to -0.09), and a separate multivariable analysis also with higher mSASSS over time (B = 2.48, 95%CI 1.55 to 2.62, p < 0.01). Similar results were found for the 12-year completers.

Conclusion: In this longstanding observational cohort study in patients with AS, no gender-attributable differences in disease activity and function over time were found. However, male gender, compared with female gender, was found to be associated with more radiographic damage, but also better QoL. It is likely that gender differences in AS are determined by both biological and psychological factors, and that male and female patients differ in the way they cope with pain and disability.

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Serum Biomarkers Associated With Changes in ASDAS and MRI Following Treatment of Ankylosing Spondylitis with Golimumab.

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Background/Purpose: Serum biomarkers that can predict subsequent clinical or imaging outcomes would aid decision-making in the management of ankylosing spondylitis (AS). Using data from the golimumab (GLM) study, GO-RAISE, in patients with active AS, we analysed correlations between multiple serum biomarkers and inflammation as detected by magnetic resonance imaging (MRI) and AS Disease Activity Score (ASDAS).

Methods: In GO-RAISE, patients with moderately to severely active AS were randomized to SC GLM 50mg, 100mg, or PBO q4wks. PBO-treated patients crossed over to receive GLM at wk16 or 24. Signal MRIIs in the sagittal plane were acquired using 1.5T scanners with T1 and short tau inversion recovery (STIR) sequences at BL and wk14. 98 patients were scored for activity (ASPMRI-Ra) and structural (ASPMRI-Rc) scores, radiographs and MRIIs were accessed by 2 readers who were blinded to treatment and image time order. Mean scores were used for analyses. Sera were collected from 140 patients at baseline and wk14 for analysis of markers by ELISA and/or using a multiplex platform (Rules Based Medicine). Spearman correlation analyses with Bonferroni p-value adjustment and logistic regression were conducted to assess the relationship between 76 serum biomarker levels and, ASDAS using C-reactive protein (ASDAS), ASPMRI-Ra, or MRI-Rc score at various time points.

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Results: Baseline ASDAS showed significant correlations with serum biomarkers for inflammation (IL-6, ICAM-1, haptoglobin, amyloid P) and lipid metabolism (Complement C3). BL IL-6 or TIMP-1 correlated with the reduction of A SppM II at wk14 in GLM-treated patients (Table). Wk4 change in IL-6 and C3 also showed correlation with change in A SppM II a at wk14. Development of new fatty degeneration in the spine at wk14 correlated with BL biomarkers involved in lipid metabolism (leptin, C3) and tissue remodeling (TIMP-1). Previously described predictors such as insulin, MMP-3, VEGF, or bone resorption markers did not have significant correlations with clinical or imaging outcomes.

Conclusion: This analysis suggests that serum biomarkers IL-6, TIMP-1 and C3 may be linked to a reduction in spinal inflammation in AS patients following GLM treatment. In addition, ICAM-1, haptoglobin and amyloid P correlate with baseline disease activity and may implicate novel roles for these factors in AS-related inflammation.

Disclosures: R. D. Inman, Abbvie, Amgen, Jansen, Pfizer, UCB, 5; X. Baraliakos, Janssen R and D, LLC, 2; K. G. A. Hermann, Janssen R and D, LLC, 2; J. Braun, None; A. A. Deodhar, Abbott, Amgen, Jansen, Novartis and Pfizer UCB Pharma, 2, Abbott, Amgen, Jansen, Novartis, Pfizer and UCB Pharma, 5; D. van der Heijde, None; S. Xu, Jansen R and D, LLC, 2; B. Ha, Jansen Research & Development, LLC, 3.

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Short-Term Non-Steroidal Anti-Inflammatory Drug (NSAID) Use Induces Subclinical-Kidney-Injury in Spondyloarthritides Patients: Urinary Biomarker Study. A. Shukla, M. Kumar Rai, N. Prasad and V. Agarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: NSAIDs are the first-line therapy for spondyloarthritis (SpA) patients and are associated with the risk of kidney injury. Long-term NSAID use is known to cause poor urine concentrating abilities. Short-term NSAID induced subclinical-kidney-injury is not well studied. Herein, we studied the effect of short-term NSAID use on kidney injury by measuring serum and urine biomarkers.

Methods: In cross-sectional study, 40 healthy controls with minimal-NSAID-exposure (cohort-A) and 40 SpA patients on regular-NSAIDs for >3 months (cohort-B) were included. In another cohort, 17 SpA-patients with minimal baseline NSAID-exposure (cohort-C) were treated with regular-NSAIDs for 6 weeks. Urine and serum samples were collected at 0, 1 and 6 weeks. In addition, 6 healthy volunteers (cohort-D) were treated with 7 days of daily NSAID. Daily urine and weekly blood samples were collected for 14 days; including 7 days after the drug was stopped. Biomarkers like NGAL, KIM1, cystatin-C and micro-albumin (ELISA) were measured. Creatinine (i.e. this method) was measured in all samples.

Minimal-NSAID-exposure was defined as nil in last week, <15 tablets in last month, <2 tablets/week in last year or <1000 tablets lifetime exposure. Normal-renal-function was ensured in all subjects as eGFR >90 ml/min, <1 dipstick proteinuria and inactive urine sediments.

Results: Mean age of cohort-A and B was 27 (IQR 26-35) and 30 (IQR 24-36) years respectively with male to female ratio of 3:1. Duration of NSAID use in cohort-B was 7 (IQR 5-12.5) months. There was no significant difference in serum creatinine and eGFR in both cohorts while biomarker levels were raised in cohort-B compared to cohort-A (mann-Whitney test, table).

Mean age of cohort-C was 35 (IQR 28-40) years and male to female ratio of 9:8. Urine biomarker levels showed a significant rise on treatment with NSAIDs at 1 week, (Wilcoxon test) cystatin C p = 0.01, NGAL p = 0.02, KIM1 p = 0.08 and micro-albumin p = 0.01. There was a further significant rise in urine and serum levels at 6 weeks (Friedman test, table). Cohort-D showed a rise in urine and serum levels of biomarkers at 7 days followed by a fall to baseline in urine levels at 10th day while serum levels showed partial fall at 14th day.

Conclusion: Short-term NSAID use may induce subclinical-kidney-injury represented by rise of urine and serum biomarkers, even in absence of changes in serum creatinine or eGFR. These levels start rising as early as 7 days of NSAID use.

Table

Changes in urine and serum levels of Kidney-Injury Biomarkers

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Cohort-A</th>
<th>Cohort-B</th>
<th>p value</th>
<th>Cohort-C</th>
<th>Cohort-D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Creatinine mg/dl</td>
<td>0.18 (0.17-0.18)</td>
<td>0.35 (0.30-0.35)</td>
<td>0.54</td>
<td>0.15 (0.13-0.16)</td>
<td>0.85 (0.69-0.86)</td>
<td>0.74</td>
</tr>
<tr>
<td>U H-CRP ng/ml</td>
<td>117 (106-127)</td>
<td>180 (100-139)</td>
<td>0.37</td>
<td>187 (103-212)</td>
<td>123 (103-154)</td>
<td>0.38</td>
</tr>
<tr>
<td>U KIM1 pg/ml</td>
<td>105 (105-106)</td>
<td>0.21 (0.23-0.23)</td>
<td>0.001</td>
<td>0.24 (0.24-0.25)</td>
<td>0.21 (0.19-0.24)</td>
<td>0.02</td>
</tr>
<tr>
<td>U NGAL ng/ml</td>
<td>187 (132-187)</td>
<td>132 (105-132)</td>
<td>0.001</td>
<td>221 (106-248)</td>
<td>397 (321-449)</td>
<td>0.001</td>
</tr>
<tr>
<td>S Creatinine mg/dl</td>
<td>0.15 (0.13-0.16)</td>
<td>0.38 (0.32-0.42)</td>
<td>0.07</td>
<td>0.17 (0.16-0.18)</td>
<td>0.07 (0.06-0.08)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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Ankylosing Spondylitis and Non- Radiographic Axial Spondyloarthritides: The Same Syndrome or Different Diseases? Analysis from Esporanza Cohort. A. Zucena Hernandez-Sanz, V. Victoria Navarro-Compan, C. Cristina Fernandez-Carballedo, C. Carlos Montilla-Morales, J. Munuelo and Eugenio De Miguel. "H. Virgen de la Salud, Toledo, Spain, "University Hospital La
Profile Ankylosing Spondylitis Patients Likely to Respond to NSAID Treatment.
Mohamed Bedaiwi,1,2 Arane Thavaneswaran,2 Nilgir Haroon,1,2 Anmeepta Anton3 and Robert D. Inman4. 1Clinical and research fellow, Toronto, ON, 2University of Toronto, Toronto Western Hospital, Toronto, ON, 3Toronto Western Research Institute, Toronto, ON, 4University Health Network, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with unpredictable course of progression. Treatment of AS thus should be tailored according to disease manifestation. There is group of patient with ankylosing spondylitis controlled with non-steroidal anti-inflammatory drugs alone, while the other subset may show high disease activity despite conventional treatments with NSAIDs and may require further therapeutic agents. The aim of study is to compare AS patients well controlled with NSAIDs alone with the other group requiring biologic therapy because of NSAID-norresponsiveness.

Methods: This retrospective study involved data collection from the last clinic visit for 417 patients with a diagnosis of AS based on the modified New York criteria for AS. NSAID-treated patients (n = 124) were defined as having a BASDAI ≤ 4 at the last clinic visit while being treated with only NSAIDs. Biological-treated patient (n = 177) had failed to respond to a trial of ≥ NSAIDs. The comparison of NSAID treated (NS-TR) and biologic treated (B-TR) was done in relation to multiple social, clinical and laboratory variables.

Results: NS-TR patients were found to have a lower incidence of smoking (P < 0.0009), lower CRP (p < 0.01), lower incidence of kidney stones (P = 0.02), increase in hyperlipidemia (P = 0.02) and better spinal mobility (P < 0.0001). There were no significant differences in the following variables: gender, age of onset, eye disease, hypertension, diabetes, cardiac disease, uveitis, psoriasis, inflammatory bowel disease.

Conclusion: This study showed that the NSAID-responsive AS patients tend to be non-smokers, with lower baseline CRP, and less impairment in spinal mobility at baseline. Conversely, age, gender, and B27 status which have previously been implicated as markers of severity, did not correlate with NSAID-responsiveness. This analysis begins to provide a profile of AS patients who at baseline are likely to require biologic therapy for their disease.

Table 1. Comparison of NSAID and biological treated patient with AS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (sd) or Frequency (%)</th>
<th>NS-TR N = 124</th>
<th>B-TR N = 187</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M ales)</td>
<td>96 (77.4%)</td>
<td>137 (73.3%)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.1 (14.9)</td>
<td>37.6 (12.0)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Age at start of back pain</td>
<td>22.8 (10.7)</td>
<td>23.0 (8.4)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of AS</td>
<td>27.7 (12.2)</td>
<td>29.7 (10.6)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Duration of AS</td>
<td>13.3 (12.5)</td>
<td>14.6 (11.1)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Current smoking status</td>
<td></td>
<td></td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>86 (70.5%)</td>
<td>104 (55.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>19 (15.6%)</td>
<td>57 (30.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>17 (13.9%)</td>
<td>26 (13.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>14.9 (18.3)</td>
<td>19.1 (17.7)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>11.0 (14.6)</td>
<td>17.6 (27.5)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>5 (5.6%)</td>
<td>20 (13.7%)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4 (3.5%)</td>
<td>1 (0.6%)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Iritis</td>
<td>28 (22.6%)</td>
<td>47 (25.1%)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>3 (2.6%)</td>
<td>7 (3.9%)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (11.3%)</td>
<td>19 (10.2%)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>1 (0.8%)</td>
<td>2 (1.3%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>M1 ever</td>
<td>0 (0%)</td>
<td>3 (1.6%)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>13 (17.1%)</td>
<td>25 (23.2%)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Urethritis</td>
<td>2 (2.1%)</td>
<td>1 (0.7%)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Kidney stones ever</td>
<td>1 (1.1%)</td>
<td>13 (8.4%)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>CV/A</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>6 (6.3%)</td>
<td>13 (8.3%)</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

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How to Classify Spondyloarthritis after a Two Year Follow up? Results from the French Recent onset spondyloarthritides Cohort. Pierre Gazeau1, Divi Connex, Marie Agnes Timis1, Valerie Devauchelle1, Sandrine Jousse1, Thierry Mahrour4, Emmanuel Nowak5, Maixme Dougados6, and Alain Saraux6.

Background/Purpose: In early arthritis, after a two years follow up, rheumatologist diagnosis of rheumatoid arthritis agrees well with 2010 ACR/EULAR criteria (Saraux A et al. Arthritis care and Research 2013;65:1227-34). Today, we do not have straightforward rules to diagnose spondyloarthritides (SpA) after a two year follow up, and we do not know the gap between rheumatologist diagnosis and SpA defined using all potential methods to classify patients having inflammatory low back pain (IBP).

Methods: We used the nationwide, longitudinal, prospective cohort (DESIR) of patients with IBP suggestive of SpA at baseline. After 2 years, patients were classified based on: imaging (MRI, X-rays), the certainty with which the rheumatologist diagnosed SpA (evaluated on 0-100 visual analogue scales), treatment used (non-steroidal anti-inflammatory drugs [NSAID] and/or TNF-alpha blockers) and classification criteria (any among axial spondyloarthritis, ESSG, ASAS) and validated classification criteria (AMOR, ESSG, and ASAS) as gold standards. Then, we evaluated agreement between all potential methods to classify patients having IBP based on Cohen’s kappa coefficient in the whole group and in the group having a MRI.

Results: On the 708 patients initially included, 548 had information on rheumatologist’s certainty after 2 years. Using ROC curves, we found that a certainty of diagnosis ≥75% gave the best balance of sensitivity and specificity. This certainty of diagnosis increased with the follow up (357 of 548 (65.1%) patients had a certainty ≥75% after a two year follow up versus 265 (48.2%) patients at inclusion). Certainty of diagnosis ≥75% after a two year follow up was statistically associated with all classification criteria (AMOR p = 0.005; ESSG p = 0.003; ASAS p < 0.0001) and the ASAS criteria had the best agreement, although it was low (kappa 0.09, 0.11 and 0.25 for AMOR, ESSG and ASAS, respectively). None of the various other potential classifications items had a better agreement.

Conclusion: Rheumatologist diagnosis of SpA certainty after 2 years does not agree well with the various previously published criteria for SpA.

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Fatigue in Ankylosing Spondylitis: A Multivariable Analysis Implicates Inflammation As the Key Determinant of Disability. Mohanned Bedawi1, Arane Thavaneswaran2, Nigil Haroon2, Aimeo Anton3 and Robert D. Inman4.

Background/Purpose: Fatigue is one of the cardinal features of ankylosing spondylitis (AS). The clinical and laboratory correlates of fatigue in AS however are not well defined. In the current study we undertake a systematic analysis of fatigue in a longitudinal observation cohort of AS patients.

Methods: A systematic review of 950 AS patients (671 male and 279 female) followed in a longitudinal clinic which contains regular clinic visits using a standardized protocol. Fatigue was recorded using the Fatigue Severity Scales (FSS). T tests were used to compare continuous variables and Chi-Squared tests for categorical variables. Multiple analysis was conducted using logistic regression to assess associations between FSS and various clinical features. P-value < 0.05 was used to define statistical significance.

Results: In the univariate analysis there were a number of clinical variables showing association with FSS. This was followed by logistic regression analysis. Figure 1 outlines selected covariates based on a p-value <0.05 in univariate models and included in the full model. Speical select are used to determine the variables most associated with FSS. In the reduced model the clinical domains with the strongest correlation with FSS were morning stiffness, Bath AS Functional Index (BASFI), and Short Form (SF-36) Health Survey (SF36-MCS). For patients with morning stiffness, there is an expected 2.13 increase in the FSS. For every unit increase in the BASFI, there is a 0.37 increase expected in the FSS. For every unit increase in the SF36-MCS, there is a 0.11 decrease in FSS.

Conclusion: Fatigue continues a frequent and sometimes disabling aspect of AS. The strong correlation with stiffness suggests that these two variables may reflect a common underlying process. Since morning stiffness is considered a surrogate indicator of inflammation, fatigue may fall into this conceptual framework as well. The level of disability as measured by BASFI shows stronger correlation with fatigue than with SF36-MCS suggesting this fatigue may impose greater functional restrictions on patients than structural progression of the disease does. The reversed SF36-MCS correlation with FSS indicates more vitality, bodily pain, emotional, social and mental health functionality impairment in fatigued AS patient.

Disclosure: M. Bedawi, None; A. Thavaneswaran, None; N. Haroon, None; A. Anton, None; R. D. Inman, None.

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Background/Purpose: Spondyloarthritides (SpA) are a group of chronic inflammatory rheumatic diseases. Extra-articular manifestations affect approximately 30% of patients with SpA, and gastrointestinal manifestations...
(GI) represents about 5 to 10%. The relationship between gut and joint inflammation suggests that there is an increase in intestinal permeability and abnormal levels of intestinal bacteria that stimulate pathologic immune responses. The persistence of joint disease activity is primarily associated with intestinal inflammation. Therefore, the aim of this study is to investigate the association between gastrointestinal symptoms, disease activity of SpA and the presence of auto-antibodies including patients with inflammatory bowel disease (IBD).

**Methods:** A cross-sectional study was designed, including 103 patients with SpA fulfilling ESSG classification criteria and 117 healthy subjects (HS). Twenty nine patients had a diagnosis and clinical activity compatible with IBD as confirmed by histologic examination.

Anti-Saccharomyces cerevisiae IgG/IgA (ASCAS), 6 antigen associated with anti polymorphonuclear neutrophil (ANCA), anti-transglutaminase (TG) IgG/IgA, anti-deamidated gliadin peptide (DGP) IgG/IgA auto-antibodies. ANAS and IgA were measured in all patients by ELISA technique. A specific questionnaire was applied asking for GI symptoms in the SpA and IBD group. Descriptive epidemiology was analyzed and association between clinical manifestations and auto-antibodies were evaluated using chi square test and Mann Whitney U-Test as appropriate.

**Results:** Mean age in SpA patients was 42.2 years (SD 15.5) with a predominance of uSpA subtype (59.8%). BASFI > 4 was reported in 60.6% and BASDAI > 4 in 67.7%. Respect to treatment, 49 % of patients were receiving anti-TNF therapy. HLA-B27 was positive in 39%.

ASCAS IgG/IgA were positive in 28.2% of SpA patients and 75.8% of them were IgG isotype. ANCA was present in 8.8% (six antigens evaluated), anti-airway auto-antibodies (1%) and ANAS (49.5%). In HS, 2.6% were ASCAS positive (50% of these were IgA subtype) and 6.8% were ANCAS positive. There was a significant difference in the frequency of autoantibodies IgG/IgA ASCAS, p-ANCAS and ANAS between SpA and HS (p = <0.001), and SpA and IBD (p = <0.001). Significant association was found between BASDAI > 4 and the presence of abdominal pain (p = 0.003), diarrhea (p = 0.017), abdominal inflammation (p = <0.001), discomfort (p = 0.004) and total IgA levels (p = 0.005); as well as between abdominal inflammation and BASFI > 4 (p = 0.028).

A significantly different frequency was found in the presence of abdominal pain between SpA (54.4%) and IBD (27.5%) patients (p = 0.012). Both groups (SpA and IBD) had similar frequency of mucus (30% vs 31%).

**Conclusion:** The presence of ASCAS IgG/IgA, p-ANCAS, ANAS, IgA and the reporting of GI symptoms, are associated with higher disease activity in SpA. There are differences in the presence of GI manifestations according to SpA subtypes, but not differences between IBD and SpA regarding the presence of mucus. It may suggest that subclinical IBD should be actively screened in Colombian SpA patients probably due to environmental conditions. In our cohort of axSpA treated with biological agents, only one third achieved ID according to ASDAS-CRP. Even with the limitations of the small sample size, ID does not correlate with the principle patient- and disease-related features but is inversely associated with NSAIDs intake. Further studies are needed to optimize the targeted treatment of axSpA and to identify potential predictive factors of ID.

**References:**
Background/Purpose: The interleukin-20 (IL-20) is a pro-inflammatory cytokine of the IL-10 family and sequence amino acid is very similar. It has been reported to be involved in the pathogenesis of several autoimmune diseases, but pathophysiologic importance is poorly understood. TNF alpha plays an important role in AS patients with axial and peripheral joint involvement. It has been reported that TNF alpha induce IL-20 in macrophage and synovial cells. For this reason, we investigated serum IL-20 levels in patients with AxSpA.

Methods: A total of 326 patients with AxSpA (195 M; 39.8 ± 10.6) from four centers, who contribute to TURKBIO, a biological database in Turkey, were included in this study. Of these patients 208 had AS according to the modified New York criteria and 118 patients had nr-axSpA. (20% fulfilling ASAS criteria).

Results: Baseline demographics and clinical characteristics are summarized in the table 1. Patients with nr-axSpA were significantly younger, had a shorter disease duration and had a higher female predominance than patients with AS. After three months of treatment with TNF inhibitors, mean BASDAI and ASDAS decreased significantly (Table 1). The response rates for minimal clinical improvement (JASDAS ≥1.1) and major clinical improvement (JASDAS ≥2) were similar in patients with nr-axSpA (66% vs 72%) and those with AS (43.8% vs 39.1%). Similarly good response rates were observed for BASDAI 50 in the two groups (56.8 % and 58.5%, respectively).

Conclusion: The results of our study suggest that TNFα, which have been clearly shown to be effective in treating signs and symptoms of AS, seem to be equally effective in the treatment of nr-AxSpA.

Table 1. Demographics and clinical characteristics of the AxSpA and AS patients.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.8 (±9.6)</td>
<td>41.5 (±10.7)</td>
</tr>
<tr>
<td>37.2 (±6.4)</td>
<td>12.56 (±8.4)</td>
</tr>
<tr>
<td>3.6 (±3.3)</td>
<td>71.5 (±6.4)</td>
</tr>
<tr>
<td>53.4</td>
<td>32.7</td>
</tr>
<tr>
<td>20.1 (±3.2)</td>
<td>24.9 (±3.2)</td>
</tr>
<tr>
<td>20 (±3)</td>
<td>20.213</td>
</tr>
<tr>
<td>1.4 (±1.2)</td>
<td>85</td>
</tr>
<tr>
<td>3.2 (±0.8)</td>
<td>5.06 (±2.58)</td>
</tr>
<tr>
<td>5.3 (±1.8)</td>
<td>3.93 (±1.8)</td>
</tr>
<tr>
<td>3.1 (±0.98)</td>
<td>3.65 (±1.08)</td>
</tr>
<tr>
<td>3.4 (±2.37)</td>
<td>3.1 (±2.24)</td>
</tr>
<tr>
<td>1.7 (±1.2)</td>
<td>1.75 (±1.1)</td>
</tr>
</tbody>
</table>

*In the patients with available data.
weeks of standardized treatment with NSAIDs, there were 44% of all axSpA pts with a BASDAI \( \geq 4 \) (AS 42% and nr-axSpA 46%), while 33% of all axSpA pts (AS 32% and nr-axSpA 34%) had an ASDAS \( > 2.1 \). Overall, the two scores were in agreement in 81%. In 15% of pts, the BASDAI score would have possibly led to treatment with TNF blockers - despite an ASDAS \( < 2.1 \) and, on the other hand, in 4% of cases the ASDAS would have initiated anti-TNF treatment but not the BASDAI. In the univariate logistic regression analysis both, ASDAS (OR: 3.6, \( p = 0.001 \)) and BASDAI (OR: 1.8, \( p = 0.002 \)) predicted the eligibility for anti-TNF therapy after 4wk of NSAID therapy at BL.

Conclusion: These data challenge the concept of only using the BASDAI cut-off \( \geq 4 \) for the treatment decisions of initiation of TNF-blocker therapy. The question on whether BASDAI or ASDAS should be used as the appropriate cut-off for such treatment needs to also include the comparison of the subject's perception on disease activity with CRP and MRI data and by assessing the predictive value of the response to NSAIDS for the response to TNF blockers in future studies.

Disclosure: X. Baraliakos, None; U. Kiltz, None; F. Heldmann, None; H. Appel, None; F. Dybowski, None; M. Igelmann, None; L. Kaltheim, None; D. Krause, None; H. J. Menn, None; F. Saracibai, None; E. Schmitz-Bortz, None; J. Braun, None.

2613

Positive Spine MRI for Inflammation Predicts Radiographic Progression in Patients with Ankylosing Spondylitis. WP Maksymowych1, S. Wichuk1, Z. Zhao2, P. Chownhamisawat1, RG Lambert1 and SJ Pedersen4. 1University of Alberta, Edmonton, AB, 2PLA General Hospital, Beijing, China, 3Mahidol University, Bangkok, Thailand, 4Copenhagen Center for Arthritis Research, Copenhagen, Denmark.

Background/Purpose: Inflammation at vertebral corners on MRI has been shown to predict development of syndesmophytes in patients with AS. However, it is unclear at a patient level whether a positive spine MRI for inflammation identifies patients at higher risk for radiographic progression and whether this is also associated with the degree of spinal inflammation. We used the SPARCC MRI spine score to assess whether the proposed cut-off of \( \geq 2 \) for positive spine MRI and the absolute score are predictive of radiographic progression.

Methods: Spinal inflammation was scored blinded to time point (baseline, 2 years) using the SPA RCC spine score by two readers and an adjudicator using pre-specified rules for adjudication. MRI scans were assessed from a prospective cohort of 195 AS patients (mean age 40.3 years, mean symptom duration 16.6 years, 59% on anti-TNF) followed for mean 2.3 years. Two readers and an adjudicator independently scored pairs of radiographs (baseline, 2 years) from the same patients using the mSASSS. Radiographic progression was compared in patients with and without positive spine MRI (SPARCC \( \geq 2 \) or \( < 2 \)) and the degree of spinal inflammation at baseline (absolute SPARCC score) was compared in patients with and without radiographic progression (mSASSS \( > 0 \) or \( = 0 \)) using Mann-Whitney and cumulative probability. Multivariate regression analyses included variables significant in univariate analyses (age, sex, symptom duration, CRP, baseline mSASSS) and treatment.

Results: Radiographic progression was significantly greater in those with positive spine MRI \( (p = 0.004) \) (figure), and especially in patients who only received non-biologic therapy \( (p = 0.006) \). Baseline SPARCC spine inflammation scores were significantly higher in those who developed radiographic progression compared to those without \( (14.5 vs 8.7, p = 0.002) \). Positive spine MRI and the degree of spinal inflammation score were both significantly associated with radiographic progression in multivariate analysis \( (\beta = 0.26, p = 0.019 \) and \( \beta = 0.066, p = 0.036 \), respectively).

Conclusion: Both a positive spine MRI for inflammation and the degree of spinal inflammation are significantly associated with radiographic progression in patients with AS.

Disclosure: W. Maksymowych, None; S. Wichuk, None; Z. Zhao, None; P. Chownhamisawat, None; R. Lambert, None; S. Pedersen, None.

2614

Reliability of Electronic Patient Self-Assessment of Swollen and Tender Joints in Psoriatic Arthritis: A Comparison Study with B-Mode Ultrasonography, Physician and Nurse Assessments. Agnes Szentpetyey1, Muhammad Haroon1, Eileen O’Flynn2, Phil Gallagher3, Shafeeq A’Iraq3 and Oliver FitzGerald1. 1St. Vincent’s University Hospital, Dublin, Ireland, 2Cork University Hospital, Cork, Ireland.

Background/Purpose: 68 tender (TJC) and 66 swollen joint counts (SJC) are recommended for disease activity assessment in psoriatic arthritis (PsA). However, there are time constraints and these counts may not be performed. It has been shown in rheumatoid arthritis that patient’s self-reported joint counts correlate well with functional disability, pain and global disease severity. Information concerning patients’ self-assessed joint counts however is limited in PsA.

The aim of this study was to evaluate the reliability of patient self-assessed joint counts versus joint counts obtained by a physician, a nurse and B-mode ultrasonography (US) in PsA.

Methods: PsA patients fulfilling the CASPAR criteria were recruited. Following a training session on the detection of tender and swollen joints by a nurse, each patient assessed their 68 joints using an electronic digital mannequin on touchscreen. A joint examination by a different nurse and a rheumatologist, both blinded to the patients’ clinical data was completed. US evaluation was performed by a further consultant rheumatologist on 34 joints assessing wrists, MCPs and PIPs, ankles and MTPs, and all extensor/flexor tendons of the fingers and toes. Presence of joint effusion, synovial proliferation and tenosynovitis on grayscale (GS); and synovitis/tenosynovitis on power Doppler (PD) was scored.

Results: 50 patients (33 female and 17 male) were enrolled to the study with a mean age of 50 (±13.7) years. Patients mean GVAS was 47 (±24) mm. Focusing on the 34 joints also assessed by US, mean TJC assessed by the patient, physician and nurse was 9 (±8), 7 (±7) and 7 (±7), mean SJC was 4 (±6), 1 (±2) and 3 (±3) respectively. Mean number of affected (swollen or tender) joints as per patient, physician, nurse and US evaluation was 10 (±8), 7 (±7), 8 (±7) and 6 (±4.5), respectively.

Patient and nurse-assessed SJC was significantly higher than physician-counts \( (p = 0.0005; p = 0.01, respectively) \). Similarly, patient and nurse-assessed SJC was significantly higher compared to physician-counts when using 28, 44 or 68 joint counts.

Patients scored their number of affected joints significantly higher than physicians irrespective of using 26, 34, 44 or 68 joint counts. The number of affected joints was higher as evaluated by patients compared to US \( (p = 0.01) \) and lower compared to physicians \( (p = 0.04) \). Joint effusion was detected in 74% synovitis in 78% on GS and 68% on PD and 30% of the patients had tenosynovitis.

TJC did not correlate significantly with any of the US measurements irrespective of the assessors. Patients SJC significantly correlated with US-assessed joint effusion, and with synovitis (GS and PD). Physician and nurse-reported SJC correlated with US-derived synovitis scores. The number of affected joints as assessed by patients and physician correlated with the US measurements \( (r = 0.28, p = 0.008; r = 0.29, p = 0.04, respectively) \).

Conclusion: Patients scored their SJC and number of affected joints higher than physicians and US measurements. Patient-reported SJC correlated with both effusion and synovitis as detected by US suggesting that patients’ self-evaluated SJC may be valid in routine clinical practice for monitoring disease activity in PsA.

Disclosure: A. Szentpetyey, None; M. Haroon, None; E. O’Flynn, None; P. Gallagher, None; S. A’Iraq, None; O. FitzGerald, Pfizer, Abbott, BM S, MSD, Roche, UCB, 2, Pfizer, Abbott, BM S, MSD, Jansen, Roche, 5.

2615

Preliminary Assessment of a Multi-Biomarker Disease Activity Test for Axial Spondyloarthritis. WP Maksymowych1, Stephanie Wichuk1, P. Scott Eastman2 and Eric H. Sasso3. 1University of Alberta, Edmonton, AB, 2Crescendo Bioscience, Inc., South San Francisco, CA, 3Crescendo Bioscience Inc., South San Francisco, CA.
Background/Purpose: There has been limited validation of soluble biomarker measures of disease activity in patients with axial spondyloarthritides (SpA). C-reactive protein (CRP) is most commonly used in clinical practice but sensitivity in ankylosing spondylitis (AS) is only 40–50%. The Ankylosing Spondylitis Disease Activity score (ASDAS) has been proposed as a treat-to-target outcome measure for effective suppression of disease activity in patients with SpA. BASDAI has also been used but does not incorporate objective measures of disease activity. We have performed an exploratory study of the association between a multi-biomarker disease activity (MBDA) score, which measures 12 serum biomarkers and has been validated in RA and clinically-based measures of disease activity in patients with axial SpA.

Methods: Disease activity measures based on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ASDAS, and BASDAI were analyzed for 40 patients with axial SpA who met modified New York criteria from a systematic, prospective follow-up cohort. The MBDA score was measured in serum and is based on the following 12 biomarkers: vascular cell adhesion molecule 1, epidermal growth factor, vascular endothelial growth factor A, interleukin 6, TNF receptor I, matrix metalloproteinases 1 and 3, bone glycophosphoryl 39 (YKL-40), leptin, resistin, serum amyloid A and CRP. These biomarkers were measured by electrochemiluminescence-based multiplexed immunoassays on the Meso Scale Discovery Multi-Array platform.

Results: Patients were of mean (SD) age, 43 (11) years; number (%) males, 26 (65); mean (SD) disease duration, 19 (10) years; number (%) B27+, 30 (75). Significant differences were observed in MBDA scores between patients with ASDAS-CRP >3.5 versus those with ASDAS ≤1.3 (57 vs. 25, p = 0.002) and patients with BASDAI >4 versus BASDAI ≤4 (51 vs. 37, p = 0.01). Several of the MBDA biomarkers, including CRP, correlated strongly with the clinical composite measure. For ASDAS-CRP, serum concentrations of CRP, SAA, IL-6, TNF-R1, and YKL-40 correlated at r > 0.5 (range 0.51–0.71).

Conclusion: The MBDA score was associated with available measures of clinical activity that were measured in patients with axial SpA and correlated most strongly with the ASDAS.

Disclosure: W. Maksymowych, None; S. Wichuk, None; P. S. Eastman, Crescendo Bioscience, 3; E. H. Sasso, Crescendo Bioscience, Inc., 3.

2616


2617

Background/Purpose: Chronic inflammatory arthritis is associated with increased cardiovascular disease (CVD) risk. The mechanisms behind this link include chronic inflammation, comorbidities and disease-related drugs. CV risk management according to local guidelines with aggressive suppression of inflammation for patients with RA, AS and PsA has been recommended. However, in contrast to RA where the bulk of supporting evidence exists, fewer studies have addressed CVD risk in AS. Moreover, the beneficial impact of anti-TNF agents, which are increasingly used in AS, has been extensively reported biasing somehow the link between AS per se and CVD risk. We aimed to compare subclinical atherosclerosis burden between AS patients to healthy controls and patients with RA.

Methods: We examined 81 consecutive non-diabetic AS patients free of clinical CVD (age 46.8±13.3, 85% men, disease duration 10 years (2–24), BASDAI 1.4 (0.4–3.2), BASFI 2.0 (0.95–2.85)). Current smokers were 62% of patients, 16% had dyslipidemia and 31% had hypertension, whereas 62% were receiving anti-TNF treatment. A subgroup of 68 AS patients could be exactly matched 1:1 with healthy controls for age, gender, smoking, dyslipidemia and hypertension. We also matched 14 AS patients with more than 10 years of disease duration 1:1 to non-diabetic RA patients, for age, gender and disease duration. Finally, we identified 24 of the 31 anti-TNF treatment-naïve patients whom we were able to match 1:1 for age and gender, smoking dyslipidemia and hypertension with 24 healthy controls. We evaluated subclinical atherosclerosis in aortic and femoral arterial beds (presence of plaques), arterial hypertrophy (intimal-medial thickness adjacent to plaques when present; cross sectional area), and arterial carotid/aortic stiffness (by ultrasound and pulse wave velocity).

Results: Fewer patients with AS than controls had plaques (n=24 vs n=32, respectively, p=0.163). This observation was extended to the subgroup of 35 AS patients with more than 10 years of disease duration (n=14 vs n=22, respectively, p=0.056). Even when taking into consideration anti-TNF-naïve patients, there were no differences compared to controls. Neither BASDAI nor BASFI scores were found to be associated with the presence of plaques. Finally, and despite the small number of matched patients, presence and multiple localization of plaques were more prevalent in RA than in AS patients with more than 10 years disease duration (p=0.053 and 0.045, respectively). Notably, all indices of arterial hypertrophy and arterial carotid/aortic stiffness were comparable between AS patients and their matched controls.

Conclusion: In this group of relatively young Greek patients, AS (even long-standing disease) - in contrast to RA - does not associate with accelerated atheromatosis compared with very closely matched healthy controls. The differential CVD risk between AS and RA requires further investigation as it may have significant clinical implications in terms of prevention strategies.

Disclosure: A. I. Arida, None; M. Konsta, None; A. Filipopoulos, None; M. Tektonis-dou, None; G. K Konstantonis, None; G. K. Dimitrakopoulou, None; A. D. Protogerou, None; P. P. Sikaklis, None.

2618

Impact of Ustekinumab on Active Inflammation and Post-Inflammatory Structural Changes As Detected By Magnetic Resonance Imaging in Patients with Active Ankylosing Spondylitis: Results of a 28-Week, Prospective, Open-Label, Proof-of-Concept Study. Denis Poddubnyy1, Kay-Geert Hermann2, Johanna Calhöff1, Joachim Listing2 and Joachim Sieper1

1Charité Universitätsmedizin Berlin, Berlin, Germany, 2German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: Ustekinumab - a fully human monoclonal antibody against interleukins 12 and 23 - has been shown to be effective in reduction of symptoms of active ankylosing spondylitis (AS) in a proof-of-concept study (TOPAS) [1]. The purpose of the current work was to investigate the impact of ustekinumab on active inflammation and post-inflammatory structural changes in the sacroiliac joints (SIJ) and in the spine as detected by magnetic resonance imaging (MRI) in the TOPAS study.

Methods: In the TOPAS study, ustekinumab in a dose of 90 mg was administered subcutaneously at baseline, week 4 and week 16 in 20 patients with active AS (BASDAI score of ≥ 4 at screening) despite treatment with non-steroidal anti-inflammatory drugs. MRI of the SIJ and of the spine was performed at baseline and at week 24. Images were scored according to the Berlin scoring system for active inflammation and for chronic changes, including a detailed fatty degeneration score for SIJ, independently by two trained readers in a concealed and randomly selected order, blinded for all clinical data.

Results: Complete MRI sets (baseline and follow-up) were available in 17 patients (13 ASAS40 responders and 4 non-responders; in 3 ASAS40 non-responders no follow-up MRI sets were available). There was a significant reduction of active inflammation on MRI at week 24 as compared to baseline both in the SIJ (osteitis change score -2.2±3.8 corresponding to 41% reduction) and in the spine (osteitis change score -1.2±2.3 corresponding to 31% reduction) - table. Reduction of active inflammation after 24 weeks was more prominent and statistically significant in patients with clinical response (ASAS40): osteitis change score in the SIJ was -3.1±3.8 in responders as compared to -0.6±1.3 in non-responders, p=0.015; similarly, osteitis change score in the spine was -1.9±1.9 in responders as compared to +1.0±2.4 in non-responders, p=0.023. Notably, clinical response (ASAS40) to ustekinumab was associated with higher level of inflammation at baseline in the SIJ (osteitis score 6.7±4.9 in responders vs. 2.0±1.7 in non-responders, p=0.030), and in the spine (4.9±3.6 in responders vs. 3.6±4.1 in non-responders, p=0.2).

There were no substantial changes in the scores for post-inflammatory lesions including fatty lesions in the entire group - table. However, the SIJ fatty lesion score increased significantly in patients with improvement of SIJ ostesitis score by at least one point at week 24 (n=11): +0.8±1.1 vs. +0.4±0.8 in patients without osteitis improvements, p=0.022.

Conclusion: Ustekinumab effectively reduced active inflammation in the axial skeleton as detected by MRI in patients with AS after 24 weeks of treatment with a clear correlation between clinical and MRI responses. Higher level of active inflammation at baseline was associated with good clinical response.

Reference:

2619

Low Socioeconomic Status (SES) As Measured By Education Is (not) Associated with Worse Outcome in SLE: Data from the 1000 Canadian Faces of Lupus. Angela George, Christine Peschken, Earl Silverman, Christian A. Pineau, C. Douglas Smith, Hector Arjilla, Michel Zummer, Ann Clarke, Sashka Benabky, Marie Hudson, Carol A. Hitchon, Paul R. Fortin and Janet E. Pope.

1University of Western Ontario, London, ON, 2University of Minnesota, Winnipeg, MB, 3Toronto Hospital for Sick Children, U of Toronto, Toronto, ON, 4McGill University Health Center, Montreal, QC, 5TOH Riverside Campus, Ottawa, ON, 6Lethbridge Rheumatology practice, Lethbridge, AB, 7U of Montreal, Montreal, QC, 8University of Manitoba, Winnipeg, MB, 9McGill University Health Center, Calgary, AB, 10McGill UHC/RVH, Montreal, QC, 11Dalhousie University, Division of Rheumatology, Centre de Recherche du CHU de Quebec and Department of Medicine, Quebec City, QC, 12St Joseph Health Care, London, ON.

Background/Purpose: To determine whether socioeconomic status, as measured by education, impacts disease activity (measured by SLAM-2, ACR/ARHP Poster Session C Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Epidemiology, Women’s Health, Cardiovascular and Central Nervous System. Tuesday, November 18, 2014, 8:30 AM - 4:00PM

ACR/ARHP Poster Session C Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Epidemiology, Women’s Health, Cardiovascular and Central Nervous System. Tuesday, November 18, 2014, 8:30 AM - 4:00PM

2619

Low Socioeconomic Status (SES) As Measured By Education Is (not) Associated with Worse Outcome in SLE: Data from the 1000 Canadian Faces of Lupus. Angela George1, Christine Peschken2, Earl Silverman3, Christian A. Pineau4, C. Douglas Smith5, Hector Arjilla6, Michel Zummer7, Ann Clarke8, Sashka Benabky9, Marie Hudson10, Carol A. Hitchon11, Paul R. Fortin12 and Janet E. Pope13.

1University of Western Ontario, London, ON, 2University of Minnesota, Winnipeg, MB, 3Toronto Hospital for Sick Children, U of Toronto, Toronto, ON, 4McGill University Health Center, Montreal, QC, 5TOH Riverside Campus, Ottawa, ON, 6Lethbridge Rheumatology practice, Lethbridge, AB, 7U of Montreal, Montreal, QC, 8University of Manitoba, Winnipeg, MB, 9McGill University Health Center, Calgary, AB, 10McGill UHC/RVH, Montreal, QC, 11Dalhousie University, Division of Rheumatology, Centre de Recherche du CHU de Quebec and Department of Medicine, Quebec City, QC, 12St Joseph Health Care, London, ON.

Background/Purpose: To determine whether socioeconomic status, as measured by education, impacts disease activity (measured by SLAM-2, ACR/ARHP Poster Session C Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Epidemiology, Women’s Health, Cardiovascular and Central Nervous System. Tuesday, November 18, 2014, 8:30 AM - 4:00PM

ACR/ARHP Poster Session C Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Epidemiology, Women’s Health, Cardiovascular and Central Nervous System. Tuesday, November 18, 2014, 8:30 AM - 4:00PM
SLEDAI-2K or disease damage (measured by SLICC SDI) in patients with systemic lupus erythematosus (SLE).

**Methods:** Data from the 1000 Canadian Faces of Lupus, a multi-center, prospective cohort database included adult SLE patients from June 2005 onward. Socioeconomic status, as measured by education was defined as being either low (did not complete high school) or high (completed high school or further). The relationships between education and SLE outcomes were evaluated using one-way ANOVA and logistic regression analyses.

**Results:** 489 patients met inclusion criteria (mean age 47 years, 91.5% female, mean disease duration of 10 years); 80.4% had completed high school education or higher and 19.6% had not. One-way ANOVA analyses demonstrated: SLEDAI-2K (p < 0.01), SLAM-2 (p < 0.3) and SLICC (p = 1.0). Proportionately more Aboriginal people were in the low education group (6.4% in high education vs. 17.9% in low education) and work disability was twice as common in low education group (13.6% vs. 28.4%). Income was higher in high education stratum. Logistic regression did not demonstrate significance between education and SLEDAI-2K when adjusting for age, sex, ethnicity, and disease duration. See table for results.

<table>
<thead>
<tr>
<th>Ethnicity†</th>
<th>Mean (SD), years</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
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<tbody>
<tr>
<td>Caucasian</td>
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<tr>
<td>Asian</td>
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</tr>
<tr>
<td>Aboriginal</td>
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<tr>
<td>Work Disabled</td>
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<tr>
<td>Disease Duration</td>
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<td>Income Level††</td>
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<td>19 (20)</td>
</tr>
<tr>
<td>&lt;$15,000</td>
<td>47 (12.1)</td>
<td>68</td>
<td>16 (8.4)</td>
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<tr>
<td>$30,000-$59,999</td>
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<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>$60,000+</td>
<td></td>
<td>0.01</td>
<td>0.01</td>
</tr>
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</table>

**Conclusion:** This was mostly a prevalent, cohort so low income and work disability could be a result of SLE disease activity and damage. This cohort was literate and had access to lupus specialists so data may not be generalizable. Socioeconomic status, as measured by education, did not impact damage or disease activity in this cohort.

**Disclosure:** S. Heredia, None; J. Narvaez, None; A. Zacarias, None; M. Ricse, None; G. Albert, None; E. Armen-Gol, None; H. Borrell, None; O. Capdevila, None; F. Mitjavila, None; T. Rozadilla, None; X. Juanola, None; J. M. Nolla, None.

## 2621

**Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus.** Jin-She Lai1, Karen Kaiser2, Jennifer Beaumont3, Sally Jensen4, Amy H Kao5, David Van Brunt6 and Shih-Yin Chen7. 1Northwestern University, Chicago, IL, 2Biogen Idec, Cambridge, MA, 3Formerly of Biogen Idec, Cambridge, MA.

**Background/Purpose:** Systemic lupus erythematosus (SLE) is a multi-organ chronic autoimmune disease that can negatively affect patients’ health-related quality of life (HRQOL). This cross-sectional study collected HRQOL data from a sample of SLE patients using questionnaires from the Patient-Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Disorders (Neuro-QoL) to assess its association with patient-reported SLE disease severity.

**Methods:** Individuals with SLE were recruited via patient advocacy organizations to complete an online survey consisting of the PROMIS-29 health profile, PROMIS Psychosocial Illness Impact-Negative, and Neuro-QoL Applied Cognition. Patients self-rated their SLE disease severity to be negligible, mild, moderate, or severe. PROMIS and Neuro-QoL scores have mean = 50, standard deviation (SD) = 10 in the US general population. Analysis of variance was used to compare HRQOL scores between SLE disease severity groups.

**Results:** Of the 333 survey participants (mean age: 45 years; 92% female; 26% Black; mean disease duration = 12 years), 55.6% reported their SLE disease severity as moderate or severe. Mean HRQOL scores were worse than those of the general population by half a SD or more with the greatest deficits observed in Fatigue, Applied Cognition, Psychosocial Illness Impact-Negative, Pain Interference, and Physical Function [Figure 1] [Figure 2]. Greater patient-reported SLE disease severity was associated with worse mean HRQOL scores (all p < 0.05). Reliability exceeded 0.70 for all PROMIS and Neuro-QoL scores.

**Conclusion:** Relative to the general population, patients with SLE reported substantial deficits in HRQOL that correlated with their severity disease, especially in fatigue, pain, cognition, physical function and psychosocial ill health impact. These deficits should be monitored in clinical practice in care for SLE patients and considered when investigating new therapies.
Background/Purpose: To describe the demographic, clinical and immunological manifestations in male patients with Systemic Lupus Erythematosus (SLE).

Methods: Patients diagnosed of SLE that were in the RELESSER database (National Registry of Patients with Systemic Lupus Erythematosus of the Spanish Society of Rheumatology) were included. This is a multicenter retrospective cross-sectional study. We analyzed 3658 patients with SLE. All met the ACR criteria. Socio-demographic variables, comorbidities, classification, clinical and immunological manifestations were evaluated. Pearson’s chi-square test, t-Student, ANOVA and multivariate logistic regression analysis were performed.

Results: A total of 3658 patients were included: 353 men (9.7%) and 3296 women (90.2%), with an average onset of symptoms of 37 ± 17 and 32 ± 14 years of age respectively. In 70.1% the gender was known. The male/female ratio was 9:1. The age of onset of symptoms and age at diagnosis was higher in men than in women (P < 0.0001). Diagnosis in males was sooner than in females (P = 0.04). The most common age range at diagnosis in both genders was 21-49 years (P < 0.0001).

### Table 1 Clinical manifestations

<table>
<thead>
<tr>
<th></th>
<th>Missing N</th>
<th>Male (N=353)</th>
<th>Female (N=3298)</th>
<th>Value of P</th>
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<tbody>
<tr>
<td><strong>Systemic MANIFESTATIONS</strong></td>
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</tr>
<tr>
<td>Weight loss</td>
<td>68</td>
<td>48 (13.7%)</td>
<td>309 (9.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lymphopenody</td>
<td>74</td>
<td>49 (14%)</td>
<td>320 (9.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>108</td>
<td>19 (5.5%)</td>
<td>99 (11.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Extremity</td>
<td>62</td>
<td>19 (5.4%)</td>
<td>215 (6.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CUTANEOUS MANIFESTATIONS</strong></td>
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<tr>
<td>Alopecia</td>
<td>86</td>
<td>54 (15.8%)</td>
<td>229 (7.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>OSTEOARTICULAR MANIFESTATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive arthritis</td>
<td>60</td>
<td>20 (5.8%)</td>
<td>342 (10.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>PULMONARY MANIFESTATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fibrosis</td>
<td>33</td>
<td>18 (5.1%)</td>
<td>86 (2.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Cardiovascular MANIFESTATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Libman Sachs endocarditis</td>
<td>103</td>
<td>7 (2%)</td>
<td>28 (0.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Angina or coronary bysses</td>
<td>54</td>
<td>19 (5.4%)</td>
<td>50 (1.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>61</td>
<td>24 (6.9%)</td>
<td>47 (1.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>79</td>
<td>20 (5.8%)</td>
<td>84 (2.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Puncarditis</td>
<td>52</td>
<td>15 (4.3%)</td>
<td>59 (1.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular manifestations</td>
<td>45</td>
<td>8 (2.3%)</td>
<td>23 (0.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>50</td>
<td>24 (6.9%)</td>
<td>129 (3.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>142</td>
<td>80 (23.7%)</td>
<td>1114 (35%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>89</td>
<td>156 (44.8%)</td>
<td>933 (29%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 50 irreversible</td>
<td>112</td>
<td>31 (9.1%)</td>
<td>161 (5.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria &gt; 3.5g/24h</td>
<td>126</td>
<td>21 (6.1%)</td>
<td>114 (3.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Terminal renal insufficiency</td>
<td>146</td>
<td>16 (4.7%)</td>
<td>82 (2.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neuro psychiatric manifestations</td>
<td>89</td>
<td>10 (2.9%)</td>
<td>204 (6.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lupus headache</td>
<td>76</td>
<td>32 (9.2%)</td>
<td>156 (4.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seizures</td>
<td>89</td>
<td>36 (10.3%)</td>
<td>574 (17.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>99</td>
<td>37 (10.5%)</td>
<td>149 (4.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ac anti DNA positive</td>
<td>99</td>
<td>27 (7.7%)</td>
<td>234 (7.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ac anti RO positive</td>
<td>96</td>
<td>94 (27.5%)</td>
<td>1300 (40.8%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Women had more frequently a history of autoimmune thyroid disease (P < 0.0001). Males have more cardiovascular comorbidities (P < 0.0001). Comparing comorbidities in men with SLE by age range, it was found that SLE patients over 50 years of age had more comorbidity with p = 0.05. A total of 68% (236) of males with SLE required hospitalization in comparison with 53% (1713) female (P < 0.001). During follow-up 208 patients died, 30% (3.3%) were male and 178 (5.9%) women (p = 0.02). On multivariate analysis, the only statistically significant variable was age. It was seen that patients over 50 year-old had a higher mortality than those under 50 year-old, regardless of gender, delay in diagnosis, risk factors and clinical features OR: 5.32 (CI: 3.61 to 7.84) P < 0.001.

Conclusion: Patients with SLE older than 50 years old are at increased risk of mortality. In male patients with SLE: the age at diagnosis and the onset of symptoms is higher that in women. The diagnostic delay is lower in men than in women. Men have more cardiovascular comorbidities, especially those over 50 years old and also more serositis, renal and cardiovascular involvement than women.

Disclosure: A. Riveros-Frutos: None; I. Casas: None; I. Rúa-Figueroa: None; J. M. Pego-Reigosa: None; M. J. García de Yebenes: None; A. Olive: None; J. Rosas: None; P. Vela: None; M. Ibanez Barcelo: None; V. Torrente: None; I. Castelli: None; J. Narváez: None; M. Moreno: None; R. Blanco Alonso: None; V. Martinez: None.
Impact of Provider Specialty on the Diagnosis and Management of Systemic Lupus Erythematosus in the American Indian/Alaska Native Population. John McDougall Jr., Charles G. Helmick, S. Sam Lim, Caroline Gordon and Elizabeth Ferucci. 1Dartmouth Hitchcock Medical Center, Lebanon, NH, 2Centers for Disease Control and Prevention, Atlanta, GA, 3Emory University School of Medicine, Division of Rheumatology, Atlanta, GA, 4Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, 5Alaska Native Medical Center, Anchorage, AK.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex disease that is traditionally diagnosed and managed by specialists, typically rheumatologists. Higher SLE prevalence in racial/ethnic minorities such as American Indian/Alaska Native (A/I AN) people, often residing in areas with less access to rheumatologists, may necessitate diagnosis and management of SLE by primary care providers (PCP) in some cases. The purpose of this analysis was to identify areas of potential difference between PCP and specialist diagnosis and management of SLE in a population-based lupus registry of A/I AN people.

Methods: All individuals with SLE meeting our inclusion criteria were selected from the 2009 American Indian Health Service lupus registry population. Inclusion in this analysis was limited to individuals with a final diagnosis of SLE made by a PCP or specialist (dermatologist, nephrologist or rheumatologist) and documented in the medical record. Based on medical record abstraction, SLE classification criteria were validated for each individual. Testing for biologic markers and medication use at any time during the course of the disease were also abstracted.

Results: Of the 320 patients identified with a documented physician diagnosis of SLE, 71 had been diagnosed by a PCP. SLE diagnosis by a specialist was associated with a higher median number of American College of Rheumatology (ACR) classification criteria (5 vs. 2), a higher percentage of patients meeting the definition of SLE by ACR criteria (79% vs. 22%), the Boston Weighted criteria (82% vs. 32%), and an abridged version of the Systemic Lupus International Collaborating Clinics (SLICC) criteria (83% vs. 35%) (p<0.001 for all comparisons). Additionally, specialist diagnosis was associated with an increased proportion with any testing for anti-double-stranded DNA antibody (93% vs 73%) and complement C3 and C4 (84% vs 52%) documented in the medical record (p<0.001 for all). Lastly, specialist diagnosis was associated with ever treatment with hydroxychloroquine (86% vs. 64%, p<0.001) as documented in the medical record at any time during their disease course.

Conclusion: Within the population studied, specialist diagnosis of SLE was associated with a higher number of SLE classification criteria met, a higher percentage of patients tested for biomarkers of disease, and a higher percentage of patients ever treated with hydroxychloroquine.
naire (WPAI) was performed. The association between clinical characteristics with work productivity was examined by standard statistical tests. **Results:** 171 patients were included, 91 % women, age was 40 (SD 12.13), 39 % white, 51 % mestizo and 10 % Afro Latin American. Hundred and thirty six patients (80 %) had more than 12 years of education and 59 (35.5 %) had no health insurance. SLE disease duration was: 10.3 years (SD 9.2), SLEDAI score was 2 (SD 3.2), SLICC-SDI score was 0 (range 0–7), fatigue visual analogue scale (VAS) was 4 (SD 3), pain VAS was 3.5 (SD 4.8), patients global VAS was 1.7 (SD 2) and physician global VAS was 2.8 (SD 2.8). Charlson comorbidity index was 1 (1–2.5).

LupusQuol in the different domains was: physical health 72.2 (SD 23.5), emotional health 64.6 (SD 23.4), burden to others 56.1 (SD 33.5), intimate relationships 67 (SD 32.6), body image 69.5 (SD 28.3). Eighty seven patients (51 %) were working, 84 (49 %) were not working (unemployed, retired, housewives and students). Seventy one patients (83 %) perform or sedentary jobs by Soler Pujol scale. Absentseeism and presenteeism were measured in employed SLE patients with WPAI questionnaire. Fifty four (62 %) patients did not miss hours of work in the past week, 21 (24 %) of patients miss == 8 hours of work last week. M ean of missed hours of work last week due to SLE was 2.8 (SD 7.8), the average hours worked last week was 29 (SD 20.6).

Presenteeism: 41 % of patients (n = 36) presented some degree of work impairment. The degree of work impairment performance on 0–10 likert scale was 2.4 (SD 2.8).

Employed patients with SLEDAI > 6 did not experienced significantly reduced work productivity than employed patients with SLEDAI < 6 (p = 0.099), patients with SLICC-SDI > 1 did not experienced significantly reduced work productivity than employed patients with SLICC-SDI < 1 (p = 0.96). Work productivity was reduced among employed SLE patients with more severe pain (p < 0.001), fatigue (p < 0.001) and worse scores in LupusQuol physical (p < 0.0001) and emotional domains (p < 0.0001).

In the multiple regression analysis considering work impairment as dependent variable (adjusting by age, disease duration, VAS pain, VAS fatigue, LupusQuol physical and emotional domains), we found the physical domain of LupusQuol (OR 0.84 CI 0.71–0.98) as unique associated variable.

**Conclusion:** SLE patients with worse physical domain of LupusQuol showed higher work productivity compromise. Reduction of work productivity was not associated with more active SLE neither with more damage.

**Disclosure:** None; S. Munoz; None; P. Alba; None; C. A. Helling; None; S. Roverano; None; J. Sarano; None; S. Malim- Green; None; A. Secco; None; M. Daniels; None; D. Medina Bornachera; None; A. Alvarez; None; A. Eimon; None; D. Perera; None; C. N. Plisoli; None.

### 2626

**Relationship of Socio-Demographic and Disease Factors with Loss-to-Follow-up and Appointment Noncompliance in Indigent Patients with Systemic Lupus Erythematosus**

**Background/Purpose:** The relationship of medical noncompliance with socio-demographic characteristics, clinical features and autoantibody profile in indigent patients with systemic lupus erythematosus (SLE) is being evaluated. The association of noncompliance with socio-demographic and disease factors has been poorly studied and inconsistently identified. In past studies, noncompliance in SLE has been defined as rate of loss to follow-up (LTF) of scheduled outpatient appointments. Reported LTC rates have ranged from 24% to 48%. We investigate the relationship of socio-demographic and disease factors with noncompliance and focus on self-reported damage, health status, and depression in a predominantly indigent Black cohort.

**Methods:** We selected a sample of indigent SLE patients from the Grady Lupus Clinic who are surveyed annually on disease status, and depression in a predominantly indigent Black cohort. The association of noncompliance with socio-demographic and disease factors. Our data show that lower compliance is seen in patients with depression, shorter disease duration, higher income, and higher self-reported disease activity. With these factors in mind, targeted intervention for improved outcomes can be tailored for those within this vulnerable population.

**Table 1** Risk factors of lost to follow-up in indigent SLE patients. Multivariable analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 score &gt;= 10</td>
<td>5.26</td>
<td>0.036</td>
</tr>
<tr>
<td>Age at diagnosis (5-year increase)</td>
<td>1.06</td>
<td>0.61</td>
</tr>
<tr>
<td>Disease duration (1-year increase)</td>
<td>0.90</td>
<td>0.19</td>
</tr>
<tr>
<td>Education (3-year increase)</td>
<td>0.97</td>
<td>0.94</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Below 100% the poverty threshold</td>
<td>0.05</td>
<td>0.015</td>
</tr>
<tr>
<td>Married/diving with partner</td>
<td>0.96</td>
<td>0.95</td>
</tr>
<tr>
<td>No insurance or under-insured</td>
<td>2.50</td>
<td>0.18</td>
</tr>
<tr>
<td>Disease Activity Moderate (SLAQ &lt; 11–16)</td>
<td>1.52</td>
<td>0.89</td>
</tr>
<tr>
<td>Severe (SLAQ &gt;= 17)</td>
<td>1.88</td>
<td>0.53</td>
</tr>
<tr>
<td>Organ damage (SA-BILD &lt;= 1)</td>
<td>1.58</td>
<td>0.41</td>
</tr>
<tr>
<td>Poor or fair health</td>
<td>0.28</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Disclosure:** None; A. Pham; G. Bao; GlaxoSmithKline, 2; S. S. Lim; None; C. Drenkard, NIH, 2; Emory, 3; GlaxoSmithKline, 2.

### 2627

**Comparison of Disease Characteristics and Organ Damage in Patients with Juvenile and Adult-Onset Systemic Lupus Erythematosus in Large Cohorts of United States, Asia, Europe, and Turkey**

**Background/Purpose:** Systemic lupus erythematosus (SLE) is a multi-systemic disease that may cause a broad spectrum of clinical and immunological manifestations. Age at onset has been shown to effect the clinical course and outcome of the disease. Herein, we aimed to define the differences in clinical characteristics and organ damage between patients with juvenile-onset (jo-SLE) and adult-onset (ao-SLE) SLE followed up in two tertiary referral centres.

**Methods:** This analysis included 935 patients 846 of whom attended the lupus outpatient clinic at Istanbul Faculty of Medicine between 1975 and May 2012 and 89 of whom were followed in the paediatric rheumatology outpatient clinic at Cerrahpaşa Faculty of Medicine between 2004 and 2013. At the time of recruitment, all patients fulfilled the ACR classification criteria for SLE. The data presented was the cumulative clinical and serological manifestations throughout the follow-up period. jo-SLE was defined as diagnosis at the age of 18 or younger according to the Paediatric Rheumatology International Trials Organization (PRINTO). Seven hundred nineteen (76.9 %) patients with ao-SLE and 216 (23.1 %) patients with jo-SLE were examined. Demographic characteristics, clinical features, autoantibody pro-

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**Tuesday, November 18**
files and damage data (SLICC damage index) were compared between the groups. Statistical analyses were performed using SPSS, version 17.

**Results:** Comparison of demographics revealed significant differences in age at onset (13.5 ± 3.5 vs 34 ± 11.3 years) and duration of disease (86.5 ± 96.2 vs 111.6 ± 83.9 months) between juvenile and adult groups respectively (p < 0.05). Of clinical symptoms, photosensitivity (71.6 vs 56.5%), malar rash (73.6 vs 45.6%) and oral ulcers (23.1% vs 15.4%) were significantly more frequent in jo-SLE (p < 0.05). As was previously reported, renal involvement was significantly more prevalent in the jo-SLE affecting 53.2% of the patients compared to patients with ao-SLE (28.9%) (p < 0.05). A autoimmune haemolytic anaemia (AIHA) did also occur more often in the jo-SLE (33.3 vs 9.5%, p < 0.05) whereas reverse was true for pleuritis (11.6 vs 18.4%, p < 0.05). Of the autoantibodies, a higher frequency of anti-dsDNA (78.7 vs 69%), antiphospholipid IgG (31.9 vs 21%) and IgM (36.6 vs 19.3%) were observed in the jo-SLE group. According to the SLICC damage index, renal damage was significantly more frequent in the jo-SLE (22.8%) than the ao-SLE (8.4%) (p < 0.05). However, damage in musculoskeletal system, namely avascular necrosis was more prominent in the ao-SLE (14.1 vs 8.4%, p < 0.05).

**Conclusion:** Our study confirms that clinical and serological differences exist between jo-SLE and ao-SLE. jo-SLE was associated with a higher frequency of renal involvement and damage. We also report a higher frequency of cutaneous symptoms, oral ulcers, AIHA and anti-dsDNA positivity in the jo-SLE. As renal involvement is a major predictor of prognosis and outcome, this study highlights the importance of awareness of the age of onset of SLE and supports the necessity of vigilant follow-up of this subgroup.

**Disclosure:** B. Artim-Esen None; O. Kasapcopur None; S. Sahin None; K. Barut None; A. Omma None; Y. Sahinkaya None; S. Kamali None; L. Ocak None; M. Iancu None.

**2628**


**Background/Purpose:** Systemic immune dysregulation associated with chronic autoimmune diseases such as systemic lupus erythematosus (SLE) as well as immunomodulatory medications used for their treatment have been associated with an increased risk of malignancy. The pathogenesis of cutaneous lupus erythematosus (CLE) is similar to SLE. It is unclear whether CLE is associated with an increased risk of malignancy. Hence, we estimated the cumulative incidence of malignancy in a population-based cohort of patients with CLE, and compared the risk with an age- and sex-matched cohort without CLE.

**Methods:** Patients with subtypes of CLE (discoid, subacute cutaneous lupus, lupus panniculitis and bullous lupus) were identified from a population-based cohort without CLE. Patients with CLE, and compared the risk with an age- and sex-matched cohort without CLE.

**Results:** We identified 66 patients with CLE (mean age at time of CLE diagnosis, 54 ± 14y; 64% females; 68% Caucasian; mean BMI, 27.3 ± 7.2 kg/m²; 34.8% smokers), who were followed over a median follow-up of 12.0 years (interquartile range [IQR], 8.1–17.3y). Positive antinuclear antibody, anti-SSA and anti-SSB were seen in 48%, 47% and 18% of patients with CLE, respectively. Median ESR was 11 mm/hour (IQR, 4.0–25.0) and CRP 2.9 mg/dl (IQR 1.5–3.9). Overall, we observed 14 cases of incident cancer (including 5 cases of non-melanoma skin cancer). The cumulative 1-, 5- and 10-year incidence of any malignancy after diagnosis of CLE was 3.4%, 10.9% and 14.6%, respectively. As compared to age- and sex-matched non-CLE controls, the overall risk of malignancies was not increased in patients with CLE (hazard ratio [HR], 1.09; 95% CI, 0.51–2.37; p = 0.81) (Figure 1). The cumulative 1-, 5- and 10-year incidence of all malignancies except non-melanoma skin cancers in patients with CLE was 1.7%, 7.1% and 11.1%, respectively. As compared to matched controls, the risk of all malignancies except non-melanoma skin cancer in patients with CLE was not increased (HR, 0.88; 95% CI, 0.36–2.14; p = 0.78).

**Conclusion:** The 10-year risk of any malignancy in a population-based cohort of patients with CLE is 14.6%. This risk is not increased as compared to age- and sex-matched subjects without CLE.

**Disclosure:** A. G. Singh None; C. S. Crowson None; M. Davis None; H. Maradit Kremers None; E. L. Atteson None; V. Chowdhary None.
adult-onset SLE at presentation. This study differs from previous studies in the large proportion of Hispanic patients included and that the studied population was all adults at the time of inclusion. As these findings differ from previous, more studies are necessary within this population.

Disclosure R. Neal, None; K. DeQuattro, None; E. C. Ortiz, None; F. P. Quismorio Jr., None.

2630

An Evaluation of Quality of Life of Patients with Systemic Lupus Erythematosus Attending Rheumatology Clinic in Kenyatta National Hospital, Nairobi, Kenya. Jackie Odhiambo University of Nairobi, Nairobi, Kenya.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects all organs of the body. Due to its chronicity SLE has been known to affect the quality of life (QoL) of those affected by it. There is minimal data on SLE in East Africa and especially in Kenya. The quality of life of SLE patients in this country has never been assessed.

Methods: Patients diagnosed with SLE as by the ACR criteria and confirmed by a rheumatologist were recruited into the study. Informed consent (assent for minors), was obtained from all participants. The patient's demographic data and last prescription was acquired from the file. Patients' clinical history was taken and a physical exam was then done looking for the presence of malar rash, discoid rash, arthritis/arthralgia, serositis and photosensitivity. These were defined as per the ACR criteria. After this the patient was given the LUPUS QOL questionnaire to fill. All the patients who attended the clinic at the study period were included in the study. Demographic variables (age) were summarized into means/medians while gender, was presented using percentages. Correlation of HRQOL and age, duration of illness and medication used was done using regression analysis.

Results: Sixty two patients were recruited into the study, 96% were female. Mean age of the population was 37.3yrs (12.2), ranging from 14–17 years. All the patients had some form of education with 61% having some form of tertiary education. Mean age at diagnosis was 34.5 yrs (12.2).

Majority of the patients (88.7%) had arthritis or arthralgia. This was followed by oral ulcers at 32.3%, malar rash at 59.7, photosensitivity at 58.1%, serositis at 32.2%, CNS involvement at 27.4%. The least common clinical feature was discoid rash 17.7%.

On assessment of the HRQOL, The population scored globally poor in all the domains. The domain with the highest scores was planning (63.7), followed by burden to others, (58.9), fatigue (57.5), pain (56.6), physical health (54.0), body image (47.1) and the lowest intimate relationships (41.1).

On Immunosuppressives

<table>
<thead>
<tr>
<th>Drug</th>
<th>On Immunosuppressives at Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>46(74.2%)</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCQ)</td>
<td>43(69.4%)</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>34 patients (54.8)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>37.1%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>14 (22.6%)</td>
</tr>
<tr>
<td>Mycophenolate Mofetil (MMF)</td>
<td>5(8.1%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2(3.2%)</td>
</tr>
</tbody>
</table>

Quality of life scores of the population were correlated with age for each domain. Positive correlation was found between Physical health (r=0.36 p=0.016), burden to others (r=0.272 p=0.032) and emotional health (r=0.315, p=0.013) and advance in age.

There was found to be no significant association between HRQOL and the duration of illness or drugs used in all the domains.

Conclusion: This study demonstrates that patients with Lupus in Kenya have a poor quality of life. Lupus affects all aspects of their lives both physically and emotionally. In this study, older patients were found to have better quality of life when it came to physical health and emotional health. They were also found to be less affected by fatigue and thought of themselves as being less of a burden to others. The drugs used by the patients and the duration since diagnosis did not affect their quality of life.

Disclosure J. Odhiambo. None.

2631

Overall Cause and Cause-Specific Mortality in a Multinational Inception Cohort of SLE. Murray B. Urowitz1, Dafna D. Gladman2, Nicole Anderson2, Dominique Ibanez2 and Systemic Lupus International Collaborating Clinics (SLICC)3. 1University of Toronto, Toronto Western Hospital, Toronto, ON; 2Toronto Western Hospital Research Institute, Toronto, ON; 3University of Toronto, Toronto Western Hospital (Coordinating Center), Toronto, ON.

Background/Purpose: A large multicenter multinational inception cohort was established initially to study risk factors for atherosclerosis (AS) in SLE. The aim of this study was to determine all cause and cause-specific mortality and their risk factors during the first 10 years of observation.

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Deaths are recorded as they occur and the cause of death was coded according to ICD9. Overall and Cause-Specific Survival curves were obtained using a Cumulative Incidence Competing Risk Analysis. Prediction models for overall survival and cause-specific for the three major causes were done using time-dependent covariate analysis for competing risks using date of birth as time zero. Variables included were geography of origin, ethnicity, sex, disease duration, disease activity, damage and medication use. The selection of variable retained was done using the stepwise approach.

Results: 1677 patients had follow-up beyond enrolment. At the time of data cut 78 patients had died. Cause of death included: atherosclerosis 11, active SLE 17, infection 27 and all other causes 23 (cancer in 5, other in 8, and unknown in 10). At enrolment 89.0% were female with a mean age at diagnosis of 34 ± 13.4 yrs and a disease duration of 0.5 ± 0.4 yrs. Mean SLEDAI-2K was 5.4 ± 5.4, SDI 0.12 ± 0.50 (SDI > 0.131 (7.9%)). Patients on steroids 1167 (69.8%), on antimalarials 1124 (67.3%) and on immunosuppressives 671 (40.2%). 825 (49.2%) were Caucasian, 275 (16.4%) Black, 260 (15.5%) Hispanic, 255 (15.2%) Asian and 61 (3.6%) other. Geography of origin included USA 460 (27.4%), Canada 398 (23.7%), Europe 450 (26.8%), Mexico 160 (9.5%), and Asia 209 (12.5%). The Competing Risk analysis is presented in the Table.

<table>
<thead>
<tr>
<th>Cause-Of-Death</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL CAUSES</td>
<td>4.02</td>
<td>2.30, 7.02</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>0.90</td>
<td>0.82, 0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>SLEDAI-2K</td>
<td>1.47</td>
<td>1.29, 1.66</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>On Steroids at Visit</td>
<td>3.97</td>
<td>0.201, 7.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>On Antimalarials at Visit</td>
<td>0.56</td>
<td>0.35, 0.89</td>
<td>0.01</td>
</tr>
<tr>
<td>ATHEROSCLEROSIS</td>
<td>1.56</td>
<td>1.17, 2.06</td>
<td>&lt;.0002</td>
</tr>
<tr>
<td>SLEDAI-2K</td>
<td>4.02</td>
<td>1.17, 2.06</td>
<td>&lt;.0002</td>
</tr>
<tr>
<td>Disease Duration</td>
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<td>0.82, 0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>On Steroids at Visit</td>
<td>1.47</td>
<td>1.29, 1.66</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>On Antimalarials at Visit</td>
<td>3.97</td>
<td>0.201, 7.92</td>
<td>&lt;.0001</td>
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<tr>
<td>On Immunosuppressives at Visit</td>
<td>0.56</td>
<td>0.35, 0.89</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Damage was an important risk factor for all cause and cause-specific mortality. Demographic factors, disease activity and treatment contribute differently to mortality both all cause and cause specific. Anti-malarials are protective for all-cause mortality and mortality due to infection.

Conclusion: Risk factors differ for all cause mortality and mortality related to active lupus, atherosclerosis and infection and all must be considered in pursuing preventive strategies.

Disclosure: M. B. Urowitz, None; D. D. Gladman, None; N. Anderson, None; D. Ibanez, None; S. L. I. C. C. (SLICC), None.
sure. But it remains uncertain whether the utility values obtained by direct or indirect methods are comparable and which approach is the most appropriate in Systemic Lupus Erythematosus (SLE) population. The objective of this study was to compare the utility values obtained using an indirect method based on the EuroQol scale (EQ-5D) and direct utility instruments, the standard gamble (SG) and visual analog scale (VAS), in patients with SLE.

**Methods:** 240 consecutive patients with stable SLE underwent assessment of disease activity SLE Disease Activity Index (SLEDAI) and damage [Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)] and completed a disease-specific health-related quality of life (HRQol) measure, LupusQoL, and 3 utility measures: VAS, SG, and EQ-5D. Pearson’s correlations were calculated between the LupusQol domains and the utility measures to assess validity. To assess reliability, intraclass correlations or kappa coefficients were calculated between first and second assessments, performed from 2 weeks apart. In patients without important clinical change in disease activity, multiple regression models were performed for VAS and SG to determine predictor of utility.

**Results:** Disease activity from SLEDAI varied from 0 to 25 (median = 2). All domains of the LupusQol correlated well with the VAS (r: 0.329-0.632, 95% confidence interval [CI] 0.30, 0.56) and EQ-5D value (r: 0.299-0.757, 95% CI [0.35, 0.69]) except body image (r = 0.162 and 0.165, p = 0.018 and 0.016, respectively), and poorly with the SG [maximum r = 0.360, CI (0.0, 0.375); minimum r = 0.044, CI (0.0, 0.375)]. Test-retest reliability intraclass correlations for the VAS [ICC = 0.973, 95% CI (0.707, 0.856)], SG [ICC = 0.770, 95% CI (0.676, 0.839)] were good. The kappa coefficients were poor (0.024) for the EQ-5D domain of Anxiety/Depression, adequate (0.382) for mental health, and excellent (Mobility: 0.786; Self-care: 0.849; Usual activities: 0.972; Pain/Discomfort: 0.796) for the remaining domains. A model incorporating the SLEDAI score and LupusQol domains of emotional health and pain were good predictors of VAS (R² = 0.56) and SG (R² = 0.221) utility measures.

**Conclusion:** The VAS, EQ-5D, and to some extent, SG, when compared with the disease-specific HRQol survey LupusQol, are valid and reliable measures to assess HRQol in a group of patients with SLE and have emerged as promising outcome measures for future research in this population. It may also be used as a basis for further studies to obtain utility data with larger samples across SLE patients and provide helpful information to seek for theoretical basis for reasonable allocation of health resources.

**Disclosure:** S. Wang. None; L. Lu. None.

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**2633**

Factors Associated with Damage Accrual and Survival in Chinese Patients with Systemic Lupus Erythematosus (SLE): A Prospective Cohort Analysis of 747 Patients. Chi Chu Mok1, Sau Mei Tse1, Ling Yin Ho2 and Chi Hung To2.1 Tuen Mun Hospital, Hong Kong, Hong Kong, 2 Chelsea Heights, Hong Kong, Hong Kong.

**Background/Purpose:** To evaluate the factors associated with accrual of organ damage in a longitudinal cohort of Chinese patients with SLE.

**Methods:** A longitudinal cohort of 747 southern Chinese patients who fulfill >=4 of the 1997 ACR criteria for SLE from 1995 to 2014 was studied. Organ damage in 12 systems was assessed by the ACR SLICC damage scores (SDI). The cumulative rate of survival was studied by Kaplan-Meier’s plot. In those who died or were lost for follow-up, data were censored at the time of death or last visit, respectively. Early damage, defined as damage accrual that occurred within one year of SLE onset, was compared with the accrual of organ damage (SDI≥1) within the first year of SLE onset. Factors associated with damage accrual and mortality over time were studied by multivariate regression models.

**Results:** 747 SLE patients were studied. There were 691 women (93%) and 56 men (7%). The mean age at SLE onset was 33.0±13.5 years and the mean duration of follow-up was 111±91.1 months. Seventy-six patients (10%) died and 284(3%) patients were lost to follow-up. Early damage occurred in 191 (26%) patients. The frequency of organ damage in these patients, in decreasing order, was neuropsychiatric (29%), musculoskeletal (19%), renal (17%), dermatological (16%), pulmonary (9.4%),ocular (8.9%), cardiovascular (8.4%) and peripheral vascular (5.8%). Compared with those patients without early damage, patients with early organ damage were older at onset of SLE (37.4±15.2 vs 31.4±12.5 years; p<0.001) and were more likely to be men (13% vs 6%; p=0.009). Patients with early damage had accrued a significantly higher cumulative SDI score than those without (1.59±1.6 vs 0.84±1.5; p<0.001). Logistic regression analysis revealed that the male sex (RR 2.20 [1.22-3.95]; p=0.008) and the age of SLE onset (RR 1.04 [1.02-1.05]; p<0.001) were independently associated with early damage after adjustment for the use of corticosteroids, antimalarials and immunosuppressive agents that included cyclophosphamide, azathioprine and mycophenolate mofetil. In the entire cohort, 344 patients (46%) eventually developed organ damage (SDI≥1) and the median time to damage was 28 months. The cumulative survival of the patients studied was 90% at 12 months, 96% at 36 months, 86% at 60 months and 86% at 120 months. The SDI score was associated with mortality (and age and sex adjusted HR for each point of increase in SDI 1.31[1.18-1.44]; p<0.001). Cox regression analysis showed that early damage (HR 6.49[3.84-11.0]; p<0.001) was independently associated with mortality after adjustment for age of SLE onset, sex and the use of medications that included prednisolone, cyclophosphamide, azathioprine, mycophenolate mofetil and hydroxychloroquine.

**Conclusion:** In this large longitudinal cohort of Chinese patients with SLE, the male sex and older age of onset were associated with early organ damage, which occurred most frequently in the neuropsychiatric, musculoskeletal and renal systems. The presence of early organ damage increased SLE mortality by more than 6-fold.

**Disclosure:** C. C. Mok, None; S. M. Tse, None; L. Y. Ho, None; C. H. To, None.

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**2634**

A Signal of Improvement in Lupus Disease Activity at 3 Months Predicts Further Valid Improvement at 6 Months. Zahi Touma, Dafna D. Glidanu, Dominique Ibanez and M urray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

**Background/Purpose:** In patients with active disease, physicians look for an early signal in response to treatment to guide their therapeutic decisions. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) measures disease activity in 24 descriptors, generates a total score describing disease activity overall. SLEDAI-2K records descriptors of disease activity as present or absent. In the SLEDAI-2K Responder Index 50 (S2K RI-50), each of the 24 descriptors has a definition for a ≥ 50% improvement resulting in an appropriate score for the corresponding descriptor and a total score describing disease activity overall.

We aimed to determine if a signal of improvement in disease activity at 3 months predicts further improvement at 6 months.

**Methods:** Consecutive active lupus patients who attended the clinic between 2012 and 2014 were screened for inclusion. Patients were included if they: 1) had at least 1 of the following 5 SLEDAI-2K clinical organ systems active (vascular, renal, musculoskeletal, serosal or skin); central nervous system was excluded and 2) started or increased prednisone therapy and/or immunosuppressants. All patients had to have a follow-up visits at 3 and 6 months.

**Outcome measures:** Disease activity was measured by SLEDAI-2K at all visits and by S2K RI-50 at 3 months.

**Study definitions:** Signal of improvement by SLEDAI-2K is defined as a decrease by ≥1 in SLEDAI-2K score at 3 months. Signal of improvement by S2K RI-50 is defined as a decrease by ≥1 in S2K RI-50 score at 3 months.

**Study endpoints:** Based on the change in the total SLEDAI-2K score (baseline – last visit), each of the patients at last visit were grouped as: 1) improved (SLEDAI-2K decreased by ≥4) and not improved (SLEDAI-2K decreased <4). First, we identified the patients with SLEDAI-2K signal at 3 months and those who did not have a SLEDAI-2K signal were further evaluated for possible S2K RI-50 signal. Patients with signals were reevaluated at 6 months to determine if they had further improvement.

**Results:** 87 patients with mean SLEDAI-2K at baseline visit was 8.9±5.1 were studied. 90% were female, age at baseline visit was 40.0±12.4 and disease duration was 13.2±9.6 years.

**Signals of improvement:** Of the 87 patients, 54 (62%) had a SLEDAI-2K signal at 3 months. Of the 33 patients who did not have a SLEDAI-2K signal, a S2K RI-50 signal was identified in 11 (33%) patients.

**Study endpoints:** Of the 54 patients with SLEDAI-2K signal at 3 months, 28 (52%) patients improved at 6 months. Of the 11 patients with S2K RI-50 signal at 3 months, 5 (46%) improved at 6 months.

**Conclusion:** A signal of improvement at 3 months predicts further improvement in disease activity at 6 months. S2K RI-50 signal at 3 months, which is not discern by SLEDAI-2K, predicts improvement in half of the patients at 6 months. S2K RI-50 can identify non responders at 3 months who will respond at 6 months.
Noncalcified Plaque Progression in Systemic Lupus Erythematosus. Afshan Kiani1, Amin Zadeh2, Joao Lima3, Laurence S. Magder4 and Michelle Petri5. 1Johns Hopkins University, Baltimore, MD, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Coronary atherosclerosis is a major cause of morbidity and mortality in SLE. New technology, computed tomography (CTA) can measure non-calcified coronary plaque (NCP), which is more inflammatory, unstable and more prone to rupture. The aim of our current study was to determine the progression of noncalcified coronary plaque in SLE.

Methods: Repeat computed tomography angiography (CTA) was done in 11 (73% female, 91% Caucasian, 9% African-American, mean age 53 years) SLE patients after a baseline CTA. The CTA scans were evaluated quantitatively by a radiologist, using dedicated software. The correlation coefficient between the overall NCP score between 2 observers was 0.93. The kappa statistic for the assessment of noncalcified plaque (present or absent) in the 71 vessel segments was 0.42. The Noncalcified plaque score was the sum of plaque severity multiplied by the plaque composition, divided by the number of vessels examined.

Results: Figure 1 shows the baseline and second CTA results in these 11 patients. Nearly all (9/11) had progression of noncalcified plaque. One patient had no NCP and one patient had regression of noncalcified plaque. Four of five patients who progressed on calcified plaque, also had progression of noncalcified plaque. Out of 11 patients, 6 were on statins, 2 mycophenolate mofetil and 1 azathioprine. All 3 on immunosuppression showed progression. This, in particular, is disappointing, as in lupus mice, mycophenolate has been proven to reduce progression of atherosclerosis. Our study proves that NCP can be the outcome in intervention trials in SLE.

Conclusion: Noncalcified plaque – the most risky coronary plaque– progressed in the majority of SLE patients. All those with progression were under the care of a dedicated cardiologist; 5 were on statin therapy. Even the 3 on immunosuppression showed progression. This, in particular, is disappointing, as in lupus mice, mycophenolate has been proven to reduce progression of atherosclerosis. Our study proves that NCP can be the outcome in intervention trials in SLE.

Disclosure: A. Kiani, None; A. Zadeh, None; J. Lima, None; L. S. Magder, None; M. Petri, None.

Vitamin D Improves Endothelial Function in Patients with Clinically Stable Systemic Lupus Erythematosus (SLE). John A. Reynolds5, David W. Ray5, Terence O’Neill5, Y vonne Alexander6 and Ian N. Bruce5. 1Athritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, United Kingdom, M anchester, United Kingdom, 2Institute of Human Development, The University of Manchester, Manchester, United Kingdom, 3University of Manchester, Manchester, United Kingdom, 4Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: SLE patients after a baseline CTA. The CTA scans were evaluated quantitatively by a radiologist, using dedicated software. The correlation coefficient between the overall NCP score between 2 observers was 0.93. The kappa statistic for the assessment of noncalcified plaque (present or absent) in the 71 vessel segments was 0.42. The Noncalcified plaque score was the sum of plaque severity multiplied by the plaque composition, divided by the number of vessels examined.

Methods: Clinically stable female SLE patients were recruited from a single site (Central Manchester). Serum 25(OH)D was measured by LC-MS and patients were classed as deficient (<20ng/ml) or replete (>30ng/ml). Patients were treated by their general practitioner according to local protocols (typically 400,000IU cholecalciferol over 10 days then 20,000IU weekly). Replete patients were not treated and acted as controls. Patients were assessed at baseline and after 3 months. Endothelial function was measured using flow-mediated dilatation (FMD) and expressed as endothelium dependent/ endothelium independent (ED/EI) dilatation. A arterial stiffness (pulse-wave velocity, aPWV) was measured using Arteriograph. Cytokines were measured by ELISA. Disease activity was measured using the SLEDAI-2K and BILAG-2004 indices.

Results: We recruited n=22 vitamin D deficient patients and n=18 replete patients (median 25(OH)D 13.1 and 34.5ng/ml respectively). All patients were female and 36/40 (90%) had ≥4 ACR criteria. Deficient patients were younger (47.0 vs 57.9 years, p=0.007) and more likely to have a history of lupus nephritis (31.8% vs 5.6%, p=0.039) or require steroid (45.4% vs 5.6%, p=0.005) or immunosuppressant therapy (54.5% vs 11.1%, p=0.004).

FMD was strongly influenced by age and the baseline brachial arterial diameter. ED/EI in contrast was not related to either age or arterial diameter. Serum 25(OH)D significantly increased in the deficient/treated group compared to the replete/untreated (median change 28.6 vs -0.62ng/ml, p<0.0001) and PTH significantly decreased (-8.6 vs 2.5pg/ml, p=0.039). There was no change in aPWV, disease activity, serum complement or cytokines (IL-6, TNFα, IP-10 or BAFF).

Change in 25(OH)D was strongly correlated with the change in ED/EI (r=0.650, p=0.006) in the treated group but not the replete group (r=0.462, p=0.115) (figure). No association was seen between change in ED/EI and calcium, PTH or blood pressure. In an ordered logistic regression model the change in ED/EI remained associated with change in 25(OH)D after adjustment for age (OR 1.12 [1.021;1.24], p=0.017).

Conclusion: Increase in serum 25(OH)D significantly improved endothelial function over a short time period. This improvement was not due to changes in blood pressure or lupus disease activity. Vitamin D may be a novel vascular protective agent for SLE patients even in the absence of active disease.

Disclosure: J. A. Reynolds, None; D. W. Ray, None; T. O’Neill, None; Y. Alexander, None; I. N. Bruce, None.
Assessment of Plaque Thickness and Area in Patients with SLE As M easures of Atherosclerosis - Associations with Disease Activity. Sara Croca1,2, Maura Griffin3,4, David Isenberg5, Anisur Rahman1. 1University College London, London, United Kingdom, 2Acu lar Screening and Diagnostic Centre, London, United Kingdom, 3Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, 4University of Nicosia, Cyprus, Nicosia, Cyprus.

Background/Purpose: SLE is an independent risk factor for cardiovascular disease (CVD). Traditional risk stratification tools underestimate CVD risk in patients with SLE. Previous vascular ultrasound (US) studies have reported intima-media thickness (IMT) and presence of plaques in the carotid arteries of patients with SLE. However, some patients have femoral but not carotid plaques and alternative measures such as plaque thickness (pT) and plaque area (pA) may be more sensitive and informative than IMT.

Methods: We carried out carotid and femoral US of 100 patients fulfilling ACR classification criteria for SLE with no history of CVD. Mean IMT of the common carotid artery (CCA) was measured using automated software. Plaque was defined as a focal structure of thickness >1.2 mm from media-adventitia interface to intima-lumen interface. Where plaque was present, pT was measured using manual callipers and pA measured using image analysis software.

Statistical analysis using Spearman's correlation was carried out to investigate association between IMT, pA, pT and auto-antibody profile, lipids and homocysteine levels, blood pressure (BP), treatment and smoking status. Anti-apolipoprotein A1 (anti-ApoA1) IgG and IgM and anti-HDL antibodies were measured using direct ELISA protocols. Other clinical/serological data were obtained from medical records/patient interview.

Results: No patients had thickened CCA IMT (>0.1cm) but 37 had plaque in at least one site and 15 had plaque in ≥3 sites. The factors associated with pT, pA and CCA IMT are summarized in Tables 1 and 2. Whereas CCA IMT was primarily influenced by traditional risk factors such as BP, total cholesterol and LDL, pT and pA correlated with a wider range of variables including higher disease activity, elevated homocysteine, cholesterol/HDL ratio and IgG anti-HDL level.

Table 1: Factors associated with CCA IMT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman Correlation (r²)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at scan (yrs)</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>0.39</td>
<td>0.0002</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean BP</td>
<td>0.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of sites with plaque</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total plaque area (sq mm)</td>
<td>0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total plaque thickness (mm)</td>
<td>0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>0.36</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>0.31</td>
<td>0.002</td>
</tr>
<tr>
<td>Anti-ApoA1 IgG in early disease</td>
<td>0.24</td>
<td>0.02</td>
</tr>
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</table>

Table 2: Factors associated with plaque area and thickness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation with plaque area (Spearman r²)</th>
<th>p-value</th>
<th>Correlation with plaque thickness (Spearman r²)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at scan (yrs)</td>
<td>0.56</td>
<td>&lt;0.0001</td>
<td>0.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>0.29</td>
<td>0.004</td>
<td>0.32</td>
<td>0.0001</td>
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<tr>
<td>Systolic BP</td>
<td>0.27</td>
<td>0.007</td>
<td>0.29</td>
<td>0.004</td>
</tr>
<tr>
<td>No of sites with plaque</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean CCA IMT</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-La positivity</td>
<td>-0.33</td>
<td>0.001</td>
<td>-0.33</td>
<td>0.001</td>
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<tr>
<td>Persistent moderate/high disease activity</td>
<td>0.21</td>
<td>0.035</td>
<td>0.18</td>
<td>0.07</td>
</tr>
<tr>
<td>Persistent low disease activity</td>
<td>-0.21</td>
<td>0.035</td>
<td>-0.18</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum homocysteine</td>
<td>0.31</td>
<td>0.04</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum triglyceride</td>
<td>0.27</td>
<td>0.007</td>
<td>0.28</td>
<td>0.005</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>0.25</td>
<td>0.013</td>
<td>0.23</td>
<td>0.02</td>
</tr>
<tr>
<td>IgG anti-HDL</td>
<td>0.21</td>
<td>0.03</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>No of BILAG A flares of disease activity</td>
<td>0.23</td>
<td>0.023</td>
<td>0.21</td>
<td>0.03</td>
</tr>
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</table>

Conclusion: Although some authors have hypothesised a link between disease activity and atherosclerosis in SLE, this has not been shown convincingly in studies of IMT. More sensitive measurements such as pA and pT may help in linking disease activity and serology with atherosclerosis in SLE. This could help us target CVD risk reduction therapies to appropriate patients.

Disclosure: S. Croca, None; M. Griffin, None; D. Isenberg, None; A. Nicolaidis, None; A. Rahman, None.

The Protective Effects of Statins for Thrombosis in Patients with Systemic Lupus Erythematosus Positive for Antiphospholipid Antibodies.

Toshiyuki Watanabe, Kenji Oku, Olu Ameugna, Eni Sugawara, Ina Hisada, Kazumasa Ohmura, Tomoko Fukui, Sanae Shimamura, Ikuma Nakagawa, Atsushi Noguchi, Haruki Shida, Michihito Kono, Yuka Shimizu, Takashi Kurita, Toshiyuki Ohshigaki, Tetsuya Horita, Shinshuke Yasuda and Tatsuya Asutomi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Thrombosis is one of the most frequent manifestations in patients with systemic lupus erythematosus (SLE). Although antiphospholipid antibodies (aPL) are well recognized risk factors for thrombosis in SLE, few studies have addressed the potential effect of additional factors in the development or in the prevention of thrombosis in those patients.

Objective: To identify risk and protective factors for developing thrombosis in SLE with or without aPL.

Methods: One hundred fifty two newly diagnosed consecutive patients with SLE without history of thrombotic events were recruited at Hokkaido University Hospital from April, 1997 to February, 2014. All patients, 138 woman and 14 men, fulfilled the 1997 American College of Rheumatology revised criteria for SLE. Seventy-eight patients (51.3%) had aPL. The development of thrombosis and death caused by thrombosis were defined as the study endpoint.

Results: The median follow-up period in all patients was 58 months (IQR 20–115 months). In 78 patients with aPL, the median follow-up period was 69 months (IQR 27–118 months). Fifteen patients with aPL (19.2%) developed thrombosis during the follow-up period. Cerebral infarction (CI) was observed in 6 patients, pulmonary embolism (PE) in 5 and deep vein thrombosis (DVT) in 6. Multivariate analysis with Cox’s proportional hazards model showed that older age at SLE onset and anticardiolipin antibodies (aCL)-IgG positivity, HR 1.80 for every ten age, 95%C.I. 1.11–2.94 and (HR 6.87, 95%C.I. 1.74–27.1), respectively, are statistically significant risk factor for thrombosis. Statin therapy appears as a statistically significant protective factor against thrombosis (HR 0.12, 95%C.I. 0.01–0.97) (Figure 1). Disease activity, anti-thrombotic drug therapy and classical risk factors for atherosclerosis were not related to thrombosis. On the other hand, in 74 patients without aPL (median follow-up period 46 months, IQR 15–110 months), 7 patients (9.5%) developed thrombosis. CI was observed in 4 patients, intestinal infarction in 1, PE in 1 and DVT in 1. With Cox’s proportional hazards model, older age at SLE onset represents a statistically significant risk for thrombosis (HR 2.73 for every ten age, 95%C.I. 1.17–6.37).

Conclusion: This study suggests that, in aPL positive patients, the late disease onset and the presence of aCL-IgG represent additional risk factors for thrombosis. Statin treatment appeared as a thrombotic protective factor.

Disclosure: T. Watanabe, None; K. Oku, None; O. Ameugna, None; E. Sugawara, None; I. Hisada, None; K. Ohmura, None; T. Fukui, None; S. Shimamura, None; I. Nakagawa, None; A. Noguchi, None; H. Shida, None; M. Kono, None; Y. Shimizu, None.
We aimed to determine the prevalence of ECG-CV abnormalities in a cohort of lupus patients and to examine the factors associated with ECG-CV abnormalities.

**Methods:** A standard digitally recorded 12-lead resting supine ECG was performed on consecutive patients attending the Lupus Clinic between October 2012-May 2014. Coded ECGs were reviewed and interpreted by a cardiologist using the Minnesota code classification system.

The frequency of the ECG-CV abnormalities was determined. In the univariate analysis normal ECG and ECG-CV abnormalities were compared (T-test and chi-squared test). Covariates with p<0.1 in addition to age, sex, and ethnicity were evaluated with a stepwise logistic regression model to predict the ECG-CV abnormalities.

**Results:** 461 patients were studied. Of the 461 resting ECGs, 39.5% were abnormal: 7.6% axis deviation, 3.5% atrial enlargement, 11.3% arrhythmia and 6.7% pathological Q waves. ECG-CV abnormalities were present in 120 patients and included: ST-segment abnormalities and/or T-wave abnormalities in 17.4%, LVH in 8.9%, left-axis deviation in 4.1% and BBB in 6.3%.

Of the 120 patients with ECG-CV abnormalities, 65.0% had 1 abnormality, 26.7% had 2, 6.7% had 3 and 1.7% had all 4 abnormalities.

In the univariate analysis, in the group of ECG-CV abnormalities, patients were older, had a longer lupus duration, higher damage index, higher cumulative dose of corticosteroids, history of previous CAD event, presence of Coombs’, LA, LE cells, SCL70 and anti phospholipid lupus antibodies (table 1).

In the multivariate analysis, older age (OR =1.03; 95% CI: 1.01, 1.05; p=0.002), presence of damage (OR =1.33; 95% CI: 1.17, 1.52; p<0.0001) and positive Coombs’ (OR =2.37, 95% CI: 1.34, 4.21; p=0.003) were associated with ECG-CV abnormalities.

**Conclusion:** Of 461 resting ECGs 39.5% were abnormal. 26% had ECG-CV abnormalities. Older age, damage and Coombs' test were associated with ECG-CV abnormalities. These patients are at higher risk of developing CV events.

### Table 1. Comparison of normal ECG and ECG-CV abnormalities

<table>
<thead>
<tr>
<th>Normal ECG (n=279)</th>
<th>ECG-CV abnormalities (n=120)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91.0%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>57.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Black</td>
<td>15.8%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Asian</td>
<td>11.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Other</td>
<td>15.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Age @ SLE Dx at CAD First visit closest</td>
<td>30.6 ± 11.2</td>
<td>0.84</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG-Disease Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>@ ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLEDAI≥20 First available in clinic at visit closest ECG</td>
<td>45.9 ± 13.0</td>
<td>52.3 ± 14.8</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDI &gt; 0 at visit closest ECG</td>
<td>60.4%</td>
<td>80.3%</td>
</tr>
<tr>
<td>SDI at visit closest ECG</td>
<td>1.29 ± 1.53</td>
<td>2.82 ± 2.62</td>
</tr>
<tr>
<td>SDI (Excluding Cardiac) at visit closest ECG</td>
<td>1.24 ± 1.48</td>
<td>2.46 ± 2.39</td>
</tr>
<tr>
<td>Steroids at visit closest ECG</td>
<td>87.5%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Cumulative Dose at visit closest ECG (gr)</td>
<td>33.8 ± 34.9</td>
<td>61.3 ± 55.6</td>
</tr>
<tr>
<td>CAD First available in clinic at visit closest ECG</td>
<td>0% 4.3%</td>
<td>1.7% 17.5%</td>
</tr>
<tr>
<td>Coombs First available in clinic at visit closest ECG</td>
<td>32.2% 63.8%</td>
<td>40.7% 80.5%</td>
</tr>
<tr>
<td>LA First available in clinic at visit closest ECG</td>
<td>18.3% 33.6%</td>
<td>22.2% 47.5%</td>
</tr>
<tr>
<td>LE First available in clinic at visit closest ECG</td>
<td>37.2% 58.1%</td>
<td>47.8% 73.0%</td>
</tr>
</tbody>
</table>
Background/Purpose: Cardiac complications of SLE are common and include both acute and chronic manifestations: pericarditis, myocarditis, valvular disease, pulmonary hypertension, atherosclerosis, ischemic and non-ischemic cardiomyopathy. Cardiovascular magnetic resonance (CMR) imaging is a non-invasive, non-radiating imaging modality which can evaluate cardiac function and structure, myocardial inflammation, ischemia, and fibrosis. In this study we sought to assess indications for CMR use and CMR findings in SLE patients.

Methods: Chart review was performed for all patients with SLE diagnosis who underwent CMR for clinical indications from 2004 to 2014 at a single academic center. CMR results, cardiac risk factors, medications, SLE history, laboratory results, SLEDAI-2K (within 30 days of CMR), were recorded. Descriptive statistics were performed.

Results: During this time period, 31 SLE patients underwent 48 CMR. The patients were 45 ± 11.7 years, 77% female, duration SLE 9.5 ± 9.5 years, SLEDAI-2K 5.5 ± 5.9, and 13% had antiphospholipid antibody syndrome. (Table 1). The following cardiovascular risk factors were present: diabetes mellitus (23%), hypertension (58%), dyslipidemia (16%), congestive heart failure (16.1%), current smoker (27%), history of myocardial infarction (6%). Clinical indications for obtaining CMR were chest pain (40%), dyspnea (4%), abnormal echocardiogram (31%), arrhythmia (4%) and other/unknown (12%). Half of the patients who underwent CMR stress testing had abnormal perfusion (Table 2). The most common abnormalities on non-stress CMR testing included abnormal myocardial T2 signal (29.8%), late gadolinium enhancement (21.3%), pericardial thickening (14.6%) and valvular abnormalities (21.7% aortic, 23.9% mitral, 17.4% tricuspid).

Conclusion: Cardiac complications of SLE are common and impart significant morbidity and mortality. In this study, CMR imaging identified several abnormalities not evident on other cardiovascular (CV) imaging modalities including increased T2 signal in myocardium (suggesting myocardial inflammation) and late gadolinium enhancement (suggesting fibrosis from prior ischemia or inflammation). CMR allows simultaneous evaluation of cardiac function, structure, inflammation, and fibrosis and, with stress imaging, ischemia. As SLE cardiac complications are myriad, CMR is a promising tool to assess the breadth of potential CV complications in the SLE patient presenting with CV symptoms.

Table 1: SLE Participant Characteristics

<table>
<thead>
<tr>
<th>Age, mean ± SD years</th>
<th>44.9 ± 11.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%) female</td>
<td>31 (77.4%)</td>
</tr>
</tbody>
</table>

SLE Characteristics

<table>
<thead>
<tr>
<th>Duration SLE mean ± SD years</th>
<th>9.5 ± 9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI-2K (within 30 days of CMR), mean ± SD</td>
<td>5.5 ± 5.9</td>
</tr>
<tr>
<td>History of lupus nephritis, no. (%)</td>
<td>5/31 (16.7%)</td>
</tr>
<tr>
<td>History of antiphospholipid antibody syndrome, no. (%)</td>
<td>4/31 (12.9%)</td>
</tr>
<tr>
<td>History of pericarditis, no. (%)</td>
<td>8/31 (26.8%)</td>
</tr>
<tr>
<td>History of positive dsDNA antibody, no. (%)</td>
<td>15/31 (48.4%)</td>
</tr>
<tr>
<td>History of positive anti-Smith antibody, no. (%)</td>
<td>14/31 (45.2%)</td>
</tr>
</tbody>
</table>

Cardiovascular History

| Diabetes mellitus, no. (%) | 3/31 (22.6%) |
| History of hypertension, no. (%) | 18/31 (58.1%) |
| History of constrictive heart failure, no. (%) | 5/31 (16.1%) |
| History of ischemic stroke, no. (%) | 3/31 (9.7%) |

Table 2: Cardiac Magnetic Resonance (CMR) Imaging in SLE Patients

<table>
<thead>
<tr>
<th>Clinical Indicators for Obtaining CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, no. (%)</td>
</tr>
<tr>
<td>Dyspnea, no. (%)</td>
</tr>
<tr>
<td>Abnormal echocardiogram, no. (%)</td>
</tr>
<tr>
<td>Arrhythmia, no. (%)</td>
</tr>
<tr>
<td>Other/unknown, no. (%)</td>
</tr>
</tbody>
</table>

CMR Results

| CMR stress testing performed, no. (%) | 11/48 (22.9%) |
| CMR stress with abnormal perfusion, no. (%) | 5/36 (13.9%) |
| LV normal, no. (%) | 24/46 (52.1%) |
| LV ejection fraction ± SD, % | 60.4 ± 11.9 |
| LV diastolic dysfunction present, no. (%) | 3/46 (6.5%) |
| Abnormal LV peak circumferential strain, no. (%) | 2/46 (4.3%) |
| RV function normal, no. (%) | 44/46 (95.6%) |
| Myocardium with abnormal T2 signal, no. (%) | 14/47 (29.8%) |
| Pericardial thickening, no. (%) | 7/48 (14.6%) |
| Late gadolinium enhancement, no. (%) | 10/47 (21.3%) |
| Pulmonary artery enlargement, no. (%) | 2/46 (4.3%) |
| Abnormal aortic valve, no. (%) | 10/46 (21.7%) |
| Abnormal mitral valve, no. (%) | 12/46 (26.1%) |
| Abnormal pulmonic valve, no. (%) | 0% |
| Abnormal tricuspid valve, no. (%) | 6/46 (13.0%) |

Abnormalities: CMR = cardiac magnetic resonance imaging; LV = left ventricle; RV = right ventricle.

Disclosures: A. Meara; None; N. Dhillon; None; K. Fisher; None; P. Jensen; None; S. P. Ardoin; None.

2014

Cardiac Magnetic Resonance Imaging in Systemic Lupus Erythematosus: A Population-Based Study


The Ohio State University, Columbus, OH, 1University of Pittsburgh Medical Center, Pittsburgh, PA, 2The Ohio State University Wexner Medical Center, Columbus, OH, 3The Ohio State University, Nationwide Children’s Hospital, Columbus, OH, 5Ohio State University College of Medicine, Columbus, OH.

Risk of Cardiovascular Events in Patients with Cutaneous Lupus Erythematosus: A Population-Based Study

transient ischemic attack, peripheral arterial disease) were collected via medical record review for a random sample of 66 of the 156 patients with CLE and the non-CLE subjects matched to them. The cumulative incidence of CVD was estimated using a Kaplan-Meier method. Cox models were used to estimate the relative risk of CVD in patients with CLE compared to non-CLE after adjustment for age, sex and calendar year.

Results: We identified 66 patients with CLE (mean age at time of CLE diagnosis: 55±14y; 64% females; 68% Caucasian; mean BMI: 27.3±7.2 kg/m²; 35% current smokers), who were followed over a median follow-up of 12.0 years (interquartile range [IQR]: 8.1-17.3y). Positive antinuclear antibody, anti-SSc and anti-SS-B were seen in 48%, 47% and 18% of patients with CLE, respectively. Median ESR was 11 mm/hour (IQR: 4.0-25.0) and CRP 2.9 mg/dL (IQR 1.5-3.9). In this cohort, 9% were diabetic, 59% were hypertensive, 35% had hyperlipidemia and 8% had a family history of CAD; these risk factors were comparably distributed in 66 age- and sex-matched controls, except a higher prevalence of hyperlipidemia (53%, p=0.036). During follow-up, we observed 24 cardiovascular events (including 7 cases of myocardial infarction) in patients with CLE. The cumulative 1-, 5- and 10-year incidence of cardiovascular events after diagnosis of CLE was 7.3%, 15.3% and 33.2%, respectively. As compared to subjects without CLE, the risk of all cardiovascular events (hazard ratio [HR], 1.37; 95% confidence interval [CI], 0.77–2.49; p=0.29) or myocardial infarction (HR, 1.18; 95% CI, 0.77–2.49; p=0.61) was not significantly higher in patients with CLE (Figure).

Conclusion: The 10-year risk of cardiovascular events in a population-based cohort of patients with CLE is 33%. This risk is not increased as compared to age- and sex-matched non-CLE controls.

Disclosure: A. G. Singh, None; C. S. Crowson, None; M. Davis, None; H. Maradit Kremers, None; E. L. Mattson, None; V. Chowdhary, None.

2644

Carotid Intima-Media Thickness and Plaque in Mexican Mestizos with Systemic Lupus Erythematosus: A Case-Control Study.


Background/Purpose: Systemic lupus erythematosus (SLE) patients are at risk of premature cardiovascular disease (CVD). The specific reason of this situation is still debatable. Subclinical atherosclerosis prevalence and characteristics in Mexican mestizo patients with SLE is unknown. The objective of this study is to evaluate the presence of carotid plaque (CP) and carotid intima-media thickness (CIMT) in Mexican mestizos with SLE and to compare them to a control group.

Methods: An observational, cross-sectional study in a Mexican mestizo population was realized. 69 SLE patients, age ranging from 18 to 53 years, and 69 age-sex-diabetes-hypertension matched controls were included. Their demographic profile, biochemical, anthropometric measurements, traditional risk factors for atherosclerosis and disease-related factors were recorded. Carotid evaluation was realized by B mode carotid Doppler ultrasonography. CP was defined as presence of focal thickening at least 50% greater than that of the surrounding wall or CIMT ≥ 1.2 cm. The CIMT was measured at 1 cm proximal to the start of the carotid bulb dilatation of the common carotid artery in the far wall. The maximum CIMT value was recorded.

Results: Demographic differences between groups included a higher prevalence of CVD familiar history in the SLE group (p=0.001), higher diastolic and systolic blood pressure in the SLE group (p=0.001), and higher weight in the control group (p=0.013). Only 2 subjects of each group had diagnosis of hypertension, and 1 subject of each group had diagnosis of diabetes at the time of the enrollment to the study.

The mean CIMT value in SLE patients was 0.514 ± 0.098 mm while the control group had a mean of 0.516 ± 0.108 mm (p=0.830). CP was found in 11 patients with SLE and 4 in the control group (p=0.360). SLE patients with CP had lower levels of total cholesterol (p=0.021), low density lipoprotein cholesterol (p=0.030) and glucose (0.003) compared with the control group with CP.

Patients in the SLE group with steroid use for more than five years were more likely to have CP or increased CIMT (p=0.023). Use of synthetic DMARD was associated with lower probability of CP or increased CIMT (p=0.048). This association was not found with biological DMARD (p=0.422).

Conclusion: Our study has shown that despite high prevalence of traditional cardiovascular risk factors among Mexicans SLE patients, the CP/CIMT findings were not completely attributable to them. These findings
agree with most previously published reports in other populations including Arians, Caucasians and African-Americans. The actual evidence suggests that SLE itself is an independent predictor of atherosclerosis in our patients, and we recommend their systematic use.

Disclosure: I. J. Colunga-Pedraza, None; D. A. Galarza-Delgado, None; A. Cardenas-de La Garza, None; L. L. Sanchez-Nunez, None; S. L. Segarra-Linares, None; R. A. Castillo-Palacios, None; D. Vega-Morales, None; F. Gangoa-Rivera, None; M. A. Garza-Elimundo, None.

Table 1

<table>
<thead>
<tr>
<th>Manifestation (n)</th>
<th>Cumulative CYC dose (mg)</th>
<th>Duration of follow-up (mean weeks)</th>
<th>Outcomes &amp; type, median (IQR)</th>
<th>Major side-effects</th>
</tr>
</thead>
</table>

### Mood Disorders in Systemic Lupus Erythematosus (SLE): Results from an International, Cohort Study


### Methods:

A prospective study of newly diagnosed SLE patients was performed by an international network of 32 academic centers in 11 countries. Patients were evaluated at enrollment and annually for up to 14 years. Data were

### Background/Purpose:

Neuropsychiatric (NP) events in patients with SLE may include mood disorders. We determined the frequency, characteristics, clinical and autoantibody associations of mood disorders in a large, multiethnic/racial, inception cohort of SLE patients.
collected at each assessment on demographic and clinical manifestations, medications, SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). Nervous system events were recorded using the ACR case definitions for 19 NP syndromes. These include mood disorders, determined by clinical judgment (based on Diagnostic and Statistical Manual, DSM-IV, criteria) and consisting of: (i) major depressive-like episode, (ii) mood disorder with depressive features, (iii) mood disorder with manic features and (iv) mood disorder with mixed features. Lupus anticoagulant, IgG autoantibodies to cardiolipin, β2-glycoprotein I, ribosomal P and NMDA glutamate receptor 2 were measured at enrollment. Pre-defined rules determined the attribution of NP events to SLE and non-SLE causes. Cox regression was used to examine the associations of various factors with the occurrence of first mood disorder and first SLE-attributed mood disorder.

Results: Of 1,827 SLE patients, 88.9% were female, 48.9% Caucasian with mean age 35.1 ± 13.3 years. At enrollment, mean SLE duration was 5.6 ± 4.8 months. SLEDAI-2K was 5.3 ± 3.45 years. The mean follow-up was 4.73 ± 3.45 years. Over the study 863 (47.2%) patients had 1,627 NP events of which 503 (30.9%) were attributed to SLE. Mood disorders were the second most frequent NP event: 232 patients experienced 256 mood disorders of which 98/256 (38.3%) were attributed to SLE. The predominant mood disorders were major depressive-like episodes (134/256, 52.3%) followed by mood disorder with depressive features (114/256, 44.5%) and the remaining two mood disorders accounted for only 8/256 (0.03%) events. The estimated cumulative incidence of any mood disorder and any SLE-attributed mood disorder after 10 years was 17.7% (95% CI=[15.1, 20.2%]) and 7.9% (95% CI=[6.0%, 9.9%]), respectively. A total of 110/256 (43.0%) mood disorders occurred in isolation without other concurrent NP events. Multivariate analysis revealed a greater risk of mood disorders in patients with other concurrent NP events (p=0.01) and a lower risk with Asian race/ethnicity (p=0.0043), anti-Smith (RR = 1.518, p = 0.0551), renal involvement (urine dipstick protein positive 3+) (RR = 2.888, p = 0.0177) and current prednisone dose (RR = 9.960, p < 0.0001) were independently associated with a higher risk of incident seizure. SELENA-SLEDAI was not predictive and hydroxychloroquine was not protective after adjusting for the other variables in the model.

Conclusion: Seizure in SLE is multi-factorial. The risk of seizure in SLE is independently increased in those patients with prior psychosis, neuropathy, proteinuria, anti-Sm, low C3 and current corticosteroid use. Anti-Sm is of particular interest as it has also been incriminated in other CNS-SLE syndromes.

Disclosure: X. Huang, None; L. S. Magder, None; M. Petri, None.

2648

Predictors Is a Risk Factor for Incident Depression in Systemic Lupus Erythematosus. Xiangyang Huang, Laurence S. Magder and Michelle Petri. 1Sichuan University School of Medicine, Sichuan, China, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Depression affects as many as 30% of SLE patients. Most studies of risk factors for depression among SLE patients have been cross-sectional, and thus unable to identify risk factors prospectively. The aim of this study was to identify the risk factors that preceded incident depression in a large prospective longitudinal cohort of patients without a history of depression.

Methods: A prospective study was performed using data from the Hopkins Lupus Cohort. Demographic variables, SLE manifestations, laboratory tests, Physician's Global Assessment (PGA), Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), cumulative organ damage (SLICC/AMERICAN College of Rheumatology Damage Index (SDI)) and depression events were recorded at enrollment and each quarterly visit. A patient was considered to have depression if (1) there was a record of persistent depression (two or more mentions of depression separated by several weeks in rheumatology clinic notes) and/or a diagnosis of affective disorder was made by a psychiatric professional and (2) treatment for those symptoms with psychotherapy or antidepressant medications was documented. Rates of incident depression were calculated overall, and in subgroups defined by demographic and clinical variables. Adjusted estimates of association were derived using pooled logistic regression.

Results: The analysis was based on 1609 cohort members who did not have a history of depression prior to joining the cohort. Of these, we found that 282 (17%) experienced a first depression episode during follow-up. The incidence of depression was 29.7 episodes per 1000 person years. In the multivariable analysis, recent SLE diagnosis, non-Asian ethnicity, disability, cutaneous activity, longitudinal myelitis and higher doses of prednisone were independent predictors of incident depression (Table 1).

Table 1. Independent predictors of incident depression in the Hopkins Lupus Cohort based on a multivariate model

<table>
<thead>
<tr>
<th>Variables</th>
<th>Comparison</th>
<th>Adjusted Rate Ratio (95% Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since SLE dx</td>
<td>Per 10 year difference</td>
<td>0.7 (0.5, 0.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>East Asian vs. others</td>
<td>0.1 (0.01, 0.8)</td>
<td>0.031</td>
</tr>
<tr>
<td>Disability</td>
<td>Yes vs. no</td>
<td>1.4 (1.0, 1.8)</td>
<td>0.034</td>
</tr>
<tr>
<td>Income</td>
<td>Income &gt;100,000</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Year of enrollment</td>
<td>Year after 2005</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Recent Cutaneous activity</td>
<td>Some vs. none</td>
<td>1.7 (1.2, 2.2)</td>
<td>0.0008</td>
</tr>
<tr>
<td>History of longitudinal myelitis</td>
<td>Yes vs. no</td>
<td>4.5 (1.6, 12.2)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Recent dose of prednisone</td>
<td>20 mg/day + vs. less</td>
<td>2.0 (1.3, 2.9)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Conclusion: These results suggest that depression in SLE is multi-factorial, with only certain types of SLE activity (skin and myelitis) playing a role. Interestingly, prednisone exposure appeared to increase the risk, even after adjustment for disease activity. This provides yet another motivation for prednisone sparing in management of SLE patients.

Disclosure: X. Huang, None; L. S. Magder, None; M. Petri, None.

2647

Predictors of Incident Seizure in Systemic Lupus Erythematosus. Xiangyang Huang, Laurence S. Magder and Michelle Petri. 1Sichuan University School of Medicine, Sichuan, China, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: We identified the rate and risk factors for first occurrences of seizure based on a large closely followed longitudinal cohort of patients with systemic lupus erythematosus.

Methods: Rates of incident seizure were calculated overall and in subgroups defined by demographic and clinical variables. A adjusted estimates of association of risk factors were derived using pooled logistic regression.

Results: Of 2203 patients with no history of seizure prior to SLE diagnosis, 157 (7.1%) had the first seizure occurrence at the time of 37 patients, 1.63% or after the diagnosis of 120 patients, 5.44% SLE. The rate of incident seizure was 4.9 per 1000 person-years. The risk of seizure occurring around the time of SLE diagnosis was higher in patients with a history of malar rash (p = 0.002), proteinuria (p = 0.004), and psychosis (p < 0.0001). Multivariable analysis of the first seizure occurring after the diagnosis of SLE showed that history of low C3 (RR = 1.763, p = 0.0007), psychosis (RR = 2.432, p < 0.0001), cranial or peripheral neuropathy (RR = 2.212, p = 0.0043), anti-Smith (RR = 1.518, p = 0.0551), renal involvement (urine dipstick protein positive 3+) (RR = 2.888, p = 0.0177) and current prednisone dose (RR = 9.960, p < 0.0001) were independently associated with a higher risk of incident seizure. SELENA-SLEDAI was not predictive and hydroxychloroquine was not protective after adjusting for the other variables in the model.

Conclusion: Seizure in SLE is multi-factorial. The risk of seizure in SLE is independently increased in those patients with prior psychosis, neuropathy, proteinuria, anti-Sm, low C3 and current corticosteroid use. Anti-Sm is of particular interest as it has also been incriminated in other CNS-SLE syndromes.

Disclosure: X. Huang, None; L. S. Magder, None; M. Petri, None.
2649


Background/Purpose: There is currently no standardized tool to assess for NPSLE, and comprehensive neuropsychological testing can be lengthy and expensive. The Automated Neuropsychological Assessment Metrics (ANAM) is a computerized battery of tests which has been successfully used to test cognitive function in SLE. The Cognitive Stability Index (CSI) is a web-based tool for assessing neurocognitive function which measures similar domains to the ANAM. However, it has not been studied in patients with SLE. Furthermore, in contrast to ANAM, CSI summary scores are not solely based on response speed, and thus may have a significant advantage over ANAM. Additionally, CSI can auto-invalidate subtests performed with insufficient patient effort. We aimed to evaluate and compare the utility of ANAM and CSI to assess NPSLE in the outpatient setting.

Methods: Subjects enrolled in the Einstein Lupus Cohort were eligible to participate. Subjects completed an ANAM screening questionnaire (Mosca et al, 2011), with the presence of NPSLE defined by a screening score of >17 (NPSLE (+)). Subjects completed the ANAM and CSI tests (each taking ~30 minutes to complete). Eight cognitive domains were assessed by the ANAM and four by the CSI. The ANAM composite score measures average performance on all domains and is reported as a z score; four individual CSI factor scores for each cognitive domain are reported as standard scores (mean 100 ± 15). Mann Whitney U tests assessed differences between NPSLE (+) and NPSLE (-) subjects. Pearson correlations were obtained for ANAM and CSI scores.

Results: 31 subjects completed the CSI, of which 20 also completed the ANAM. Of the 31 subjects, median age was 39 years, 94% were female, 42% were Hispanic and 63% were black. 74% were treated with corticosteroids (median prednisone dose 10 mg).

The median composite ANAM z-score, adjusted for sex/age, was -1.39 (-2.59, -0.98). Median age-adjusted CSI standard factor scores ranged from 84-98 across the four cognitive domains. The median composite ANAM score was significantly different in the NPSLE (+) patients compared to those who were NPSLE (-) (p = 0.03). Of the eight domains evaluated by ANAM, learning, attention and spatial working memory differed significantly by screening score. Of the four CSI domains, response speed and memory differed significantly between the NPSLE (+) and NPSLE (-) subjects (p = 0.03 and 0.01, respectively). The composite ANAM score and CSI factor scores correlated significantly with each other. Finally, anti-dsDNA antibodies, C3, C4, SLEDAI scores, and medications were not significantly associated with NPSLE.

Conclusion: Median cognitive test scores on both ANAM and CSI fell below the standard mean for normals, independent of NPSLE status. CSI factor memory scores were significantly lower in NPSLE (+) subjects, independent of their response speed. Since this cannot be inferred from the ANAM composite score, CSI may provide a more specific assessment of cognitive functioning. Overall, NPSLE was associated with significantly lower scores on both ANAM and CSI, suggesting that these are valuable "point of care" tools that can be easily implemented in the clinical setting for the diagnosis of NPSLE.

Disclosure: D. Rybak, None; N. Jordan, None; N. Schwartz, None; T. Rubinstein, None; B. Freilich, None; I. Blanco, None; C. Putterman, None.

2650

Cognitive Impairment in SLE and Non-Criterion Anti-Phospholipid Antibodies. Michael Luggen1, Gaurav Gulati2, Rohan Willis2 and Emililo B. Gonzalez2. 1University of Cincinnati College of Medicine, Cincinnati, OH, 2University of Texas Medical Branch, Galveston, TX.

Background/Purpose: The pathogenesis of cognitive impairment (CI) in patients with SLE is unknown. Anti-phospholipid antibodies (APL) have been implicated in some studies, but not in others. The APL which have been evaluated have variably included anti-cardiolipin (ACL) antibodies, lupus anticoagulant (LAC), and antibodies to beta-2 glycoprotein I (β2GPI). Few studies have examined all of the above and none have examined other APL (so-called non-criterion APL). We evaluated the association of CI with a broad spectrum of both criterion and non-criterion APL.

Methods: Subjects meeting the revised criteria for classification of SLE were recruited from 3 different patient populations. Cognitive function was assessed with the ANAM (Automated Neuropsychologic Assessment Metrics), a validated computer-based assessment tool which measures multiple cognitive domains. The TTS (total throughput score= number of correct responses/time) was used as the primary outcome measure. It was summed over 8 separate domains. Demographic, clinical, treatment, disease activity and damage information was obtained. The following APL of all three isotypes were assessed by ELISA using standardized techniques: ACL, anti-β2GPI, anti- phosphothyrdiol ethanalamine (aPE), anti-phosphothyrdiol choline (aPC), anti-phosphothyrdiol inositol (aPI), anti-phosphothyrdiol serine (aPS), anti-phosphothyrdiol glycerol (aPG), anti-phosphothydric acid (aPA). The data were analyzed by Fisher’s exact test, Wilcoxon rank sum test, and multiple linear regression.

Results: Fifty-seven (57) patients were evaluated. Clinical characteristics are shown in Table 1. Of the 57, 12 had definite CI (<1.5 SD below the mean of an age, sex, and race matched RA population). The two groups were significantly different with regard to age, ethnicity, and family income. There was no significant difference between groups with regard to the presence or absence of any APL, or any specific APL, criterion or non-criterion. When titters of specific APL were compared with TTS, no significant correlations were found. Using multiple linear regression and adjusting for age, ethnicity, income, opioid and hydroxychloroquine use, and simple reaction time, neither the presence nor the titer of any APL significantly decreased TTS. However, the presence of aPG (IgM) (b = 0.352, p = .0007) and aPA (IgG) (b = -0.242, p = .02) appeared to increase TTS (model R²=.731, p<.0001).

Conclusion: In this cross-sectional study, neither criterion nor non-criterion APL of any isotype was associated with a significant decrease in cognitive performance as measured by the TTS of the ANAM. Somewhat surprisingly, aPG (IgM) and aPA (IgG) appeared to increase TTS, possibly reflecting protection against other pathogenic factors. Confirmation and further analysis of this finding is in progress.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALL SUBJECTS (n=57)</th>
<th>CD (n=12)</th>
<th>NO CD (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs [SD])</td>
<td>49.9 (11.2)</td>
<td>54.9 (8.8)</td>
<td>48.5 (11.5)*</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>13.1 (10.1)</td>
<td>17.5 (13.9)</td>
<td>12.0 (8.6)</td>
</tr>
<tr>
<td>Family Income (% &lt;= $20K)</td>
<td>45.6</td>
<td>75.0</td>
<td>37.8*</td>
</tr>
<tr>
<td>Education (% ≤ 12 yrs)</td>
<td>36.8</td>
<td>50.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>36.8</td>
<td>8.3</td>
<td>44.4*</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>3.6 (3.4)</td>
<td>3.2 (4.3)</td>
<td>3.8 (3.3)</td>
</tr>
<tr>
<td>SLICC</td>
<td>2.75 (2.4)</td>
<td>3.4 (2.1)</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>Pain (100 mm VAS)</td>
<td>40.0 (28.2)</td>
<td>49.6 (29.1)</td>
<td>36.2 (27.7)</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>53.7 (22.6)</td>
<td>58.8 (22.6)</td>
<td>52.3 (22.7)</td>
</tr>
<tr>
<td>Depression (Beck Depression Inventory)</td>
<td>16.0 (12.3)</td>
<td>17.6 (10.2)</td>
<td>14.4 (12.6)</td>
</tr>
<tr>
<td>Fatigue (FACIT)</td>
<td>24.6 (13.5)</td>
<td>26.1 (10.8)</td>
<td>23.3 (14.3)</td>
</tr>
<tr>
<td>APL Positive (%)</td>
<td>38.6</td>
<td>25.0</td>
<td>42.2</td>
</tr>
<tr>
<td>Prednisone (% use)</td>
<td>53.7</td>
<td>54.5</td>
<td>53.9</td>
</tr>
<tr>
<td>Prednisone &gt; 20 mg/d (%)</td>
<td>15.8</td>
<td>25.0</td>
<td>13.3</td>
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<tr>
<td>Immunosuppressants (%)</td>
<td>48.2</td>
<td>36.4</td>
<td>51.2</td>
</tr>
<tr>
<td>HCO (%)</td>
<td>70.0</td>
<td>50.5</td>
<td>74.4</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>14.8</td>
<td>18.2</td>
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<tr>
<td>ASA (%)</td>
<td>38.9</td>
<td>27.3</td>
<td>41.9</td>
</tr>
<tr>
<td>Anti-depressant (%)</td>
<td>31.5</td>
<td>36.4</td>
<td>30.2</td>
</tr>
<tr>
<td>Opioid (%)</td>
<td>25.9</td>
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<td>20.9</td>
</tr>
<tr>
<td>NSAID (%)</td>
<td>22.2</td>
<td>18.2</td>
<td>23.3</td>
</tr>
</tbody>
</table>

*C/D vs non-C/D, p < .05

Disclosure: M. Luggen, None; G. Gulati, None; R. Willis, Louisville APL Diagnostics Inc; S. E. B. Gonzalez, None.

2651

Predictors of Therapeutic Outcomes in Patients with Neuropsychiatric Systemic Lupus Erythematosus. Kenichi Ichinose1, Kazuhiko Arima2, Masataka Umeda3, Shioichi Fukui4, Ayako Nishino5, O yoshikazu Nakashima6, Takahisa Suzuki7, Yoshiro Horai7, Tomohiro Koga8, Shin-ya Kawashiri9, Naoki Iwamoto1, Mami Tamai1, Hideki Nakamura1, Tomoki Origiuchi1 and Atsushi Kawakami1. 1Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki.

The relationship between disease activity and cognitive function in patients with systemic lupus erythematosus (SLE) is not well established. This study was conducted to evaluate the association between disease activity and cognitive function in patients with SLE.
Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious organ disorder with a variety of symptoms. Despite advances in the understanding of the immunopathogenic and clinical aspects of SLE, NPSLE remains a diagnostic and therapeutic challenge. The therapeutic outcomes among very few published controlled studies are diverse, because of the variability in the manifestations of NPSLE and the absence of appropriate diagnostic criteria.

Methods: This study was conducted to investigate the immunopathogenic and clinical aspects and treatment outcomes of NPSLE. We analyzed the laboratory data, symptoms, treatment regimen, and therapeutic outcomes 1 year after treatment, and the prognostic factors of 28 NPSLE patients admitted to our hospital in an 8-year period from 2006 through 2013 and 27 cytokine, chemokines and growth factor profiles in pretreatment samples of their cerebrospinal fluid (CSF) using the Bio-Plex Human 27-plex panel.

Results: There were 26 females (92.9%) and 2 male. The median age at the onset of NPSLE was 35 years, ranging from 15 to 53 years old. The median duration from SLE onset to first neuropsychiatric event was 7 years. The median safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at the disease onset of NPSLE was 13. Twelve patients were responders at 1 year post-treatment, their median age at NPSLE onset was 29 years versus 39 years in the non-responders (p = 0.009). The median duration from SLE onset of NPSLE was 1.5 years in responder versus 11 years in non-responder (p = 0.0069). Patients with more than two NPSLE symptom types had significantly poorer outcomes (p = 0.0159). The CSF interleukin (IL)-10, interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels before the treatment were significantly higher in the non-responders as compared with the responders (p = 0.0029 and p = 0.001, respectively). The cytokines/chemokines to distinguish responder from non-responder by weighted-voting algorithm showed that the combination of IL-10, TNF-α, IL-6, IFN-γ, IL-4 and IL-13 had a highest Matthews correlation coefficient.

Conclusion: Younger, shorter disease duration and single-symptom NPSLE patients had significantly better therapeutic outcomes. The lower cytokine value of IL-10, IFN-γ and TNF-α before the treatment in CSF may provide better NPSLE outcomes. Additionally, measurement of multiple cytokines in pretreatment such as IL-10, TNF-α, IL-6, IFN-γ, IL-4 and IL-13 could distinguish responder from non-responder patients. Our findings may suggest the importance of making a diagnosis at an earlier phase for better therapeutic response and measuring multiple cytokines to predict therapeutic outcomes of NPSLE.

Disclosure: K. Ichinohe, None; K. Arima, None; M. Umeda, None; S. Fukushima, None; A. Nishio, None; Y. Nakashima, None; T. Suzuki, None; Y. Horai, None; T. Koga, None; S. Y. Kawaiishi, None; N. Ishiwatari, None; M. Tamai, None; H. Nakamura, None; T. Orizuchi, None; A. Kawakami, None.

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Clinical Features in Patients with Anti-Triphosphate Isomerase Antibody-Positive Neuropsychiatric Systemic Lupus Erythematosus

Shuzo Sato, Hiroshi Watanabe, Tomoyuki Aso, Hiroko Kobayashi, Hiro-masa Ohira and Makiko Yashiro. Fukushima Medical University School of Medicine, Fukushima, Japan.

Background/Purpose: Although several autoantibodies of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) have been reported, none of these autoantibodies were conclusively established as pathogenic. We have reported that autoantibodies to triphosphate isomerase (TPI), which is an important glycolytic enzyme in red blood cells or neuronal cells, are associated with NPSLE pathogenesis. We have detected the presence of anti-TPI antibodies in sera of human NPSLE patients. However, clinical features regarding anti-TPI antibody-positive NPSLE patients are unknown.

The aim of this study was to determine the clinical features of anti-TPI antibody-positive NPSLE patients.

Methods: Clinical data was retrospectively collected from 24 NPSLE patients (mean age: 26.41 ± 8.93 years old, 4 males and 20 females). NPSLE manifestations were determined according to the ACR case definitions for NPSLE. NPSLE patients were divided into 2 groups (anti-TPI antibody-positive or negative), and compared clinical features as follows: age, sex, disease duration, NPSLE manifestation, other SLE manifestations, SLEDAI, and laboratory data. Serum samples collected from all NPSLE patients were analyzed by Western blotting to detect anti-TPI antibodies using rabbit muscle TPI protein.

Results: 7 of 24 NPSLE patients were positive for anti-TPI antibodies (29.1%). Age, the rate of female, and SLEDAI were not significantly different between 2 groups. In laboratory data, the platelet count was significantly elevated in anti-TPI positive NPSLE patients (221,800 vs 158,300 /μL, p = 0.047). In NPSLE manifestation, Lupus headache was more frequently observed in anti-TPI antibody-positive NPSLE patients (28.5% vs 0%, p =
Cerebral Small Vessel Disease in Systemic Lupus Erythematosus: Histopathological Study. Jamal A. Mikdashi, Rupal I. Mehta, and Rudy J. Castellani. 1Univ of Maryland Sch of Med, Baltimore, MD, 2University of Maryland School of Medicine, Baltimore, MD, 3University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: Little is known about cerebral small vessel disease (CSVD) in SLE, compared to the mounting evidence of relating cardiovascular risk factors and inflammation to larger vessel disease and atherosclerosis. Our aim is to examine the clinical features of CSVD in SLE, and determine the risk factors associated with CSVD.

Methods: This is a postmortem study of consecutive autopsy brain of subjects drawn from the Maryland Lupus Cohort, between 2002 and 2014. A total of 15 eligible patients were identified, and central nervous system and systemic autopsy histopathology were reviewed. Four patients with limited autopsy data were excluded. Histopathological evidence of CSVD included microthrombomicroangiopathies, glial hyperplasia, neuronal loss, microaneurysms, lacunar infarcts, and microbleeds. Demographics, clinical SLE features, cardiovascular risk factors, neuromaging findings and therapeutic options were examined among those with CSVD and those with no CSVD. Multivariate analysis and non-parametric studies were used to determine factors associated with CSVD. SLE disease activity (SLEDAI-2k), SLE damage index (SDI) and duration of SLE were adjusted for during analyses.

Results: Only four out of 11 SLE patients (36.4%) had histopathological evidence of CSVD (n=4, mean age = 26.4 +/- 9.2 years, 100% women, 100% African American, mean duration of disease = 3.4 +/- 0.7 years), as compared to SLE patients with no CSVD (n=7, mean age = 26.2 +/- 8.8 years, 86% women, 86 % African American, and mean duration of disease = 3.7 +/- 1.7 years). CSVD patients presented with less acute CNS disease process and tended to accumulate more damage overtime as compared with no CSVD patients. Stroke and cognitive impairment were more frequent among CSVD patients compared to no CSVD group.

Histopathological CSVD findings correlated well with neuromaging evidence of CSVD including, the presence of recent subcortical infarcts, lacunar of vascular origin, white matter hyperintensity, and brain atrophy (Pearson correlation coefficient: 0.633; p value < 0.036). CSVD was manifested largely as microinfarction in the subcortical and cortical areas of the frontal and parietal regions (75%), with volume loss (50%), non-inflammatory vasculopathy (50%), and inflammatory vessel disease (25%). Independent risk factors associated with the occurrence of CSVD included, elevated dsDNA and low levels of C3 (odds ratio; 2.0; 95 % CI: 0.8-5.6, p value < 0.050). This association was independent of age, hypertension, diabetes, smoking, alcohol intake, anti-phospholipid antibodies, C-reactive protein, prior use of immunosuppressive therapy, or presence of microscopic evidence of small vessel disease in other organs such as the kidney, skin, cardiac, or pulmonary systems.

Conclusion: The present study highlights the nature of CSVD in SLE which is of considerable importance related to stroke and cognitive impairment. CSVD in SLE appears to be associated with chronic inflammation in the absence of classic cardiovascular risk factors, or effective treatment of hypertension and SLE. Identifying novel risk factors that shed light on CSVD pathogenesis in SLE may offer potential therapeutic targets.
assessments. In 2010, a 27-item questionnaire was developed to identify NPS in SLE (1); in the present study we aim to compare the capability to detect NPS by means of this questionnaire and routine clinical assessment in SLE.

Methods: The questionnaire was administered to consecutive SLE patients from two European Countries as a physicians’ administered tool in one cohort (PhQ) and a self-administered questionnaire in the other (PaQ). On the same day the routine clinical assessment was performed by a physician, NPS were captured by the questionnaire. The concordance level of NP symptoms as reported by questionnaires and clinical evaluation were calculated. The questionnaire was considered positive in presence of at least one symptom recorded.

Results: Overall, 137 patients were enrolled; the PhQ was administered to 70 patients (96% female, mean age at enrollment 42.3 ± 12. years, disease duration 12.5 ± 8.6 years) while the PaQ to 67 patients (92% female, mean age at enrollment 47 ± 13 years, disease duration 14.9 years). Previous NP involvement was present in 25% of patients in PhQ cohort and in 21% in PaQ cohort. According to the clinical records and irrespectively from their attribution, NPS were recorded in 23 patients (32%) in the PhQ cohort, and in 23 (34.3%) in the PaQ cohort; overall, there were neurologic symptoms in 15% and psychiatric symptoms in 14% of cases. According to questionnaires, at least one NPS was captured in 61 patients (87%) of the PhQ cohort and 62 (92%) in PaQ cohort. In the PhQ cohort, among the 61 patients with at least one symptom as captured by the questionnaire PhQ, 20 (32.7%) have also NPS recorded in the clinical chart; in all the 8 patients with negative questionnaire, no NPS were recorded in the clinical chart (agreement p = 0.057). Similarly, among the 62 patients with positive PaQ, 20 (29.8%) have also NPS recorded in the clinical chart (agreement p = 0.07). Cognitive impairment, depression and anxiety were the most overlooked symptoms in the clinical charts.

Conclusion: These data demonstrated that some NPS can be overlooked by the physician during routine clinical assessment. Although the clinical significance of these observations are under evaluation, this screening questionnaire can be a useful aid, for identifying patients with NPS requiring further evaluation.

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Brain Gray and White Matter Volume Losses and Their Associations with Glucocorticoid Use in Patients with Newly Diagnosed Systemic Lupus Erythematosus (SLE) - a Prospective M R Study. A. C. Araujo, None; S. Vagnani, None; R. Talarico, None; C. Mateus, None; S. Bombardieri, None; N. Riso, None; M. Mosca, None.

Background/Purpose: To examine cognitive symptoms and its relation to disease related factors including disease activity, antiphospholipid antibody, previous neuropsychiatric history (NPSLE) and non-disease related factors such as anxiety and depression over time.

Methods: Cognitive symptoms inventory (CSI) was used to measure perceived cognitive impairment serially at 3 time-points 12 months apart. Disease activity was measured by SLEDAI. Depressive and anxiety symptoms were measured by HADS-A and HADS-D respectively.

Results: 304 SLE patients were recruited at baseline (T0) among whom 144 had first re-evaluation (T1) and 34 had second re-evaluation (T2) at 12-month interval. Majority (73.5%, 25/34) of patients had stable CSI whereas 5.9% (2/34) of patients had persistently worsened CSI over 24 months. At T0, multivariate analysis revealed that higher CSI was associated with history of NPSLE (p < 0.005) and psychiatric disease (p = 0.04), higher HADS-A (p < 0.001) and HADS-D (p < 0.001) scores. CSI of active patients (SLEDAI > 6) was not different from inactive patients and did not change despite regression of disease activity in 12 months. There was no difference in CSI between T0 and T1 regardless of history of NPSLE, psychiatric history, change in depressive status at T1 (HADS-D < 11 as cutoff) but CSI was significantly different in patients who demonstrated change in anxiety status at T1 (HADS-A < 11 as cutoff) (p = 0.03). Multivariate linear regression analysis revealed change in HADS-A as the only significant predictive factor of change in CSI over time (β = 0.27, 95% CI 0.43 – 1.12, p < 0.001).

Conclusion: 5.9% of unselected SLE patients reported persistent cognitive symptoms. Patients with history of NPSLE and psychiatric illness, high...
Neurofilament H Is Associated with White Matter Lesions in Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa1, Mariana Postal1, Nailu A. Sinicato1, Lucas Ferreti Silveira2, Fernando Cendes3, Roberto Marini4 and Simone Appenzeller2.1 State University of Campinas, Campinas, Brazil, 2Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil, 3Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Imaging findings in systemic lupus erythematosus (SLE) patients are diverse; and diffuse or regional atrophy and white matter hyperintensities (WMH) have been described in variable frequency. Studies have shown that the subunit of high molecular weight neurofilament (NF-H) is more resistant to degradation and therefore can be found in large quantities in the serum of patients with CNS injury. However the prevalence and clinical significance of WMH and it’s association with serum NF-H levels in childhood-onset SLE (cSLE) is still unknown. We aimed to determine if serum NF-H protein levels are associated with WMH in cSLE patients.

Methods: We included consecutive cSLE patients (disease-onset before the age of 18) followed in a cohort at the Pediatric Rheumatology Unit at the State University of Campinas. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. MRI scans were obtained through a standardized protocol (3Telsa Philips). WMH were analyzed in T2-weighted images using a semiautomated computer program developed in our laboratory (Neuroline) and validated against standard MRI segmentation programs. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and cumulative SLE-related damage was determined using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI). Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Cognitive impairment (CI) was defined when scores were ≤2 standard deviations from controls in 1 or more subtests. Magnetic resonance imaging (MRI) scans were performed in a 3T Philips scanner using a standardized protocol and T2 weighted images were used for analyze. Quantification of lesion load and volume of WMH were performed by using a semi-automatic computer program (Neuroline®). Non-parametric tests were used for statistical analysis.

Results: cSLE was observed in 11 (17.4%) cSLE patients and in none of the controls (p<0.001). We observed a higher hip circumference (p=0.030), waist-to-hip ratio (p=0.001) and hyprotiglyceridermia (p=0.005) in cSLE patients when compared to controls. Controls had a higher height (p=0.003) and higher levels of HDL (p=0.004). We observed an inverse correlation between height and total corticosteroid dose adjusted by weight in cSLE patients (r=-0.285; p=0.022). CI was present in 32 (50.8%) cSLE. No association between M etS and CI was observed (p=0.3). Rey complex picture on memory subset correlated with BMI (r=-0.249; p=0.05) and TG levels (r=0.282; p=0.028) and Boston Naming Test had an inverse correlation with total cholesterol levels (r=-0.258; p=0.047). WMH were observed in 53 (82.5%) cSLE patients and in 4 (6.3%) controls. The presence of WMH lesions was associated with serum glucose levels (p=0.039).

Conclusion: cSLE patients with lipid profile and glucose levels were associated with some cognitive functions and with WMH in cSLE. This findings suggest that M etS complications go beyond the cardiovascular risk factors and should be routinely screened and treated.

Disclosure: N. A. Sinicato, None; A. T. Lapa, None; M. Postal, None; B. Bellini, None; P. T. Fernandes, None; R. Marini, None; S. Appenzeller, None.

Serum Neuronal Biomarkers and Brain Atrophy in Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa1, Mariana Postal1, Nailu A. Sinicato1, Renata Barbosa2, Fernando Cendes3, Roberto Marini3 and Simone Appenzeller3.1 State University of Campinas, Campinas, Brazil, 2Faculty of Medical Science, State University of Campinas, Campinas, Brazil, 3Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: We aimed to investigate the association of serum biomarkers and regional and diffuse brain atrophy in cSLE.

Methods: We included consecutive cSLE patients (disease-onset before the age of 18) followed in a cohort at the Pediatric Rheumatology Unit at the State University of Campinas and age and sex matched healthy controls. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and cumulative SLE-related damage was determined using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI). Magnetic resonance imaging (MRI) scans were obtained through a standardized protocol (3Telsa Philips) and normalized volumetric 1mm T1 weighted images were used for manual volumetric measurements. Volumes ≤2 standard deviation from the means of controls were considered abnormal. Serum biomarkers (S100a, NF-H and antibosbom P (Anti-P) and anticardiolipin antibodies levels were measured by enzyme-linked immunosorbent assay using commercial kits from Biovendor, Inc(Czech Republic). Anti-double stranded DNA (dsDNA) antibodies were determined by indirect immunofluorescen-
Olfactory functions were evaluated using the Sniffin' Sticks test, in 3 stages: threshold, discrimination, and identification of different odors (TDI).

**Results:** We included 120 SLE patients (93.3% female; mean age 40.3 years; SD 11.3 years) and 135 healthy volunteers (91.1% female; mean age 37.6 years; SD 12.4 years). Anxiety was observed in 81 (67.5%) SLE patients and in 49 (39.2%) controls (p = 0.003). Depression was identified in 62 (51.6%) SLE patients and in 39 (28.8%) controls (p = 0.004). Anti-ribosomal P antibodies were identified exclusively in SLE patients and were present in 13 (10.8%) of them (p = 0.001). Olfactory changes were observed in 62 (51.6%) SLE patients and in 40 (29.6%) controls (p = 0.001). SLE patients had significantly lower mean in all phases of the olfactory assessment. The olfactory was also inversely associated with anxiety (p = 0.004, R = -0.18), depression (p = 0.01, R = -0.232), cumulative damage (p = 0.002, R = -0.289) and age (p = 0.001, R = -0.355). The TDI was correlated with a CNS involvement, and patients with NP manifestations [mean of 28.35 (SD ± 5.30)] points, whereas patients without NP manifestations had a mean TDI of 30.8 (SD ± 4.51) points (p < 0.001). Anti-ribosomal P antibodies were not associated with CNS involvement (p = 0.730), but when we analyzed each manifestation separately, we observed an association between the presence of anti-ribosomal P antibodies and psychosis (p = 0.046). We also observed an association between anti-ribosomal P antibodies and disease activity (p = 0.036).

**Conclusion:** SLE patients have a significant decrease of smell when compared to healthy controls. Olfactory changes are associated with a history of neuropsychiatric symptoms, anxiety, depression, cumulative damage, and age. Anti-ribosomal P antibodies were exclusively observed in SLE patients compared to healthy controls and they were associated with psychosis and disease activity.

**Disclosure:** R. Barbosa, None; K. O. Pellicari, None; A. T. Lapa, None; N. A. Sinicato, None; M. Postal, None; R. Marini, None; M. Govoni Sr., None; S. Appenzeller, None.

**2663 Sense of Smell, Anti-Ribosomal P Antibodies and Neuropsychiatric Manifestations in Systemic Lupus Erythematosus:**

**Background/Purpose:** Neuropsychiatric manifestations occur in 12–95% of SLE patients. Recent studies have demonstrated the high specificity of anti-ribosomal P antibodies for SLE. Anti-ribosomal P antibodies are able to bind to neuronal cells in areas of the limbic system which are responsible to the olfactory. We aimed to analyze the prevalence of olfactory disorder in SLE, correlate olfactory with presence of neuropsychiatric manifestations, disease activity and the presence of anti-ribosomal P antibodies.

**Methods:** Consecutive SLE patients followed at the rheumatology unit of the State University of Campinas were enrolled in this study. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity (SLE Disease Activity Index (SLEDAI)), damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index), and anti-ribosomal P antibody was performed by Enzyme Linked Immuno Sorbent Assay. Olfactory functions were evaluated using the Sniffin' Sticks test, in 3 stages: threshold, discrimination, and identification of different odors (TDI).

**Results:** We included 120 SLE patients (93.3% female; mean age 40.3 years; SD ± 11.3 years) and 135 healthy volunteers (91.1% female; mean age 37.6 years; SD ± 12.4 years). Anxiety was observed in 81 (67.5%) SLE patients and in 49 (39.2%) controls (p = 0.003). Depression was identified in 62 (51.6%) SLE patients and in 39 (28.8%) controls (p = 0.004). Anti-ribosomal P antibodies were identified exclusively in SLE patients and were present in 13 (10.8%) of them (p = 0.001). Olfactory changes were observed in 62 (51.6%) SLE patients and in 40 (29.6%) controls (p = 0.001). SLE patients had significantly lower mean in all phases of the olfactory assessment. The olfactory was also inversely associated with anxiety (p = 0.004, R = -0.18), depression (p = 0.01, R = -0.232), cumulative damage (p = 0.002, R = -0.289) and age (p = 0.001, R = -0.355). The TDI was correlated with a CNS involvement, and patients with NP manifestations [mean of 28.35 (SD ± 5.30)] points, whereas patients without NP manifestations had a mean TDI of 30.8 (SD ± 4.51) points (p < 0.001). Anti-ribosomal P antibodies were not associated with CNS involvement (p = 0.730), but when we analyzed each manifestation separately, we observed an association between the presence of anti-ribosomal P antibodies and psychosis (p = 0.046). We also observed an association between anti-ribosomal P antibodies and disease activity (p = 0.036).

**Conclusion:** SLE patients have a significant decrease of smell when compared to healthy controls. Olfactory changes are associated with a history of neuropsychiatric symptoms, anxiety, depression, cumulative damage, and age. Anti-ribosomal P antibodies were exclusively observed in SLE patients compared to healthy controls and they were associated with psychosis and disease activity.

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Increased Risk of Hematological Malignancies in Children Born to Women with SLE. Evelyne Vinet1, Ann E. Clarke2, Christian A. Pineau3, Susan Scott3, Robert W. Platt4 and Sasha Bernatsky4. 1McGill University Health Centre, Montreal, QC, 2University of Calgary, Calgary, AB, 3McGill University Health Centre, Montréal, QC, 4McGill University, Montreal, QC.

Background/Purpose: Patients with SLE have an increased risk of hematological malignancies, particularly non-Hodgkin lymphoma, compared to the general population. Recently, in utero exposures, such as chronic maternal autoimmune conditions, have been associated with the development of childhood hematological malignancies. However, until now, no one has assessed the risk of hematological cancers in children born to women with SLE. Thus, in a large population-based study, we aimed to determine if SLE offspring have an increased risk of hematological malignancies, versus controls.

Methods: The “Offspring of SLE mothers Registry (OSLER)” includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained hematological malignancies based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up.

We performed multivariate logistic regression analyses, using generalized estimating equations, to adjust for maternal demographics and comorbidities, sex of child, and gestational diabetes. In a subsample analysis of children with maternal drug coverage throughout pregnancy, we further assessed relevant in utero medication exposures.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age and follow-up were respectively 30.3 (SD 5.0) and 9.1 (SD 5.8) years. Children born to women with SLE experienced more hematological malignancies (9/719) compared to controls (38/8493) (1.25% [95% CI 0.61, 2.15] versus 0.45% [95% CI 0.32, 0.62]), difference 0.80% (95% CI 0.14, 2.01). The most frequent type of hematological cancer in both groups was acute lymphoblastic leukemia. Of note, primary non-Hodgkin lymphoma of bone was observed in 2/719 SLE offspring as opposed to 6/8493 control children (0.28% [95% CI 0.05, 1.12] versus 0.07% [95% CI 0.01, 0.16], difference 0.21% [95% CI -0.04, 1.05]). In multivariate analyses (n=9212), children born to women with SLE appeared to have an increased risk of hematological cancers versus controls (OR 2.80, 95% CI 1.33, 5.92).

In the subsample of children with drug coverage (n=1925), in utero medication exposures were rare in the 10 hematological cancer cases: none was exposed to antimalarials, corticosteroids, or immunosuppressants.

Conclusion: Our data suggest that compared to children from the general population, children born to women with SLE may have an increased risk of hematological malignancies. However, it must be emphasized that this outcome is extremely rare and our findings should be interpreted by other study methods. The lack of association with in utero drug exposures may be viewed as somewhat re-assuring, though this too is preliminary.

Disclosure: E. Vinet, None; A. E. Clarke, None; C. A. Pineau, None; S. Scott, None; R. W. Platt, None; S. Bernatsky, None.

Risk of Hydrocephalus and/or Macrocephaly in Children Born to Mothers with SLE. Catherine Huang1, Sasha Bernatsky2, Christian A. Pineau3, Susan Scott3, Ann E. Clarke2, Robert W. Platt4 and Evelyne Vinet3. 1McGill University, Montreal, QC, 2University of Calgary, Calgary, AB, 3McGill University Health Centre, Montreal, QC, 4McGill University Health Centre, Montreal, QC.

Background/Purpose: Evidence suggests that both hydrocephalus and macrocephaly could be potential manifestations of neonatal lupus. In a recent study of 87 children born to mothers with anti-Ro antibodies (Boros et al., Arthritis Rheum, 2007), prevalence of hydrocephalus was high at 8.0% and mean head circumference was substantially larger than the age-matched normal values. Although up to 40% of women with SLE display anti-Ro antibodies, to date, no one has assessed the occurrence of hydrocephalus and/or macrocephaly in SLE offspring. Thus, in a large population-based study, we aimed to determine if children born to women with SLE have an increased risk of hydrocephalus and/or macrocephaly compared to children born to women without SLE.

Methods: The “Offspring of SLE mothers Registry (OSLER)” includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained hydrocephalus and macrocephaly based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up. We performed multivariate logistic regression analyses, using generalized estimating equations, to adjust for maternal demographics and comorbidities, sex of child, and gestational diabetes.

Results: A total of 719 children were born to 509 women with SLE, and 8493 children were born to the 5824 matched controls. Compared to controls, children born to women with SLE showed only a slight trend towards more records of hydrocephalus and/or macrocephaly diagnosis (8 per 1000 persons [95% CI 4.18] versus 6 per 1000 persons [95% CI 5.8], difference 2 per 1000 persons [95% CI -3.13]). Similarly there was only a slight trend towards younger age at time of hydrocephalus and/or macrocephaly diagnosis in SLE offspring versus controls (respectively 0.6 year [95% CI 0.2, 1.0] and 1.1 years [95% CI 0.5, 1.7]). Of note, among the 6 cases of hydrocephalus and/or macrocephaly identified in SLE offspring, none had a diagnosis of cardiac conduction disturbance, suggesting no strong association with neonatal lupus. In multivariate analysis, the point estimate for the outcome was consistent with a trend for higher risk of hydrocephalus and/or macrocephaly in SLE offspring compared to controls, although the confidence interval was wide and precluded definitive conclusions (OR 1.37, 95% CI 0.58, 3.22).

Conclusion: Compared to children from the general population, there was a slight trend for higher frequency (and earlier age at diagnosis) of hydrocephalus and/or macrocephaly among children born to mothers with SLE, but the results do not strongly suggest an important increase in the risk of hydrocephalus and/or macrocephaly.

Disclosure: C. Huang, None; S. Bernatsky, None; C. A. Pineau, None; S. Scott, None; A. E. Clarke, None; R. W. Platt, None; E. Vinet, None.

Causes of Stillbirths in Women with SLE. Evelyne Vinet1, Geneviève Genest1, Susan Scott1, Christian A. Pineau1, Ann E. Clarke1, Robert W. Platt1 and Sasha Bernatsky1. 1McGill University Health Centre, Montreal, QC, 2University of Calgary, Calgary, AB, 3McGill University, Montreal, QC.

Background/Purpose: It is believed that pregnant women with SLE face an increased risk of stillbirths, although there are few precise or recent estimates of the magnitude of the effect. As well, no one to date has investigated the causes of stillbirths in SLE pregnancy. Using the “Offspring of SLE mothers Registry (OSLER)”, we explored the incidence of stillbirths and the cause of their death in SLE mothers versus those without SLE.

Methods: OSLER is a large population-based cohort, which includes all women who had one or more hospitalizations for delivery after SLE diagnosis, identified through Quebec's healthcare databases (1989–2009). OSLER also includes a randomly selected control group of healthy women, matched at least 4:1 for age and year of delivery. We identified stillbirths (defined as intrauterine deaths occurring at or after 20 weeks of gestational age) from SLE mothers and their matched controls and ascertained the cause of death as indicated on the death certificate. We performed a multivariate logistic regression analysis, using generalized estimating equations, to estimate the risk of stillbirths in SLE offspring versus controls, adjusting for maternal education, comorbidities (i.e. hypertension, diabetes, asthma, depression), and multiple births.

Results: 509 women with SLE had 729 births, including 9 stillbirths (1.4%), while 5829 matched controls had 8541 births including 47 stillbirths (0.6%). Compared to controls, women with SLE had an increased risk of having a stillbirth (adjusted OR 2.16, 95% CI 1.05, 4.44). Among women having a stillbirth, median maternal age was identical for both SLE and control mothers [respectively 31.0 years (IQR 29.0, 32.0) and 31.0 years (IQR 30.5, 32.5)]. There was a trend for women with more female stillbirths born to women with SLE (6 of nine stillbirths were female) compared to controls (22/47) (OR 2.27, 95% CI 0.54, 9.41). In addition, stillbirths in SLE mothers occurred at a younger median gestational age compared to controls [29 weeks (IQR 28, 31) versus 35 weeks (IQR 27, 38)].
Table 1. Causes of death among SLE and control stillbirths

<table>
<thead>
<tr>
<th>Causes</th>
<th>SLE stillbirths (n=9)</th>
<th>Control stillbirths (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorders, n (%)</td>
<td>2 (22)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Placental abruption, n (%)</td>
<td>2 (22)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Placental disorders, n (%)</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Congenital abnormality, n (%)</td>
<td>1 (11)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Umbilical cord abnormality, n (%)</td>
<td>1 (11)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Obstetrical complications, n (%)</td>
<td>1 (11)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Maternal medical condition, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>1 (11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>1 (11)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Unknown n (%)</td>
<td>0 (0)</td>
<td>7 (15)</td>
</tr>
</tbody>
</table>


Disclosures: E. Vinet, None; G. Genest, None; S. Scott, None; C. A. Pinaud, None; A. E. Clarke, None; R. W. Platt, None; S. Bernatsky, None.

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First-Trimester Disease Activity Does Not Predict Pre-Eclampsia in SLE Pregnancy.

Khaled Alderaan1, Laurence S. Magder2 and Michelle Petri3.

1King Fahad Specialist Hospital, Dammam, Saudi Arabia, 2University of Maryland, Baltimore, MD, 3Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Pre-eclampsia complicates up to 35% of lupus pregnancies compared to 8% of general population pregnancies. SLE has up to a 3-fold increased rate of preeclampsia. The aim of this cohort study was to determine whether variables measured in the first trimester could help predict which women will develop pre-eclampsia.

Methods: Only pregnancies with a clinic visit during the first trimester were included. All women were diagnosed with SLE either before or during pregnancy, according to the American College of Rheumatology (ACR) revised classification criteria. Pre-eclampsia was defined according to the American College of Gynecology (ACOG), as follows: systolic blood pressure of 140 mm Hg or higher or diastolic of 90 mm Hg or higher in patients with previously normal blood pressure, taken on two occasions, measured after 20 weeks of gestation; and proteinuria, defined as urinary protein excretion of more than 0.3 g in a 24-hour urine collection. Rates of pre-eclampsia were calculated in subgroups defined by variables measured in the first trimester, defined as the first 13 weeks of pregnancy.

Results: A total of 280 pregnancies from 234 different women were included in this analysis. The patients were 62% Caucasian, 28% African American, and 10% other ethnicities. Twenty-nine (10%) of the pregnancies met the definition of pre-eclampsia. Table 1 shows the rates of pre-eclampsia by patient subgroups. There was not strong evidence of an association between lupus-related variables such as anti-dsDNA, low complement, global disease activity and risk of pre-eclampsia. Also, there was not strong evidence of a relationship between medications such as prednisone, hydroxychloroquine and risk of pre-eclampsia.

Conclusion: Pre-eclampsia development in SLE patients cannot be predicted in the first trimester. Disease activity, serologic activity, proteinuria, antiphospholipid antibodies and prednisone are not predictive.

Disclosure: K. Alderaan, None; L. S. Magder, None; M. Petri, None.

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Background/Purpose: Systemic lupus erythematosus (SLE) typically presents in women of childbearing age. As such, it is important to understand how the clinical characteristics of SLE affect pregnancy outcomes. This research question is being assessed in a secondary analysis of the Hopkins Lupus Pregnancy Cohort.

Methods: Data from the Hopkins Lupus Pregnancy Cohort for pregnancies occurring on or after 01 Jan 2000. Maternal clinical characteristics in the 6 months prior to or during pregnancy that were analyzed included comorbidities (pregnancy-induced hypertension, placental abruption, pre-eclampsia, gestational diabetes, proteinuria, hypertension and thrombocyto-
penia), concomitant medications (corticosteroids, other immunosuppressants, NSAIDs, anti-malarials and heparin) and lab tests (low C3/C4, anticardiolipin antibodies and anti-dsDNA). We evaluated whether maternal clinical characteristics were associated with low birth weight (LBW; <2500 g) pregnancy outcome for live births. Fischer exact p-values were calculated in this analysis (WEUK BRE5887 & WEUK BRE4566; 114256).

**Results:** In this analysis, there were 213 pregnancies in 190 women (median age: 30 years; median SLE duration: 5.5 years; 51% white, 37% black, 12% other). There were 16 (7.5%) spontaneous miscarriages, 6 (2.8%) stillbirths and 188 (88.3%) live births (median gestational age: 38 weeks). The outcome was unknown in two of the pregnancies. The live births (20.2%) were preterm, 15 (8.0%) were small for gestational age (SGA; defined as weight <10th percentile for gestational age) and 41 (21.8%) were LBW. Compared to mothers of infants with normal birth weight (Table 1), mothers of infants with LBW had a greater frequency of hypertension (34.1% vs. 17.0%; p = 0.01), proteinuria (12.2% vs. 3.4%; p = 0.03) and higher dose steroid use (7.5 mg/day) in the 6 months prior to or during pregnancy (63.4% vs. 47.6%; p = 0.03).

**Table 1**: Association of maternal clinical characteristics and low birth weight pregnancy outcome in the Hopkins Lupus Pregnancy Cohort

<table>
<thead>
<tr>
<th>Co-Morbidities</th>
<th>Total Live Births (n=190)</th>
<th>Normal Birth Weight (≥2500g) (n=147)</th>
<th>Low Birth Weight (&lt;2500g) (n=41)</th>
<th>Fischer Exact p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>39 (20.7)</td>
<td>25 (17.0)</td>
<td>14 (34.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>7 (3.7)</td>
<td>5 (3.4)</td>
<td>2 (4.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>1 (2.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>16 (8.5)</td>
<td>6 (4.1)</td>
<td>10 (24.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>10 (5.3)</td>
<td>5 (3.4)</td>
<td>5 (12.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2 (1.1)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (6.4)</td>
<td>8 (5.4)</td>
<td>4 (9.8)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Medications:**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Total Use (n=190)</th>
<th>Low Birth Weight (&lt;2500g) (n=41)</th>
<th>Fischer Exact p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7.5 mg/day</td>
<td>96 (51.1)</td>
<td>26 (63.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;7.5 mg/day</td>
<td>91 (48.4)</td>
<td>15 (36.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mising</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Other immunosuppressants</td>
<td>56 (29.8)</td>
<td>15 (36.6)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**NSAIDs:**

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Total Use (n=190)</th>
<th>Low Birth Weight (&lt;2500g) (n=41)</th>
<th>Fischer Exact p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>154 (81.9)</td>
<td>33 (80.5)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>39 (20.7)</td>
<td>8 (19.5)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Lab Values:**

<table>
<thead>
<tr>
<th>Low C3/C4</th>
<th>Total Use (n=190)</th>
<th>Low Birth Weight (&lt;2500g) (n=41)</th>
<th>Fischer Exact p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 (58.5)</td>
<td>26 (63.4)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>14 (7.4)</td>
<td>3 (7.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>IgG</td>
<td>6 (3.2)</td>
<td>1 (2.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>IgM</td>
<td>9 (4.8)</td>
<td>2 (4.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>IgA</td>
<td>3 (1.6)</td>
<td>1 (2.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>100 (53.2)</td>
<td>22 (53.7)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**Conclusion:** In this analysis, certain maternal clinical characteristics were associated with LBW in infants born to mothers with SLE. A greater frequency of higher dose steroid use was observed in mothers of infants with low birth weight, it is possible that treatment with higher dose steroids (≥7.5 mg/day) has a direct effect on low birth weight. Data from this analysis will complement planned analyses for the Emerge Pregnancy Registry, an ongoing international, prospective cohort study of women exposed to commercially-supplied belimumab within 4 months prior to and/or during pregnancy (WEUK BRE5887 & WEUK BRE4566; 114256).

**Disclosure:** M. Petri, GlaxoSmithKline, 5; A. Eudy, GlaxoSmithKline, 3; M. Powell, GlaxoSmithKline, 1, GlaxoSmithKline, 3; G. Giugni, GlaxoSmithKline, 3; Q. Fu, GlaxoSmithKline, 1, GlaxoSmithKline, 3; D. Hill, GlaxoSmithKline, 1, GlaxoSmithKline, 3.
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Pregnancy Delivery in Patients with Systemic Lupus Erythematosus.
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Background/Purpose: Premature delivery (PD) is one of the most important difficulties in perinatology. An incidence on developing countries of around 19% and 5–7% in developed nations is estimated. In Systemic Lupus Erythematosus (SLE) preterm delivery and stillbirth are still concerns, particularly in relation to pregnancies in patients with renal involvement, the presence of antiphospholipid antibodies (a-PL) or anti Phospholipidic Syndrome (APS). The aim of this study was to evaluate the prevalence of PD in patients with SLE and analyze the relationship between different factors related to the disease with fetal outcomes and neonatal mortality.

Methods: Patients with SLE (1997 ACR criteria) with ≥ 1 pregnancy from 1987–2011 were analyzed. Premature delivery was defined as live birth before 37 weeks of gestation. We compared the outcomes among PD pregnancies versus term pregnancies. The statistical analysis was performed with Chi-square test or test of Student as appropriate.

Results: 166 pregnancies were recorded in 124 SLE patients. In 132/166 (79.5%) pregnancies were live birth. 46/132 (34.8%) were PD. Main causes of PD were: premature rupture of fetal membranes (21.7%), gestosis (19.6%) and placental insufficiency with intrauterine growth restriction (13%). Eight preterm newborn (17.4%) died in the neonatal period, 4 of them were part of the seven cases of extreme preterm birth (<32 weeks of gestation).

Preterm 46 Term 98 p OR CI
APS 51% 32.6% 0.65 2.063 0.94–4.49
Previous nephropathy 32.6% 30.6% 1.00 1.063 0.46–2.39
Infections 24% 18.3% 0.505 1.39 0.54–3.52
Proteinuria 43.75% 10.2% 0.002 3.85 1.42–10.51
a-PL 77% 52.6% 0.006 3.06 1.27–7.49
Hydroxychloroquine 37% 40% 0.855 0.887 0.40–1.93
Pre-eclampsia 19.6% 11.2% 0.201 1.92 0.66–5.54
Cesarean delivery 58.7% 47% 0.212 1.61 0.74–3.48
Low birth weight 82.6% 10% <0.0001 41.8 13.9–132
Neonatal Death 17.4% 4% 0.019 4.94 1.24–20.9

Conclusion: 34.8% of the 132 live newborns from mothers with SLE were preterm deliveries. Proteinuria during the course of the pregnancy and anti phospholipid antibodies were significantly associated with PD. Patients with PD had increased the risk of having newborn with low birth weight as well as increased mortality in the neonatal period, especially when the delivery occurred before 32 weeks of gestation.

Disclosure: V. Arturi, None; P. Sansinena, None; M. A. Pera, None; A. P. Salas, None; J. Marcos, None; A. C. Costi, None; C. E. Pena, None; M. A. Garcia, None.

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Impact of Glucocorticoid Dose on Maternal and Fetal Outcomes in Lupus Patients.
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Background/Purpose: Lupus flares during pregnancy can be treated with short courses of low to moderate doses of glucocorticoids (GCs). GCs are associated with several maternal and fetal complications during pregnancy, however information about the role of the dose in the development of these complications is limited.

Methods: We prospectively studied a cohort of pregnant women with SLE (ACR 1997) between January 2009 and August 2013. The patients were assessed every 4 to 6 weeks and postpartum by a rheumatologist and a gynecologist. Clinical, biochemical and immunological characteristics of women, along with maternal and fetal complications, were recorded. For analysis, the patients were first assigned to one of two groups: pregnancies exposed to GCs vs those not exposed. Secondly, to evaluate the dose effect of GCs, we compared three dose ranges throughout pregnancy: prednisone ≤10 mg daily, prednisone >10–24 mg daily and prednisone >25 mg daily. Statistical analysis included descriptive statistics, chi square, Student t test, Fisher’s exact test, ANOVA and Scheffe’s test as post-hoc and logistic regression; relative risk (RR) with confidence intervals (CI) of 95% were calculated. For the analysis each pregnancy was considered as an independent event.

Results:

• We included 143 pregnancies in 136 patients. There were 111 pregnancies exposed to GCs and a greater exposure to azathioprine (55% vs 21.9%, p=0.001) in comparison with those not exposed to GCs. There were no differences in maternal complications in the analyzed groups by dose ranges. Major fetal complications were dose-related: low weight, low height, and preterm birth. In the multivariable analysis, the use of prednisone >25mg daily was associated with preterm birth (RR 3.3, CI 95% 1.39–8.04, p=0.0002), low birth weight (RR 3.25; CI 95% 1.37–7.18, p=0.0001).

Conclusion:

• This study suggests that fetal complications associated with the use of prednisone are dose-related (>25 mg). The use of low to moderate doses of prednisone during pregnancy is safe.

Disclosure: D. Miranda, None; M. A. Saavedra, None; E. Gomez, None; A. D. Rocha Muñoz, None; J. G. Ramos, None; L. J. Jara, None.

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Maria N. Antonio1, Cecilia Reimundes1, Cecilia Catoggio1, Analia V. Longo1, Analia P. Alvarez2 and Carlos Perandones1. 1CEMIC, Buenos Aires, Argentina, 2Hospital Penha, Buenos Aires, Argentina.

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) present factors associated with the reproductive system that can increase the risk of the disease, but the literature is controversial.

The reproductive system variables are influenced by multiple social, ethnic, economic and cultural factors that can function as confounding variables. For this reason, the optimal SLE population control should be matched by age and sociodemographic features.

We compared reproductive variables of a group of women with SLE with pair-matched healthy controls.

Methods: A case-control study was performed using a cross-sectional survey to analyze variables of the reproductive system in patients with SLE. We included women over 18 years-old with SLE according to ACR criteria. Each case was matched with a healthy control belonging to her sociocultural environment and having her age ± 5 years.

The survey included multiple demographic and disease variables, as well as reproductive system features: age of menarche and menopause, number of pregnancies and fetal losses, and contraceptive methods. Paired t test and McNemar’s test or Fisher exact test were applied for continuous and categorical variables, respectively.

Results: We included 83 cases with a mean age of 39.2 ± 10.8 years (range19–66) and the mean age at SLE diagnosis was 26.9 ± 10.3 years. Previous treatments were as follows: 91% hydroxychloroquine, 32% cyclophosphamide, 31% azathioprine, 24% mycophenolate mofetil, and 16% methotrexate.

<table>
<thead>
<tr>
<th>Cases Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche (age ± SD)</td>
</tr>
<tr>
<td>Menopause (age ± SD)</td>
</tr>
<tr>
<td>Previous Oral Contraceptives (%)</td>
</tr>
<tr>
<td>Fetal Loss (mean ± SD)</td>
</tr>
<tr>
<td>Children (mean ± SD)</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
</tr>
<tr>
<td>Infertility Treatment (%)</td>
</tr>
</tbody>
</table>

Fisher exact test p 0.17
When cyclophosphamide was analyzed as a risk factor for early menopause there were no difference between exposed and non exposed patients.

Conclusion: There were no differences in the age of menarche, previous oral contraceptives, number of pregnancies, fetal losses and children, and the need of infertility treatment between SLE patients and pair-matched controls.

The age of menopause is significantly different but cannot be related only to cyclophosphamide.

Disclosure: M. N. Antoniol, None; C. Reimundes, None; C. Catoggio, None; A. V. Longo, None; A. P. Alvarez, None; C. Perandones, None.


ACR/ARHP Poster Session C
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: T and B Cell Signaling and Genetic Variants
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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High-Throughput Sequencing of 219 Candidate Genes for Identification of SLE-Associated Risk Variants.
Fabiana Farias1, Maria Wilbe2, Johanna Dahlqvist3, Dag Leonard4, Sergey Kozyrev1, Gerli Pielpberg5, Maaja-Leena Eloranta2, Lars Rönblom2, and Kerstin Lindblad-Toh1. 1Uppsala University, Science for Life Laboratory, Uppsala, Sweden; 2Department of Medical Sciences, Scilife Lab, Rheumatology, Uppsala University, Uppsala, Sweden; 3Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China; 4Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China; 5Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease, believed to arise from environmental triggering events in genetically predisposed individuals. To date, more than 50 genes have been associated with SLE through genome-wide association studies. However, only about 15% of the heritability of SLE is explained by these findings. In this study we aimed to identify novel rare genetic variants of functional importance for SLE.

Methods: One hundred and forty Swedish SLE patients, fulfilling the ACR classification criteria for SLE, and 12 healthy controls were included in the study. We sequenced the exomes, promoter regions and putative regulatory regions of 219 genes selected on basis of their role in immune response, autoimmunity or known association with SLE or SLE-related disease complexity in dogs. Selected gene regions were targeted using Roche NimbleGen arrays and the Illumina HiSeq2000 reaching approximately 250x coverage per individual.

Results: We detected 4276 novel single-nucleotide polymorphisms (SNPs; not present in 1000Genomes or dbSNP137) out of which 1258 SNPs were case-only variants. Seventeen genes showed > 5 novel variants private to cases. Of these, three genes have previously been associated with human SLE and 14 are novel candidate genes. Six SNPs (allele frequencies 0.01–0.03 in patients) located in non-coding sequences with potential regulatory function were selected for further studies based on their characteristics in terms of conservation, DNA sequence hypersensitivity, ENCODE data on histone marks and ChIP-seq peaks. The SNPs were validated by genotyping in all patients and in 96 additional healthy controls, to confirm their increased frequency in the patient cohort. Using electrophoretic mobility shift assay, binding of protein complexes was investigated for all six SNPs and they were currently evaluated for their effect on gene expression. The clinical disease manifestations of the patients harboring each of the six SNPs are being followed in a separate pool. The pools were paired-end sequenced using Illumina HiSeq2000 reaching approximately 250x coverage per individual.

Conclusion: This proof-of-principle study highlights the importance of analysis of non-coding putative regulatory DNA regions for the identification of rare variants associated with complex disease.

Disclosure: F. Farias, None; M. Wilbe, None; J. Dahlqvist, None; D. Leonard, None; S. Kozyrev, None; G. Pielpberg, None; M. L. Eloranta, None; L. Rönblom, None; K. Lindblad-Toh, None.

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The Effect and Mechanisms of Icaritin on Regulating Foxp3/IL17a Expression in CD4+ T Cells from SLE.
Jieyue Liao1, Yiu Liu2, Ming Zhao3, Hai Jing Wu4 and Qianjin Lu1. 1Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China; 2Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China; 3Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China; 4Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is a female predominant autoimmune disease characterized by overproduction of autoantibodies. The pathogenesis of SLE is complex. Several studies have revealed that the balance between Treg cells and Th17 cells is destroyed in autoimmune diseases such as SLE.

Icaritin (ICT) is an active ingredient extracted from Chinese herbaeds Epiredium genus. It has been used as an aphrodisiac, tonic and antirheumatic in China. Our previous studies have found that ICT has a wide range of pharmacological and biological activities, including inhibiting T cell activation and enhancing Treg cells suppressive activities. In this study, we explored the effect and mechanisms of Icaritin on regulating Foxp3/IL17a expression in systemic lupus erythematosus.

Methods:
1. CD4+ T cells were isolated from SLE patients by positive selection using magnetic beads. CD4+ T cells were treated with 40uM/L ICT for 72h. Foxp3 and IL17a mRNA levels were determined by real-time RT-PCR. Foxp3 protein level was examined by western blotting. Detection of IL17a level was performed by ELISA.
2. Amounts of H3K4me3 and H3K9me3 and H4 acetylation within the foxp3 and IL17a promoters were analyzed by chromatin immunoprecipitation (ChIP) and real-time PCR.
3. The transcription factor regulating both Foxp3 and IL17a expression was determined by microarray. STAT5b-siRNA and control-siRNA were transfected into CD4+ T cells by transient electroporation. Then CD4+ T cells were treated with 40uM/L ICT for 24h. STAT5b, Foxp3 and IL17a mRNA levels were evaluated by real-time PCR. STAT5b protein levels were examined by western blotting.

Results:
1. Compared to control group, Foxp3 mRNA and protein level were significantly increased in ICT-treated group, while IL17a mRNA and protein level were significantly decreased in ICT-treated group.
2. Compared to control group, H3K4me3 enrichment at the Foxp3 promoter was significantly increased in ICT-treated group; H3K9me3 enrichment at the IL17a promoter was significantly increased in ICT-treated group. There was no significant difference in H4 acetylation level at Foxp3 and IL17a promoter region.
3. Compared to control-siRNA group, STAT5b mRNA level and protein level were significantly decreased. After down-regulating STAT5b expression, Foxp3 and IL17a had no significant changes in ICT-treated group.

Conclusion:
1. ICT can increase the expression level of Foxp3 while decrease IL17a gene expression in CD4+ T cells from SLE.
2. ICT can increase H3K4me3 enrichment at the foxp3 promoter and H3K9me3 enrichment at the IL17a promoter in CD4+ T cells from SLE.
3. Down-regulating STAT5b in CD4+ T cells can inhibit the effect of ICT on the modulation of Foxp3/IL17a balance in CD4+ T cells from SLE.

Disclosure: J. Liao, None; Y. Liu, None; M. Zhao, None; H. J. Wu, None; Q. Lu, None.

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The Selective Loss of SLAMF4+ CD8+ T Cells Contributes to the Decreased Cytotoxic Capacity Observed in Systemic Lupus Erythematosus.
Katalin Kis-Toth, Denis Comte, Maria Karampatsou, Lakshmi Kannan and George C. Tsokos. Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: Signaling lymphocytic activation molecule family member 4 (SLAMF4) engagement by its ligand SLAMF2 can mediate the cytotoxicity of CD8+ T cells and natural killer cells. SLE CD8+ T lymphocytes are reportedly defective in cytotoxicity. The aim of this study was to investigate the expression and function of SLAMF4 on SLE CD8+ T cells.

Methods: The expression of SLAMF4 and its adaptor SAP in healthy and SLE T cells were measured by Q-PCR, flow cytometry and western blot. T cells were treated with immobilized anti-SLAMF4 antibodies and the cytotoxic capacity of the T cells was monitored by the cell surface expression of CD107a, reflecting exocytosis of lytic granules.
Results: We found significant downregulation of SLAMF4 and the adaptor molecule SAP gene and protein expression in SLE T cells compared to normal controls. Characterization of the T cell subsets revealed that SLE patients have significantly less SLAMF4 and CD8 T cells compared to normal control T cells, switching the SLAMF4/SLAMF7 ratio in the favor of SLAMF4 and CD8 T cells which have less SAP expression and decreased cytotoxic capacity. SLAMF4 engagement triggers the degranulation of CD8 T cells and SLE T cells have decreased degranulation compared to normal controls. In the effort to explain the loss of SLAMF4 and CD8 T cells in SLE we found that these cells are more likely become double negative T cells and/or die by apoptosis.

Conclusion: Based on our results we conclude that the selective loss of SLAMF4 and CD8 T cells may contribute to the ineffective capacity of fighting against infections in SLE.

Disclosure: K. Kis-Toth, None; D. Comte, None; M. Karampetsou, None; L. Kannan, None; G. C. Tsokos, None.

Background/Purpose: The interplay between effector and regulatory T cells (Tregs) is a key element among peripheral tolerance mechanisms in Systemic Lupus Erythematosus (SLE). Resistance to suppression has been recently acknowledged as part of the defects shown by T cells from SLE patients. The E3 ligase Cbl-b has been shown to modulate T cell unresponsiveness in SLE. However its potential role in the regulation of peripheral Tregs tolerance has not been fully addressed. The aim of this study was to assess the expression of Cbl-b and its relationship to the resistance to suppression phenotype in SLE patients.

Methods: We included 25 patients with SLE (10 in remission and 15 with active untreated disease) according to the classification criteria of the American College of Rheumatology and 25 age and gender-matched healthy controls. PBMCs were isolated by density gradient and effector (CD4/CD25+) and Tregs (CD4/CD25+/CD127+) were purified by magnetic selection. The expression of Cbl-b and p27kip1 was analyzed by Western blotting. Interaction between Cbl-b and p27kip1 was addressed by immunoprecipitation (IP). Proliferative responses were assessed in allogeneic and autologous cocultures by CFSE. Differences were assessed by t Student test, p < 0.05 was considered as statistically significant. In all cases, an informed consent was obtained, and the ethics committee approved this study.

Results: We found diminished Cbl-b expression in Tregs from SLE patients in comparison to healthy controls (1.3 ± 1.0 vs 2.8 ± 1.8, p = 0.002), which was associated with resistance to suppression in proliferation assays (r = 0.553, p = 0.041). Moreover, this phenomenon was related to deficient expression of the cell cycle regulator p27kip1 in Tregs from SLE patients when compared to healthy controls. We also found by IP assays, that p27kip1 interacts with Cbl-b in Tregs. We found no significant differences regarding to disease activity.

Conclusion: Our data suggest that the ligase Cbl-b is able to regulate the interplay between effector and Tregs, particularly, the resistance to suppression in SLE patients. The E3 Ligase Casitas B Lineage Lymphoma b (Cbl-b) Modulates T Cell Receptor Activation Threshold.

Disclosure: D. Gómez-Martín, None; J. Romo-Tena, None; J. Merayo-Chalico, None; A. Barrera-Vargas, None; J. Alcocer-Varela, None.

Background/ Purpose: Down-regulation of MAP kinase pathway has been recognized in T cells from patients with SLE that result in hypo-methylation of DNA. RasGRP1 is an intracellular signaling protein highly expressed in T cells and activates the Ras signaling pathway downstream of TCR engagement. RasGRP1 deficient mice develop late-onset lymphoproliferative autoimmune syndrome. Previously we reported that defective (alternatively spliced) RasGRP1 transcripts correlate with lower levels of RasGRP1 protein in SLE T cells. Serin/arginine-rich splicing factor 1 (SRSF1) is a member of the serine arginine family of splicing proteins that binds pre-mRNA to regulate alternative splicing. For instance, SRSF1 binds to the 3’UTR of CD3 zeta and enables normal splicing of this signaling protein. (Moulton V et al J Biol Chem. 2010). The purpose of this study is to determine the relationship between aberrant splicing of RasGRP1 and SRF1 expression in SLE T cells.

Methods: Forty-five SLE patients and eighteen healthy subjects were included in this study. T cells were collected from peripheral blood of each subject and RNA was isolated. Expression levels of SRSF1, normally spliced RasGRP1 and DNM1T1 transcripts were assessed by real time quantitative PCR. Immunoprecipitations (IP) were performed to confirm the direct binding of SRSF1 to RasGRP1 mRNA. SRSF1 specific siRNA was used to suppress the expression levels of the RasGRP1 in Jurkat T cell.

Results: Expression levels of SRSF1 transcripts were significantly lower in SLE patients compared with healthy subjects (p = 0.001, t-test). In patients with SLE, expression levels of SRSF1 correlated with those of normally spliced RasGRP1 and DNM1T1 (r = 0.517, p = 0.023 [RasGRP1]; r = 0.555, p = 0.013 [DNMT1]). IP studies suggested that SRSF1 binds directly to RasGRP1 exon11 RNA. RasGRP1 protein level was decreased in Jurkat T cell when exposed to SRSF1 specific siRNA (Figure).

Conclusion: SRSF1 binds to RasGRP1 mRNA and controls its expression. Low SF2A/5SF levels in SLE T cells correlate with the expression levels of RasGRP1 and DNM1T1. We propose that SRSF1 regulates the alternative splicing of important genes in SLE T cells including RasGRP1 and CD3 zeta.

Acknowledgment: This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Disclosure: T. Kurita, None; S. Yasuda, None; V. Moulton, None; Y. Shimizu, None; M. Kono, None; H. Koido, None; K. Oku, None; T. Bohgaki, None; O. Amengual, None; T. Horita, None; G. C. Tsokos, None; T. Atsumi, None.

UC-MSCs Inhibit T Cell Autophagy and Apoptosis in Patients with Systemic Lupus Erythematosus through Mitochondrial Transfer.

Jinyun Chen, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that causes inflammation and immune complex deposition in multiple organs. B lymphocytes, CD4+ and CD8+ T cells are involved in the pathogenesis of SLE. We hypothesized that UC-MSCs may inhibit T cell autophagy and apoptosis via activating mitochondrial transfer.

Methods: We assessed autophagy and apoptosis in T cells from SLE patients and healthy controls using the Autophagy Activity Assay Kit and Annexin V/PI detection kit. UC-MSCs and T cells were cocultured in the presence of 5% serum. By the time the T cells were harvested, autophagy and apoptosis levels were measured. The mitochondrial transfer activity of UC-MSCs was assessed by MitoTracker Green FM staining and mitochondrial DNA detection.

Results: Compared to healthy controls, T cells from SLE patients had significantly increased autophagy and apoptosis levels in both autophagy and apoptosis detection kits. UC-MSCs co-cultured with T cells from SLE patients inhibited autophagy and apoptosis levels and reduced mitochondrial transfer activity. UC-MSCs Inhibit T Cell Autophagy and Apoptosis in Patients with Systemic Lupus Erythematosus through Mitochondrial Transfer.
Background/Purpose: This study is aimed to investigate the role of umbilical cord derived mesenchymal stem cells (UC-MSCs) on autophagy and apoptosis in T cells from SLE patients, and to explore the underline mechanisms involved in this process.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from SLE patients and healthy donors, and cultured under stimulation with anti-CD3/28 antibodies in the presence or absence of autophagy inhibitor 3-MA (5mM for 6h) or activator rapamycin (50nM for 48h). Autophagy levels and apoptotic rates were measured by flow cytometry with the detection of LC3II and Annexin V respectively. To determine the effects of MSCs on T cell autophagy and apoptosis, UC-MSCs were cocultured with T cells at the ratio of 1:10 directly or in transwell system. To observe the changes of pathways upstream of autophagy after MSC treatment, an AMPK activator was added to the cocultures. Meanwhile, mitochondria transmembrane potential (ΔΨm), which was closely related to APPK activation, was marked and measured in MSCs and T cells by MitoTracker Deep Red (MADR).

Results: T cells from SLE patients had both elevated autophagy level and apoptotic rate compared with those from normal controls, which were further increased after anti-CD3/CD28 stimulation. Apoptotic rate of T cells significantly correlated with autophagy level (r=0.570, p<0.0001 for CD4+T; r=0.508, p=0.0011 for CD8+T). Inhibition of autophagy with 3-MA decreased the apoptotic rate of T cells, whereas activation of autophagy with rapamycin increased the apoptotic rate. UC-MSCs significantly inhibited T cell autophagy (22.5±2.4 vs. 36.4±6.3 for CD4+T; 27.2±1.9 vs. 39.2±5.4 for CD8+T, both p<0.05) and T cell apoptosis (22.2±2.6% vs. 49.1±5.7% for CD4+T; 23.3±2.4% vs. 53.2±2.3% for CD8+T, both p<0.05) after cell-to-cell contact coculturing, yet the effect was diminished in transwell system. When AMPK activator added to the cultures, the ability of UC-MSCs to regulated T cell apoptosis was greatly improved. As shown in Figure 1, mitochondria in UC-MSCs could be transferred to SLE T cells when directly cocultured. Consequently, the elevation of ΔΨm in T cells was downregulated after MSC treatment (242.5±8.4 vs. 315.8±5.5, p=0.003 for CD4+T; 139.8±23.5 vs. 199±35.7, p=0.06 for CD8+T), along with the reduction of AMPK.

Conclusion: Autophagy levels are elevated in T cells from SLE patients, leading to aberrant apoptosis. UC-MSCs may inhibit T cell autophagy and apoptosis through mitochondrial transfer.

Figure 1 Transfer of MSC mitochondria to lupus T cells. Mitochondria in MSCs were marked by MitoTracker Deep Red. After cell-to-cell contact coculture, MSC-derived mitochondria were detectable in T cells.

Disclosure J. Chen, None; X. Feng, None; L. Sun, None.

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DNA Hydroxymethylation Changes in CD4+ T Cells from Patients with Systemic Lupus Erythematosus. Ming Zhao, Wei Liao, Bochen Zhu, Ruifang Wu and Qianjin Lu. Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Recent studies have uncovered 5-hydroxymethylcytosine (5hmC) as the sixth base of the genome, and that the Ten-eleven translocation (TET) family proteins is responsible for the generation of 5hmC from 5mC in mammalian cells. 5hmC may function as another epigenetic mark by altering chromatin structure or contributing to the recruitment or exclusion of other DNA-binding proteins that affect transcription. However, the report about DNA hydroxymethylation in CD4+ T cell is SLE is poor, though DNA hypomethylation has been confirmed to contribute to dysregulated mucosal immunity in SLE.

Conclusion: Our study primarily demonstrates that MAIT cells are numerically and functionally deficient in SLE. In addition, we report a novel finding that this MAIT cell deficiency is associated with NK T cell deficiency and elevated PD-1 expression. These abnormalities possibly contribute to dysregulated mucosal immunity in SLE.

Disclosure: J. H. Kang, None; Y. N. Cho, None; H. M. J. Jin, None; H. J. Jun, None; S. J. Lee, None; S. J. Kee, None; Y. W. Park, None.

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DNA Hydroxymethylation Changes in CD4+ T Cells from Patients with Systemic Lupus Erythematosus. Ming Zhao, Wei Liao, Bochen Zhu, Ruifang Wu and Qianjin Lu. Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Recent studies have uncovered 5-hydroxymethylcytosine (5hmC) as the sixth base of the genome, and that the Ten-eleven translocation (TET) family proteins is responsible for the generation of 5hmC from 5mC in mammalian cells. 5hmC may function as another epigenetic mark by altering chromatin structure or contributing to the recruitment or exclusion of other DNA-binding proteins that affect transcription. However, the report about DNA hydroxymethylation in CD4+ T cell in SLE is poor, though DNA hypomethylation has been confirmed to contribute to dysregulated mucosal immunity in SLE. In this study, we will investigate DNA hydroxymethylation in genome-wide in lupus CD4+ T cells.

Methods: 36 SLE patients and 36 healthy controls were recruited. CD4+ T cells were isolated by magnetic beads. The age and sex were matched. All patients fulfilled at least 4 of the SLE classification criteria of ACR. The content of 5hmC in genome was detected by dot blot: hmDBP-NimbleGen Human 3×720K Promoter Plus CpG Island Arrays was completed for identification of genes with different 5hmC modifications between SLE CD4+ T cells and normal controls. mRNA expression levels were measured by real-time RT-PCR. Gene ontology (GO) was analyzed by the Database for Annotation, Visualization and Integrated Discovery (DAVID). Student's t-test for equality of means was used to compare values. P-values < 0.05 were considered as significant.

Results: Compared with normal controls, the content of 5hmC was increased significantly in lupus CD4+ T cells according to the result of dot blot: hmDBP-NimbleGen Human 3×720K Promoter Plus CpG Island Arrays was completed for identification of genes with different 5hmC modifications between SLE CD4+ T cells and normal controls. mRNA expression levels were measured by real-time RT-PCR. Gene ontology (GO) was analyzed by the Database for Annotation, Visualization and Integrated Discovery (DAVID). Student's t-test for equality of means was used to compare values. P-values < 0.05 were considered as significant.

Conclusion: Compared with normal controls, the content of 5hmC was increased significantly in lupus CD4+ T cells according to the result of dot blot: hmDBP-NimbleGen Human 3×720K Promoter Plus CpG Island Arrays was completed for identification of genes with different 5hmC modifications between SLE CD4+ T cells and normal controls. mRNA expression levels were measured by real-time RT-PCR. Gene ontology (GO) was analyzed by the Database for Annotation, Visualization and Integrated Discovery (DAVID). Student's t-test for equality of means was used to compare values. P-values < 0.05 were considered as significant.

Disclosure: M. Zhao, None; W. Liao, None; B. Zhu, None; R. Wu, None; Q. Lu, None.
Activated SLE-T Cells Enhance the Interferon-Alpha Production By Plasmacytoid Dendritic Cells Stimulated By RNA-IC.

**Background/Purpose:** A prominent interferon-α (IFNα) signature is seen in several autoimmune diseases including systemic lupus erythematosus (SLE). Plasmacytoid dendritic cells (pDCs) are the main IFNα producing cells and produce large amounts of IFNα in response to immune complexes containing nucleic acids (ICs). Produced IFNα activates the immune system in a number of ways, including polarization of naïve T helper cells to Th1 cells, expansion and activation of cytotoxic CD8 T cells and enhanced B-cell differentiation and antibody production. Thus, once pDCs are activated they strongly promote the adaptive immune response. However, much less is known about the effects on pDCs by different adaptive immune cells. B-cell differentiation and antibody production. Thus, once pDCs are activated

**Methods:** Human T cells were activated by anti-CD3/CD28 antibodies. T cells or supernatant from T cell cultures were co-cultured with pDCs stimulated by RNA-IC (>20-fold). The frequency of pDCs expressing intracellular IFNα increased when co-cultured with activated CD4+ T cells (5.8%) or CD8+ T cells (6.8%) compared to pDCs cultured alone (0.2%). When cytokines were added to the RNA-IC stimulated pDCs at the same concentration as in the supernatant from activated T cells, both GM-CSF and IL-3 demonstrated a strong stimulatory effect on the IFNα response. The combination of both cytokines increased the IFNα production as much as supernatants from activated T cell. The stimulatory effect of supernatants was significantly reduced after depletion of GM-CSF (92%), blocking of GM-CSF (81%), or its receptor subunits CD131 O.

**Results:** Activated T cells or supernatants from activated T cells increased the IFNα production by pDCs stimulated by RNA-IC -fold. The frequency of pDCs expressing intracellular IFNα increased when co-cultured with activated CD4+ T cells (5.8%) or CD8+ T cells (6.8%) compared to pDCs cultured alone (0.2%). When cytokines were added to the RNA-IC stimulated pDCs at the same concentration as in the supernatant from activated T cells, both GM-CSF and IL-3 demonstrated a strong stimulatory effect on the IFNα response. The combination of both cytokines increased the IFNα production as much as supernatants from activated T cell. The stimulatory effect of supernatants was significantly reduced after depletion of GM-CSF (92%), blocking of GM-CSF (81%), or its receptor subunits CD131 O.

**Conclusion:** Activated T cells enhance the IFNα production by pDCs stimulated by RNA-IC -fold. The frequency of pDCs expressing intracellular IFNα increased when co-cultured with activated CD4+ T cells (5.8%) or CD8+ T cells (6.8%) compared to pDCs cultured alone (0.2%). When cytokines were added to the RNA-IC stimulated pDCs at the same concentration as in the supernatant from activated T cells, both GM-CSF and IL-3 demonstrated a strong stimulatory effect on the IFNα response. The combination of both cytokines increased the IFNα production as much as supernatants from activated T cell. The stimulatory effect of supernatants was significantly reduced after depletion of GM-CSF (92%), blocking of GM-CSF (81%), or its receptor subunits CD131 O.

**Disclosure:** Disclosures: D. Leonard, None; M. L. Eloranta, None; N. Hagberg, None; O. Berggren, None; K. Tandre, None; G. Alm, None; L. Rönblom, None.
Conclusion: The novel splicing variants of Ng and their ectopic expression in PBM C5s may contribute to the pathogenesis of SLE through mediating Ca2+ signal transduction.

Fig 1. Three splicing variants of Ng gene. A: Comparison of IQ motif of Ng-WT, Ng-mu1 and Ng-mu2. B: Schematic diagram of forming of Ng-WT, Ng-mu1 and Ng-mu2. C: A agarose gels with the analysis of the cDNA of Ng gene fragment with primers F2 and R2 as in fig1B. D: A agarose gels with the analysis of the cDNA of Ng with specific primers F2 and R2' as in fig1B.

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Association of Adam33 Polymorphisms with Systemic Lupus Erythematosus. Seong-Wook Kang1, Seung-Taek Song2, Su-Jin Yoo, Mi-Kyoung Lim2, Dong-Hyuk Sheen3, In-Seol Yoon2, Jinhyun Kim2 and Seung-Choil Shim3. 1Chungnam National University School of Medicine, Daejeon, South Korea, 2Eulji University Hospital, Daejeon, South Korea.

Background/Purpose: A Disintegrin and Metalloprotease 33 (ADAM33) is a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloprotease domain, and is located on chromosome 20p13. Recently, the polymorphisms in ADAM33 have been found to be associated with asthma. Among the rheumatic diseases, systemic lupus erythematosus (SLE) is a prototypic Th2-mediated autoimmune disease like allergic disorders.

To assess whether genetic functional variants of ADAM33 are associated with susceptibility to SLE or development of specific phenotypes in patients with SLE.

Methods: We have identified 48 SNPs, and nine SNPs were selected with regard to the LD pattern. Genotyping for g.10918G>C, g.12433T>C and g.13506C>G in the ADAM33 gene was conducted with PCR RFLP methods, and genotyping for g.330C>T, g.517A>G, g.8227 G>A, g.9511 G>T, g.12462 C>T, g.12988 C>A polymorphisms was performed by single-base extension (SBE) using the ABI Prism SNPShot Multiplex kit (Applied Biosystems). We conducted an association study for ADAM33 polymorphisms in 190 SLE patients, 469 healthy controls, and 390 rheumatoid arthritis (RA) patients as a disease control. Haplotype analyses of related variants were performed as well.

Results: Significant associations of ADAM33 polymorphisms with susceptibility to SLE were found at g.8227 G>A, g.12988 C>A, and g.13506 C>G (P value were all below 0.001). Polymorphisms at g.8227 G>A was associated with the A NA titers among SLE patients (P = 0.012). In addition, we analysed the haplotype, and found a positive association of susceptibility to SLE with the major haplotype CGCG (P = 3.5E-11). There was no association between ADAM33 polymorphisms and RA as expected.

Conclusion: ADAM33 polymorphisms were strongly associated with susceptibility to SLE and the development of specific clinical manifestations.

Table 1. Genotype and allele analyses of the polymorphisms of Adam33gene in SLE patients and healthy controls Position

<table>
<thead>
<tr>
<th>Position</th>
<th>Genotype/Allele</th>
<th>Control n (%)</th>
<th>SLE n (%)</th>
<th>Odds ratio (95% CI)</th>
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</thead>
<tbody>
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<td>g.330C&gt;T</td>
<td>CC 426 (90.8) 168 (88.4) 1.00</td>
<td>0.347</td>
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</tr>
<tr>
<td></td>
<td>CT 43 (9.2) 22 (11.6) 1.30 (0.75–2.24)</td>
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<tr>
<td></td>
<td>TT 0 (0.0) 0 (0.0) 0.00</td>
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<tr>
<td></td>
<td>C 895 (95.4) 358 (94.2) 1.00</td>
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<td>T 43 (4.6) 22 (5.8) 1.28 (0.75–2.17)</td>
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<td>g.517A&gt;G</td>
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<tr>
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<td>AG 201 (46.7) 79 (41.6) 1.29 (0.88–1.88)</td>
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<td>GG 64 (14.9) 31 (16.3) 1.29 (0.77–2.17)</td>
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<td>g.8227 G&gt;A</td>
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<td>GA 168 (35.9) 59 (31.6) 0.86 (0.60–1.24)</td>
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<td>TT 2 (0.4) 1 (0.5) 3.75 (0.75–22.66)</td>
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<tr>
<td>g.12433 T&gt;C</td>
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<td>CT 68 (15.1) 12 (6.3) 0.38 (0.20–0.72)</td>
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<td>C 70 (15.9) 14 (7.6) 0.44 (0.25–0.79)</td>
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<td></td>
<td>C 17 (3.7) 10 (6.2) 1.65 (0.73–3.23)</td>
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<td>g.12988 C&gt;A</td>
<td>CC 327 (70.2) 170 (92.4) 1.00</td>
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<tr>
<td></td>
<td>CA 134 (28.8) 14 (7.6) 0.20 (0.11–0.36)</td>
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<tr>
<td></td>
<td>AA 5 (1.0) 0 (0.0) 0.00</td>
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<tr>
<td>g.12988 C&gt;G</td>
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<tr>
<td></td>
<td>CG 207 (46.4) 48 (26.1) 0.49 (0.33–0.73)</td>
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<td>GG 46 (10.3) 45 (24.4) 2.08 (1.28–3.36)</td>
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<td>g.13506 C&gt;G</td>
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<td></td>
<td>CG 299 (33.5) 138 (37.5) 1.19 (0.92–1.53)</td>
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*Calculated from the translation start site.

 Logistic regression analyses were used for calculating OR (95% CI; confidence interval)

Disclosure: X. Luo, None; X. He, None; C. Wu, None; J. Ni, None; L. L. Dong, None; S. Li, None.
Gene Array Analysis Reveals Unique Estrogen Signature in Peripheral Blood Mononuclear Cells of Patients with Systemic Lupus Erythematosus

Stephanie Amici1, Nicholas A. Young1, Lai-Chu Wu2, Mireia Guerau2 and Wael N. Jarjour2. 1The Ohio State University, Columbus, OH, 2The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder predominantly affecting females in the reproductive age range. Estrogen is present at higher levels in this population compared to pre-pubertal and postmenopausal women and has been shown to influence immune cell function by regulating the expression of multiple genes through activation of estrogen receptors (ER) α and β. Recent work using a chromatin immunoprecipitation with ERα has shown that this list may be much larger than what has been characterized to date. In this study, the effects of E2 were examined by comparing gene array expression in peripheral blood mononuclear cells (PBMCs) from premenopausal women with SLE and in healthy premenopausal individuals.

Methods: SLE patients meeting the revised criteria of the American College of Rheumatology, and healthy volunteers were recruited through approved IRB protocols. Whole blood was collected into heparinized tubes and PBMCs were isolated. Cells were cultured with or without 10 nM of 17b-estradiol (E2) for 48 hours. PBMCs were then collected and purified as total RNA and submitted for gene array analysis using HG-U133 Affymetrix® Human Gene Chips. Untreated PBMC arrays served as the internal baseline control for each individual sample and was subtracted from the E2-treated expression values; thus, only the estrogen mediated effect was reported. Data was analyzed using the Multiplot function within the GenePattern software program and with Ingenuity Pathway Analysis Software.

Results: While over 1000 genes were significantly up-regulated over 2-fold in SLE samples when treated with E2, only 236 were identified in corresponding healthy controls. Furthermore, E2 stimulation significantly down-regulated 2530 genes in PBMCs from SLE patients, but only 244 in healthy samples under the same conditions. In concordance, 525 and 1629 genes were found to be uniquely up or down-regulated with E2 treatment in SLE, respectively. Significant E2-mediated regulation of several methyltransferases, including PCMT1 and 9GMDT3, was identified in this analysis. Using Ingenuity Pathway Aanalysis Software, our results identified these genes to be associated with several pathways, including post-translational modification.

Conclusion: These results establish a clear estrogen effect over many genes to produce an estrogen signature, including several genes known to be associated with post-translational modification, and further reveals enhanced regulation in SLE patients when compared to healthy controls.

Table 2. The haplotype frequencies by Adam33 polymorphisms in both SLE patients and controls

<table>
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<tr>
<th>Haplotype</th>
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<th>g.12998</th>
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<tr>
<td>others</td>
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Chi-square p

3.58E-11
5.56E-14
4.1E-6
0.339
0.003
0.010
-
Nuclear Antibody Positive African-Americans Reveals Distinct Differences in Systemic Lupus Erythematosus and Healthy Anti-Nuclear Antibody Positive African-Americans Reveals Distinct Differences in T Cell and Progenitor Populations

**Background/Purpose:** Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder which arises from both genetic and environmental factors that likely affect phenotypic and functional characteristics of multiple cell lineages. Further, almost all SLE individuals are anti-nuclear antibody positive (ANA+) although ANA positivity does not obligate autoimmune disease. The differences in cellular physiology between ANA+ healthy individuals and individuals that go on to develop SLE remain a critical goal in the understanding of SLE development. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of cell isolation techniques. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of cell isolation techniques. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of cell isolation techniques. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of cell isolation techniques. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of cell isolation techniques.

**Methods:** Blood specimens and information on disease activity were collected from eight African American SLE patients. Patients were matched by age (<5 years), race, and gender to healthy individuals positive for ANA without classifiable lupus (ANA+, n=8) and ANA negative healthy controls (ANA-, n=8). Single-cell analysis of cell surface markers was completed by mass cytometry and cellular heterogeneity was analyzed using SPADE.

**Results:** Compared to both ANA+ and ANA- healthy controls, SLE patients had lower frequencies of cytotoxic CD8+ T cells, regulatory CD4+ T cells and early progenitor cell populations (P<0.05). Significant differences in progenitor cells nodes were found in CD4 and CD8 negative CD3+ T cells and surface marker null progenitor cells. Concentrations of serum sCD40 ligand were significantly lower in patients with SLE compared with ANA+ and ANA- healthy controls (P<0.05). Interestingly, sCD40L production positively correlated with a decrease in regulatory CD4+ T cell populations (P<0.01). Further, IL-7 levels were lower in both ANA+ controls and SLE patients compared with ANA- healthy individuals (P<0.05).

**Conclusion:** Our results indicate that early differences in progenitor cell populations may contribute to decreased levels of regulatory CD8+ and CD4+ T cells and autoantibody production systemically. Furthermore, the decreased production of IL-7, which is important for the differentiation of hematopoietic stem cells into lymphoid progenitors, in SLE patients and ANA+ patients may contribute to early immune defects in progenitor lymphoid populations leading to loss of tolerance in autoimmunity.

**Disclosure:** R. Lu, None; S. Slight-Webb, None; H. T. Macek, None; P. J. Utz, None; J. M. Guthridge, None; J. A. James, None.

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**2689**

The CUL4RBB E3 Ubiquitin Ligase Modulator CC-220 Induces Degradation of the Transcription Factors Ikaros and Aiolos: Immunomodulation in Healthy Volunteers and Relevance to Systemic Lupus Erythematosus

**Background/Purpose:** Systemic lupus erythematosus (SLE) is an immunomodulatory compound that binds to cereblin (CRBN), part of the CUL4RBB E3 ubiquitin ligase complex, which has been shown to ubiquitinate the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3). Polymorphisms at the IKZF1 and IKZF3 loci have been associated with risk of systemic lupus erythematosus (SLE). We explored CRBN, IKZF1, and IKZF3 gene expression in peripheral blood mononuclear cells (PBMC) from SLE patients, the effect of CC-220 on Ikaros and Aiolos protein levels and SLE autoantibody production in vitro, and the impact of CC-220 on immunological parameters in a phase 1, double-blinded, placebo-controlled, single ascending dose, healthy volunteer study.

**Methods:** CRBN, IKZF1, and IKZF3 gene expression was measured by qRT-PCR. Ikaros and Aiolos protein levels were measured by western blot and flow cytometry. Anti-dsDNA and anti-phospholipid autoantibodies were measured from SLE PBMC cultures treated for 7 days with CC-220. In the phase 1 healthy volunteer study, 56 subjects were randomized and enrolled in 7 cohorts, with 6 subjects per cohort receiving a single oral dose of CC-220 (0.03 to 6 mg) and 2 subjects per cohort receiving placebo. CD19+ B cells, CD3+ T cells, and intracellular Aiolos were measured by flow cytometry. IL-7 and IL-1β production were stimulated with anti-CD3 or lipopolysaccharide, respectively, in the TruCulture ex vivo whole blood assay system.

**Results:** Compared to normal PBMC, SLE PBMC expressed significantly higher levels of CRBN (1.5-fold), IKZF1 (2.1-fold), and IKZF3 (4.1-fold). CC-220 treatment of whole blood significantly reduced Ikaros and Aiolos protein levels in B cells, T cells, and monocytes, but not in granulocytes. In cultures of SLE PBMC, CC-220 inhibited anti-dsDNA and anti-phospholipid autoantibody production with an IC50 of ~10 nM. Following administration of single doses of CC-220 to healthy volunteers, there was a treatment-related decrease in intracellular Aiolos, with minimum mean percent of baseline values of ~12% to 28% in B cells and ~0% to 33% in T cells for 0.3 to 6 mg. There was also a treatment-related decrease in absolute CD19+ B cells and CD3+ T cells, with minimum mean percent of baseline values of ~41% to 67% for B cells and ~66% to 73% for T cells for 2 to 6 mg. CC-220 administration also resulted in increased IL-2 (maximum mean percent of baseline values ranging from 247% to 1.896% for 0.1 to 6 mg), and a decrease in IL-1β (minimum mean percent of baseline values of ~11% to 6 mg).

**Conclusion:** These results demonstrate that CRBN, IKZF1, and IKZF3 mRNA are overexpressed in PBMC from SLE patients. Targeting the CUL4RBB E3 ubiquitin ligase with CC-220 resulted in a potent reduction in Ikaros and Aiolos protein levels in B cells, T cells, and monocytes, and inhibited autoantibody production. A diminution of single doses of CC-220 (0.3 to 6 mg) reduced intracellular Aiolos protein expression in B cells and T cells, reduced absolute B cell and T cell counts in the peripheral blood.
increased T cell-derived IL-2 production, and decreased LPS-induced IL-10 production in whole blood ex vivo. These findings support the further development of CC-220 for the treatment of SLE and other autoimmune diseases.

Disclosure: P. H. Schaefer, Celgene, 3; Y. Ya, Celgene Corporation, 3; L. Wu, Celgene Corporation, 3; J. Rosek, Celgene Corporation, 3; Z. Yang, Celgene Corporation.

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Background/Purpose: Pre-naive B cells represent an intermediate stage in human B cell development with some functions of mature cells, but their involvement in immune responses is unknown. The aim of this study was to determine the functional role of normal pre-naive B cells and possible abnormalities in systemic lupus erythematosus (SLE) that might contribute to disease pathogenesis.

Methods: Pre-naive, naive and memory B cells from healthy individuals and SLE patients were stimulated through CD40 and were analyzed for IL-10 production and co-stimulatory molecule expression, and their regulation of T cell activation. Autoreactivity of antibodies produced by pre-naive B cells was tested by measuring IgM autoantibodies in culture supernatants after different differentiation media. Results: CD40-stimulated pre-naive B cells produce large amounts of IL-10, but did not suppress CD4+ T cell cytokine production. Activated pre-naive B cells demonstrated IL-10 mediated indirect promotion of CD4+ T cell activation, and IL-10 independent impairment of co-stimulatory molecule expression and TNF-α and IL-6 production. IgM antibodies produced by differentiated pre-naive B cells were reactive to ssDNA. SLE pre-naive B cells were defective in producing IL-10, and co-stimulatory molecule expression was enhanced, resulting in promotion of robust CD4+ T cell activation.

Conclusion: There is an inherent and IL-10 mediated mechanism that limits the capacity of normal pre-naive B cells from participating in cellular immune response, but these cells can differentiate into autoantibody secreting plasma cells. In SLE, defects in IL-10 secretion permit pre-naive B cells to promote CD4+ T cell activation, and may, thereby, enhance the development of autoimmunity.


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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by overproduction of autoantibodies by B cells and breaking self-tolerance of T cells and dendritic cells (DCs). However, little is known about the relationship between these immune cells in the etiology of SLE. Here, we found a novel DC subset and investigated the interaction among immune cell subsets in SLE.

Methods: Peripheral blood mononuclear cells were obtained from 44 patients with SLE, 20 with rheumatoid arthritis (RA), and 8 healthy controls (HD). Circulating B cells, T cells and DCs were defined based on comprehensive flow cytometric analysis for human immune system termed "the Human Immune Project" by NIH/FHOCIS.

Results: The proportion of central memory B cells, effector B cells, and plasmablasts was higher (p<0.04), while that of IgM memory B cells was lower (p<0.001) in SLE, compared to HD and RA. For T cell subsets, the proportion of effector memory T cells was highest in SLE (p=0.04). For DC subsets which were defined as CD3+CD14+CD19+CD20HLA-DR+, the percentage of CD11c+ myeloid DCs significantly decreased in SLE (p<0.001), while that of CD123+ plasmacytoid DCs was comparable among SLE, HD and RA (p=0.48). Interestingly, DCs that expressed neither CD11c nor CD123 were detected exclusively in SLE but not in the control or RA (p<0.001). To assess pathological relevance of this double-negative DC subset in SLE, we calculated the Pearson product-moment correlation coefficient among immune cell subsets and also conducted correlation clustering analysis. Among them, double-negative DCs characterized with the central memory B cells and plasmablasts, and was correlated with plasmablasts (p<0.04) and negatively with myeloid DCs (p<0.001) and plasmacytoid DCs (p=0.04). Furthermore, the percentage of double-negative DCs was correlated with scores of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) index in patients. In 13 patients with treatment-naïve in this cohort, the percentage of double-negative DCs was correlated positively with scores of SLEDAI and BILAG index as well as serum anti-dsDNA antibody levels and negatively with CH50 levels.

Conclusion: These results suggest that a novel CD123+ CD11c+ DC subset characteristically increased in relation to central memory B cells and plasmablasts in patients with treatment-naïve SLE. Furthermore, the frequencies of novel DC subsets were correlated with scores of SLEDAI and BILAG and serum levels of anti-dsDNA antibody, indicating that this DC subset may contribute to disease activity and autoantibody production. A thorough further studies are required, our findings would shed light on the activation mechanism of autoantibody production through the interaction between a novel DC subset and central memory B cells/plasmablasts in SLE and could be potentially useful in the design of new therapeutic strategies.

those with inactive disease (52.9 vs 27.6 %, p = 0.004). Finally, infiltration of CXCR4-expressing CD19+ B cells into the renal interstitium was more prominent in lupus nephritis than IgA nephropathy (p = 0.003).

Conclusion: In SLE patients with active disease, B cells with upregulated expression of CXCR4 and enhanced chemotactic responsiveness towards CCL12 were increased in circulation. These aberrant B cells may be involved in the pathogenic process of SLE by infiltrating into the inflamed organs such as kidneys.


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Hyporesponsiveness to TLR9 in Term of Cytokines Production By B Cells in SLE-Patients.

Results: SLE patients had a lower frequency of proliferating B cells upon TLR9 stimulation than HD (p<0.05). B cells from HD significantly upregulated CD38, resulting in a 3-fold increase after TLR9 stimulation, while B cells from HD significantly upregulated any of the surface markers following BLyS stimulation indicating that SLE patients exhibited significantly higher levels of IL-6 in their serum. Furthermore the SLE patients exhibited significantly higher levels of IL-6 in their serum.

Background/Purpose: The role of B cells in immunity has been mainly related to the generation of antibodies and formation of immune complexes. However, B cells can exert additional functions, such as antigen presentation, activation of T cells, formation of lymphoid organs and secretion of cytokines which has not been comprehensively explored in human autoimmunity. In systemic lupus erythematosus (SLE), which is a prototypic autoimmune disease characterized by a breakdown of tolerance toward nuclear antigens, cytokine production induced by toll-like receptor (TLR) 9 is of great interest. It remains unclear to what extent B cells from SLE patients are able to produce cytokine in reaction to TLR9 stimulation.

Methods: Peripheral B cells from 18 SLE patients and 13 healthy donors (HD) were purified from peripheral blood mononuclear cells (PBMCs) by Magnetic Activated Cell Sorting and were stimulated with CpG 2006 in vitro for 48 hours. Subsequently, cell culture supernatants were tested for 28 cytokines (Bio-Plex). In a subgroup of subjects (6 SLE, 10 HD), activation status (CD38 expression), proliferation (% Ki67 positivity), cytokine production and correlated with disease activity, anti-dsDNA titers upon TLR9 stimulation was compared regarding proliferation, activation and cytokine production in reaction to TLR9 stimulation.

Conclusions: B cells from SLE patients and HD upon TLR9 stimulation was compared regarding proliferation, activation and cytokine production and correlated with disease activity, anti-dsDNA titers and CD38 expression following BLyS stimulation indicating that SLE patients exhibited significantly higher levels of IL-6 in their serum.

With respect to monocyte activation SLE patients expressed significantly more CD80, CD86 and HLA-DR in the resting state compared to healthy controls. This baseline hyperactivated state of the SLE monocytes results in up-regulated levels of pro-inflammatory cytokines and increased production of cytokines. The role of B cells in immunity has been mainly related to the generation of antibodies and formation of immune complexes. However, B cells can exert additional functions, such as antigen presentation, activation of T cells, formation of lymphoid organs and secretion of cytokines which has not been comprehensively explored in human autoimmunity. In systemic lupus erythematosus (SLE), which is a prototypic autoimmune disease characterized by a breakdown of tolerance toward nuclear antigens, cytokine production induced by toll-like receptor (TLR) 9 is of great interest. It remains unclear to what extent B cells from SLE patients are able to produce cytokine in reaction to TLR9 stimulation.
Background/Purpose: Systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA) are autoimmune diseases which develop secondary to immune self-tolerance failure. Both diseases are characterised in part by the production of pathogenic autoantibodies. Although they are different clinically, genetically and immunologically, SLE and GPA may be treated successfully with rituximab, an anti-CD20 monoclonal antibody B cell depleting drug.

The repopulation of B cells post-rituximab is of interest as the timing may differ in different autoimmune diseases and may be associated with serum factors, such as B cell activating factor (BAFF), which promotes B cell survival or with characteristics of specific B cell subsets.

Methods: A prospective longitudinal study of 12 patients with SLE and 12 patients with GPA pre-rituximab and at set intervals post-rituximab with matched autoimmune controls was conducted. Demographic, clinical and laboratory data was obtained in all patients with comparison to healthy controls.

Flow cytometry analysis of transitional B cell, naïve mature B cell and memory B cell subsets was conducted in experiments staining isolated peripheral blood mononuclear cells with antibodies to CD19, IgD, CD27, CD24 and CD38. The expression of α4β7 integrin by B cell subsets was analysed. Plasma BAFF levels were measured by ELISA at baseline, 3 months and 6 months post-rituximab. Statistical analysis was done using GraphPad Prism version 5.

Results: B cells were found to repopulate the blood earlier after rituximab in some cases of SLE compared to GPA. There was no statistically significant difference between the pre-rituximab CD19+ B cell percentage of total lymphocytes in SLE and GPA (p<0.37), however at 3 months and 6 months post-rituximab SLE patients had a greater population of CD19+ B cells in the peripheral blood compared to GPA patients (p=0.02, p=0.001, respectively). Early repopulation was found to be independent of serum factors, but was related to the expression of α4β7 integrin by subsets of B cells. α4β7 integrin expression by T1 and T2 transitional B cells, naïve mature B cells and memory B cells was significantly lower in SLE patients compared to GPA patients pre-rituximab (p<0.0001, p=0.0003, p=0.0008 and p=0.0005, respectively). A separate analysis revealed significantly lower α4β7 integrin expression in the early repopulation group, defined as B cell count > 5 cells/μl 3 months post-rituximab, compared to SLE patients who repopulated the peripheral B cell pool later (p=0.004, p=0.004 and p=0.003, p=0.07, respectively).

Plasma BAFF levels were elevated in SLE and GPA patients pre-rituximab compared to HC (p=0.008, p=0.001 respectively) with a rise in BAFF levels detected in SLE 3 months post-rituximab (p=0.006) but no difference in SLE 6 months post-rituximab (p=0.25). Plasma BAFF levels did not change significantly in the GPA cohort post-rituximab. Plasma BAFF levels were positively correlated with percentage transitional B cells (r=0.44, p=0.04).

Conclusion: There may be an association between the early repopulation of the peripheral blood B cell pool, α4β7 integrin by subsets of B cells and rise in BAFF levels in a cohort of SLE patients.

Disclosure: P. M. K. Lutano, None; D. P. D'Cruz, Investigator; S. J. Spencer, None.

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Relationship Between Soluble sCD23 and B Cell Activation Factor in Patients with Systemic Lupus Erythematosus before and after Rituximab.

Laura Heretiu1, Maria J. Leandro2, Venkat Reddy3, David A. Isenberg1 and Geraldine Cambridge2. 1'Sf. Maria' Clinical Hospital, Bucharest, Romania, 2Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, 3Centre for Rheumatology and Musculoskeletal Medicine, University College London, London, United Kingdom.

Background/Purpose: CD23 is the low-affinity receptor for IgE (FceRII). The soluble form, sCD23 is released into the circulation and in vitro this is consistent with clearance from naïve B cells and expression of CD27 (a marker of memory B cells). BAFF (B cell activation factor) is a survival factor for predominantly naïve B cells and is involved in B cell proliferation, plasma cell differentiation and, with APRIL, also class switching. High levels of sCD23 and of BAFF can be present in sera from patients with Systemic Lupus Erythematosus (SLE) and other autoimmune diseases. The interaction between sCD23 and BAFF has not been studied in relation to Rituximab (RTX) treatment.

Aim To investigate the relationship between sCD23 and serum BAFF at baseline and after RTX in patients with SLE.

Methods: Twenty-eight patients with SLE (diagnosed according to the 1982 ACR revised criteria) were studied before B cell depletion therapy (BCDT) based on RTX and 18 SLE patients after RTX treatment. Twenty-eight healthy controls (HC) were also included. Serum sCD23 (normal range given by manufacturers; 1235–5024pg/ml) and BAFF levels were determined using ELISA. Results were analysed in relation with C3 level, anti-ds-DNA titre, IgA, IgG, IgM level and CD19+ B cell count.

Results: Before RTX, sCD23 levels were positively correlated with serum BAFF (p=0.05, r^2 0.47). There was no correlation between sCD23 levels with C3, anti-ds-DNA titre, IgA, IgG or IgM. In HC, sCD23 levels did not correlate with serum BAFF (r^2 =0.23; p=0.10). Further, in patients with levels of sCD23 above the normal range (>5024pg/ml; n=7) median BAFF levels were significantly higher than those with sCD23 within normal limits (n=21) (median BAFF levels: 3.37 and 1.35 ng/ml respectively).

In the 15/28 SLE patients with active disease (BILAG score), there was an even stronger correlation between sCD23 levels and serum BAFF (r^2=0.56, p=0.0001) but no correlation between sCD23 and anti-ds-DNA, IgA, IgG or IgM levels. There was a tendency towards lower C3 values in patients with sCD23 above the normal range. Median BAFF levels were significantly higher in this group (n=6; 5.75 ng/ml) compared to patients with sCD23 within the normal range (n=9; median BAFF: 1.25 ng/ml) (p=0.001).

After RTX, in 10 patients from whom serial samples were available, sCD23 decreased by a median of 39% at 3 months and 56% at 3-6 months consistent with removal of the majority of circulating B cells but levels did not fall below the normal range.

Conclusion: In vitro, the addition of BAFF to B cell cultures stimulated through either Toll-like receptors and the B-cell receptor significantly increased sCD23 cleavage from the B cell surface. Before RTX, serum BAFF levels were related to levels of sCD23 above the normal range in patients with SLE, most markedly in patients with active disease. Serum BAFF is raised in some SLE patients due to changes in availability of BAFF, R-B cell lymphopoenia, BAFF production, or induction by interferons. Germinal center structure is also disturbed in SLE, possibly related to high BAFF levels, which may result in decreased stringency for naïve B cell differentiation into memory phenotype, accompanied by release of sCD23. Levels of sCD23 may be a useful measure of B cell maturation in vivo.

Disclosure: L. Heretiu, None; M. J. Leandro, None; V. Reddy, None; D. A. Isenberg, None; G. Cambridge, None.
Survival in Systemic Sclerosis-Pulmonary Arterial Hypertension By Serum Autoantibody Status.

Background/Purpose: Previous studies have shown that anticientromere (AC) and isolated nucleolar (NUC) antibodies are the most common autoantibodies in patients with systemic sclerosis (SSc) and World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH). The goal of the present study was to determine the association between serum autoantibodies and survival in patients with newly diagnosed PAH who are enrolled in the PHAROS (Pulmonary Hypertension and Recognition of Outcomes in Scleroderma) Registry.

Methods: We evaluated patients from the multi-center, prospective, observational PHAROS registry who had definite PAH diagnosed by right-heart catheterization (RHC) (mean pulmonary artery pressure (mPAP) ≥ 25mmHg and pulmonary capillary wedge pressure (PCWP) ≥ 15mmHg) within 6 months of enrollment. Medical history, laboratory (including serum autoantibodies), pulmonary function test, echocardiogram, 6-minute walk distance, and RHC data were collected at baseline and biannually or as clinically indicated. Mortality data were collected from participating centers' medical records and/or the Social Security Death Index. Kaplan-Meier estimates for survival were determined for 6 different autoantibody groups. Multivariable Cox regression analyses were performed to assess risk of death by hazard ratios (HR) in each autoantibody group, controlling for age, sex, SSc disease duration (defined as duration since first Raynaud symptom), forced vital capacity (FVC) % predicted, and skin score.

Results: 163 PHAROS subjects met WHO group 1 PAH criteria and had serum autoantibody information available (7 missing autoantibody data, 7 with negative autoantibodies). More than half had either AC or NUC; 61 (36%) subjects had AC, 39 (23%) NUC, 11 (6%) AC and Scl70, 28 (16%) had mixed/other, 9 (5%) RNA polymerase III (RNApol), 8 (5%) U1RNP autoantibodies. The mean SSc disease duration at PAH diagnosis was longest for AC (19.3±13.4y) and shorter for NUC patients (12.2±9.8, compared to AC p=0.02). Thirty-two (21%) subjects died over the mean follow-up time of 2.4±1.7 (median 2.0, range 0-7.2) years. 1- and 3-year survival across all antibody groups was 93% and 77%; 1- and 3-year survival estimates were 94% and 72% for AC; 94% and 79% for NUC; 89% and 63% for Scl70; 100% and 88% for RNApol; 92% and 79% for mixed/other. No patient with RNApol or negative autoantibodies died over the follow-up period. For all autoantibody groups, unadjusted and adjusted HR

2698

Optimizing Scleroderma Centers of Excellence: Perspectives from Patients and Scleroderma (SSc) Experts.

Background/Purpose: SSc is a complex, diffuse, devastating health condition of vascular injury, inflammation and fibrosis resulting in multiple organ-system derangements with high impact on survival and quality of life. Demonstrated research activity tends to define SSc Centers of Excellence (SCoEs) certification. However, SSc complications require coordinated high-level multi-specialty expert care. The Scleroderma Foundation in partnership with the Scleroderma Australia and Scleroderma Society UK engaged SSc patients and SSc health providers (HPs) in a multi-tiered process to assess priorities in recognition of SCoEs.

Methods: A mixed methods design ensured comprehensive item collection in addressing 'important qualities and services in a certified SSc Center of Excellence'. A core of 35 patients, SSc HPs from 8 countries initiated the process through an iterative process using nominal group technique with rounds of item collection modification and review until saturation and satisfaction of proposed survey content was achieved and subsequently field-tested with a 5 point scale (critical to low importance). Participation was screened and "gate-controlled" with online survey access through a unique one-time link. Telephone interview was offered for accessibility. Responses from SSc patients showed statistically significant association between risk of death and autoantibody positivity.

Conclusion: Anticientromere and NUC autoantibodies are prevalent in SSc patients with PAH. PAH may be a late complication in AC patients, but may occur earlier in SSc patients with other autoantibodies. There does not appear to be a significant association between SSc antibody type and survival in patients with PAH.

Table 1: Clinical Characteristics for World Health Organization Group 1 (PAH) Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>25th</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56.0</td>
<td>10.8</td>
<td>57.0</td>
<td>38</td>
<td>65.0</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>55</td>
<td>36</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>Skin score</td>
<td>60</td>
<td>20</td>
<td>60</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>36.6</td>
<td>7.7</td>
<td>35.0</td>
<td>28.0</td>
<td>44.0</td>
</tr>
<tr>
<td>Forced vital capacity (FVC) % predicted</td>
<td>50.5</td>
<td>17.4</td>
<td>50.0</td>
<td>30.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>

Disclosure: The authors have nothing to disclose.
patients and HPs were compared by Pearson’s X² or Fisher’s exact tests as appropriate.

**Results:** Initial phases yielded a 54 item survey that was field-tested in 15 SSc patients and HPs. 400 patients and SSc HPs received surveys of which 299 from 19 countries (75% response rate) were completers. Expert care superseded research as a priority of ‘critical importance’ by HPs and patients respectively at 69% and 48% (p = 0.02) and by 94% and 89% (p = 0.8) when ‘critical to very important’ were collapsed. 3 questions provided internal cross-validation of this query. “SCoEs should engage in research” received 57% of patients and 48% of HPs (p = 0.02) as being critical. Further, education, rehabilitative services and support networks were consistently highly rated items with topics stratified by ratings (Tables 1 & 2). Discrepant areas of importance between patients and HPs are highlighted in tables.

**Conclusion:** Participation was robust in all project stages emphasizing the perceived global importance of this effort. Though research is of clear importance, quality expert care incorporating rehabilitative and educational provisions is a SCoE operational priority. These findings signal the need to redefine SCoE certification standards and provide a roadmap to SCoE development.

### Table 1. Selected surveys. 5-point scale represented under 3 categories: 1. Critical importance, 2. Very important and 3. Moderate importance to not important/collapsed. *P-value = bottom row groups.

<table>
<thead>
<tr>
<th>Survey Area</th>
<th>Patients</th>
<th>HPs</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Red Flag Symptoms’ to help patients recognize when to seek medical attention</td>
<td>54%</td>
<td>28%</td>
<td>49%</td>
</tr>
<tr>
<td>Overview of available treatments for SSc (with associated risks and benefits)</td>
<td>46%</td>
<td>17%</td>
<td>35%</td>
</tr>
<tr>
<td>Stress reduction, cold management, pain management strategies, and exercise</td>
<td>46%</td>
<td>21%</td>
<td>42%</td>
</tr>
<tr>
<td>Dietary/nutritional strategies to ease symptoms</td>
<td>38%</td>
<td>15%</td>
<td>34%</td>
</tr>
<tr>
<td>Current clinical trials available</td>
<td>36%</td>
<td>28%</td>
<td>35%</td>
</tr>
<tr>
<td>Over-the-counter medications or preparations for relieving symptoms</td>
<td>35%</td>
<td>13%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Specialized treatment options (like hand surgeries or stem cell transplants) ‘Helping’ tools and devices for assistance with daily living | 34% | 11% | 30% |

### Table 2. Priority of Perceived Educational Needs

<table>
<thead>
<tr>
<th>Educational Needs</th>
<th>Patients</th>
<th>HPs</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Red Flag Symptoms’ to help patients recognize when to seek medical attention</td>
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<td>Over-the-counter medications or preparations for relieving symptoms</td>
<td>35%</td>
<td>13%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Clinical association | No. of studies | Anti-SSc III positive patients | Anti-SSc III negative patients | Odds ratio (95% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>18</td>
<td>498/612</td>
<td>263/6612</td>
<td>0.46 (0.22–0.96)</td>
</tr>
<tr>
<td>Diffuse cutaneous SSc</td>
<td>26</td>
<td>512/666</td>
<td>247/6612</td>
<td>4.12 (2.72–6.24)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>16</td>
<td>36/664</td>
<td>55/74769</td>
<td>0.94 (0.68–1.29)</td>
</tr>
</tbody>
</table>

**Background/Purpose:** Anti-SSc polymerase III antibodies (anti-SSc III) are one of the most frequent antinuclear antibodies identified in systemic sclerosis (SSc), with an estimated prevalence of 11% (95% CI: 8–14) (1). Anti-SSc III has been associated with some clinical characteristics linked with a poor prognosis such as diffuse cutaneous involvement or renal crisis. More recently, anti-SSc III have been suggested to play a role in immunological response to cancer (2). This study aimed to (i) confirm this clinical phenotype in a new French cohort followed by a systematic review and meta-analysis of the literature; (ii) test whether unknown clinical associations could be highlighted by a meta-analysis.

**Methods:** One hundred and thirty tree consecutive and unselected SSc patients were tested for anti-SSc III. Clinical characteristics were retrieved from our database. PubMed and EMBase were searched for all references providing clinical characteristics of anti-SSc III positive and negative (controls) SSc patients. Meta-analysis was performed using number of anti-SSc III positive and controls patients, clinical characteristics and organ involvement.

**Results:** Twelve patients were found to be anti-SSc III positive in our cohort. Anti-SSc III was associated with diffuse cutaneous involvement (p = 0.02), myositis, renal crisis and cancer (p = 0.01). The systematic review retrieved 112 abstracts from 2003 references, which were read in full-text. Forty-five studies were finally included in the meta-analysis. The number of studies providing data for each clinical association was comprised between 4 and 26; between 256 to 1098 anti-SSc III positive patients and 2088 to 6612 controls were included in analysis. Anti-SSc III were positively associated with diffuse cutaneous involvement, joint involvement, renal crisis, heart involvement and cancer; and negatively associated with female sex. There was no association between anti-SSc III and esophageal involvement, pulmonary hypertension, interstitial lung disease, digital ulceration, and myositis (Table 1).

**Conclusion:** This meta-analysis confirmed that SSc patients with anti-SSc III are at higher risk of severe skin extension, renal crisis and cancer. Merging results from numerous studies also highlighted less known associations such as joint and heart involvement. Patients carrying anti-SSc III should benefit from an appropriate screening of these potentially severe complications.


2701

Relevance of the 6-Minute Walking Test in Assessing the Severity and Outcome of Pulmonary Arterial Hypertension Associated with Systemic Sclerosis, without Extensive Interstitial Lung Disease.

Background/Purpose: In pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc), no study has yet evaluated the correlation between the 6-minute walking test (6MWT) distance and the right-heart hemodynamic parameters, in SSc-PAH patients without extensive interstitial lung disease (ILD). As the ILD correlation between the baseline 6MWT total distance and the RHC hemodynamic variables remains important in this test, during follow-up, a weak correlation persists between Δ6MWT and ΔmPAP, but not with ΔCI. These results question the relevance of the 6MWT as an outcome measure for SSc-PAH patients.

Methods: Patients with definite SSc (according to ACR 1987 and/or Leroy criteria), RHC-proven pre-capillary PAH and no extensive ILD on chest HRCT were enrolled. The Δ6MWT (total distance was non-significantly and weakly correlated with ΔmPAP (r = 0.20, p = 0.15) and with ΔPVR (r = 0.17, p = 0.22). Similar results were found on the validation cohort, but reached statistical significance (ΔmPAP : r = 0.20, p = 0.03 ; ΔPVR : r = 0.29, p = 0.008). There were no correlation between Δ6MWT total distance and ΔCI in both cohorts.

Conclusion: To our knowledge, this study is the first to prove a correlation between the baseline 6MWT total distance and the RHC hemodynamic parameters, in SSc-PAH patients without extensive ILD. As the CI explains only 8–21% of the distance, the weight of confounding comorbidities remains important in this test. During follow-up, a weak correlation persists between Δ6MWT and ΔmPAP, but not with ΔCI. These results question the relevance of the 6MWT as an outcome measure for SSc-PAH patients.

Disclosure: S. Sanges, None; D. Launay, None; R. L. Rhee, None; O. Sitbon, None; E. Hachulla, None; L. Mouton, None; L. Guillemin, None; L. Rottat, None; P. Cleson, None; J. F. Cordier, None; S. M. Kawut, None; G. Simonneau, None; M. Humbert, None.

2702

Key Roles for Mir-155 and Mir-21 in Progressive Lung Fibrosis Associated with Systemic Sclerosis (SSc-ILD).

Background/Purpose: We have already reported that macrophage activation, and up-regulation of TGF-beta and interferon-regulated genes are involved in progressive SSc-ILD. Micro-RNAs (miRNA) are a class of small noncoding RNAs that control gene expression and are eventually involved in most biological processes. Therefore, we analyzed simultaneously miRNA and mRNA in the same prospective cohort of SSc-ILD patients in order to explore their complex network and the miRNA’s involvement in progressive lung disease.

Methods: Lung tissue was obtained by open lung biopsy in 22 consecutive SSc-ILD patients (11 diffuse and 10 limited cutaneous SSc patients; 5 controls). High-resolution computerized tomography (HRCT) was performed on baseline and 2–3 years after treatment that was based on lung histologic classification. Microarray analysis (mRNA and miRNA) was performed and the results correlated (Pearson’s) with changes in HRTC score (FibMx). MirConnX software was used to explore the gene regulatory network between mRNA and miRNA. The study was approved by the Institutional Review Boards from both universities (Brazil and USA).

Results: As already shown, despite treatment, most of SSc-ILD patients progressed based on delta FibMx (p < 0.01). Lung mRNA microarray analysis distinguished SSc-ILD from controls (FDR-corrected, q < 0.25) with 185 miRNA genes (present in 25%) that had significant differential expression. The miRNA microarray analysis also confirmed the altered expression of hundreds of genes in our SSc-ILD cohort and MirConnX simultaneous analysis of miRNA and mRNA showed 4 relevant miRNAs in the center of this multifaceted regulation (graphical): mir-182, mir-141, mir-155, and mir-195 (graphical). Pearson’s correlation between miRNAs and the top-50 most upregulated miRNAs in SSc-ILD compared to controls showed that mir-155 was strongly correlated (r = 0.5) with 32/top-50 genes, such as IL12A and DHFR. mir-21 was the second most correlated (22/top-50 genes), followed by mir-195 (21/top-50 genes), mir-141 (22/top-50 genes), and mir-182 (19/top-50 genes). mir-155 and mir-21 were also strongly negatively correlated with several top-downregulated mRNA genes, including IL12A, with r = 0.70. A heatmap of the most informative miRNAs showed mir-155 clustering together with mir-21, a known mRNA involved in idiopathic lung fibrosis; and both mir-155/mir-21 expression were strongly correlated (r = 0.6). Surprisingly, only 4 miRNAs were correlated to the delta FibMx: mir-155 (r = 0.65), mir-182 (r = 0.49), mir-27a (r = 0.49), and mir-21 (r = 0.47).

Conclusion: Mir-155 and mir-21 were the center of this complex altered gene expression in the lungs of SSc-ILD. Moreover, these miRNAs were key for the progression of the lung fibrosis based on a CT score. Together, anti-miRNA therapy might be a novel target to prevent progressive SSc-ILD.
Elevated Serum Levels of Endostatin in Mixed Connective Tissue Disease - Association with Pulmonary Fibrosis and Digital Ulcers. Siilje Reiseter1, Ragnar Gunnarsson2, Torhild Garen3, May Britt Lund1, T. Mogens Aalokken4, Anna M. Hoffmann-Vold1, Øyvind Molberg1 and Thor Ueland5. 1 Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 2 Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway. 3 Department of Respiratory Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway. 4 Department of Radiology, Oslo University Hospital Rikshospitalet, Oslo, Norway. 5 Research Institute for Internal Medicine, University of Oslo, Oslo, Norway.

Background/Purpose: Mixed Connective Tissue Disease (MCTD) is a chronic, immune-mediated disorder defined by the combined presence of serum anti-RNP antibodies and selected clinical features of Systemic Sclerosis (SSc), Systemic Lupus Erythematosus and Polymyositis. Previous studies have revealed increased values of endostatin and Vascular Endothelial Growth Factor (VEGF) in MCTD (1) and SSc (2), suggesting that an altered angiogenic balance might play a pathogenic role in both diseases. The aim of this study was to evaluate the serum levels of endostatin and VEGF in MCTD, compared to SSc and Healthy Controls (HC).

Methods: Sera of MCTD patients (N=169) from the cross-sectional nationwide Norwegian MCTD cohort (n=136) and the Norwegian Systemic Tissue Disease and Vasculitides Registry (NOSVAR) (n=33) were assessed. 170 SSc patients (N=310) were included from NOSVAR. Age- and sex-matched healthy blood donors were included as HC (N=100). Clinical parameters examined in MCTD patients were: digital ulcers (N=136), pulmonary fibrosis (N=158) and Forced Vital Capacity (FVC) % of predicted value (N=142). Pulmonary fibrosis was defined according to the Fleischner Society classification system for high-resolution CT Abnormalities. Serum levels of endostatin and VEGF were assessed by ELISA and compared by Means (M) and Standard Deviation (SD) in all groups. Statistical differences were analyzed by the independent sample t-test with significance level P < 0.05.

Results: The levels of endostatin were higher in the MCTD group (M:SD) 83.0(24) ng/ml compared to HC 65.1(12) ng/ml (P < 0.001), but lower compared to SSc 93.0(37) ng/ml (P < 0.001). The levels of VEGF in MCTD were not different compared to HC and SSc. However, levels of VEGF were elevated in SSc vs. HC (251.8(185) vs. 186.1(130) ng/ml, P < 0.001). MCTD patients with digital ulcers had higher endostatin levels than MCTD patients without digital ulcers (79.6(21) ng/ml, P < 0.05). Mean endostatin levels were increased in MCTD patients with pulmonary fibrosis 90.5(33) ng/ml compared to MCTD without pulmonary fibrosis 79.9(20) ng/ml (P < 0.05). Correspondingly, MCTD patients with VFC < 80% had higher endostatin levels 94.5(33) ng/ml than MCTD patients with VFC ≥ 80% 81.8(21) ng/ml (P < 0.05).

Conclusion: MCTD patients have significantly elevated serum levels of endostatin, but not elevated serum levels of VEGF. Increased circulating levels of endostatin can indicate dysregulation of angiogenesis in MCTD, particularly in patient subgroups with digital ulcers and pulmonary fibrosis.

References:

Disclosure: S. Reiseter, None; R. Gunnarsson, None; T. Garen, None; M. B. Lund, None; T. M. Aalokken, None; A. M. Hoffmann-Vold, None; Molberg, None; T. Ueland, None.

2704

Fatigue in Systemic Sclerosis. Didem Uzunaslan1, Caner Saygin2, Tufan Torun2, Mehmet Ozdemir2 and Gulen Hatemi2. 1 University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey. 2 Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: Fatigue is a frequently reported disabling symptom for patients with systemic sclerosis (SSc). It has a major impact on overall quality of life including work, family and social life. Our aim is to evaluate the frequency of fatigue among SSc patients compared to healthy and diseased controls and to delineate the factors associated with fatigue.

Methods: We included SSc and rheumatoid arthritis (RA) patients who visited our outpatient clinic for their routine follow-up and healthy controls recruited from hospital staff. Comprehensive physical examination with nailfold capillaroscopy and assessment of Rodnan skin score (RSS) were performed by a single physician. Health assessment questionnaire disability index (HAQ-DI), multidimensional assessment of fatigue (MAF) scale, fatigue impact scale (FIS), Beck depression inventory (BDI) were filled by all participants. Having a score of ≥ 5 in FSS was tabulated as having fatigue for statistical analysis. Multivariate regression analysis was performed to determine the factors associated with high fatigue scores in SSc.

Results: Seventy patients with SSc, 52 RA patients and 100 healthy controls were included in this study. MAF scores were significantly higher among RA patients (p < 0.0001), followed by SSc patients (p < 0.013) compared to healthy controls. Similarly, HAQ scores in SSc were higher than healthy controls. The frequency of fatigue, determined by FSS score, was significantly higher with 77% among RA patients (40 out of 52 scored ≥ 4 on the FSS) (χ² = 47.58, df = 2, p = 0.0001), followed by SSc patients of whom 60% (42 out of 70) reported high FSS scores (χ² = 9.402, df = 1, p = 0.002). SSc patients who experienced fatigue had higher frequency of skin pigmentation (72.9% vs. 45.5%, p = 0.002), GI involvement (70% vs 35%, p = 0.007), and higher HAQ (1.26 vs 0.54) and BDI scores (24.7 vs 12, p < 0.001). The components of HAQ-DI which were significantly higher among SSc patients with fatigue were VAS-Raynaud (1.53 vs 0.32), VAS-digital ulcer (1.36 vs 0.32), VAS-GI (1.2 vs 0.39), and VAS-general (1.87 vs 0.76). In multivariate analysis, RSS (p = 0.016, β = 0.365, 95%CI = 0.28–0.45), pulmonary arterial hypertension (p = 0.043, β = 0.258, 95%CI = 0.009–0.504), VAS-digital ulcer (p = 0.036, β = 0.339, 95%CI = 0.009–0.271), and VAS-GI (p = 0.016, β = 0.169, 95%CI = 0.032–0.297) were independent predictors of fatigue.

Conclusion: A round two-thirds of our SSc patients reported higher levels of fatigue. This increase in fatigue correlated with the extent of skin sclerosis, pulmonary hypertension and patient-reported digital ulcer and gastrointestinal involvement severity.

Disclosure: S. Reiseter, None; R. Gunnarsson, None; T. Garen, None; M. B. Lund, None; T. M. Aalokken, None; A. M. Hoffmann-Vold, None; Molberg, None; T. Ueland, None.

Table 1: Comparisons among SSc, RA and Healthy Controls.

<table>
<thead>
<tr>
<th>Systemic Sclerosis (n=70)</th>
<th>Rheumatoid Arthritis (n=52)</th>
<th>Healthy Controls (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs</td>
<td>46.95 ± 11.96</td>
<td>54.07 ± 14.84</td>
<td>45.97 ± 10.39</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>65.5 (13)</td>
<td>40.12 (3.3)</td>
<td>96.4 (16)</td>
</tr>
<tr>
<td>Multidimensional assessment of fatigue scale</td>
<td>24.1 ± 14.08</td>
<td>33.9 ± 14.4</td>
<td>16.8 ± 6.06</td>
</tr>
<tr>
<td>Fatigue severity scale</td>
<td>4.61 ± 1.87</td>
<td>5.1 ± 1.8</td>
<td>3.97 ± 1.43</td>
</tr>
<tr>
<td>Fatigue impact scale</td>
<td>63.6 ± 39.4</td>
<td>61.9 ± 38.16</td>
<td>35.03 ± 28.67</td>
</tr>
<tr>
<td>Beck depression inventory</td>
<td>19.55 ± 12.34</td>
<td>17.15 ± 13.89</td>
<td>11.32 ± 9.55</td>
</tr>
</tbody>
</table>
Background/Purpose: Systemic sclerosis (SSc) is a systemic disease characterized by cutaneous and visceral fibrosis, presence of autoantibodies and vasculopathy. The central nervous system has, however, been rarely studied. Therefore the aim of this study is to determine cerebral and corpus callosum abnormalities in SSc and to determine the possible relationship between atrophy and SSc related features.

Methods: A total of 41 SSc patients (37 female; mean age = 50.8; SD = 13.2) and sixty-six health age and sex matched volunteers (37 female; mean age = 51.4; SD = 12.3) were included. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Cognitive evaluation was performed using the Montreal Cognitive Assessment (MoCA). Individual scores 26 were considered impaired. Mood disorders were determined through Beck’s Depression and Beck’s Anxiety Inventories. SSc patients were further assessed for clinical and laboratory SSc manifestations, disease activity (Valentini Activity Index), severity activity (Medsger Severity Index). Total dose of corticosteroids and other immunosuppressant medications used since the onset of the disease were calculated. MRI scans were performed in a 3T Phillips® scanner. Sagittal T1 weighted were used for cerebral volume and corpus callosum volume in both dSSc (r = -0.05; p = 0.02) and lSSc (r = -0.06; p = 0.14) or corpus callosum volume (r = -0.06; p = 0.14).

Conclusion: dSSc have significant smaller cerebral and corpus callosum volumes when compared to lSSc and healthy controls. Structural abnormalities are observed in SSc patients with cognitive impairment and mood disorders. Disease activity and organ damage showed no correlation with cerebral volume and corpus callosum volume in this population.

Disclosure: S. Dertkigil, None; T. N. Amaral, None; A. T. Lapa, None; F. Peres, None; R. Frittioli, None; A. P. del Rio, None; J. F. Marques-Neto, None; S. Appenzeller, None.

2706

Ulnar and Radial Stenosis in Systemic Sclerosis. María Eugenia Lara1, Mariano Rivero1, Julia Romero1, Guadalupe Palacios1, Ignacio Carrillo2, Claudia L. Giraldo3, Amalia Schiell4, Hugo Armando Laborde4, Marina Khoury4, Saez Diego4, Gustavo Citera5, Oscar L. Rillo5 and Juan C. Barreira6. 1British Hospital, Buenos Aires, Argentina, 2Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, 3Hospital Gral. de Agudos Dr. E. Tomú, Buenos Aires, Argentina, 4Hospital General de Agudos Dr. E. Tomú, Buenos Aires, Argentina.

Background/Purpose: Systemic sclerosis (SSc) is a chronic, autoimmune disease. Endothelial damage has been recognized as the initial pathogenic factor. The involvement of the microvasculature is well defined, whereas the prevalence of large vessels disease is still unknown. We aim to describe the frequency of ulnar and radial stenosis in SSc patients and analyze the correlation between arterial stenosis and digital ulcers.

Methods: We included 57 SSc consecutive patients who fulfilled ACR 1980 classification criteria and 21 healthy controls. SSc patients were classified in two groups: those with present or past digital ulcers and those without them. We collected demographic, clinical and laboratory information. The control group was constituted with volunteers who attended spontaneously to our hospital to make an image study. All participants have done an arterial ecodoppler of both arms, looking for ulnar and radial stenosis. Statistical analysis: Mann-Whitney, Fisher test p<0.05, Odds Ratio (OR), Forward Stepwise Hosmer and Lemeshow test.

Results: The prevalence of stenosis in at least one arterial was observed in 18 of 57 patients with SSc (31%) and in none of the 21 controls (p=0.003). Stenosis occurred in at least one radial artery in 9 of 57 SSc patients (15%) and in one of 21 controls (p=0.19). Univariate analysis is shown in Table 1. In the multivariate model, the best predictors of digital ulcers were age at onset of Raynaud phenomenon before 40 years (OR 5.3 95%CI 1.54–18.22, p=0.008) and presence of late SD pattern (OR 4.4 95%CI 1.29–15.63, p=0.018). The area under ROC = 0.76 and the Hosmer and Lemeshow test was not significant (p=0.54). Ulcers probability calculated by the model and observed in the sample by combining groups with different predictors is presented in Table 2.

Conclusion: In the present series, ulnar stenosis was observed frequently in SSc patients. However, the size of the sample did not allow adjusting for potential confounders. Stenosis of large vessels in SSc patients was not associated with presence or history of digital ulcers. The best predictors of digital ulcers were age at onset of Raynaud phenomenon before 40 years and the presence of late SD pattern.

Table 1. Clinical features between SSc patients with present or past digital ulcers (A) versus those without them (B).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>A (%)</th>
<th>B (%)</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 45 years</td>
<td>20 (5)</td>
<td>34 (11)</td>
<td>0.02</td>
<td>4.2 (1.22-16.64)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (4)</td>
<td>12 (4)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Age at first non-Raynaud symptom years ± SD</td>
<td>37 ± 14</td>
<td>50 ± 9</td>
<td>0.0018</td>
<td></td>
</tr>
<tr>
<td>Raynaud phenomenon onset ≤ 40 years</td>
<td>28 (7)</td>
<td>46 (15)</td>
<td>0.005</td>
<td>5.3 (1.68-17)</td>
</tr>
<tr>
<td>Radial stenosis</td>
<td>12 (3)</td>
<td>18 (6)</td>
<td>0.4</td>
<td>0.59 (0.13-2.64)</td>
</tr>
<tr>
<td>Ulnar stenosis</td>
<td>32 (8)</td>
<td>31 (10)</td>
<td>0.9</td>
<td>1.03-3.18</td>
</tr>
<tr>
<td>Esophageal involvement</td>
<td>52 (13)</td>
<td>50 (16)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Rodman skin score &gt; 14</td>
<td>28 (7)</td>
<td>34 (11)</td>
<td>0.079</td>
<td>2.8 (0.88-8.87)</td>
</tr>
<tr>
<td>HAQ score ≤ SD</td>
<td>0.69 ± 0.7</td>
<td>0.46 ± 0.56</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Positive ANA (IF/IF)</td>
<td>84 (22)</td>
<td>81 (26)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Anti-Scl70 positive (ELISA)</td>
<td>20 (5)</td>
<td>19 (6)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Late SD pattern</td>
<td>70 (14)</td>
<td>30 (7)</td>
<td>0.013</td>
<td>4.5 (1.43-14.37)</td>
</tr>
</tbody>
</table>

Table 2. Chance of ulcers according to the combination of predictor factors.

<table>
<thead>
<tr>
<th>Predictor factors</th>
<th>Value prediction model</th>
<th>Value observed in the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>18.5%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Raynaud phenomenon onset ≤ 40 years</td>
<td>50.5±4.7%</td>
<td>47.8%</td>
</tr>
<tr>
<td>Raynaud phenomenon onset &gt; 40 years and late SD pattern</td>
<td>84.4%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Disclosure: M. E. Lara, None; M. Rivero, None; J. Romero, None; G. Palacios, None; I. Carrillo, None; C. L. Giraldo, None; A. Schiel, None; H. A. Laborde, None; M. Khoury, None; S. Diego, None; G. Citera, None; O. L. Rillo, None; J. C. Barreira, None.

2707

Systemic Sclerosis Related Calcinosi...
Background/Purpose: Calcinosis is a disabling, rarely discussed manifestation of SSc for which the natural history and management is poorly understood. Last year, the Scleroderma Clinical Trials Consortium (SCTC) established a task force to develop a calcinosis specific patient reported measure (PROM). This investigation is the 1st phase of a multi-tiered project.

Methods: Four focus groups and individual interviews in the US and UK were recorded and transcribed verbatim. To capture both pathophysiologic and life impact, 2 questions were asked: 1. Since developing calcinosis how has your life changed over time? 2. How has the calcinosis changed over time? Patients were also asked to frame questions to help a physician learn if calcinosis was better, worse or the same. Transcripts underwent an iterative inductive process (no preconceived coding, content drives coding and analysis) by at least 5 independent analysts including at least one research team member with SSc. Concepts were triangulated to identify a comprehensive set of meaningful concepts with occurrence quantified per participant.

Results: Twenty-three patients (22/23 female, 19/23 white, with mean disease duration 14.8 years) were consented and interviewed. Responses broadly included concepts of self-management strategies and recurrent hypotheses relating calcinosis development to trauma, Raynaud’s and cold exposure. We identified discrete concepts which are described in Table 1 along with the proportion of patients declaring personal relevance.

Cold exposure and Raynaud’s were a perceived association to calcinosis severity - “when they are cold mine always open back up”. Several described a disabling core body phenomenon involving decreased core temperature with sensation of freezing, feeling of being cold, “like ice”, and all described a feeling of intense rigidity - “it’s like intense - it racks your whole body”. Calcinosis tended to present along with or soon after SSc diagnosis and remained throughout disease duration.

A majority of patients engage in strategies to extrude calcinosis with either pressure +/- soaking or at home surgical techniques. “I actually have homemade surgical tools to get these out.” The following anchors were consistently indicated to assess calcinosis severity: pain level, size, frequency, number and functional impairment.

Conclusion: Patient observations and self-management behavior provide opportunities to learn from and to preemptively educate physicians and patients. Patients are eager for self-management guidance. These concepts provide the groundwork for PROM development. However, as suggested by patients, a composite of scales anchored in pain, size, frequency, number and related impairment may reasonably serve as an interim instrument for SSc calcinosis until that time.

Table 1. Concepts from patient focus groups and interviews. The participants not represented by either affirmations or denials did not discuss the designated issue.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Yes %</th>
<th>No %</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud’s (%)</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (female)</td>
<td>96%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Race (white)</td>
<td>82%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Time from Diagnosis (mean)</td>
<td>14.8 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold exposure decreases core body temperature with sensation of systemic symptoms</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Patient Report</th>
<th>Yes %</th>
<th>No %</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingers</td>
<td></td>
<td>87%</td>
<td>3%</td>
<td>“I got a spreading infection in there and then I had it amputated”</td>
</tr>
<tr>
<td>Palms</td>
<td></td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrists</td>
<td></td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbows</td>
<td></td>
<td>48%</td>
<td></td>
<td>“I thought it was a bone chip”</td>
</tr>
<tr>
<td>Scalp</td>
<td></td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face, Lips, Eyelids or Ears</td>
<td></td>
<td>26%</td>
<td></td>
<td>“most painful ones are on the eyelid”</td>
</tr>
<tr>
<td>Feet (including toes)</td>
<td></td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (back, chest, buttock, armpit)</td>
<td></td>
<td>22%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calcinos Physical Properties

| Rock-like/soft calcinosis | 52% | “... hard as a rock” |
| Paste-like                | 22% | “It was quite like toothpaste” |
| Fluid/Leaking             | 44% | “I’ve always had peeling and leaking” |

Extrudes with warm soaking 23% –
Calcinos recurrent, once appears in any site 30% –

Effects/Sensations of Calcinos

- Pain
  - Constant 43% –
  - Tender 91% –
  - Throbbing 91% –
  - Like skin has been burned (hot, coals, flame etc) 26% –
  - Sharp - ‘like glass shards’ 22% –
  - Tight with pressure 57% – “feels like something is trying to get out” –

- Feel calcinos growing 48% –
- Relief with extrusion of calcinos 70% –
- Itchy 9% –
- Development of Ulcer secondary to calcinos 52% –
- Infection related to calcinos 70% –

Functional Effects of Calcinos

- Interferes with ADL’s 87% – “I can’t even hold her” (referring to baby)
- Interferes with work 91% –
- Interferes with walking 22% –

Perceived Influencing Factors

- More frequent in cold or not practicing cold prevention 35% – “I know winter’s coming because these come up... Become tight”
- More frequent when Raynaud’s worse 43% –
- Trauma or banging interferes with healing 43% –
- Response to warmth or prevention against cold 35% – “I haven’t taken the kind of care I’m used to with my gloves on... now it’s the first time again with this”
- Response to cyclophosphamide 13% – “not since I was treated with Cytoxan... they totally stopped coming”
- Response to vasodilating medications 9% –
- Response to colchicines 4% – “she gave me colchicine, it was doing exactly what she said softening the calcinos”

Self-Management

- Self-Manages with topical antibiotics 30% –
- Self-Manages with cushioning (if malatial doesn’t hurt) 70% –
- Self-Manages by extrusion with pressure +/- warm soak 35% – “contact with viater helps them to drain”
- Self-Manages by extrusion with instruments at home 22% – “I just got a large darning needle and pushed it in”
- Need Self-Management Protocols for Calcinos 87% –

Patient-suggested anchors to assessment questions

- Pain 91% –
- Interferes with work / daily activities 74% –
- Size 61% –
- Number 43% –
- Ask about wounds 1st then proceed to ask about calcinos 13% –
- Location 9% –

Disclosure: A. Christensen, None; S. Khalique, None; S. Cenac, None; K. Fligelstone, None; A. Mawdsley, None; T. Frech, None; J. K. Gordon, None; M. Baron, None; E. Busman, None; V. D. Steen, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berthing, 2, Intermune, 2, Bayer, 5; L. A. Saketkoo, None.

Tuesday, November 18
Background/Purpose: Vascular involvement is a key feature of Systemic sclerosis (SSc) and involves both the micro and macrovasculature. Vascular changes are central in the disease’s pathogenesis and the assessment of vascular involvement has a prognostic value; therefore vascular assessment has a pivotal significance, both for research and clinical purpose.

A non invasive technique to monitor cutaneous vascular function is the response to a physiological challenge using laser speckle contrast imaging. This technique has proven effective and reproducible for the assessment of skin blood flow in SSc patients, either with or without dynamic challenge.

The aim of our study was to evaluate post-occlusive reactive hyperemia test (PORH) in consecutive SSc patients and to test whether PORH is a useful tool to discriminate different disease subsets within SSc population.

Methods:

Patients

Starting from to april 2011 to june 2014, 54 consecutive SSc patients were enrolled (mean age 56 ±15 years, F/M =18). Patients were divided into limited SSc (n=29), Diffuse SSc (n=8) and Very early SSc (VEDOSS) (n=17) according to literature definition.

Laser Speckle Contrast Analysis

Cutaneous blood flow was measured throughout the experiments using a high frame rate LSKI (Pericam PSI system, Perimed, Jarfalla). The occlusive ischemic test was performed by inflating for 4 minutes a cuff placed on the left arm to 30 mm Hg above the systolic pressure. The recovery time (time needed to recover the basal flux after occlusion in seconds), the peak flux (hyperemic peak reached after occlusion) and the area under the hyperemic curve were recorded.

Statistical analysis

Correlation between clinical data and laser measurements were performed by non parametric tests and contingency tables for cathegorical variables (StatView, SAJ). In view of the high number of comparisons involved, only p values equal or below 0.01 were considered significant.

Results: A statistical significant difference was detected in the post-ischemic hyperemic peak flow between very early SSc and established SSc (424 vs 137% p = 0.0001). PORH peak flow decreased according to capillaroscopic pattern (early=435%, active=173%, Late=145% P<0.005). Moreover a strong correlation between capillary density and peak flow was unveiled (rho=0.56, p < 0.0001).

Conclusion: These data show a different pattern of vascular involvement in early SSc as compared to established disease that mirror capillaroscopic changes. In this context, functional features of early and established disease seem to be the physiologic counterpart of abnormalities detected by capillaroscopy. PORH test might be a useful aid for further characterization of vascular involvement in SSc.

Disclosure: A. Della Rossa, None; A. d’Ascanio, None; M. Cagnoni, None; C. Stagnaro, None; A. Parma, None; M. Mosca, None; S. Bombardieri, None.

Table 1. Validity indexes for new ACR-EULAR 2013 SSc classification criteria global score, and by items and subitems

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LHR +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal and distal scleroderma</td>
<td>66.3</td>
<td>98.6</td>
<td>95.6</td>
<td>86.2</td>
<td>46.2</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>95.9</td>
<td>88.0</td>
<td>79.0</td>
<td>97.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Finger edema</td>
<td>68.4</td>
<td>74.2</td>
<td>55.4</td>
<td>83.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Any finger involvement</td>
<td>66.3</td>
<td>98.6</td>
<td>95.6</td>
<td>86.2</td>
<td>46.2</td>
</tr>
<tr>
<td>Digital Ulcers</td>
<td>43.9</td>
<td>92.3</td>
<td>72.9</td>
<td>77.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Pitting Scars</td>
<td>43.9</td>
<td>92.3</td>
<td>72.9</td>
<td>77.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Any ischaemiculcer</td>
<td>46.9</td>
<td>91.9</td>
<td>73.0</td>
<td>78.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>51.0</td>
<td>95.7</td>
<td>84.7</td>
<td>80.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Capillaroscopic changes</td>
<td>81.6</td>
<td>90.4</td>
<td>80.0</td>
<td>91.3</td>
<td>8.5</td>
</tr>
<tr>
<td>PAH (confirmed by RHC)</td>
<td>6.1</td>
<td>97.1</td>
<td>50.0</td>
<td>68.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td>25.5</td>
<td>95.2</td>
<td>71.4</td>
<td>73.2</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Joining Tendon Involvement Predict Severe Disease Progression in Systemic Sclerosis: A Prospective Study.

Disclosure: P. E. Carreira, None; L. Carmona, None.

Table 2. Validity indexes for all cutpoints for the global score of the new ACR-EULAR 2013 SSc classification criteria

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Correctly Classified</th>
<th>L R +</th>
<th>L R -</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt; = 0)</td>
<td>100.00%</td>
<td>0.00%</td>
<td>31.92%</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 2)</td>
<td>100.00%</td>
<td>17.70%</td>
<td>43.97%</td>
<td>1.125</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 3)</td>
<td>100.00%</td>
<td>25.36%</td>
<td>49.19%</td>
<td>1.339</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 4)</td>
<td>100.00%</td>
<td>62.20%</td>
<td>74.27%</td>
<td>2.645</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 5)</td>
<td>100.00%</td>
<td>64.11%</td>
<td>75.57%</td>
<td>2.786</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 6)</td>
<td>100.00%</td>
<td>84.21%</td>
<td>89.25%</td>
<td>6.333</td>
<td>0.000</td>
</tr>
<tr>
<td>(&gt; = 7)</td>
<td>98.98%</td>
<td>86.60%</td>
<td>90.55%</td>
<td>7.388</td>
<td>0.012</td>
</tr>
<tr>
<td>(&gt; = 8)</td>
<td>98.98%</td>
<td>93.78%</td>
<td>95.44%</td>
<td>15.912</td>
<td>0.011</td>
</tr>
<tr>
<td>(&gt; = 9)</td>
<td>97.96%</td>
<td>94.74%</td>
<td>95.77%</td>
<td>18.612</td>
<td>0.015</td>
</tr>
<tr>
<td>(&gt; = 10)</td>
<td>91.84%</td>
<td>96.65%</td>
<td>95.11%</td>
<td>27.419</td>
<td>0.025</td>
</tr>
<tr>
<td>(&gt; = 11)</td>
<td>86.73%</td>
<td>98.56%</td>
<td>94.79%</td>
<td>60.425</td>
<td>0.136</td>
</tr>
<tr>
<td>(&gt; = 12)</td>
<td>83.67%</td>
<td>99.04%</td>
<td>94.14%</td>
<td>87.436</td>
<td>0.168</td>
</tr>
<tr>
<td>(&gt; = 13)</td>
<td>76.53%</td>
<td>99.52%</td>
<td>92.18%</td>
<td>159.948</td>
<td>0.235</td>
</tr>
<tr>
<td>(&gt; = 14)</td>
<td>73.47%</td>
<td>100.00%</td>
<td>91.53%</td>
<td>265.53</td>
<td>0.256</td>
</tr>
<tr>
<td>(&gt; = 15)</td>
<td>60.20%</td>
<td>100.00%</td>
<td>87.30%</td>
<td>398.00</td>
<td>0.390</td>
</tr>
<tr>
<td>(&gt; = 16)</td>
<td>59.18%</td>
<td>100.00%</td>
<td>86.97%</td>
<td>408.42</td>
<td>0.408</td>
</tr>
<tr>
<td>(&gt; = 17)</td>
<td>55.10%</td>
<td>100.00%</td>
<td>85.67%</td>
<td>489.40</td>
<td>0.450</td>
</tr>
<tr>
<td>(&gt; = 18)</td>
<td>45.92%</td>
<td>100.00%</td>
<td>82.74%</td>
<td>540.80</td>
<td>0.508</td>
</tr>
<tr>
<td>(&gt; = 19)</td>
<td>41.84%</td>
<td>100.00%</td>
<td>81.43%</td>
<td>581.03</td>
<td>0.567</td>
</tr>
<tr>
<td>(&gt; = 20)</td>
<td>28.57%</td>
<td>100.00%</td>
<td>77.20%</td>
<td>714.23</td>
<td>0.743</td>
</tr>
<tr>
<td>(&gt; = 21)</td>
<td>26.53%</td>
<td>100.00%</td>
<td>76.55%</td>
<td>734.73</td>
<td>0.757</td>
</tr>
<tr>
<td>(&gt; = 22)</td>
<td>22.45%</td>
<td>100.00%</td>
<td>75.24%</td>
<td>755.75</td>
<td>0.757</td>
</tr>
<tr>
<td>(&gt; = 24)</td>
<td>8.16%</td>
<td>100.00%</td>
<td>70.68%</td>
<td>918.14</td>
<td>0.918</td>
</tr>
<tr>
<td>(&gt; = 24)</td>
<td>0.00%</td>
<td>100.00%</td>
<td>68.08%</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Disclosure: P. E. Carreira, None; M. J. Garcia de Yebenes, None; B. E. Joven, None; E. Loza, None; L. Carmona, None.

2711

Joint and Tendon Involvement Predict Severe Disease Progression in Systemic Sclerosis: A Prospective Study.

Joining synovitis (HR, 1.26, 95% CI 1.00–1.58) and TFRs (HR: 1.67, 95% CI 1.01–2.75) were independently predictive of overall disease progression, as were also the diffuse cutaneous subset (HR: 1.30, 95% CI 1.05–1.61) and positive antitopoisomerase-I antibodies (HR: 1.25, 95% CI 1.02–1.53).

The mean change of mRSS over the follow-up period was 9.4±4.11, and 99/123 patients (80%) had a progression of at least 5 points. Joint synovitis (HR: 1.63, 95% CI 1.05–2.55) and TFRs (HR: 1.67, 95% CI 1.01–2.75) were independently predictive of overall disease progression.

Conclusion: This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of baseline synovitis and extended previous data for tendon friction rubs in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

Disclosure: J. Avouac, None; U. Walker, None; E. Hachulla, None; G. Riemekasten, None; G. Cuomo, None; P. E. Carreira, None; P. Caramaschi, None; L. P. Ananieva, None; M. MatsuC-Cerinic, None; L. Czirjak, None; C. P. Denton, None; U. Muller-Ladner, None; Y. Allanore, None.

2712

Nailfold Videocapillaroscopy in Healthy Children and Adolescents: Description of Patterns of Normality.

Daniela Piotto, Julianna Sekiyama, Cristiane Kayser, Mariana Yamada, Claudia A. Len and Maria Teresa Terreri.

Joint synovitis was predictive of the occurrence of new digital ulcer(s) (HR: 1.45, 95% CI 1.08–1.96) and decreased left ventricular ejection fraction (HR: 2.20, 95% CI 1.06–4.57); TFRs were confirmed to be an independent predictor of scleroderma renal crisis (HR: 2.33, 95% CI 1.03–6.19).

Conclusion: This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of baseline synovitis and extended previous data for tendon friction rubs in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

Disclosure: J. Avouac, None; U. Walker, None; E. Hachulla, None; G. Riemekasten, None; G. Cuomo, None; P. E. Carreira, None; P. Caramaschi, None; L. P. Ananieva, None; M. MatsuC-Cerinic, None; L. Czirjak, None; C. P. Denton, None; U. Muller-Ladner, None; Y. Allanore, None.

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Background/Purpose: Video capillaroscopy (VCP) allows for the evaluation of capillary dimensions and to quantify the degree of microangiopathic alterations in autoimmune diseases. However, studies in healthy subjects and specially in children and adolescents are limited. To describe the normal pattern of capillaries by VCP in healthy children and adolescents, and to evaluate the inter and intraobserver concordance in capillary measurements.

Methods: Cross-sectional study of 100 healthy participants aged 5 to 18 years by VCP. The capillary dimensions (capillary loop length, capillary width, inter capillary distance) and the number of capillaries/mm were evaluated under 100x magnification, acquiring three consecutive images of nine capillaries per individual, totaling 900 capillaries examined and photographed. Four age groups were studied: 5-7 years (17 individuals); 8-10 years (24 individuals); 11-14 years (30 individuals) and 15-18 years (29 individuals). The intra and inter observer concordance was tested in 25% of subjects by two professionals with experience in this method.

Results: The capillary dimensions (mean ± SD) were: capillary loop length 278.6 ± 60.3 μm, inter capillary distance 124.1 ± 28.1 μm, capillary width 15.0 ± 2.6 μm and 7.8 ± 1.5 number of capillaries/mm. The only significant difference between males and females was the inter capillary distance which was higher in girls (p = 0.011). When comparing the four age groups, only the intercapillary distance remained constant over time (p = 0.088). Teenagers between 15 and 18 years had longer and thicker capillaries (318.7 ± 50.4 μm) and (16.2 ± 3.3 μm) resp. when compared to other age groups (p < 0.001 and p = 0.012 respectively). We also found an increase in the number of capillaries/mm with age: 6.1 capillaries/mm (5–7 years); 7.0 (8 to 10 years); 8.0 (11–14 years) and 9.3 (15–18 years) (p < 0.001). There was a good intra and interobserver concordance in the analysis of capillary dimensions and the number of capillaries/mm by VCP. In VCP, 11% had enlarged capillary (capillary width percentile> 97.5) and 10% avascular areas (inter capillary distance percentile> 97.5). There was a negative correlation between the distance and the number of capillaries/mm.

Conclusion: This study evaluated the normal pattern of VCP in healthy children and adolescents and stratified patients by age groups. The number of capillaries/mm, the length and thickness of the capillary increased with age, while the intercapillary distance was maintained over the years.

Disclosure: D. Piotto, None; J. Sekiyama, None; C. Kayser, None; M. Yamada, None; C. A. Len, None; M. T. Terreri, None.

2714


Background/Purpose: The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) suggested the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc), due to the lack of sensitivity for early and limited SSc of the 1980 ACR classification criteria.

The aim of this study was to determine how many patients with Raynaud phenomenon are reclassified as SSc by the 2013 ACR/EULAR classification criteria for SSc and to analyze the predictive variables of the new classification criteria in those patients.

Methods: We applied the 2013 ACR/EULAR classification criteria for SSc to 60 patients who had been diagnosed as SSc according to the 1980 ACR classification criteria (SSc group) and 64 patients who presented Raynaud phenomenon with or without autoimmune disease, but did not fulfill the 1980 ACR classification criteria (Raynaud phenomenon group). We analyzed the discrepancy between the previous and the new classification criteria when subjects were categorized as those with SSc.

Results: All patients who were diagnosed as SSc according to the previous classification criteria fulfilled the new criteria. Furthermore, 17 of 64 patients (26.5%) in Raynaud phenomenon group were reclassified as SSc by the new criteria. Reclassified SSc patients in Raynaud phenomenon group significantly showed less frequency of scleroderma, sclerodactyly, finger pitting scar, interstitial lung disease and higher frequency of telangiectasia than those in SSc group (Table 1). Eleven of 17 patients who were reclassified as SSc (64.7%) had anti-centromere antibody. But none of 17 patients had anti-topoisomerase 1, meanwhile 29 of 60 patients who had been diagnosed as SSc (43.8%) had anti-topoisomerase 1 (Table 1). On multivariate linear regression analysis using variables with significance, puffy finger, sclerodactyly and telangiectasia were significant predictive values for the new classification as SSc in Raynaud phenomenon (RR = 23.7, 29.5, 14.2; p values <0.001, 0.015, 0.031).

Conclusion: 26.5% patients, who presented Raynaud phenomenon but did not fulfill the 1980 ACR classification criteria for SSc, were reclassified as SSc according to the 2013 ACR/EULAR classification criteria. Also, we suggest that physicians should pay attention to puffy finger, sclerodactyly and telangiectasia in patients with Raynaud phenomenon for the early diagnosis of SSc.

Table 1. Comparison of characteristics, clinical manifestations and autoantibodies between reclassified systemic sclerosis patients in Raynaud phenomenon group (New SSc) and patients in systemic sclerosis group (SSc).

<table>
<thead>
<tr>
<th>Variables</th>
<th>New SSc (n=17)</th>
<th>SSc (n=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP duration (years)</td>
<td>3.4 ± 2.4</td>
<td>9.6 ± 6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>1.25 ± 1.25</td>
<td>6.4 ± 5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2013 ACR/EULAR score</td>
<td>10.8 ± 1.8</td>
<td>19.1 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Disclosure: J. Ziemek, None; A. Man, None; R. W. Simms, None; R. Lafyatis, None.
Scleroderma (N(%) 0 (0) 40 (66.7) <0.001
Puffy finger (N(%) 12 (70.5) 27 (45.0) 0.062
Sclerodactyly (N(%) 6 (35.3) 55 (91.6) <0.001
Digital tip ulcer (N(%) 2 (11.8) 20 (33.3) NS
Fingertip pitting scar (N(%) 0 (0) 19 (31.7) 0.008
Telangiectasia (N(%) 5 (29.4) 5 (8.3) 0.022
Abnormal nailfold capillaries (N(%) 17 (100) 56 (93.3) NS
Pulmonary artery hypertension (N(%) 1 (5.9) 3 (5.0) NS
Interstitial lung disease (N(%) 2 (11.8) 29 (48.3) 0.007
ANA (centromere) (N(%) 9 (52.9) 12 (20.0) 0.007
Anti-centromere (N(%) 11 (64.7) 13 (21.7) 0.001
Anti-topoisomerase 1 (N(%) 0 (0) 29 (48.3) <0.001

Values given as n (%). p values < 0.05 NS, not significant.

Disclosure J. S. Park, None; H. J. Park, None; Y. J. Ha, None; Y. B. Park, None; S. K. Lee, None; W. L. Lee, None.

2715

Background/Purpose: The Duruöz Hand Index (DHI) is a reliable tool for the evaluation of hand’s function in patients with scleroderma. The aim of our study was to adapt and to validate the DHI questionnaire in an Argentinian population with scleroderma.

Methods: For validation, 3 rheumatologists adapted and translated to Spanish the original version in French and the final version was re-translated to French by a bilingual person. To evaluate the construct validity, we used the patient global visual analogue scale (VAS), VAS for questions for the same activity, the health assessment questionnaire (HAQ) and the Rodnan. A subsample attended a second visit to evaluate reproducibility, with no modifications in the treatment in relation to the previous visit. Continuous variables were expressed as mean and standard deviation (SD) or medians with their interquartile range (IQR). Spearman’s correlation coefficient was used to quantify the degree of correlation between the different VAS, HAQ and Rodnan with the total score. The intraclass correlation coefficient (ICC) was used to assess reproducibility and Cronbach’s alfa to evaluate internal consistency.

Results: 45 patients diagnosed with scleroderma were included in the study. 84.44% were women, mean age of 51 ± 13.72 years (SD). 48.89% were Mestizos, while 46.67% were Caucasians with a disease duration of 24 months (IQR: 18–60). 64.44% patients had diagnostic of limited scleroderma: 77.78% were right handed and 53.33% had extra cutaneous manifestations. Raynaud was present in 93.33%, pitting scars in 33.33% and digital ulcers in 26.67%. The median score of the total questionnaire was 4.5 (IQR: 0–26) of the global VAS 49 (IQR: 10–50), of HAQ 0.3 (IQR: 0–1) and of Rodnan 5 (IQR: 2–11). The correlation between the total score of DHI and the patient global VAS was 0.58, with the HAQ was 0.63 and with Rodnan 0.08. The correlation coefficient between the VAS and each group of questions for the same activity in the DHI questionnaire, indicated good correlation for the questions that refer to activities of dressing (0.69; 0.65; 0.57), for hygiene (0.61; 0.56), and for the office questions (0.56; 0.73). There was excellent level of correlation with those related to fine motor activities with a maximum r value of 0.78. The reproducibility was 0.88 (CI 95% 0.76–0.99) and the internal consistency according to Cronbach’s alfa was 0.98.

Conclusion: The results from this study show the DHI to be a reliable and valid test for this Argentinian population with scleroderma.

Disclosure V. Duarte, None; G. Crespo, None; M. Manzano, None; M. V. Martíre, None; S. Scarafia, None; L. Marino, None; F. Romanini, None; M. Mamani, None; A. Secco, None.

2716
Development of a “Renal Crisis Prevention Card” As an Educational Tool Aimed at Improving Outcomes in High-Risk Patients with Systemic Sclerosis. Lee S. Shapiro,2,4,5 Lesley Ann Saketko,2,4,5 Jessica F. Farrell,2,4 and Kim Filigelstone3. 1The Center for Rheumatology, Albany, NY; 2Louisiana State University Health Sciences Center, New Orleans, LA; 3Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom.

Background/Purpose: Scleroderma renal crisis (SRC) is a devastating complication of SSC. The introduction of effective treatment with ACE inhibition (ACE-I) in 1979 dramatically reduced death as a near-immediate consequence of SRC. However, poor outcomes still occur with great frequency including chronic or temporary dialysis or death. Individuals with early, rapidly progressive diffuse disease and RNA polymerase III antibody positivity are at high risk for SRC. Prophylactic use of ACE-I in high risk patients has not demonstrated improved outcomes and may have negative consequences. Our goals were to identify associative causes of poor outcome and develop a targeted preventive intervention to address in accordance with findings.

Methods: A retrospective chart review at Royal Free Hospital scleroderma clinic between 1994–1999 identified and stratified 44 cases of SRC for long term outcomes (death, long-term dialysis, short-term dialysis, and no dialysis). Cases were then assessed for factors potentially related to outcomes: onset of symptoms, time to medical attention, and therapeutic management. Results directed development of SRC preventive intervention.

Results: Death or long-term dialysis was the outcome in approximately 50% of the cases reviewed. Three subgroups emerged as associated with poor outcomes:

1. SSc patients with no previously established SSc diagnosis presenting as “malignant hypertension”
2. SSc patients with an established SSc diagnosis but uninformated about SRC and misinterpreted symptoms or failed to recognize the urgency of seeking medical attention
3. SSc patients who presented promptly for urgent outpatient medical care informing physician of SSc diagnosis, but were incorrectly treated with therapies other than ACE-I or initiation of ACE-I was without sufficiently rapid dose adjustment to achieve blood pressure control.

Poor outcomes were correlated to delayed therapy, rather than drug failure. All patients in the ‘no dialysis/death’ group were treated with ACE-I according to protocol. From these findings, a “scleroderma renal crisis prevention card” was developed. See image.

Conclusion: Despite availability of effective therapy, SRC is associated with poor outcomes often consequential to treatment delay and lack of knowledge of initial treating physicians. A “renal crisis prevention card” may improve health outcomes of high-risk patients as a method of educating patients and health care providers.

Disclosure: L. S. Shapiro, None; L. A. Saketko, None; J. F. Farrell, None; K. Filigelstone, None.
Comparison of PROMIS® survey Between Scleroderma Patients in an Academic Center and Patient-Based Scleroderma Foundations. Vivek Nagaraja1, Veronica Berrocal1, Keri Connolly1, Ann Kennedy2, Daniela Seelmann2 and Dinesh Khamán2. 1University of Michigan, Ann Arbor, MI, 2Scleroderma Foundation, Boston, MA, 3Federation of European Scleroderma Associations, Tournai, Belgium, 4Universidad de Los Andes, Santiago, Chile.

Background/Purpose: The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). It has comprehensive item banks that assess physical, mental, and social well-being. The aim of this study was to compare the PROMIS survey between the scleroderma patients at an academic center and patient-based foundations as this has implications for large epidemiological studies (such as Scleroderma Patient Intervention Network).

Methods: A study titled ‘PROMIS in rheumatology’ was created in the Assessment center website. This study contained 13-PROMIS instruments. Patients seeking care in the academic Scleroderma clinic were approached to participate in the PROMIS survey. Patients were also recruited from the Scleroderma patient-based foundations (SF) namely – the Scleroderma Foundation and the Federation of European Scleroderma Associations through the respective social media pages and e-newsletters. Averager T-scores of the patient-based foundation scleroderma cohort were compared with those of the UM scleroderma patient cohort.

Results: Thirty-six patients at UM and 241 patients from SF have so far completed the survey. In both groups, the T-scores in the following domains were approximately 1 standard deviation worse than the United States (US) general population (GP) – fatigue, physical function, pain interference, satisfaction in roles and activities. Anger and social isolation banks were comparable to US GP. In comparison to the UM scleroderma cohort, the T-scores of the SF patient cohort was significantly worse for pain behavior and social isolation (Table, p < 0.05); however, the differences were not clinically meaningful.

Conclusion: The patients with SSc have decrements in health-related quality of life on PROMIS measures when compared to the US general population. There were no meaningful differences in the two cohorts, suggesting that patients from scleroderma clinic and patient foundations can be approached for non-pharmacologic intervention trials.

Table 1: Comparison of T-scores of UM and SF patient cohorts

<table>
<thead>
<tr>
<th>PROMIS item banks</th>
<th>UM Scleroderma</th>
<th>Scleroderma patient foundations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Anger</td>
<td>36</td>
<td>51.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>36</td>
<td>55.1</td>
</tr>
<tr>
<td>Depression</td>
<td>36</td>
<td>54.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>60.4</td>
</tr>
<tr>
<td>Pain behavior</td>
<td>36</td>
<td>56.4</td>
</tr>
<tr>
<td>Pain interference</td>
<td>36</td>
<td>59.3</td>
</tr>
<tr>
<td>Physical function</td>
<td>36</td>
<td>39.5</td>
</tr>
<tr>
<td>Physical function with mobility aid</td>
<td>36</td>
<td>41.7</td>
</tr>
<tr>
<td>Satisfaction in roles and activities</td>
<td>36</td>
<td>43.8</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>36</td>
<td>56.7</td>
</tr>
<tr>
<td>Sleep related impairment</td>
<td>36</td>
<td>58.1</td>
</tr>
<tr>
<td>Social activities (Ability to participate)</td>
<td>36</td>
<td>45.2</td>
</tr>
<tr>
<td>Social isolation</td>
<td>36</td>
<td>48.7</td>
</tr>
</tbody>
</table>

* Lower score (T-score <50) means worse than average

Disclosure: V. Nagaraja, None; V. Berrocal, None; K. Connolly, None; A. Kennedy, None; D. Seelmann, None; D. Khamán, None.

2718

The UCLA Gastrointestinal Tract Questionnaire (GIT) 2.0 and GI Visual Analogue Scale(GI-VAS) Reflect Different Aspects of GI Involvement in Systemic Sclerosis. Y ossra Suliman1, Yasser Shaweesh2, Suzanne Kafaja3, Lewis Duan4 and D. E. Furst5. 1Fatih Sultan Mehmet State Hospital, Istanbul, Turkey, 2Trakya University Medical Faculty, Edirne, Turkey, 3Medical Faculty, Edirne, Turkey, 4Scleroderma Foundation and the Federation of European Scleroderma Associations, Tournai, Belgium, 5University of California Los Angeles, Los Angeles, CA.

Background/Purpose: UCLA GIT2.0 is a validated measure for assessing the severity of gastrointestinal involvement in systemic sclerosis patients (SSc) patients; GI VAS is also a widely used measure of GI effect in patients as a component of SSc health assessment questionnaire (SHAQ). GIT2.0 includes 34 questions in 7 domains (reflux, distention, soilage, diarrhea, social function, emotional wellbeing and constipation). GI VAS is a 100 mm VAS that asks the patient; how much GI symptoms interfere with patient function. Both are measures of present state.

Objectives
1) Is there a correlation between GI-VAS and total GIT2.0?
2) Is a correlation between GI-VAS and GIT2.0 domains?
3) Does total GIT2.0 or GI-VAS predict patient global.

Methods: We extracted baseline data in 38 consecutive SSc patients, with respect to: age, sex, SSc subtype, disease duration, HAQ-DI, VAS for; pain, raynaud’s ulcer, breathing, GIT2.0 domains and patient global. An analysis: Correlation between GI-VAS and domain and individual domains by Pearson correlation Coefficient. Univariable linear regression using patient global as dependent variable against total GIT2.0 or GI-VAS as separate independent elements. Independent variables were: SSc subtype, age, gender, disease duration, VAS for: raynaud’s, ulcer, fingers and breathing in each model.

Results: Of total 98 patients available for analysis, 84 were females, 59 were diffuse subtype, mean age 54.6 (SD 14), mean disease duration 9.6 years (7.6), total GIT2.0 mean 50.51 (0.49) – moderate, GI-VAS mean 52.34 (2.77)– mild, HAQ-DI mean 0.98 (0.76) and patient global mean 3.77(2.69).

Conclusion: Correlation between GI-VAS and GIT2.0 (total and individual domains) are listed in table. Even though the correlation between GIT2.0 and GIT VAS is (r=0.6) and weighted kappa is 0.59 – moderate, thirty four percent of the patients showed disagreement between the two measures by at least 1 category (total of four categories). Linear regression analysis demonstrated that GIT2.0 and GI-VAS were independent predictors of patient global as well as VAS for breathing and ulcer (p<0.007). A desired r squared for GIT2.0 was 0.49and for GI-VAS was 0.51.

Table 1: Correlation between GI VAS and GIT2.0 (total and individual domains)

<table>
<thead>
<tr>
<th>GI VAS</th>
<th>Reflux</th>
<th>Distention</th>
<th>Soilage</th>
<th>Diarrhea</th>
<th>Constipation</th>
<th>Social function</th>
<th>Emotional wellbeing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.61</td>
<td>0.56</td>
<td>0.54</td>
<td>0.32</td>
<td>0.26</td>
<td>0.33</td>
<td>0.58</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Disclosure: Y. Suliman, None; Y. Shaweesh, None; S. Kafaja, None; L. Duan, None; D. E. Furst, None.

2719

Performance of the New ACR Criteria in Systemic Sclerosis: A Multi-center Study. Necati Cakir1, Omer Nuri Pamuk2 and Mehmet Ali Balci3. 1Fatih Sultan Mehmet State Hospital, Istanbul, Turkey, 2Trakya University Medical Faculty, Edirne, Turkey.

Background/Purpose: Reliable and validated classification criteria are needed to conduct high quality clinical research in systemic sclerosis (SSc). The most widely used classification criteria for SSc are ACR criteria published in 1980. Recently, ACR and EULAR Collaborative Initiative has proposed a new set of criteria for the classification of SSc. In our study, we aimed to compare the sensitivity and specificity of the new ACR/EULAR criteria to the ACR criteria in our SSc population.

Methods: Two rheumatology centers from Turkey participated in this study. The features present at disease onset in patients with SSc seen between 2008-2013 were retrospectively reviewed. For the evaluation of specificity, patients admitted to each center between the same time period for conditions other than SSc, in whom AANA was deemed necessary within the diagnostic work-up, were included as controls.

Results: Onehundradandtwo SSc patients (93 females, 9 males, mean age: 47.9±13.9) and 80 controls (70 females, 10 males, mean age: 48.4±11.6) were included into the study. AANA was positive in 89.2%,
anti-Scl-70 in 31.7%, and anti-centromere in 21.6% of the patients. Digital ulcers were present in 34.7% of SSc patients, pulmonary hypertension in 42.2%, interstitial lung disease in 36.3%, and renal crisis in 2%.

The sensitivity of ACR/EULAR and ACR1980 criteria were, respectively, 92.2% and 78.4%. The specificity of ACR/EULAR and ACR1980 criteria were, respectively, 89.3% and 76.7%. According to the new criteria more patients were misclassified, and according to ACR1980 criteria 18 patients were classified. The sensitivity of ACR 1980 criteria was significantly better in SSc patients with interstitial lung disease when compared to others (91.7% vs. 74.1%, p=0.036). According to the New criteria set, however, the sensitivity tended to be higher in the group with anti-Scl-70 positivity (91.7% vs. 74.1%, p=0.09). The sensitivity and the specificity of the criteria were not different in patients with certain other clinical features or other antibody positivities.

Conclusion: We observed that the new ACR/EULAR SSc classification criteria had better sensitivity and specificity in our SSc patients; and it led to misclassification in a larger number of patients.

Disclosure: N. Cakir, None; O. N. Pamuk, None; M. A. Baldi, None.

2720
Prevalence and Features of Metabolic Syndrome in Systemic Sclerosis.
Tiago N. Amaral1, Karina Pereira2, Naiul A. Sinicato1, Sandra Gasparini1, Fernando Augusto Peres3, Maria Carolina de Souza1, Ana Paula del Rio4, João Francisco Marques-Neto5 and Simone Appenzeller6. 1State University of Campinas, Campinas, Brazil, 2State University of Campinas, Limeira, Brazil, 3University of Campinas, Campinas, Brazil, 4State University of Campinas, Limeira, Brazil, 5University of Campinas, Campinas, Brazil, 6Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resulted fibrosis of skin and internal organs. Vascular impairment in SSc involves both micro and macrovascular circulation and maybe a sign of endothelial dysfunction. Metabolic syndrome (MetS) in SSc.

Methods: We screened consecutive SSc patients followed in a longitudinal cohort from 2011 to 2013 and age and sex matched controls. We excluded patients with overlapping rheumatic diseases. Predefined outcome measures were collected. This included demographics (age, gender, disease duration), physical examination [skin score, joint count, blood pressure, height, weight, waist circumference (WC) and hip circumference (HC)], disease activity (Valentini Disease Activity Index) and severity (Medger Disease Severity Scale) scores and laboratory data (total and fractions of cholesterol, fasting glucose levels, basal insulin, C3, C4, erythrocyte sedimentation rate and hemoglobin/hematocrit levels). MetS was assessed using the definition recommended by the 2009 Joint Interim Statement (JIS). Nonparametric tests and correlation were used for statistical analysis.

Results: A total of 131 SSc (121 female; mean age = 51.70; SD=13.12) and 79 health subjects (69 female; mean age=40.66; SD=13.38) were included in the study. Seventy-eight (59.54%) patients had limited SSc (lSSc), 42(32.06%) had diffuse SSc (dSSc) and 11(8.4%) SSc sine scleroderma disease (ssSSc). Active disease was observed in 18(13.74%) SSc (10 lSSc); 42(32.06%) had diffuse SSc (dSSc) and 11(8.4%) SSc sine scleroderma disease (ssSSc). Active disease was observed in 18(13.74%) SSc patients. Hypertension was identified in 35 (26.72%) SSc and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients, and in 8 dSSc) patients. Hyperension was identified in 35 (26.72%) SSc patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients. Hypertension was identified in 35 (26.72%) SSc patients and 8 dSSc) patients.

Conclusion: This is the first study to determine the prevalence and features of MetS in SSc. MetS is frequently observed in SSc and not associated with disease related features in this cohort. However MetS should be routinely screened since it can influence athosclerosis and cardiovascular mortality in SSc.
ACR/ARHP Poster Session C
T cell Biology in Lupus, Vasculitis, Myositis and Other Autoimmunity
Tuesday, November 18, 2014, 8:30 AM – 4:00 PM

2722
Rapamycin Corrects GATA-3 Deficiency in Lupus Treg.
Hiroshi Kato and Andras Perl. SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: As demonstrated by the negative correlation between Treg frequency or suppressive function and SLE disease activity index score, it is tempting to speculate that a Treg defect contributes to dysregulated immune response in SLE. GATA-3 is not only indispensable for Th2 differentiation, but also plays critical roles in homeostasis and function of Tregs as exemplified when Treg-specific deletion of GATA-3 leads to spontaneous development of inflammatory disorder. GATA-3 deficient Tregs have reduced FoxP3 expression and are poised to express IL-17 in the presence of IL-6. However, roles of GATA-3 in lupus Treg biology remain undefined.

Methods: CD3+ T cells were isolated from 9 pairs of matched SLE and healthy control (HC) subjects. A part of the CD3+ T cells were stained with CD4, CD8, and CD25 followed by GATA-3 and FOXP3. The rest of the cells were cultured in RPMI culture media with 10% FCS, 1% Penicillin/Streptomycin, and 1% L-glutamine for 3 days in the presence of plate-bound anti-CD3 and soluble anti-CD28 with or without 100 nM rapamycin. After 3 days of culture period, cells were stained as previously described. GATA-3 expression by CD4+, CD8+, and CD4+ CD8+ double-negative (DN) T cells as well as CD4+ CD25+ FOXP3+ Treg was assessed by flow cytometry. MFI fluorescence intensity was normalized to that of HC samples on day 0.

Conclusion: The data points to GATA-3 deficiency in SLE Treg as a potential mechanism underlying the functional incompetence. Rapamycin may correct Treg function by restoring GATA-3 expression in SLE.

Disclosure: H. Kato, None; A. Perl, None.

2723
Programmed Death 1 Inhibits T-Cell Adhesion By Regulating Rap1.
Inbar Alagut1, Marianne Straza2 and Adam Mor3. 1NYU, New York, NY; 2NYU Langone Medical Center, New York, NY.

Background/Purpose: Programmed Death-1 (PD-1) is an inhibitory co-receptor that is highly expressed in T lymphocytes. The binding of PD-1 to its ligands, PD-L1 or PD-L2, is vital for the physiologic regulation of the immune system. Likewise, a major function of the PD-1 signaling pathway is the inhibition of self-reactive T cells, which serve to protect against autoimmune disease. PD-1 transmits its inhibitory effects by dephosphorylation of physiologically associated proximal signaling molecules that are downstream of the T cell receptor complex.

At the cellular level, PD-1 activation can lead to depression of T-cell proliferation, impaired survival, and decreased interleukin-2 release.

Methods: Preliminary studies have shown that PD-1 also inhibits T cell adhesion, but little is known how this is mediated. In order to fill this gap, we investigated the role of PD-1 in T-cell adhesion by analyzing the major players in its TCR signaling pathway. We hypothesized that PD-1 inhibited adhesion by inhibiting Rap1, a small GTPase vital for effective T cell motility and adhesion.

Results: We identified that when PD-1 binds to its ligand PD-L2 there is an inhibition of Rap1 activation and LFA-1 mediated adhesion. We continued to show that C3G, a vital component of activating Rap1 and a more upstream element in the TCR signaling cascade, is dephosphorylated by PD-1.

Moreover, this was mediated by the phosphatases SHP-1 and SHP-2. Interestingly, we did not see these results downstream the inhibitory coreceptors, CTLA-4, proving that PD-1 works by a distinct mechanism.

Conclusion: We concluded that PD-1 inhibits Rap1 mediated adhesion by dephosphorylation of C3G utilizing the phosphatases SHP-1 and SHP-2. Further studies are underway to further characterize the regulation of these enzymes by PD-1.

Disclosure: I. Alagut, None; M. Straza, None; A. Mor, None.

2724
Deficiency of Ro52/TRIM21 in Different Subsets of Peripheral Blood Mononuclear Cells from Patients with Inflammatory Myopathies.
Andreas Galindo-Feria1, Jadranka Gamo-Martin2, Ana Barrera-Vargas3, Javier Merayo-Chalico and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Background/Purpose: The detection of Ro52/TRIM21 autoantibodies has been considered an independent prognostic marker in different rheumatic conditions. However, the information about the expression of Ro52/TRIM21 in subsets of peripheral blood mononuclear cells (PBMCs) in autoimmune diseases is scant. Specifically, its role in idiopathic inflammatory myopathies (IIM) has not been elucidated, and the evaluation of its expression in these diseases is the aim of the present study.

Methods: We included active, untreated patients with recent diagnosis (<1 month) of IIM according to Bohan and Peter’s criteria, who attended a referral center from March 2013 to April 2014. Patients with diagnosis of dermatomyositis (DM), polymyositis (PM) and antisynthetase syndrome (AAS), as well as age and gender-matched healthy controls were recruited. All subjects gave informed consent and the study was approved by the institutional ethics committees. PBMCs were isolated by Ficoll-Hypaque method and different subsets of PBMCs (CD4+, CD8+, CD14+) were purified by magnetic selection. The expression of Ro52/TRIM21 was evaluated by Western Blot. Descriptive statistics are shown with mean and standard deviation. Student’s T test or Mann-Whitney U test was used to analyze differences between groups.

Results: We included 14 patients with IIM (1 PM, 3 AAS, 10 DM), as well as 14 healthy controls. Sixty percent of subjects were female, with a mean age of 43 ± 15 years. CPK levels at diagnosis were 4534 ± 2235 U/L and lymphocyte count was 1021 ± 170 cells/µL. The presence of myositis-specific and associated autoantibodies was assessed by ELISA. The autoantibodies found in DM patients were anti-Ro52 (20%) anti-PL7 (20%), anti-Ku (20%), anti-PL12 (10%), anti-SRP (10%) and anti-Mi2 (10%). In AAS patients, anti-Ro52 (33.3%), anti-Jo1 (33.3%) and anti-PMSc17 (33.3%) were identified. We did not find any specific nor associated autoantibodies in the patient with PM. Patients with IIM showed decreased protein expression of Ro52/TRIM21 in comparison to healthy controls in different PBMC subsets: total PBMC: 0.971 ± 0.603 vs 1.849 ± 0.927, p = 0.016, CD4+ lymphocytes: 0.797 ± 0.540 vs 2.413 ± 0.786 p = 0.007, and monocytes: 0.875 ± 0.358 vs 1.890 ± 0.209 p < 0.001. CD8+ lymphocytes from IIM patients also showed a trend towards lower Ro52/TRIM21 expression (0.902 ± 0.708 vs 0.540, p = 0.133). We did not find significant differences among each of the IIM groups.

Conclusion: Our findings suggest that patients with IIM are characterized by deficient expression of the ubiquitin ligase Ro52/TRIM21 in different PBMC subsets (CD4+ lymphocytes and monocytes). Further insights into the function of this protein will have profound implications for the understanding of IIM. TRIM21 deficiency could be particularly related to decreased IRF ubiquitination and degradation, which could enhance type 1 interferon signaling.

Disclosure: A. S. Galindo-Feria, None; D. Gómez-Martin, None; A. Barrera-Vargas, None; J. Merayo-Chalico, None; J. Alcocer-Varela, None.

2725
S.L. M. Blockland1, M.R. Hillen1, A.A. Krötz1, A. Kizlat2, S. Melier3, B. Homey3, G.M. Smithson3, J. Zalevsky4, T.R.D.J. Radstake5 and J.A.G. van Roon5. 1University Medical Center Utrecht, Utrecht, Netherlands; 2University of Düsseldorf, Medical Faculty, Düsseldorf, Germany; 3Takeda Pharmaceuticals International, Chicago, IL; 4Takeda California, San Diego, CA.

Background: Primary Sjogren’s Syndrome (pSS) is a systemic autoimmunity disease characterized by the presence of anti-Ro/SSA (SS-A) and anti-La/SS-B (SS-B) autoantibodies in >90% of affected individuals. Diffuse disease of salivary glands is a frequent feature of pSS. CCR9, a member of the chemokine receptor family, is expressed on T follicular helper (Tfh) cells and Tfh-like cells and on naïve T cells. A main role of CCR9 is to facilitate the homing of Tfh-like cells to secondary lymphoid tissues. CCL25 is a ligand for CCR9 and plays a central role in Tfh cell development. Upregulation of CCL25 levels in salivary glands of pSS patients may favor the accumulation of Tfh-like cells in the gland and contribute to disease pathogenesis. In this study we aimed to investigate the expression of CCR9 and CCL25 in salivary glands of primary Sjogren’s syndrome patients (pSS).

Methods: A few milligrams of the salivary glands were harvested from 12 patients with pSS and six controls. Frozen sections were used for immunohistochemistry (antibodies against CCR9, CCL25, CD3, CD20, and CD38). CCR9+/CD3+ and CCR9+/CD38+ cells were quantified using ImageJ software. CCR9 and CCL25 expression levels were determined by qRT-PCR and Western Blot.

Results: The expression of CCR9 and CCL25 was significantly higher in pSS patients compared to healthy controls. The percentage of CCR9+ cells was increased in pSS patients (p<0.05). Similarly, the expression of CCL25 was significantly higher in pSS patients (p<0.05).

Conclusion: The expression of CCR9 and CCL25 is significantly increased in salivary glands of pSS patients compared to healthy controls. This finding suggests that CCR9+ and CCL25+ cells may contribute to the pathogenesis of pSS.

Disclosure: None.
Background/Purpose: In primary Sjögren’s syndrome (pSS) B cell activation and autoantibody secretion are hallmark immunopathological features. Specific lymphoid organization (including germinal centers) is associated with increased risk for development of extraglandular manifestations and lymphoma. Thus better understanding of the cellular and molecular pathways that underlie formation of ectopic lymphoid structures is of pivotal importance. Tfh cells, expressing ICOS and cytokines like IL-21 play a critical role in the formation of such structures and in activation of B cells. Recently, a novel subset of CD4+ T cells was found to have Tfh-like characteristics and was found to be specifically attracted to mucosal sites by CCL25, the ligand for CCR9.

Objective: To investigate the presence of CCL25 and CCR9-expressing Tfh-like cells in pSS patients.

Methods: Levels of CCL25 were measured in the serum of patients with pSS (n = 13), non-Sjögren’s sicca (nSS, n = 15) and healthy controls (HC, n = 10) by Luminex was determined. Secretion of CCL25 by labial salivary gland (LSG) biopsy samples from pSS (n = 14) and nSS (n = 14) patients was assessed and CCL25 mRNA was quantified (n = 9 vs n = 9). CCR9-expressing cells were assessed in the circulation of HC and pSS patients and expression of Tfh markers including CXCR5, ICOS and PD-1 was analyzed.

Results: Increased CCL25 levels were observed in serum of pSS and nSS patients as compared to HC (pSS 2984 ± 286, nSS 2692 ± 177, HC 2140 ± 154, p = 0.02 and p = 0.03 resp). CCL25 serum levels in pSS correlated with the presence of chemokines involved in formation of ectopic lymphoid structures CXCL13 and CCL19 (r = 0.594, p = 0.04) and proinflammatory cytokines IL-12 (r = 0.615, p = 0.03) and TWEAK (r = 0.621, p = 0.03). In addition, pSS patients displayed a 10 fold increase in CCL25 mRNA levels in LSG (p < 0.05) and an increase in CCL25 protein levels in LSG washouts compared to nSS patients (2029 ± 2986 vs 974 ± 188 pg/mL, p = 0.03). In contrast, CCL25 protein levels in HC did not increase. The number of CCR9-expressing T cells in the circulation as compared to HC (14.1% vs 7.9%, p < 0.05). Interestingly, to CCL25 a substantial proportion of CCR9+ cells expressed CXCR5, PD-1 and ICOS.

Conclusion: Our results suggest that enhanced expression of CCL25 in the labial salivary gland might promote elevation of CCR9-expressing Tfh-like cells at the site of inflammation. Considering the expression of ICOS and the capacity of CCL25 to induce proinflammatory cytokine secretion it suggests that the CCL25/CXCR5/CCR9 axis might play a role in the immunopathology of pSS, representing a novel therapeutic target in this disease.

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2727

T Cells Trigger Intestinal Pneumonia in Polyomaviruses. Akira Takeda1, Y asut suku Fukushima2, Takaji Matsutani3, Y ichiro Hagi3, Chisun M in4, Ryo Rokutanda3, Y asuhiro Suyama5, Mitsu masa Kishimoto6, Ken-ichi Yamaguchi7, and Masao Okada8.

The lung is frequently affected in connective tissue diseases (CTDs). Polyomaviruses (PM) is a major CTD characterized by idiopathic inflammatory lesions of muscle and other organs including critical pulmonary involvement. Intestinal lung diseases, mainly interstitial pneumonia (IP), have been recognized in 30–70% of PM patients, which often have a poor prognosis and a high risk of mortality. While the presence of myositis-specific autoantibodies suggests an autoimmune etiology of PM, the pathogenesis of PM-associated IP remains unclear. The aim of this study was to elucidate the role of T cells in this pulmonary complication. Lung tissue was utilized in this study with the approval of the IRB.

Methods: We had advantage of a rare opportunity to be able to precisely study the lesions caused by PM by using a video-enhanced thoracoscopic surgery after successful video-assisted thoracoscopic surgery from the cases of earliest-stage IP associated with PM: one patient with IP of early usual (IP) pattern and another patient with IP of nonspecific IP (NISP) pattern. It lead us to immunohistochemically characterize the phenotype of lung-infiltrating lymphocytes from the lung biopsy specimens, and to analyze T-cell receptor (TCR) and T-cell receptor (TCR) alpha-chain (TCR V alpha) and TCR beta-chain (TCR V beta) variable region repertoires of T-cells infiltrating the lungs tissue using a validated adaptor ligation polymerase chain reaction (PCR)-based microplate hybridization assay, comparing these to peripheral blood lymphocytes (PBL). We considered it important to perform TCR analysis from lung tissue in the earliest stage of IP because TCRs diversify with disease progression due to "determinant spreading" in which autoreactive T-cell responses, initiated by a single antigenic epitope, evolve into multispecific responses.

Results: The study with lung tissues of the initial stage of IP demonstrated substantial pulmonary CD3+ predominated T cell infiltrates. In both cases, patient A (early UIP pattern) and patient B (NISP pattern), most of the mononuclear cells were CD3+ T-cells, accompanied by a subtle infiltration of B-cells (CD20+), and a minimal number of monocytes (CD14+). Of infiltrating T-cells, most CD4+ than CD8+ cells (in the ratio of four to one) were noted in both patients. The usage of repertoires of TCR V alpha/beta in the lung differed from those in PBL, with certain TCR V gene families detected more frequently in lung tissue, suggesting a pivotal role for T cells in the pathogenesis of IP associated with PM. This is the first robust demonstration of selective TCR repertoire usage and its differential expression in lung tissue.

Background/Purpose: Inflammatory infiltrates of muscles in polymyositis patients are cytotoxic to autologous muscle cells in vitro via perforin-dependent mechanisms. J ayesh Pandya1, Paulius Venalis2, Lubna Al-Khalili1, Mohammad Shahadat Hos sain3, Ingrid E. Lundberg4, Vivianne Malmstrom1, and Andreas E. R. Fath1.

1Department of Rheumatology, 2Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden; 3Karolinska Institute, Stockholm, Sweden; 4KTH - Royal Institute of Technology, Stockholm, Sweden.

CD28null T Cells from Polymyositis Patients Are Cytotoxic to Autologous Muscle Cells in Vitro Via Perforin-Dependent Mechanisms. Jayesh Pandya1, Paulius Venalis2, Lubna Al-Khalili1, Mohammad Shahadat Hossain3, Ingrid E. Lundberg4, Vivianne Malmstrom1, and Andreas E. R. Fath1.

The lung is frequently affected in connective tissue diseases (CTDs). Polyomaviruses (PM) is a major CTD characterized by idiopathic inflammatory lesions of muscle and other organs including critical pulmonary involvement. Intestinal lung diseases, mainly interstitial pneumonia (IP), have been recognized in 30–70% of PM patients, which often have a poor prognosis and a high risk of mortality. While the presence of myositis-specific autoantibodies suggests an autoimmune etiology of PM, the pathogenesis of PM-associated IP remains unclear. The aim of this study was to elucidate the role of T cells in this pulmonary complication. Lung tissue was utilized in this study with the approval of the IRB.

Methods: We had advantage of a rare opportunity to be able to precisely study the lesions caused by PM by using a video-enhanced thoracoscopic surgery after successful video-assisted thoracoscopic surgery from the cases of earliest-stage IP associated with PM: one patient with IP of early usual (IP) pattern and another patient with IP of nonspecific IP (NISP) pattern. It lead us to immunohistochemically characterize the phenotype of lung-infiltrating lymphocytes from the lung biopsy specimens, and to analyze T-cell receptor (TCR) and T-cell receptor (TCR) alpha-chain (TCR V alpha) and TCR beta-chain (TCR V beta) variable region repertoires of T-cells infiltrating the lungs tissue using a validated adaptor ligation polymerase chain reaction (PCR)-based microplate hybridization assay, comparing these to peripheral blood lymphocytes (PBL). We considered it important to perform TCR analysis from lung tissue in the earliest stage of IP because TCRs diversify with disease progression due to "determinant spreading" in which autoreactive T-cell responses, initiated by a single antigenic epitope, evolve into multispecific responses.

Results: The study with lung tissues of the initial stage of IP demonstrated substantial pulmonary CD3+ predominated T cell infiltrates. In both cases, patient A (early UIP pattern) and patient B (NISP pattern), most of the mononuclear cells were CD3+ T-cells, accompanied by a subtle infiltration of B-cells (CD20+), and a minimal number of monocytes (CD14+). Of infiltrating T-cells, most CD4+ than CD8+ cells (in the ratio of four to one) were noted in both patients. The usage of repertoires of TCR V alpha/beta in the lung differed from those in PBL, with certain TCR V gene families detected more frequently in lung tissue, suggesting a pivotal role for T cells in the pathogenesis of IP associated with PM. This is the first robust demonstration of selective TCR repertoire usage and its differential expression in lung tissue.
versus PBL. As expected, no TCR signals were detected from non-IP lung tissue controls.

**Conclusion:** These findings clearly suggest a pathogenic contribution of organ-specific oligoclonal T cell accumulation through antigen-driven immune responses, implying potential elucidation of causative antigens as well as development of immuno-specific treatments such as molecular-targeted therapies.

**Disclosure:** A. Takenaka, None; Y. Fukushima, None; T. Matsutani, None; Y. Haji, None; C. Min, None; R. Rokutanda, None; Y. Suyama, None; M. Kishimoto, None; K. I. Y. Yamaguchi, None; M. Okada, None.

**2728**

**Reduction of MAIT Cell Frequency Associated with Reduced Cell Proliferation and Enhanced Cell Death in Systemic Lupus Erythematosus**

Asako Chiba, Naoto Tamura, Eri Hayashi, Ran Matsuda, Yoshibari Takasaki and Sachiko Miyake. Juntendo University School of Medicine, Tokyo, Japan.

**Background/Purpose:** Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes which are restricted by the MHC-related molecule-1 (MRC1) and express a semi-invariant TCR α chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. MAIT cells uniquely recognize microbial-derived vitamin B metabolites presented by MRC1. Like other innate-like lymphocytes, MAIT cells have been suggested to play both proinflammatory and regulatory roles in autoimmune models. Although MAIT cells are rare in mice, human MAIT cells have been suggested to play both proinflammatory and regulatory roles in autoimmune diseases. Previously we have revealed that the frequency of MAIT cells was reduced and reflected the disease activity in multiple sclerosis. In this study, we sought to investigate whether MAIT cells are involved in the pathogenesis of systemic lupus erythematosus (SLE).

**Methods:** Whole blood samples or peripheral blood mononuclear cells (PBMC) of SLE patients as well as healthy volunteers were stained with anti-human mononuclear antibodies (mAb) against CD3, γδ TCR, Vαα7.2TCR, CD161, CD45RA,CCR7, CD69, CD95 (FAS) and 7-AAD. MAIT cells were identified as CD3γδ TCR Vαα7.2 TCR CD161α T cells by FACsLSR Fortessa. In some experiments, costaining of intracellular active caspase-3 of MAIT cells was performed. MAIT cells and other T cell subsets were single-cell sorted by using FACs Aria II, and the usage of Vαα7.2-Jα33 TCR of single-cell sorted cells was examined by PCR. PBMC labeled with Cell Trace Violet Dye were stimulated with anti-CD3 mAb and anti-CD28 mAb or Fcγ receptors on activated naive CD4 T cells. Although the frequencies of naive cells were increased in lupus γδ T cells, most MAIT cells displayed an effector memory phenotype and there was no increase of naive cells among lupus MAIT cells.

**Conclusion:** This study demonstrates that the frequency of MAIT cells was significantly reduced in SLE. The increased cell death and reduced cell proliferation of activated MAIT cells were in part responsible for the decrease of MAIT cells in SLE. The limited recruitment of recent thymic emigrants of naive MAIT cells also contributed the profound reduction of these cells in SLE.

**Disclosure:** A. Chiba, None; N. Tamura, None; E. Hayashi, None; R. Matsuda, None; Y. Takasaki, None; S. Miyake, None.

**2729**

**To Live or Let Die... the Battle Between PD-1 and OX40 on SLE T Cells.**

Jule Kristine Laustsen1, Stein Greisen2, Bent Deleuran3 and Tue Kruse Rasmussen4.

1Aarhus University, Aarhus C, Denmark; 2Aarhus University Hospital, Aarhus, Denmark.

**Background/Purpose:** Programmed cell death 1 (PD-1) is a co-inhibitory receptor, which inhibits T cell proliferation and survival by inhibiting IL-2 signalling. By this PD-1 has been speculated as a key player in maintaining and restoring self-tolerance. In contrast, OX40 is a surface receptor that induces IL-2R expression and OX40 has been suggested to allow possible autoreactive effector T cells to develop into memory T cells. These two molecules could therefore represent two opposite sides of the balance in immune regulation - a balance crucial for maintaining peripheral tolerance. In systemic lupus erythematosus (SLE) this balance is disrupted, and disease progression is characterized by antibody production and autoreactive lymphocytes. In this study, we investigated cellular expression and soluble (s) levels of PD-1 and OX-40.

**Methods:** Plasma levels of sPD-1 and sOX40 from SLE patients (n=19) and healthy controls (HCs) (n=18) were quantified by ELISA. PBMCs from SLE patients and HCs were stained with monoclonal antibodies against PD-1, OX40, CD4, and CD8. Cells were gated based on flow cytometry. Skin biopsies from SLE patients and HCs were stained with anti-OX40 and anti-PD-1 antibodies and analyzed by confocal microscopy. Statistics were assessed by Mann-Whitney’s test, and Spearman’s ranked correlation. Data are expressed as median (IQR).

**Results:** In SLE patients, sPD-1 was significantly increased (445 pg/ml (319 pg/ml – 897 pg/ml)) compared to HCs (244 pg/ml (173 pg/ml – 343 pg/ml), p<0.001) and correlated positively with the SLE disease activity score SLEDAI (r=0.69, p=0.01). Soluble OX40 was decreased (7.3 pg/ml (7.3 pg/ml – 16.4 pg/ml)) compared with HCs (53.5 pg/ml (41.9 pg/ml - 72.5 pg/ml), p<0.001). Furthermore, the levels of sPD-1 and sOX40 were intercorrelated positively in SLE patients (r=0.59, p=0.005), which was not the case in HCs. Co-expression of PD-1 and OX40 was seen on (9.5%) CD4+ T cells in SLE compared with (5.2%) in HCs (p<0.01). Immunofluorescence revealed that PD-1 and OX40 co-expressing cells were present in SLE skin, further supporting that the same cell expresses both PD-1 and OX40 (Fig 1).

**Conclusion:** In this study, we show that T cells expressing both PD-1 and OX40 are increased in SLE, and that the levels of the soluble isoforms intercorrelate. We also show that sPD-1 correlates strongly with SLEDAI, suggesting sPD-1 as a marker of inflammation in SLE. The observed co-expression of the death receptor PD-1 and the survival receptor OX40, could in part explain why autoreactive effector T cells survive, despite receiving apoptosis signals, and help elucidate the lack of self-tolerance in SLE patients.

**Disclosure:** J. K. Laustsen, None; S. Greisen, None; B. Deleuran, None; T. Kruse Rasmussen, None.

**2730**

**FCγRIIIa Ligation in Human Peripheral CD4+ T-Cells Generate Th17-like Population.**

Anil K. Chauhan1, Terry Moore2 and Chen Chen3. 1Saint Louis University, St. Louis, MO, 2Saint Louis University, Saint Louis, MO.

**Background/Purpose:** Cytokines produced during Th17 response, IL-17A and IL-17F drive inflammation and autoimmunity. They also act as a bridge between adaptive and innate immunity. Immune deposits are formed in vascular sites in autoimmunity and often demonstrate the excessive presence of immune complexes (ICs) and activated complement products. ICs drive nephropathic changes in SLE. Thus, we examined whether these immune reactants can activate naive CD4+ T-cells to generate Th17-like cells. Furthermore to elucidate the mechanism by which ICs triggered the generation of Th17-like population, we also examined the presence of low affinity Fc-receptors on activated naive CD4+ T-cells.
Methods: Naive CD4+CD45RA+ T-cells obtained from SLE patients were activated using plate bound ICs (10 mg/ml) and soluble Csb5-2 (5 mg/ml) in the presence of anti-CD3 (0.25 mg/ml). Post activation cells were cultured in the presence of IL-1β (25 ng), IL-2 (10 ng), IL-6 (50 ng), IL-23 (25 ng), and TGF-β1 (10 ng) in each ml of RPMI. On day 9th culture soups were analyzed for cytokines and flow analysis was performed for IL-17A, IL-17F, IL-21, and IL-22. qRT-PCR was performed for IFN and Tnf IFN pathway genes were analyzed using qRT-PCR. IFN-arrays (Applied Biosystems).

Activated cells were analyzed for binding to labeled ICs and expression of fcrγ3a gene transcripts.

Results and Conclusion: Our results demonstrate that ICs via FcγR1IIa ligation on activated naïve CD4+ T-cells generate T-cell, like population. We observed increased expression of Th1 transcripts and statistically significant increase in IL-17A, IL-17F, IL-21, and IL-22 in the culture supernatants and an increase in cytokine producing population in flow analysis in response to ICs treatment. In addition IC mediated signal in CD4+ T-cells also generated an IFN-γ+ population. ICs and complement provided a co-stimulatory signal that was strong and divergent from the traditional CD28 co-stimulatory signal. CD4+ T-cells activated anti-CD3+ICs+Csβ-9 induced expression of fcrγ3a transcripts and membrane FcγR1IIa protein. These activated cells showed statistically significant increase in binding to labeled ICs and ANG in flow analysis. These results for the first time demonstrate a possible role for FcγR1IIa in the generation of T-cell, like cells. Our IFN array analysis also showed increase in type 1 IFN genes. In autoimmune disease a co-operation between type 1 IFNs and Th17 has been observed. Our data suggest that both of these responses are driven by ICs and complement in CD4+ T-cells. Generation of Th17, like population and IFN-γ producing cells will contribute to the development of lupus nephritis, which could occur locally in the kidney. These findings are important in that the activating membrane co-stimulatory signal from CD28 and ICOS are counteracted by CTLA4 and PD1 inhibitory signal during immune contraction. An activating signal from ICs and complement in immune contraction can tip the balance in favor of activating signal that may lead to breakdown of peripheral tolerance. Thus the data present identifies a new pathway by which ICs and complement will drive the autoimmune pathology.

Disclosure: A. K. Chauhan, None; T. Moore, None; C. Chen, None.

2731

Th1 and Th17 Cytokines Drive Takayasu Arteritis Inflammation. David Saadoun1, Marion Garrido2, Cléo Comarmond3, Anne-Claire Desbois4, David Klatzman5, Pierre Fourret6, Philippe Cluzel7, Julien Gaudric8, Fabien Koskas9, and Patrice Cacoub10.

Background/Purpose: Takayasu arteritis (TA) is a large-vessel vasculitis inducing damage of the aorta and its branches. Glucocorticoids remain the gold standard of therapy in TA. However, the nature of T cell driving vascular inflammation and the effects of glucocorticoids on the systemic components of TA are not understood.

Methods: T cell homoeostasis and cytokines production were analyzed in peripheral blood and aorta inflammatory lesions using Luminex, flow cytometry, and immunohistochemistry analysis. The study included 41 TA patients fulfilling the ACR criteria [17 active (aTA) and 24 in remission (rTA)]. 30 giant cell arteritis (GCA) patients (disease control) and 20 age and sex-matched controls.

Results: We first demonstrated the promotion of Th1 and Th17 responses that correlates with TA activity. We determined whether serum from TA patients is able to modulate T cell differentiation in healthy controls. The addition of serum from active TA patients in sorted CD4+ T cell culture of healthy donors induced a significant production of IFN-γ and IL-17A. We demonstrated the strong expression of IFN-γ, and IL-6 producing T cells within vascular inflammatory infiltrates of TA. Glucocorticoid therapy were associated to decreased circulating Th1 cytokines with significantly lower IL-2 (mean±SEM: 2812.6±690.1 vs. 7228±1356 pg/ml, p=0.0196), IFN-γ (1437±367.3 vs. 7124±1818 pg/ml, p=0.0191) and TNF-α (643.3±106.4 vs. 1438±196.6 pg/ml, p=0.01) in steroid treated TA compared to steroid free TA patients, respectively. However, glucocorticoids essentially left unaffected Th17 cytokines (i.e. IL-1b, IL-6, IL-17 and IL-23).

Conclusion: We provided the first evidence that Th1 and Th17 immunity seems to be important in driving TA inflammation, both systemically and in the blood vessels. In addition, one of these pathways was amendable to glucocorticoid-mediated suppression. Glucocorticoids are associated to decrease Th1 cytokines and spared Th17 cytokines in TA.

Disclosure: D. Saadoun, None; M. Garrido, None; C. Comarmond, None; A. C. Desbois, None; F. Domont, None; L. Savey, None; B. Terrier, None; M. Rosenzweig, None; D. Klatzman, None; P. Fourret, None; P. Cluzel, None; J. Gaudric, None; F. Koskas, None; P. Cacoub, Astra Zeneca, Bayer, Boehringer Inghein, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Roche, Servier, Vifor, 5.

2732

Massive Ex Vivo Expansion of Functionally Stable Beohct's Patient-Derived Regulatory T Cell Clones. Johannes Nowatzky, Olivier M. Manches, Yusuf Y. Yazici and Juan Lafaille. New York University School of Medicine, New York, NY.

Background/Purpose: A leptime transfer of regulatory T cells (Treg) is a promising strategy for the treatment of human autoimmune diseases. Most currently tested approaches focus on the polyclonal expansion of human Th17. Our results demonstrate that ICs via FcγR1IIa ligation on activated naïve CD4+ T-cells generate T-cell, like population. We observed increased expression of Th1 transcripts and statistically significant increase in IL-17A, IL-17F, IL-21, and IL-22 in the culture supernatants and an increase in cytokine producing population in flow analysis in response to ICs treatment. In addition IC mediated signal in CD4+ T-cells also generated an IFN-γ+ population. ICs and complement provided a co-stimulatory signal that was strong and divergent from the traditional CD28 co-stimulatory signal. CD4+ T-cells activated anti-CD3+ICs+Csβ-9 induced expression of fcrγ3a transcripts and membrane FcγR1IIa protein. These activated cells showed statistically significant increase in binding to labeled ICs and ANG in flow analysis. These results for the first time demonstrate a possible role for FcγR1IIa in the generation of T-cell, like cells. Our IFN array analysis also showed increase in type 1 IFN genes. In autoimmune disease a co-operation between type 1 IFNs and Th17 has been observed. Our data suggest that both of these responses are driven by ICs and complement in CD4+ T-cells. Generation of Th17, like population and IFN-γ producing cells will contribute to the development of lupus nephritis, which could occur locally in the kidney. These findings are important in that the activating membrane co-stimulatory signal from CD28 and ICOS are counteracted by CTLA4 and PD1 inhibitory signal during immune contraction. An activating signal from ICs and complement in immune contraction can tip the balance in favor of activating signal that may lead to breakdown of peripheral tolerance. Thus the data present identifies a new pathway by which ICs and complement will drive the autoimmune pathology.

Disclosure: A. K. Chauhan, None; T. Moore, None; C. Chen, None.
functionally reported different phenotypes within the expanded CD4+ TEM cell population in peripheral blood of GPA-patients.

**Methods:** Peripheral blood of 43 GPA-patients in remission and 16 healthy controls (HCs) was stained immediately after blood withdrawal with fluorochrome-conjugated antibodies for cell surface markers (CD3, CD4, CD45RO) and chemokine receptors (CCR4, CCR6, CCR7, CRTh2, CXCR3) followed by flow cytometry analysis. Positively and negatively stained populations were calculated by dot plot analysis, determined by the appropriate isotype controls. Expression patterns of chemokine receptors CXCR3, CXCR4, CCR6, CCR7, CRTh2, CXCR3 were used to distinguish Th1, Th2, Th17 and Th1/17 cells, respectively.

**Results:** The percentage of CD4+ TEM (CD3+CD4+CD45RO+CCR7+) cells was significantly increased in GPA-patients in remission compared to HCs (median 41.93% vs 31.52%). Chemokine receptor co-expression analysis within the CD4+ TEM cell population demonstrated similar percentages of Th1 and Th2 cells between GPA-patients and HCs. Interestingly, the analysis revealed a significant decrease in the frequency of Th1/17 cells (median 9.28% vs 16.53%) with a concomitant significant increase in the Th17 cells (median 21.14% vs 16.93%) in GPA-patients compared to HCs. However, differences between these CD4+ TEM cell subsets were not related to generalized or localized disease, ANCA positivity at the time of inclusion, nor to immunosuppressive treatment regimen.

**Conclusion:** Based on chemokine receptor co-expression analysis we demonstrate an aberrant distribution in the CD4+ TEM cell compartment in GPA-patients. The identification of different phenotypes within the expanded CD4+ TEM cell population revealed a distinction between Th1/17 cells and Th17 cells. Interestingly, it has been described that the functional and molecular signature of Th1/17 cells is associated with a strong polarization of this subset and may be important in mediating chronic inflammation. Analyzing the migration capacity of Th1/17 cells might reveal their distinct tissue homing characteristic to inflamed lesions in GPA-patients.

**Disclosure:** L. L. Lintermans, None; C. A. Stegeman, None; A. Rutgers, None; P. Heeringa, None; W. H. Abdulahad, None.

### 2734

**B55β Regulates T Cell Survival through the Modulation of AKT during Cytokine Deprivation.** Jose C. Crispin1, Sokrats A. Apostolis1, Neri Rodriguez Rodriguez1, Tran Nguyen2, and George C. Tsokos1.

**Background/Purpose:** The abundance of cytokines controls the length of immune responses through poorly defined mechanisms. B55β is a molecule that triggers apoptosis in activated T cells when cytokine levels decrease. T cells from a subset of patients with systemic lupus erythematosus (SLE) exhibit resistance to apoptosis that is associated to failure to express B55β. The aim of this study was to determine the molecular mechanisms through which B55β controls the survival of activated T cells.

**Methods:** Most experiments were performed in human primary T cells obtained from healthy donors. MCF7 cells were used in some experiments. T cells were activated with anti-CD3 and anti-CD28 (1 μg/mL). After day 3, fresh RPMI and IL-2 (100 U/mL) were replenished every 48 hours. Apoptosis was quantified in T cell lysates by ELISA. AKAP79 mutants deficient for association to PKA (ΔPKA-AKAP79), PKC (ΔPKC-AKAP79) and calcineurin (ΔCN-AKAP79) were generated with QuickChange Site Directed Mutagenesis kit and confirmed by sequencing. Jurkat T cells were transfected with dual promoter pRRL-AKAP79/GFP- or control pRRL-GFP-expressing lentiviruses. For functional assays, T cells were stimulated with plate-bound anti-CD3 and soluble anti-CD28 antibodies or tPA/monocyte. RNA was isolated, IL2 transcripts quantified by quantitative real-time PCR (qPCR) and results normalized to unstimulated control. qPCR and western blotting. Statistical differences between groups were analysed by ANOVA and non-parametric Mann-Whitney U test, using GraphPad Prism software.

**Results:** IL2 transcription induced by anti-CD3/CD28 stimulation was not significantly different between SLE (n=6) and HC (n=6) T cells. However, a negative correlation between levels of AKAP79 protein and levels of AKAP79 expression and was reduced by IL2 deprivation but that the pathway is not uniformly downregulated. mTORC1 and its substrates were mostly not affected whereas other AKT substrates, in particular the pro-apoptotic protein BAD and the transcription factors Foxo1 and 3a, were activated by dephosphorylation. Accordingly, induction of pro-apoptotic genes regulated by Foxo factors was observed. Further experiments confirmed that B55β overexpression activates the Foxo factors inducing the upregulation of pro-apoptotic genes, in particular Noxa, Puma and HRK.

**Conclusion:** B55β is a key regulator of AKT. Upon its induction by IL-2 deprivation, it causes AKT dephosphorylation triggering programmed cell death. We report for the first time the induction of apoptosis associated to dephosphorylation of AKT S473. Simultaneous phosphorylation status of 18 members of the pathway using an intracellular signaling array. The results confirmed that AKT is dephosphorylated by IL-2 deprivation but that the pathway is not uniformly downregulated. mTORC1 and its substrates were mostly not affected whereas other AKT substrates, in particular the pro-apoptotic protein BAD and the transcription factors Foxo1 and 3a, were activated by dephosphorylation. Accordingly, induction of pro-apoptotic genes regulated by Foxo factors was observed. Further experiments confirmed that B55β overexpression activates the Foxo factors inducing the upregulation of pro-apoptotic genes, in particular Noxa, Puma and HRK. Our results demonstrate a novel mechanism of how AKT is regulated in activated T cells in response to cytokine abundance.

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### 2735

**Association of A Kinase Anchoring Protein-79 (AKAP79) to PKC mediates Inhibition of IL2 Transcription and Erk Activation in T Cells.**

Gabriel Criado, Marı́a J. Pérez-Lorenzo, Marı́a Galindo, José L. Pablos and Abel Suarez-Fuego. Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain.

**Background/Purpose:** A-Kinase anchoring Protein AKAP79 associates to and regulates the activity of PKA, PKC and calcineurin, key regulators of T cell activation. We have previously described that AKAP79 is overexpressed in T cells from systemic lupus erythematosus lupus patients and inhibits IL2 transcription in Jurkat T cells (Criado et al., A & R 63 (Suppl10): S5916). In the present study, we aim to analyze the effect of AKAP79 levels on IL2 production in SLE and normal T cells and characterize the role of the association to PKA, PKC and calcineurin in T cell activation and IL2 transcription.

**Methods:** T cells were isolated by negative selection from SLE patients and healthy controls (HC). RNA was purified, retrotranscribed to cDNA and levels of AKAP79 and β-actin transcripts were quantified by quantitative real-time PCR using Sybr Green technology. AKAP79 protein expression was quantified in T cell lysates by ELISA. AKAP79 mutants deficient for association to PKA (ΔPKA-AKAP79), PKC (ΔPKC-AKAP79) and calcineurin (ΔCN-AKAP79) were generated with QuickChange Site Directed Mutagenesis kit and confirmed by sequencing. Jurkat T cells were transfected with dual promoter pRRL-AKAP79/GFP- or control pRRL-GFP-expressing lentiviruses. For functional assays, T cells were stimulated with plate-bound anti-CD3 and soluble anti-CD28 antibodies or tPA/monocyte. RNA was isolated, IL2 transcripts quantified by quantitative real-time PCR (ΔqPCR) and results normalized to unstimulated control. Statistical differences between groups were analysed by ANOVA and non-parametric Mann-Whitney U test, using GraphPad Prism software.

**Results:** IL2 transcription induced by anti-CD3/CD28 stimulation was not significantly different between SLE (n=6) and HC (n=6) T cells. However, a negative correlation between levels of AKAP79 protein and induction of IL2 transcription was found in T cells, regardless of their origin (R2 = 0.53, p=0.0076). This was confirmed in Jurkat T cells by transduction with different amounts of AKAP79 (R2 = 0.57, p=0.03, n=8). Complementation of anti-CD3/CD28 stimulation by tPA, but not monocyte, restored IL2 transcription in Jurkat cells overexpressing AKAP79, suggesting that inhibition of PKC by AKAP79 was responsible for the observed reduction of IL2 transcription. Consistent with this interpretation, overexpression of ΔPKC-AKAP79 partially rescued IL2 transcription when compared to WT-AKAP79 but ΔPKA-AKAP79 and ΔCN-AKAP79 had no significant effect (GFP: 11.59 +/- 2.21, AKAP79: 8.67 +/- 0.01, ΔPKC-AKAP79: 4.86 +/- 1.24, ΔPKA-AKAP79: 0.73 +/- 0.29, ΔCN-AKAP79: 0.88 +/- 0.35). Likewise, analysis of the kinetics of Erk activation in response to antiCD3/CD28 showed that Erk activation was blocked by AKAP79 overexpression and was recued by ΔPKC-AKAP79.

**Conclusion:** Overexpression of AKAP79 inhibits IL2 transcription and Erk activation in a PKC-dependent manner. Thus, targeting AKAP79-PKC interaction could provide a therapeutic approach to modulate T cell activation.

**Disclosure:** G. Criado, None; M. J. Pérez-Lorenzo, None; M. Galindo, None; J. L. Pablos, None; A. Suarez-Fuego, None.
Female Specific Increase in T Cell Glycosylation in Lupus. Gabriela Gorelik and Bruce Richardson. University of Michigan, Ann Arbor, MI.

**Background/Purpose:** Systemic Lupus Erythematosus (SLE) is an autoimmune inflammatory disease characterized by altered T cell signaling. SLE is characterized by epigenetic mechanisms that cause hypomethylation of the inactive X-chromosome predisposing females to the disease, and a global T cell DNA hypomethylation, which causes overexpression of immune-related genes.

**Conclusion:** We demonstrate that SLE patients have reduced IL-21 signaling capacity, decreased miR-155 levels, and increased SOCS1 levels compared to HCs. The reduced IL-21 signaling in SLE could be rescued by overexpression of miR-155, suggesting an important role for miR-155 in the reduced IL-21 signaling observed in SLE.

**Disclosure:** T. K. Rasmussen, None; T. Andersen, None; R. Bak, None; G. Yiu, None; N. K. Steenbergs-Petersen, None; J. G. Mikkelsen, None; P. J. Utz, None; C. Holm, None; B. Deleuran, None.

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**Background/Purpose:** The voltage-gated potassium channel Kv1.3 is a novel target for the treatment of autoimmune disorders including psoriatic and rheumatic diseases. Shk-186 is an exquisitely specific, highly potent peptide inhibitor of Kv1.3 on activated effector memory T cells that has just entered clinical development. Here, we report on Shk-186’s safety and tolerability in phase I trials and on the evaluation of its therapeutic potential in an autoimmune kidney disease model.

**Methods:** To evaluate the safety, tolerability and pharmacokinetics (PK) of Shk-186, we conducted single ascending dose and multiple ascending dose double-blind, placebo-controlled phase I trials in healthy volunteers. In the single ascending dose trial, individuals were given increasing doses of Shk-186 subcutaneously and characterized after a single dose of drug; in the multiple ascending dose trial, individuals were given 9 doses of drug twice weekly for 4 weeks and characterized throughout. To investigate Shk-186’s potential therapeutic application in autoimmune kidney disease, we evaluated the drug in a glomerular basement membrane animal model of autoimmune glomerulonephritis. Moreover, we have begun evaluating peripheral blood and urine samples from patients with autoimmune kidney disease for expression of Kvl3 and production of cytokines in the presence and absence of Shk-186.

**Results:** Shk-186 was well tolerated with no serious adverse events reported. PK analysis revealed that the doses and dose regimens evaluated provided drug exposure in plasma surpassing the predicted therapeutic range based on therapeutic drug exposures in preclinical models of disease. Supporting the therapeutic potential of Shk-186 to treat chronic autoimmune kidney diseases, we showed that Shk-186 could lower kidney disease parameters such as urine protein and creatinine in a model of autoimmune glomerulonephritis, as well as significantly reduced histopathological changes associated with disease such as crescent formation and inflammatory cell infiltrate. Ex vivo immunophenotyping and functional studies of blood and urine from autoimmune kidney disease patients showed that Kvl3 is present in effector memory T cells.

**Conclusion:** This first-in-human clinical trial suggests that Shk-186 is a well-tolerated drug when given at doses expected to provide a therapeutic benefit. In addition to previously described indications where Kvl3 has been implicated including multiple sclerosis and rheumatoid arthritis, we provide evidence to support extending its therapeutic scope to the treatment of chronic kidney autoimmune diseases.

**Disclosure:** E. J. Muñoz-Elias, Kineta Inc, 3; K. Norton, Kineta Inc, 3; J. B. Grigg, Kineta Inc, 3; L. Bromley, Kineta Inc, 3; D. W. Peckham, Kineta Inc, 3; E. J. Tarcha, Kineta Inc, 3; J. Odgaard, None; J. Qin, None; M. Y. uasa, None; A. Stevens, None; W. H. Abdulahad, None; G. Schmunk, None; K. G. Chandy, Kineta Inc, 3; S. P. Iadonato, Kineta Inc, 3.

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**Microrna-155 Suppresses IL-21 Signaling and Production in Systemic Lupus Erythematosus.** Tue K. Rasmussen, Thomas Andersen, Rasmus Bak, Gloria Y. u, Kristian Steengaard-Petersen, Jacob G. Mikkelsen, Paul J. Utz, Christian Holm and Bent Deleuran. 1Arhus University, Aarhus C, Denmark, 2Stanford University School of Medicine, Stanford, CA, 3Aarhus University Hospital, Aarhus, Denmark.

**Background/Purpose:** IL-21 is a key regulator of B cells functions and autoantibody production and is mainly produced by follicular T help cells. The purpose of this study is to investigate the signaling capacity of interleukin (IL-21) in T and B cells and assess its possible regulation by microRNA-155 and its target gene suppressor of cytokine signaling 1 (SOCS1) in systemic lupus erythematosus (SLE).

**Methods:** The signaling capacity of IL-21 was quantified by stimulating PBMCs with IL-21 and measuring phosphorylation of pSTAT3 in CD4+ T cells, B cells, and NK cells. Induction of miR-155 by IL-21 was investigated by stimulating purified CD4+T cells with IL-21 and measuring miR-155 expression levels. The functional role of miR-155 was assessed by overexpressing miR-155 in PBMCs from SLE patients and HCs and measuring its effects on STAT3 and IL-21 production in CD4+ and CD8+ T cells.

**Results:** Induction of pSTAT3 in CD4+ T cells in response to IL-21 was significantly decreased in SLE patients compared to HCs (p<0.0001). Further, expression levels of miR-155 were significantly decreased and SOCS1 correspondingly increased in CD4+ T cells from SLE patients. Finally, overexpression of miR-155 in CD4+ T cells increased STAT3 phosphorylation in response to IL-21 treatment (p<0.01) and differentially increased IL-21 production in SLE patients compared to HCs (p<0.01).

**Conclusion:** We demonstrated that SLE patients have reduced IL-21 signaling capacity, decreased miR-155 levels, and increased SOCS1 levels compared to HCs. The reduced IL-21 signaling in SLE could be rescued by overexpression of miR-155, suggesting an important role for miR-155 in the reduced IL-21 signaling observed in SLE.

**Disclosure:** T. K. Rasmussen, None; T. Andersen, None; R. Bak, None; G. Yiu, None; N. K. Steenbergs-Petersen, None; J. G. Mikkelsen, None; P. J. Utz, None; C. Holm, None; B. Deleuran, None.

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**SHP-1 Regulates the Activation Threshold of INKT Cells.** Meng Zhao and Mitchell Kronenberg. UC-San Diego, La Jolla, CA, La Jolla Institute for Allergy and Immunology, La Jolla, CA.
**Background/Purpose:** Autoimmune invariant Natural Killer T (iNKT) cells have been implicated in several rheumatic diseases, including Systemic lupus erythematosus and Rheumatoid arthritis. iNKT cells are a unique subpopulation of lymphocytes that recognize glycolipids presented by CD1d, and that express an invariant T cell receptor (TCR). As a result of activation, iNKT cells secrete copious amount of cytokines, including IFN-γ, IL-4, IL-17 and IL-21 and they mediate immune responses in various pathological conditions. Although several potential lipid self-antigens for iNKT cell development and activation have been identified, the mechanism by which iNKT cells react to CD1d-self-antigen is not understood yet. Our discoveries therefore will help identify novel drug targets for potential translational intervention in patients with SLE, RA and other autoimmune diseases in which abnormal activation of iNKT cells is observed.

**Methods:** In detecting autoreactivity, instead of iNKT cell hybridomas that have many limitations, we will use primary cultured mouse iNKT cells. Sorted as αβLCer-CD1d tetramers “TCRβ+” iNKT cells grow exponentially in vitro, and can be transduced by retroviruses in order to modulate differential expressions of important regulators. Microarray was carried out to identify new regulators of iNKT cell autoreactivity.

**Results:** Our data show that the cultured iNKT cells have a greatly increased sensitivity to CD1d-lipid complexes derived from multiple sources, including soluble CD1d molecules produced in insect or mammalian cells, CD1d transfected cultured cells, and bone marrow-derived DCs. APCs that express a tail-deleted form of CD1d have a strongly diminished ability to stimulate the iNKT cell lines, indicating that the lines, like their primary cell counterparts in vivo, recognize auto-Ags loaded onto CD1d in endo/lysosomal compartments. Our results show that the iNKT cell lines preferentially respond to specific epithelial cells that were described previously when compared to the closely related homologs, despite their very different structures. Microarrays comparing the expression profiles of cultured and freshly isolated iNKT cells identifies SHP1/PTPN6, a tyrosine phosphatase that regulates TCR signaling, is down regulated in the iNKT cell lines. Reconstitution of the lines with the wild type but not the catalytically inactive SHP1 decreases the auto reactivity of the iNKT cell lines.

**Conclusion:** We hypothesize that iNKT cell TCR is intrinsically autoreactive, and instead of requiring a specific autoantigen, many autologous Ags are capable of stimulating iNKT cells. The threshold of activation for iNKT cells are controlled during development and immune responses through key regulators, so that in the situation when this threshold is lowered, iNKT cells are activated by common lipid antigens that are present in the DP thymocytes or APCs. In the present study, taking advantage of a new system, we show the autoreactivity of polyclonal iNKT cells and we discover the protein tyrosine phosphatase SHP1 (Ptpn6) is a critical regulator of the activation threshold of iNKT cells.

**Disclosure:** K. A. Kuhn, None; S. P. Colgan, None.

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**The Role of Fli1 in Lupus T Cell Function and Nephritis.** Thirumagal Thyagarajan, Ivan Molano and Tamara K. Nowling. *Medical University of South Carolina, Charleston, SC; Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC.*

**Background/Purpose:** The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved kidney disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells in MRL/lpr lupus mice resulted in significantly improved kidney disease. We recently demonstrated that lowering the global levels of Fli1 in the MRL/lpr lupus model has specific effects on T cells, including reducing their activation and IL-4 production when stimulated through the T cell receptor. We further showed that this was likely a result of decreased glycosphingolipid (GSL) metabolism, specifically decreased Neuraminidase1 (Neu1) expression and activity and decreased lactosylceramide (LacCer) in T cells. GSls are a heterogeneous class of lipids in the sphingolipid family that play a role in the regulation of cellular processes. LacCer is a GSL to which sialic acid residues are added by ganglioside synthases to generate ganglio- side and other GSLs in the GSL synthetic pathway. Sialic acids are then removed by NEUs from gangliosides in the GSL catabolic pathway. Lipids with distinct chain lengths are thought to possess distinct biological activities. We now demonstrate that lowering Fli1 levels significantly decreases the number of CXCR3+ T cells, T cell migration to the kidney and GSL metabolism in the kidney of MRL/lpr lupus prone mice.

**Methods:** Kidney and/or spleen were harvested from non-splenectomized 11, 14 and 18 week-old MRL/lpr Fli1+/+ and Fli1−/− mice. Kidneys and/or T cells isolated from spleen by negative selection were analyzed by flow cytometry. Supercritical Fluid Chromatography coupled with tandem mass spectrometry was performed on kidney cortex homogenates. Gene expression was analyzed by real-time RTPCR on RNA isolated from kidney cortex. Mx48-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) imaging and immunohistochemistry (IHC) for LacCer was performed on frozen kidney sections.

**Results:** LacCer levels, which are elevated in the kidneys of MRL/lpr mice controlled to controls, are significantly reduced by 50% in age-matched MRL/lpr mice that are heterozygote for Fli1 (Fli1+/−). This reduction in LacCer expression is observed across the kidney using MALDI-IMS. Although Neul expression and Neu activity is decreased in T cells, their levels are unchanged in the kidney of Fli1+/− compared to Fli1+/+ MRL/lpr mice. The percentage of T cells expressing CXCR3 is significantly reduced by ~30% in Fli1−/− compared to Fli1+/+ MRL/lpr mice and the percentage and overall number of T cells in the kidney are significantly reduced by ~50%.

**Conclusion:** Our results demonstrate that one mechanism by which reducing Fli1 levels may be protective in lupus kidney disease is to decrease GSL metabolism in T cells, reducing T cell activation, production of IL-4, expression of CXCR3, a receptor shown to be important in T cell migration.
to the kidney in lupus, and migration to the kidney. This likely contributes to the decreased inflammation and GSL metabolism in the kidney and improved kidney disease of MRL/lpr F1/+/-- mice.

**Disclosure** T. Thiyyagarajan, None; I. M. diano, None; T. K. Nowling, None.

**2742**

**Polymorphisms in the Slam Family of Molecules Play a Role in the Development and Function of Invariant Natural Killer T Cells in New Zealand Black Mice.** Yuryi Baglaenko,1 Kieran Mainion,1 Nan-Hua Chang2 and Joan E. Wither2.1 University of Toronto, Toronto, ON, 2Toronto Western Research Institute, Toronto Western Hospital, Toronto, ON, 3Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, ON, Toronto.

**Background/Purpose:** The family of signaling lymphocyte activating molecules (SLAM) have been shown to play a key role in the development of autoimmunity in spontaneous and induced mouse models. Previous work by others has shown that expression of two SLAM family members, CD150 and Ly108, plays a critical role in the development of Natural Killer T (NKT) cells, an innate-like semi-invariant population of lymphocytes, which quickly respond to lipids presented on non-classical MHCs. However, the impact of SLAM polymorphisms on NKT function is less clear. The aim of this study was to characterize both the development and function of NKT cells in B6 congenic mice with an NZB chromosome 1 interval that is known to have polymorphisms in the SLAM family of molecules.

**Methods:** NKT development and marker expression were examined by flow cytometry of de novo splenocytes and thymocytes. NKT cell function was examined by in vivo stimulation with 2μg of αGalCer, injected intravenously. Production of IFN-γ and IL-4 was measured by intracellular flow cytometry. Bone marrow derived dendritic cells (BMDCs) were generated by 7–10 day culture with recombinant human FLT3 ligand.

**Results:** Congenic mice had significantly fewer splenic NKT cells when compared to B6 controls. However, NKT cell frequencies in the thymus did not differ. The frequency of double positive thymocytes, critical for homotypic interactions between NKT cell precursors, was also unchanged. In support of previous findings, cell surface expression of SLAM family members on this cell population was altered. When compared to control animals, NZB congenic mice had significantly decreased expression of positive signaling Ly108 and CD150 molecules and increased expression of the negative SLAM signaling molecule, Lyl9. Since NKT cells have been shown to play a role in autoimmunity through production of cytokines such as IL-4 and IFN-γ, the capacity of these cells to secrete cytokines was assessed. Upon stimulation with αGalCer, the prototypic NKT cell stimulating lipid, NKT cells from NZB congenic mice produced significantly less IL-4 and IFN-γ when compared to control mice. Consistent with this being the result of the SLAM polymorphisms, analysis of subcongenic NZB strains with shorter chromosome 1 intervals revealed that both of these phenotypes localized to a small region between 171–177Mb containing the SLAM family. To determine whether the reduced NKT cytokine production in NZB congenic mice was due to altered antigen presentation or impaired NKT cell function, adoptive transfer experiments were conducted with αGalCer pulsed BMDCs from control or congenic mice. The results revealed that injection of BMDCs generated from either strain could equivalently stimulate IL-4 and IFN-γ production by NKT cells in control animals, whereas injection of control BMDCs into NZB congenic mice resulted in impaired production of these cytokines.

**Conclusion:** These data suggest that polymorphisms in the SLAM family result in reduced peripheral NKT cell numbers and an intrinsic NKT cell functional defect.

**Disclosure** Y. Baglaenko, None; K. Mainion, None; N. H. Chang, None; J. E. Wither, None.

**2743**

**CD27 Is a Key Regulator of T Cell Responses.** Michael Scully1, Nicole Wunderler2, Holger Babbe2, Yevgeniy Orlovsky3, Galina Osmolova3, Ann Ca4, Health Guay5, Jacqueline Benson6 and Tatiana Ort3.1 Immunology Research, Janssen Research and Development, LLC, Spring House, PA, 2Toronto Western Research Institute, Toronto Western Hospital, Toronto, ON, 3Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, ON, Toronto.

**Background/Purpose:** CD27 is a member of the TNF superfamily of receptors that is expressed on a majority of natural killer (NK) cells, T cells, memory B cells and antibody-secreting plasma cells in humans. CD70 is the only known ligand for CD27 and is transiently expressed on activated dendritic cells, B cells and T cells. Much of our understanding of the immunological role of CD27 comes from studies with mouse models, which suggest that CD27 is a key regulator of NK cell, T cell and B cell responses. Here, we used an in-house generated neutralizing, antagonistic antibody to evaluate the role of CD27 in regulating human and primate immune responses using in vitro and in vivo models.

**Methods:** To examine the role of CD27 in immune cell biology, we generated a neutralizing, antagonistic and non-depleting human anti-human CD27 antibody. To assess the contribution of CD27 signaling to human immune responses in vitro, we examined the effects of CD27 blockade on Ig-production by B cells, proliferation of naïve CD4+ T cells and cytokine production by healthy volunteer PBMCs in vitro. To understand the role of CD27 on immune responses in vivo, we examined the effects of CD27 blockade on T and B cell responses in a cynomolgus monkeyDelayed Type Hypersensitivity (DTH) model. To further explore the contribution of CD27 to human T cell responses in vitro, we examined the effects of CD27 blockade on human T cell engraftment in the NSG (NOD/Scid IL-2Rγ−/−) human CD45+ peripheral blood cell → mouse GVH model.

**Results:** We found that neutralizing the CD27 pathway inhibited CD70-induced Ig-secretion by activated human B cells, whereas blockade of CD27 in an autologous T cell:B cell co-culture model did not impact Ig-secretion in vitro (despite expression of CD27 on cells in this system). Treatment with an anti-CD27 antibody dose-dependently attenuated CD70-mediated induced proliferation of primary human CD4+ T cells and decreased the production of pro-inflammatory cytokines by healthy control PBMCs in vitro. Treatment with an anti-CD27 antibody reduced human CD45+ CD4+ and CD8+ T cell numbers in the spleen and peripheral blood of host mice in the human cell → NSG mouse GVH model. Blockade of CD27 reduced T cell infiltration into the challenge site in response to a neo-antigen, but did not impact antigen-specific antibody titers in a cynomolgus monkey DTH model.

**Conclusion:** These data demonstrate that CD27 can promote Ig-production by human B cells, but may play a redundant role in some types of B cell responses. In contrast, CD27 appears to play a critical role in the generation of both CD4+ and CD8+ T cell responses. These data suggest that the CD27 pathway modulates the activity of multiple human immune cell types, and that blockade of the CD27 pathway may present a novel therapeutic strategy for the treatment of immune mediated diseases.

**Disclosure** M. Scully, Janssen Research and Development, 3; N. Wunderler, Janssen Research and Development, 3; H. Babbe, Janssen Research and Development, 3; Y. Orlovsky, Janssen Research and Development, 3; G. Osmolova, Janssen Research and Development, 3; A. Cai, Janssen Research and Development, 3; H. Guay, Janssen Research and Development, 3; J. Benson, Janssen Research and Development, LLC, 3; T. Ort, Janssen Research and Development, 3.

**ACR/ARHP Poster Session C Vasculitis**

**Tuesday, November 18, 2014, 8:30 AM–4:00 PM**

**2744**

**MI-RNA Profile of Active Vascular BEHÇET’S Patients.** Ahmet Mesut Onal1, Ozan Gerenli1, Bıyımnüş Canıası2, M. Mustafa Ulası3, Gezmis Kimyon4, Ayaz Pehlivan5 and Serdar Oztuzcu6.1 Gaziantep University School of Medicine, Gaziantep, Turkey, 2Gaziantep UniversitySchool of Medicine, Gaziantep, Turkey, 3Uludag University, School of Medicine, Bursa, Turkey.

**Background/Purpose:** Behçet’s Disease (BD) is a systemic vasculitis that predominantly presented with oral aphthous ulcers and additionally at least two of the following findings like genital ulcers, eye involvement, skin lesions and pathergy reaction. Vascular involvement is devastating face of BD and thrombosis of the arterial and venous system and aneurismatic arterial disease is not rare. The flares are the typical nature of BD and the pathology of the disease is mostly constructed on vasculitis. However the satisfied mechanism of BD remains unknown. We herein tried to evaluate the micro RNA (miRNA) behavior in BD.

**Methods:** Eighty-five BD patients were enrolled in to the study group, which were divided to 3 groups of 20–25 and 25 with active vascular disease, active mucocutaneous disease and patients with at least 6 months remission, respectively. A additional 25 volunteers were the healthy controls and the 4 of the groups have no difference in the characteristics. The whole study population was male, due to difficulties of finding active women BD patients.
Serum samples were analyzed for miRNA with PCR assay and the data were analyzed statistically. A clive vascular patients had significantly higher CRP and ESR results than active mucocutaneous ones and they both had higher levels than remission and healthy groups.

<table>
<thead>
<tr>
<th>Active BD</th>
<th>Active mucocutaneous</th>
<th>Remission BD</th>
<th>Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.60 ± 4.57</td>
<td>32.60 ± 6.36</td>
<td>35.72 ± 9.21</td>
</tr>
<tr>
<td>Disease duration</td>
<td>4.2 ± 2.71</td>
<td>4.25 ± 3.31</td>
<td>4.68 ± 3.21</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>29.35 ± 36.47</td>
<td>22.53 ± 21.38</td>
<td>4.92 ± 3.11</td>
</tr>
<tr>
<td>ESR (hour)</td>
<td>34.90 ± 26.46</td>
<td>30.0 ± 24.03</td>
<td>15.56 ± 11.85</td>
</tr>
</tbody>
</table>

Results: There was no difference for any miRNA between BD patients with remission and healthy controls. The comparison of active BD patients and healthy controls revealed lower levels of miR-17-5p, miR-451A, miR-106b-5p, miR-19b-3p, miR-26b-5p, miR-93-5p, miR-250b, miR-25-3p in the disease activity, miR26b-5p was found lower only in mucocutaneous plasma (from HC, iBD or aBD). Gene expression for the five NADPH-oxidase substrates was determined by luminol/lucigenin luminescence with or without stimulation with AB (Table 1) and NADPH-oxidase expression (Table 2) was higher after stimulus with aBD or iBD plasma. PBMC displayed equivalent results. Resting and pathogen-stimulated phagocytes presented equivalent O2⁻/H2O2 production and NADPH-oxidase expression. NET formation was constitutive and NADPH-oxidase expression. NET formation was constitutively increased in aBD or iBD plasma, compared to HC neutrophils (Table 3). Similarly, neutrophils from aBD and iBD produced more extensive NET than neutrophils from HC (Table 3). We aimed to search the relation among levels of visfatin with activity of BD.

Background/Purpose: It’s a known fact that serum levels of the tumor necrosis factor alpha (TNF-α) interleukin-6 (IL-6) and other proinflammatory cytokines which are released from the adipose tissue are increased in Behçet’s disease (BD). In BD adipose tissue is not a passive energy depot, it is an active endocrine organ and releases adipokines. Visfatin is one of them. Visfatin is related to TNF-α and IL-6, IL-1 beta, co-stimators like CD40, CD54 and CD 80 and endothelial I CAM-1 and ICAM-2. We aimed to search the relation among levels of visfatin with activity of BD.

Methods: 60 BD (30 patients were in active state and 30 were in remission) patients diagnosed according to The Criteria of Working Group on International BD and 20 health subjects as controls were involved in to the study. The study of groups detected visfatin levels were compared among groups.

Results: Visfatin levels were significantly higher in both group of patients compared to the control group (both p<0.001). Serum visfatin levels in patients with active than in inactive patients were found statistically significantly higher (p<0.001). The same way in all cases statistically significant correlation between visfatin and CRP (p<0.001) and visfatin and ESR (p<0.001). Only according to the symptoms of the patients in the active group compared to visfatin levels in patients with genital aphth visfatin levels, a statistically significantly higher than in patients without genital aphth were detected (p<0.001).

Conclusion: Serum visfatin levels in patients with active and inactive causes are higher than the control group; visfatin proinflammatory cytokines have a role in chronic inflammatory reaction, and to sustain the cellular expression of the inflammatory stochiomer which induced that conclude or be due to different reasons.

Disclosure: M. E. Enecki, None; Z. Ozbalkan, None; G. Keskin, None; S. C. Sandikci, None; Y. Karaaslan, None.
Background/Purpose: Thrombosis occurs in 20% of patients with Behçet’s Syndrome (BS) and leads to significant morbidity. There is no robust association between thrombosis in BS and the presence of hereditary thrombophilia or raised inflammatory markers. It remains a challenge to distinguish those at risk of thrombosis potentially requiring aggressive preventative therapy and those whose therapy can be reduced. There is a clear need to develop biomarkers for diagnosis and risk management in BS.

Results: MPs were prepared following venepuncture of 88 BS patients who fulfilled International Study Group Criteria for diagnosis, 21 of whom had a history of thrombosis, and 39 healthy controls (HC). MPs were identified using flow cytometry by gating for particles less than 1 μm in size and staining positively with Annexin V, which binds PS, giving a total MP count. Antibodies to CD14 (monocytes), TF, CD62P (platelets), CD144 (endothelial cells) and CD66b (neutrophils) were used to identify cellular markers. MPs were measured using calibrated automated thrombography, allowing analysis of the thrombotic potential of MPs.

Conclusion: MPs are found in higher numbers in BS patients than in HCs, and in TBS patients compared to NTBS patients. MPs are associated with thrombosis in Behçet’s Syndrome (BS).

Disclosure: Y. Cheng Jr., None; X. Sun, None; Y. Chen Jr., None; C. Huang, None; H. Deng, None; Z. G. Li, None.

2749

Microparticles May Play a Role in Causing Thrombosis in Behcêt’s Syndrome and Act As a Biomarker for Risk Management.

Emon Khan, Nicola Ambrose, Michael A. Laffan and Dorian O. Haskard. Imperial College, London, United Kingdom.

Background/Purpose: Thrombosis occurs in 20% of patients with Behçet’s Syndrome (BS) and leads to significant morbidity. There is no robust association between thrombosis in BS and the presence of hereditary thrombophilia or raised inflammatory markers. It remains a challenge to distinguish those at risk of thrombosis potentially requiring aggressive preventative therapy and those whose therapy can be reduced. There is a clear need to develop biomarkers for diagnosis and risk management in BS.

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Conclusion: MPs are found in higher numbers in BS patients than in HCs, and in TBS patients compared to NTBS patients. MPs are associated with thrombosis in Behçet’s Syndrome (BS).

Disclosure: Y. Cheng Jr., None; X. Sun, None; Y. Chen Jr., None; C. Huang, None; H. Deng, None; Z. G. Li, None.

2749

The Clinical Course of Acute Deep Vein Thrombosis of the Legs in Behcet’s Syndrome. M. Elkele Mikellioglu1, Y. esim Ozguler2, Serdal Ugurlu3, Firat Cetinkaya4, Koray Tasci5, Emir Celik6, Vesil Cemolun7, Yavuz Yilmaz8, Mehmet Sayarlioglu9, Yavuz Pehlivan9, Umit Kalyoncu10, Omer Karadag11, Timucin Kasifoglu12, Eren Erken13, Salih Pay14, Ayse Cefle15, Ayten Yazici16, Muhammed Cinar17, K. Tascilar18, None; E. Seyahi19, None; V. Hamuryuden20, None; H. Yazici21. None.

Background/Purpose: Thrombosis occurs in 20% of patients with Behcét’s Syndrome (BS) and leads to significant morbidity. There is no robust association between thrombosis in BS and the presence of hereditary thrombophilia or raised inflammatory markers. It remains a challenge to distinguish those at risk of thrombosis potentially requiring aggressive preventative therapy and those whose therapy can be reduced. There is a clear need to develop biomarkers for diagnosis and risk management in BS.

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2749

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Disclosure: Y. Cheng Jr., None; X. Sun, None; Y. Chen Jr., None; C. Huang, None; H. Deng, None; Z. G. Li, None.
Results: Two hundred eighty-one BD patients (44.1%) were of mucocutaneous type, whereas 356 patients (55.9%) had major organ involvement [Uveitis: 42.4% (n = 270), neurologic involvement: 6.9% (n = 44), gastrointestinal involvement 1.9% (n = 12)]. VBD developed in 20.6% (N = 131) patients during the follow-up. When the first vascular event developed, the mean disease duration was 3.5 (0–28) years and mean age 33.2 ± 8 years. After the first vascular event, IS treatment was given to 88.5% (n = 105) and AC treatment to 62.6% (n = 76) of the patients. Minor hemorrhage (as a complication likely related to AC treatment) was observed in 3 (13%) patients. A second vascular event developed in 35.9% (n = 47). The rate of new vascular event development was similar between the patients taking only ISs and AC + IS treatments after first vascular event (27.2% vs 29.6%, p = 0.78). Relapse rate was significantly higher in group taking only ACs (91.6%, p = 0.002). During follow-up, a third vascular event developed in 23.4% (n = 11) patients. The rate of new vascular event development was again similar between the patients taking only ISs and AC + IS treatments. There was no relationship between the total duration of AC treatment and number of vascular events. However, total number of vascular events negatively correlated with the age during the first vascular event (r = −0.215, p = 0.02).

Conclusion: In this study, we did not find any additional positive effect of AC treatment used in combination with ISs in the course of vascular involvement in patients with BD. Severe complications related to AC treatment were also not detected. Our results suggest that short-duration of IS treatment is the major problem in BD patients associated with vascular relapses during follow-up.

Methods: Thirty-three (30 M/3 F) patients with BS between March 2012 and April 2014 were studied. The mean age and the mean disease duration were 32 ± 7 and 4 ± 3 years, respectively. All patients had one or more type of large vessel disease such as: deep vein thrombosis of lower extremities (n = 31), pulmonary artery involvement (n = 14), vena cava superior (n = 1) or inferior thrombosis (n = 9) and Budd-Chiari syndrome (n = 5). FDG PET/CT studies were performed within the first 2 weeks of diagnosis in 23 patients. In the remaining 10, scans were obtained for activity assessment during the follow-up. Maximum standardized uptake values (max SUVs) and visual analyses were used to interpret the FDG PET/CT images. In addition, non-enhanced CT findings obtained during FDG PET/CT were recorded.

Results: FDG PET/CT was positive (SUV ≥ 2; equal to or greater than liver uptake) in 15 (45%) patients. These included 11 patients with pulmonary artery involvement (11/14, 79%). A monolateral involvement was observed in 3 (23%) patients. FDG uptake was observed in the lung parenchyma in the form of nodules, consolidations or cavities in 8, in the hilar region suggesting lymphadenopathy in 6 patients and in 1 patient suggesting thrombus of a pulmonary artery aneurysm. Among the 19 patients with major venous involvement, FDG uptake was observed in 4 patients (4/19, 21%) and these was in the femoro-popliteal vessels.

Conclusion: This preliminary survey showed that in BS, FDG uptake was mainly observed at the pulmonary parenchyma while pulmonary arteries did not show increased uptake in disease in peripheral and major veins. On the other hand, can only occasionally be discerned by FDG PET/CT. Further studies might be still be needed among immunosuppressive naïve patients.

References:

Disclosures: E. Seyahi, None; M. Hallac, None; B. Vatanankulu, None; S. Ugrulu, None; M. Melikoglu, None; S. Yurdakul, None; H. Yazici, None.

2751
Budd-Chiari Syndrome Due to Behcet’s Syndrome: Some Patients Present Without Liver Related Symptoms and Have a Better Outcome.

Emire Seyahi, Enkan Caglar, Serdal Ugrulu, Fatih Kantarcı, Vedat Hamuryudan, Abdullah Sonmez, Melike Melikoglu, Sebahatin Yurdakul and Hasan Yazici. 1Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, 2Bakirkoy Research and Training Hospital, Istanbul, Turkey, 3Istanbul University Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, 4Cerrahpasa Medical Faculty of Istanbul University, Istanbul, Turkey, 5Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: Behçet’s syndrome (BS) is a well recognized cause of Budd-Chiari syndrome (BCS), however, information about its clinical characteristics and outcome is limited. We have presented the outcome of 40 patients with BCS due to BS at the ACR 2013 meeting (1). In further analyses, we better understood that there were patients in whom BCS could exist without the presence of any liver related symptoms/signs. In the current study we compared demographic, clinical, radiologic and prognostic characteristics of these patients to those presented with overt liver related symptoms.

Methods: We reviewed the records of about 9000 patients with BS who were registered at the multidisciplinary Behçet’s syndrome outpatient clinic at Cerrahpasa Medical Faculty between July 1977 and October 2013. We identified 43 (40 male/3 female) patients who were diagnosed as having BCS. Their outcome was evaluated between September 2012 and October 2013.

Results: 43 (40 male/3 female) patients with BCS were identified. Thirty-three patients (77%) had presented with liver related symptoms such as ascites and abdominal swelling for a median duration of 1 month [IQR:0.5–2.5 months]. These patients were defined as Group I. On the other hand, 10 (21%) were silent for liver disease at presentation and were found to have BCS while being investigated for fever (n = 4), bilateral diffuse leg swelling (n = 4) and pulmonary symptoms like hemoptysis or dyspnea (n = 4). None had liver dysfunction related symptoms/signs. These patients were classified as Group II. All were diagnosed after 1990. Group I patients were somewhat older (mean age: 32.2 vs 28.7, p = 0.06) and had longer disease duration of BCS at the onset of BCS (median: 5.1 vs 2.7, p = 0.18) than Group II patients. The level of hepatic venous outflow obstruction in Group II patients was somewhat limited (2–3). We investigated the potential of PET/CT to evaluate the extent and activity of disease in vascular disease due to BS.
involved less frequently the combined IVC and hepatic veins (30 %) while it was more likely to involve isolated hepatic veins (30 %) or isolated IVC (40 %) when compared to Group I (76 %, 26 % and 3 %, respectively) (p = 0.05). Besides that, the anatomical distribution of vessels other than those involved in BCS, and the clinical characteristics of BS were not very different than Group I. By the end of the survey, there was only 1 death in Group II, which was not due to hepatic failure. Mortality was significantly lower among Group I patients (1/10) as compared to Group II (19/33, 58 %), (p = 0.025). By the end of the survey, only 1 (1/10) in Group I, had ascites, while in the remaining surviving patients in Group I ascites had resolved within 6 to 8 months after the first visit. A final hepatic Doppler USG indicated that, the frequency of recanalisation and collateral formation was similar between the patients in Group I and II.

Conclusion: There is subgroup of patients in whom, BCS may exist without the presence of liver related symptoms/signs and these patients have a good prognosis. These patients could pass unnoticed, unless one looks carefully for hepatic veins or intra or suprahepatic segments of the IVC. The fact that, 8 of these 10 patients were diagnosed after 2000, suggests that this would help developing effective management strategies.

Methods: 120 patients, all fulfilling the International Study Group (ISG) criteria for BD. The study enrolled 120 patients, all fulfilling the International Study Group (ISG) criteria for BD. The male/female ratio was 1.6:1, with a mean disease duration of 11.6 years. Their mean age was 42 ± 8 years (min:18, max:77), while the mean age at disease onset was 24±5 years. The principal end-point was to study any potential correlation between quality of life and disease activity. Disease activity was evaluated by means of the Behcet’s Disease Current Activity Form (BDCAF), while the Italian version of the Short-form-36 (SF-36) questionnaires were filled by consecutive BS patients attending our outpatient clinic. Socioeconomic factors, each type of organ involvement during the disease course, during the previous 4 weeks, disabilities caused by each, treatment modalities and overall disease activity were tested with regression analysis as possible determinants of quality of life. Men and women were also analyzed separately.

Results: 322 patients (M/F: 166/156, mean age: 37.9±11.1 years) were included. 157 patients had eye involvement, 72 patients had vascular involvement, 67 patients had joint involvement, 20 patients had neurologic involvement, 2 patients had gastrointestinal involvement and 93 patients had only mucocutaneous involvement without major organ involvement. Determinants of BDQoL in the whole group were BSAS, household income, work disability, perception of insufficient income, neurologic and mucocutaneous involvement. Among women they were BSAS, perception of insufficient income, neurologic and mucocutaneous involvement (R²:0.47, F: 19.75, p<0.001). Among men they were BSAS, perception of insufficient income, vascular involvement during the last 4 weeks and damage caused by neurologic involvement (R²:0.06, F: 29.70, p<0.001). SF-36 scores were well correlated with BDQoL scores (r = -0.69 for physical component and r = -0.63 for mental component).

Conclusion: In addition to overall disease activity and neurologic damage, mucocutaneous involvement in women and recent eye and vascular events in men seem to impair quality of life in BS. These findings are important for developing management strategies and outcome measures.

Reference:
Seyahi E et al. ACR 2013

Disclosures: E. Seyahi, None; E. Caglar, None; S. Ugurlu, None; F. Kantarcı, None; V. Hamuryudan, None; A. Sonsuz, None; M. Melikoglu, None; S. Yurdakul, None; H. Yazıcı, None.

2753
Reduced Heart Rate Variability in Patients with Behcêt’s Disease. Jong-Wook Lee1, Seung-Geun Lee2, Eun-Kyong Park2 and Geun-Tae Kim2.

1Division of Rheumatology, Department of Internal Medicine, Busan St. Mary's center, Busan, South Korea, 2Division of Rheumatology, Department of Internal Medicine, Pusan National University Hospital, Busan, South Korea. Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea.

Background/Purpose: The autonomic nervous system, including the sympathetic and parasympathetic nervous systems, has an important role in the triggering of ventricular arrhythmias and sudden cardiac death. The aim of this study was to investigate autonomic regulations by means of heart rate variability (HRV), influence of conventional cardiovascular risk factors, and relationship with the disease activity in patients with Behcet’s disease (BD).

Methods: 50 patients with BD (Age: 43.8 ± 18.6, female: 40) and 50 age-and sex-matched healthy controls were included in this study. All the participants were screened for basic cardiovascular risk factors.

BD activity was studied with Behcet’s disease current activity form (BDCAF) and acute phase indices. HRV was calculated by time domain measures, frequency domain measures and nonlinear/complexity-based measures on 24 hours recording.

Results: Patients with BD had decreased HRV in comparison to healthy controls as reflected by decrease of the standard deviation of normal R-R intervals (SDNN) (74.0 ± 20.9 vs. 83.5 ± 15.4 ms, respectively, p<0.005).

SDNN (r = -0.45, p < 0.005 and r = -0.37, p < 0.04) and HF (r = -0.42, p < 0.01 and r = -0.35, p < 0.02) were significantly correlated with BDCAF and CRP, respectively.

Conclusion: HRV was shown to be significantly decreased, compared to healthy controls, among BD patients. Patients with BD had impaired autonomic cardiac regulation which is related to the disease activity and presence of systemic inflammation and which could contribute to the increased cardiovascular risk in these patients.

Disclosure: J. W. Lee, None; S. G. Lee, None; E. K. Park, None; G. T. Kim, None.

2754
Predictors of Quality of Life in Behcet’s Syndrome. Selma Bozcan1, Ersin Ozguler2, Koray Tasçilar2, Caner Saygin2, Didem Uzunaslan2 and Gulen Hatemi3.

1University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, 2Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: Quality of life is commonly impaired in patients with chronic inflammatory diseases. The disease itself as well as the drugs used may be responsible for this impairment. Behçet’s syndrome (BS) is a multisystem vasculitis with a wide variety of manifestations including oral ulcers, genital ulcers, nodular lesions, papulopustular lesions, arthritis, uveitis, venous thrombosis, arterial aneurysms, neurologic and gastrointestinal involvement. Determining the factors affecting quality of life in BS patients, would help developing effective management strategies.

Methods: Behçet Disease Quality of Life (BDQoL) and Short Form-36 (SF-36) questionnaires were filled by consecutive BS patients attending our outpatient clinic. Socioeconomic factors, each type of organ involvement during the disease course, during the previous 4 weeks, disabilities caused by each, treatment modalities and overall disease activity were tested with regression analysis as possible determinants of quality of life. Men and women were also analyzed separately.

Results: 322 patients (M/F: 166/156, mean age: 37.9±11.1 years) were included. 157 patients had eye involvement, 72 patients had vascular involvement, 67 patients had joint involvement, 20 patients had neurologic involvement, 2 patients had gastrointestinal involvement and 93 patients had only mucocutaneous involvement without major organ involvement. Determinants of BDQoL in the whole group were BSAS, household income, work disability, perception of insufficient income, neurologic and mucocutaneous involvement (R²:0.47, F: 19.75, p<0.001). Among women they were BSAS, perception of insufficient income, neurologic and mucocutaneous involvement (R²:0.40, F: 19.75, p<0.001). Among men they were work disability, BSAS, household income, perception of insufficient income, vascular involvement during the last 4 weeks and damage caused by neurologic involvement (R²:0.06, F: 29.70, p<0.001). SF-36 scores were well correlated with BDQoL scores (r = -0.69 for physical component and r = -0.63 for mental component).

Conclusion: In addition to overall disease activity and neurologic damage, mucocutaneous involvement in women and recent eye and vascular events in men seem to impair quality of life in BS. These findings are important for developing management strategies and outcome measures.

Disclosure: S. Bozcan, None; Y. Ozguler, None; K. Tasçilar, None; C. Saygin, None; D. Uzunaslan, None; G. Hatemi, None.

2755
Disease Activity and Quality of Life in Behçet’s Disease: The Role of Patients Reportedoutcomes. Elena Elefante1, Rosaria Talarico2, Chiara Stagnaro2, Anna D’Acsano1, Antonio Tavoni4, Chiari Tani3, Chiara Baldini3, Marta Mosca3 and Stefano Bombardieri1.

1Rheumatology Unit, Pisa, Italy, 2Rheumatology Unit, University of Pisa, Pisa, Italy, 3University of Pisa, Pisa, Italy, 4 Immunology and Rheumatology Unit, Pisa, Italy.

Background/Purpose: Behcet’s disease (BD) is a systemic vasculitis, typically characterised by recurrent oro-genital ulcers, ocular inflammation and skin manifestations; articular, vascular, gastro-enteric and neurological involvement may also occur. Since BD has a chronic-relapsing relapsing course and it can be very severe, debilitating and potentially life-threatening, it may without any doubt affect the quality of life of the patients. Moreover, it is well known that patient’s perception of own disease represents an useful tool to help physicians to improve the understanding and management of the disease itself. The primary aim of this study was to explore the role of quality of life patients reported outcomes (PRO) in better identifying the global status of BD.

Methods: The study enrolled 120 patients, all fulfilling the International Study Group (ISG) criteria for BD. The male/female ratio was 1:6:1, with a mean disease duration of 11±6 years. Their mean age was 42±8 years (min:18, max:77), while the mean age at disease onset was 24±5 years. The principal end-point was to study any potential correlation between quality of life and disease activity. Disease activity was evaluated by means of the Behcet’s Disease Current Activity Form (BDCAF), while the Italian version of the Short-form-36 (SF-36) was used to evaluate quality of life. Disease activity was compared with the global SF-36 score and with each dimension, that includes: physical functioning, physical disability, body pain, general health, vitality, social functioning, emotional disability, mental health. The statistical analysis was performed using Student t-test, Mann-Whitney-U test, ANOVA and Pearson correlation.

Results: At time of evaluation, according BDCAF, 47 BD patients (39%) had clinically active disease (18 ocular involvement, 8 joint involvement, 4 neurological involvement, 2 gastro-enteric, 15 muco-cutanous involvement). As expected, the overall SF-36 scores were significantly lower in patients
with clinically active disease. Moreover, female BD patients had statistically significant lower scores in all SF-36 domains compared with male patients. When each domain of SF-36 was evaluated, we found that physical disability (p = 0.004), body pain (p = 0.006), general health (p = 0.001), and vitality (p = 0.001) were significantly lower in patients with disease activity. Notably, vitality (p = 0.001), physical disability (p = 0.004), social functioning (p = 0.001), emotional disability (p = 0.003) and mental health (p = 0.001) were significantly lower in patients with mucocutaneous active disease, compared with the other patients with active disease.

Conclusion: The clinicians who take care of any chronic disease would like to correctly know the current status of a patient to manage him properly. In this regard, the combination data of PRO measures and disease activity have been demonstrated to add more information compared to the evaluation of disease activity alone. These considerations suggest that the correct assessment of BD need a multi-dimensional approach that fairly includes disease activity, disease activity, disease damage and quality of life.

Disclosure E. Elefante: None; R. Talarico: None; C. Stagnaro: None; A. d’Ascanio: None; A. Tavoni: None; C. Tani: None; C. Baldini: None; M. Mosca: None; S. Bombardieri: None.

2756

Background/Purpose: IL-1 blocking therapy shows promise in the treatment of Behcet’s eye disease, but its effect on mucocutaneous manifestations is unknown.

Methods: 6 patients with Behcet’s disease as determined by International Study Group criteria and active oral or genital ulcers for ≥2 months were enrolled in this open label phase I/II study. 2 patients had a history of inactive uveitis (anterior, panuveitis). Study duration was 3 months with extension up to 16 months (range 4-16). All were treated with anakinra 100mg subcutaneous daily with the option to escalate dose to 200mg in partial responders after 1 month and 300mg after 6 months. Patients recorded the number and severity of oral and genital ulcers in daily diaries. The primary outcome was remission defined as no ulcers on physical exam for 2 consecutive monthly visits from months 3-6. Secondary outcomes included the number of ulcers, the number and severity of patient-reported ulcers, patient/physician global scores, and standardized disease activity scores.

Results: 2 of 6 patients achieved the primary outcome of remission from months 3-6. All but 1 had improvement in the number of oral ulcers at month 3 (primary endpoint). Mean number of oral ulcers at baseline, month 3 and month 12 were 3.3, 1.5 and 0.5 and mean number of genital ulcers were 0.8, 0 and 0. Over the entire study, patients reported ≥1 oral and ≥1 genital ulcer on 66% (66%) and 139 (14%) days, respectively. Non-statistically significant improvements were seen in secondary outcomes including physician and patient visual analog scores and scores for Behcet’s disease current activity form (BDCAF) patient index, and Behcet’s disease quality of life (BDQOL). Behcet’s syndrome activity scale (BSA) showed significant changes at 3 and 9 months. (Table). Dose escalation to 200mg occurred in all patients prior to month 3 and was further increased in 3 to 300mg after month 6. 2 patients on baseline prednisone of 40mg and 20mg were tapered to 20mg and 0mg, respectively. On anakinra 200mg vs. 100mg, patients reported fewer days with oral ulcers (65% vs 74% days, p = 0.02) and genital ulcers (10% vs 22% days, p < 0.001) and milder ulcer severity (p=0.01). Increase of anakinra to 300mg did not result in fewer ulcers or milder ulcer severity. No ocular flares occurred during the study; however, 2 ocular flares (anterior uveitis, periorbital inflammation) occurred within a month after discontinuation of anakinra in the 2 patients with prior eye disease. A diverse influx included a serious adverse event of pulmonary hypertension suspected prior to the study and frequent viral infections.

Conclusion: In this open-label pilot study, anakinra, at an optimal dose of 200mg daily, demonstrated partial efficacy in treatment of resistant oral and genital ulcers in Behcet’s disease. Organ-specific differential effects of IL-1 blockade are likely.

NCT01441076

Table - Mean (SD) Values for Disease Activity Measurements

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcer number</td>
<td>3.3 (0.8)</td>
<td>1.5 (1.2)</td>
<td>1.5 (1.4)</td>
<td>1.5 (1.2)</td>
<td>0.8 (1)</td>
</tr>
<tr>
<td>Genital ulcer number</td>
<td>0.8 (1.3)</td>
<td>0.5 (0.8)</td>
<td>0.3 (0.8)</td>
<td>0.0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Physician global VAS</td>
<td>27.5 (39)</td>
<td>19 (34.8)</td>
<td>19 (30.8)</td>
<td>14 (17.2)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Patient global VAS</td>
<td>63.7 (29.9)</td>
<td>39.5 (32.1)</td>
<td>58.4 (25.9)</td>
<td>56.8 (32.5)</td>
<td>49.3 (40.1)</td>
</tr>
<tr>
<td>BDCAF (0–12)</td>
<td>6.7 (2.3)</td>
<td>6.2 (1.9)</td>
<td>5.5 (2.2)</td>
<td>5.6 (2.0)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>BDQOL (0–12)</td>
<td>10.2 (10.2)</td>
<td>9.4 (8.8)</td>
<td>9.2 (8.7)</td>
<td>9.1 (8.9)</td>
<td>8.7 (8.9)</td>
</tr>
</tbody>
</table>

* p < 0.05 paired t-test from baseline

Disclosure: P. C. Grayson, None; Y. Yazici, Collegen, BMS,genentech; 2; E. Novakovich, None; E. Joyal, None; R. T. Goldbach-Mansky, None; C. H. Sibley, None.

2757
Efficacy and Safety of Anti-TNF ALPHA in Behcet’s Disease: A Multinational Registry of 122 Patients. Héâne Vallet1, Sophie Rivière1, Albain Derouex2, Guillaume Moulis3, Olga Adimandana4, Caro Salvan5, Marc Lambert6, Philip Biefield6, Pascale Seje7, Jean Sibilia8, Jean Baptiste Fraison9, Yolande Schindler9, Isabelle Mariea10, Laurent Perard14, Thomas Pap10, Damien Sénéa11, Gaelle Leroux9, Valérie Royard7, Antoinette Perlitz18, Xavier Mariet17, Olivier Lido06, Olivier Fain1, Claire De Meurelj, Gilles Blaisong, Phuc Le Hoang7, Eric Hachula10, Bertrand Wechsler7, Barbara Bodagh2, Patrice Caboud2 and David Saadoun2, 1DHU 218 Internal Medicine Center, University Hospital of Pitie Hospital, Paris, France, 2Hospital, Montpellier, France, 3CHU Grenoble, Grenoble, France, 4International Internal Medicine department, Toulouse, Toulouse, France, 5Aircaspenta Maria Nuova, 1R.C.C.S., Reggio Emilia, Italy, 6Aircaspenta S Maria Nova, Reggio Emilia, Italy, 7CHRU Lille, Lille, France, 8CHU de Dijon, Dijon, France, 9CHU Lyon, Lyon, France, 10University Hospital of Strasbourg, Strasbourg, France, 11Hopital Jeanne Veyrier, Bondy, France, 12DHU 218 Internal Medicine Referral Center for Autoimmune Diseases Pitie Hospital, PARIS, France, 13CHU de Rouen, Rouen, France, 14Hospices civils de Lyon, Lyon, France, 15Hotel Bichat, Paris, France, 16Hotel Lariboisiere, Service de Médecine Interne, Paris, France, 17Chartes, Chartes, France, 18CHU de Rennes, Rennes, France, 19Université Paris-Sud, Le Kremlin Bicêtre, France, 20Hotel Croix-Saint-Simon, PARIS, France, 21Hotel Saint Antoine, DHU i2B, Service de Médecine Interne, Paris, France, 22CHU, Brest, France, 23CH, Colmar, France, 24Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Paris, France, 25National Scleroderma Centre, Lille CEDEX, France, 26Hôpital de la Pitié Salpêtrière, Paris, France, 27Groupe Hospitalier Pitié Salpêtrière, Service de Médecine Interne, DHU 12B, Paris, France.

Background/Purpose: Behcet’s disease (BD) is a systemic large vessel vasculitis with recurrent genital and oral ulceration, uveitis, cardiovascular, joints, neurological or gut symptoms. Treatment of BD is dependent of the nature and the severity of clinical manifestations. Increased levels of TNF alpha and soluble TNF receptors have been found in the serum, plasma and in the aqueous humor of patients with BD. Although, anti-TNF alpha have proven effective in refractory uveitis, few data are available relative to its efficacy in extraocular manifestations of BD. The aim of this study is to report on the efficacy and the safety of anti-TNF alpha in BD.

Methods: We performed a retrospective multicenter study of main characteristics and outcomes of 122 patients with BD treated with anti-TNF alpha.

Results: One hundred twenty two observations were collected in 21 centers. Mean ± SD age at the anti-TNF alpha introduction was 35 ± 12 years with 47% of men. Ninety one (75%) patients received at least one immunosuppressive therapy before the use of anti-TNF alpha.

The main indications of anti-TNF alpha were uveitis (n = 80, 66%), mucocutaneous manifestations (n = 26, 21%) [oral (n = 21) and genital ulcerations (n = 13)], articular (n = 29, 24%), neurologic (n = 12, 10%), cardiovascular (n = 5, 4%), and digestive manifestations (n = 9, 7%). Infliximab was frequently used (61%), followed by adalimumab (30%), etanercept (8%) and golimumab (1%). A associated therapy included prednisolone (84%), azathio-}
hypersecretory reactions (16%). Serious adverse events were reported in 13% of patients and required treatment interruption in all cases.

**Conclusion:** These results show that TNF alpha inhibitors are highly and rapidly efficient in all BD manifestations. Although tolerance seems satisfactory, infliximab is associated with more frequent and more serious side effects.

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**2759**

**Predictive Factors for the Response to Infliximab Therapy in Patients with Behçet’s Disease.** Salvatore D’Angelo, Pietro Leccese, Angela Paadula, Angelo Nigo, Michele Gilio, Antonio Carriero, Carlo Palazzi and Ignazio Olivieri. Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy.

**Background/Purpose:** To identify the clinical factors predicting a good clinical response to infliximab (IFX) therapy after 12 months in patients with Behçet’s disease (BD) refractory to conventional therapy.

**Methods:** Patients receiving IFX (5 mg/kg intravenously at weeks 0, 2, 6, and every 6–8 weeks subsequently) for BD unresponsive to conventional therapy (corticosteroids plus at least two different immunosuppressive drugs) were prospectively included. Clinical response to IFX therapy was based on the expert opinion and was graded as follows: remission, response, no response and worsening. Remission was defined as the complete disappearance of symptoms and signs of inflammation and response as at least 50% of improvement. Univariate and multivariate analyses were performed to identify factors associated with IFX good response (remission, response) at 12 months. Logistic regression analysis was performed to analyse which of the following measures at the start of treatment were associated with a good response: sex, age, disease duration, HLA-B27 status, indication for IFX treatment including uveitis, CNS involvement, severe mucocutaneous manifestations or others including arthritis, intestinal and vascular involvement; concomitant drugs including steroids (Ster), colchicine (Col), antithrombin (AHA) or cyclosporine (CSA).

**Results:** The study included 73 BD patients (47 M/26 F; mean age 33.6 ± 10.7 yrs; mean disease duration 12.3 ± 9.3 yrs; 71.2% HLA-B27 positive). Indication for IFX treatment were uveitis in 38 patients, severe mucocutaneous manifestations in 13, CNS involvement in 16, intestinal involvement in 2, arthritis in 2, vascular involvement in the remaining 2. At 12 months, 56 patients (76.7%) had a good response to IFX, 4 (5.5%) patients had stopped for adverse events, and 13 (17.8%) had stopped for primary or secondary inefficacy. In the univariate analysis concomitant use of AZA (95.6% vs 67.3%, p= 0.02) was the only factor associated with a good response. In a multivariate logistic regression analysis concomitant use of AZA was independently associated with a good therapeutic response (OR = 34.2; 95% CI 2.7–435.8; p = 0.007). None of the other variables analysed predicted response to treatment.

**Conclusion:** This study has, for the first time, shown that concomitant use of AZA at the start of IFX treatment is a factor that seems to influence the probability of achieving a good therapeutic response in patients with refractory BD. Further support from larger studies is necessary so as to optimize the management of BD patients treated with IFX.

**Disclosure:** S. D’Angelo, None; P. Leccese, None; A. Paadula, None; A. Nigo, None; M. Gilio, None; A. Carriero, None; C. Palazzi, None; I. Olivieri, None.

**2759**

**Anti-TNF Treatment for Refractory Vascular Involvement of Behçet’s Syndrome.** Yedet Hamuryudan1, Emire Seyahi1, Melike Elikoglu1, Serdal Ugrulu1, Gulen Haberal1, Selahattin Yurdakul2 and Hasan Yazici3. 1Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, 2Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

**Background/Purpose:** The optimal management of major vascular involvement in patients with Behçet’s syndrome (BS) is still a challenge.

**Methods:** We reviewed the charts of 16 BS patients (15 with vascular involvement who had been treated with anti-TNF agents following an inadequate response to traditional immunosuppressives (cyclophosphamide or azathioprine combined with glucocorticoids).

**Results:** Ten patients had pulmonary artery involvement (PAI), 5 had major vein involvement (multiple thromboses of vena cavae, deep veins and dural sinuses) and 1 had renal artery aneurysm. PAI was in the form of pulmonary artery aneurysm (PAA) in 2 patients, pulmonary artery thrombosis (PAT) in 6 patients and the combination of PAA with PAT in 2 patients. Six patients (5 with PAI) also had intracardiac thrombi formation. All patients were using immunosuppressives at the time of initiation of anti TNF therapy (for 11 ± 7 SD months in patients with PAI and for 50 ± 51 SD months in patients with other types of vascular involvement). The initial anti TNF agent was infliximab (5mg/kg) in 15 patients and adalimumab (40 mg eow) in 1 patient who had PAI and PAT in combination. Adalimumab was used in the case of high dosages of glucocorticoids and 10 used immunosuppressives (azathioprine = 7).

At the time of survey closure (December 2013) all patients were being followed, with all but 3 being still on anti TNF therapy. None of the patients experienced an exacerbation or new development of vascular involvement under anti TNF therapy during a mean of 16.5±13.6 SD months for PAI patients and 19.5±14.9 SD months for patients with other vascular involvement. Anti TNF treatment (all infliximab) had been discontinued in 5 patients (4 with PAI). In 3 patients (2 with PAI) this was due to stable disease after a mean of 22.7±12 SD months treatment. One of these patients with PAA is on maintenance treatment with azathioprine and is symptom free 8 months after withdrawal. The second patient with PAI experienced hemoptysis due to development of a new PAT 3 years after withdrawal. He responded to re-institution of infliximab, which was switched to adalimumab because of anaemia during the second induction. The third patient with extensive venous involvement developed new venous thrombosis and secondary amyloidosis 1 year after withdrawal. His clinical status improved with re-institution of infliximab but he was also switched to adalimumab because of the development of anaphylaxis. In the 2 remaining patients with PAI infliximab was withdrawn because of serious infections (lungs tuberculosis and fungal infection). The patient developing tuberculosis is still receiving treatment for tuberculosis with no immunosuppressives and the second patient with fungal infection was subsequently prescribed interferon alpha.

**Conclusion:** Our uncontrolled experience suggests that anti TNF therapy effectively suppresses signs and symptoms of major vascular involvement in BS. Relapses can be seen after withdrawal. The development of serious infections underline the importance of close follow-up.

**Disclosure:** V. Hamuryudan, None; E. Seyahi, None; M. Elikoglu, None; S. Ugrulu, None; G. Haberal, None; S. Yurdakul, None; H. Yazici, None.

**2760**

**Interferon Alfa-Associated Depression in Patients with Behçet’s Syndrome.** Yasin Keskin2, Emire Seyahi1, Cagri Poyraz2, Serdal Ugrulu2, Yilmaz Ozyazgan4 and Hasan Yazici4. 1Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, 2Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, 3Cerrahpasa Medical Faculty University of Istanbul, Istanbul, Turkey, 4Cerrahpasa Medical Faculty University of Istanbul, Istanbul, Turkey, 5Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

**Background/Purpose:** Interferon (IFN) is an effective immune-modulatory agent in the medical management of eye disease of Behçet’s syndrome (BS). The agent is frequently associated with psychiatric adverse events, such as depressive disorders and suicide attempts are the most feared complication (1). We evaluated psychiatric status of a group of BS patients in whom IFN was used for the first time. As a control group we studied BS patients who started to use drugs other than IFN.

**Methods:** We studied BS patients who were seen between January 2012 and January 2014 at the Behçet’s syndrome outpatient clinic at Cerrahpasa Medical Faculty. Patients who have a history of psychiatric illness, who use illicit drugs/alcohol, or who have parenchymal neurological involvement due to BS were not included in the study. Patients who started to use IFN for the first time (Group 1) and those who started to use drugs other than IFN (Group 2) were studied. Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) were used to measure status of depression at baseline and at week 12.

**Results:** Group 1 included 17 (14 M, 3 F) while Group 2 included 21 (13 M, 8 F) patients. During 12 weeks of follow-up, in Group 1, 6 patients used corticosteroids while 3 used colchicine in addition to IFN. Drugs that were started in Group 2 were atazanavir and cyclosporine combination (n=5), infliximab (n=2), methotrexate (n=1), azathioprine alone (n=6) and colchicine (n=7). Patients who used IFN were more likely to be male, to have longer disease duration and to have eye disease. Besides that, demographic, socio-economic and clinical characteristics were similar between the Groups. A mong patients who used IFN, both BDI and HADS scores increased significantly after 3 months of follow-up. These scores did not change among patients who used other drugs (Table 2). There was no statistically significant difference among patients who answered (I have thoughts of killing
myself but I would not carry them out) to question no: 9 was more common in
the IFN group at week 12 (35 % vs 10 %, p = 0.053). These were 24 % vs 10 %,
respectively, (p = 0.24) at baseline.

Conclusion: We found that the depression scales increased among IFN
users after 12 weeks of follow-up compared to those who used other drugs.
Additionally, after 12 weeks of follow-up, the frequency of those with
suicidal ideation also increased among the IFN users. A recent survey
indicated that BS patients with major organ involvement have already
suicidal ideation also increased among the IFN users. A recent survey
lay Sahin2, Yesim Sucullu Karadag2, Ridvan Mercan1, Abdurrahman Tufan1,

Table 1. Depression scales at baseline and at week 12

<table>
<thead>
<tr>
<th>interferon, n = 17</th>
<th>Other drugs, n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Week 12</td>
<td>p</td>
</tr>
<tr>
<td>BDI, mean ± SD</td>
<td>11.4 ± 8.7</td>
</tr>
<tr>
<td>HADS, mean ± SD</td>
<td>5.0 ± 4.5</td>
</tr>
<tr>
<td>BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale</td>
<td></td>
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</tbody>
</table>

References:

Disclosure: Y. Keskin None; E. Seyahi None; C. Poyraz None; S. Ugurlu None; Y. Ozyagcan None; H. Yazici None.

2761

Increased Risk of Parenchymal Neurological Involvement in Behçet’s Syndrome Patients with Panuveitis. Berivan Bitik1, Bema Goker2, Kubilay Sahin3, Y esim Sucullu Karadag4, Ridvan Mercan1, Abdurrahman Tufan1, Mehmet Akif Ozturk1, Fikri Ak1, Yasar Karrayan1 and Semin Haznedaroğlu1. 1Gazi University School of Medicine, Ankara, Turkey, 2Ankara Numune Education and Research Hospital, Ankara, Turkey, 3Hilt University, Corum, Turkey.

Background/Purpose: Behçet’s Syndrome (BS) is a systemic vasculitis
which may involve multiple organ systems simultaneously. Most frequently,
clinical findings in BS fit into well recognized patterns such as the association
between papulopustular skin lesions and arthritis. Neurological involvement
in BS is a serious condition which could lead to significant disability. It could
either be parenchymal or vascular. The pathogenesis of these two types of
Neuro-Behçet’s Syndrome (NBS) are suggested to be different. The purpose
of this study is to evaluate the association between the parenchymal Neuro-Behçet’s Syndrome and panuveitis.

Methods: We retrospectively reviewed the clinical records of 288 patients
with BS, who met the international classification criteria for BS, diagnosed
two major rheumatology clinics from 2000 to 2014. Patient demographics,
opthalmic examinations, clinical and radiologic patterns of neurological
involvement were recorded. Pearson’s Chi-square test was used for analysis.

Results: In this cohort of a total of 288 patients, 93 developed panuveitis
and 38 had NBS (28 men and 10 women, median age 33 (28–54)). Of the 38 patients
with neurological involvement, 28 had parenchymal and 10 had vascular disease.
Venous sinus thrombosis was the only vascular involvement in NBS patients.
Those with panuveitis were significantly more likely to have parenchymal
involvement than without panuveitis (22.6% vs 3.6%, p = 0.001) (Table 2). 21 of the 28 parenchymal NBS patients had panuveitis either
prior to or during the course of neurological involvement. Panuveitis was
significantly associated with parenchymal-NBS (OR 7.83 95% CI 3.19–19.21).

Table. The association between panuveitis and parenchymal neurological
involvement in patients with BS.

<table>
<thead>
<tr>
<th>BS Patients</th>
<th>Parenchymal neurological involvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panuveitis</td>
<td>Present 72</td>
<td>Absent 18</td>
</tr>
<tr>
<td>Absent</td>
<td>21</td>
<td>7</td>
</tr>
</tbody>
</table>

Conclusion: Among our 288 patients with BS, over one out of five
cases with panuveitis had neurological involvement during their disease course. Our findings suggest a significant association between these two major organ involves.
This association might also be defined as a recognized clinical pattern
similar to the association of papulopustular skin lesions with arthritis. BS patients
with panuveitis should be educated about possible signs and symptoms of neurological involvement which could progress quite rapidly and early initiation
of treatment is the key for success.

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Atrophy of Hippocampal Region in Chronic Progressive Neuro-Behçet’s Disease. Hiroshi Kikuchi1, Kurumi Asako1, Makiko Takayama2, Yoshikata Kimura1, Akiko Okamoto1, Toshihiro Nanki2, Hajime Kono1 and Shunsei Hirohata1. 1Teikyo University School of Medicine, Tokyo, Japan, 2Teikyo University, Tokyo, Japan, 3Kitasato University School of Medicine, Sagamihara, Japan.

Background/Purpose: Central nervous system involvement in Behçet’s
disease, usually called neuro-Behçet’s disease (NB), can be classified into
acute NB (ANB) and chronic progressive NB (CPNB) based upon the differences
in clinical courses and responses to corticosteroid treatment. Previous studies demonstrated that brainstem atrophy was significantly more
frequently observed in CPNB than in ANB or non-NB. Noteworthy, in addition to truncal ataxia, neurobehavioral changes are frequently observed
in CPNB, which cannot be accounted for by brainstem atrophy. In the present
study we examined the volumes of hippocampus in order to determine the responsible lesions for neurobehavioral changes in CPNB.

Methods: A total of 26 patients were studied, including 13 patients with
CPNB (11 males and 2 females, age 51.2 ± 12.1 [mean ± SD]) and 13 non-NB
(10 males and 3 females, age 54.4 ± 11.4). All the patients satisfied the
international classification criteria for Behçet’s disease. CPNB was defined as
intractable, slowly progressive neurobehavioral changes and/or ataxia accompa-
An MRI scan is significant in CPNB than in ANB or non-NB. The severity
of gray matter loss in the hippocampal region and whole brain were investigated
by the software for Voxel-Based Specific Regional A nalysis System for Alzhei-
mer’s Disease (VSRAD) (Eisai Co., Ltd), calculating the indicators of the degrees
of hippocampal region atrophy (HAI) and those of whole-brain atrophy (WBAI).
The areas of midbrain tegmentum and pons were measured on mid-sagittal
sections of T1-weighted images of brain MRI using image analysis software
Image (NIH, U.S.).

Results: The VSRAD analysis showed that HAI was significantly
increased in CPNB (1.46 ± 0.70 [mean ± SD]) compared with in non-NB
(0.77 ± 0.40) in ANB (p = 0.0016) (Fig. 1). Although less markedly, WBAI was
significantly higher in CPNB (1.06 ± 5.00) than in non-NB (0.69 ± 1.7)
(p = 0.0240). Neither HAI nor WBAI was correlated with age. Whereas all the patients with CPNB showed brainstem atrophy, there was no significant
correlation between HAI and the rate of brainstem atrophy (Fig. 2).
Conclusion: These results indicate that hippocampus, in addition to brainstem, is a commonly affected lesion in CPNB, accounting for progressive neurobehavioral changes. The lack of correlation between brainstem atrophy and hippocampal atrophy suggest that there might be some predisposing factors determining the preference of affected lesions in CPNB.

Disclosure: H. Kikuchi, None; K. Asako, None; M. Takayama, None; Y. Kimura, None; A. Okamoto, None; T. Nanki, None; H. Kono, None; S. Hirohata, None.

2763

Long-Term Outcome of Chronic Progressive Neurological Manifestations in Behcet’s Disease. Shunsei Hirohata1, Hiroshi Kikuchi2, Tetsuji Sawada3, Hiroko Nagafuchi4, M. K. Kuwana5, M. Takeno6 and Yoshiaki Ishigatsubo7. 1Kitasato Univ School of Med, Kanagawa, Japan, 2Tokyo University School of Medicine, Tokyo, Japan, 3Tokyo Medical University, Tokyo, Japan, 4St. Marianna University School of Medicine, Kanagawa, Japan, 5Ko e University School of Medicine, Tokyo, Japan, 6Yokohama City University Hospital, Yokohama, Japan, 7Yokohama City Grad Schi of Med, Yokohama, Japan.

Background/Purpose: Chronic progressive neurological manifestations in Behcet’s disease (BD) is characterized by progressive deterioration leading to disability either with or without a history of previous attacks, thus called chronic progressive neuro-Behcet’s disease (CPNBD). ATough high doses of steroids, including steroid pulse therapy, cyclophosphamide and azathioprine have been anecdotally used in the treatment of CPNBD, the prognosis of the patients treated with such drugs have been usually miserable. Notably, methotrexate has been found effective for CPNBD in prospective open trials with a small number of patients. However, its influence on the long-term outcome in a larger population remain unclear. The present study was designed to explore the effects of various treatment regimens, including methotrexate, on the prognosis of patients with CPNBD.

Methods: Thirty-seven patients, who met the international classification criteria for BD, and developed chronic progressive manifestations of NBD after 1988, were followed up until October 2013. The effects of various treatment regimens on prevention of death or severe disability of bedridden state were examined by Kaplan-Meier analysis. Cox’s proportional hazard model was used for multivariate analysis in Cox proportional hazard model.

Results: In 37 patients with CPNBD, 28 patients (75.7%) received methotrexate. Among the 28 patients with methotrexate, no patients died and only 5 patients progressed to the bedridden state. By contrast, among the 9 patients without methotrexate, 5 patients died and 3 patients progressed to the bedridden state. Thus, methotrexate significantly improved the survival of patients with CPNBD (HR 0.0507, 95% CI: 0.0077–0.334, p = 0.020 as calculated by Mantel-Cox test) (figure), but any of steroid pulse, methotrexate or cyclophosphamide did not. Methotrexate also significantly reduced the proportion of the patients who were progressed into the bedridden state or death (HR 0.0694, 95% CI: 0.0047–0.7327, p = 0.0258 as determined by multivariate analysis in Cox proportional hazard model).

Conclusion: These results indicate that methotrexate, but not high doses of steroids, azathioprine or cyclophosphamide, is effective to prevent the progression of CPNBD. Thus, it is recommended that methotrexate should be started as soon as possible the diagnosis of CPNBD is made.

Disclosure: S. Hirohata, None; H. Kikuchi, None; T. Sawada, None; H. Nagafuchi, None; M. Kuwana, None; M. Takeno, None; Y. Ishigatsubo, None.

2764

S100B Astrocyte Protein May Serve As a Prognostic Factor in Reversible Cerebral Vasoconstrictive Syndromes. Juan J. Maya1, Vikram Puvenna2, Chanda Brennan3, Seby John4, Ken U Chino5, Leonhard H. Calabrese6, Damir Janigro7 and Rula Hajj-Alil8. 1Cleveland Clinic Foundation, Cleveland, OH, 2Cleveland Clinic Lerner College of Medicine, Cleveland, OH.

Background/Purpose: Reversible Cerebral Vasoconstrictive Syndromes (RCVS) are a group of disorders characterized by acute onset of recurrent thunderclap headaches with or without neurologic deficits. Radiologically, RCVS is characterized by reversible vasoconstriction; however at a molecular level the pathophysiology is poorly understood. Blood-brain barrier disruption has been linked to a variety of neurological disorders. S100B is as an astrocytic protein considered to be an important peripheral blood marker of Blood-brain barrier disruption and correlates with the presence or absence of enhancements on MRI scans. S100B serum levels have been used to study Blood-brain Barrier Disruption after traumatic brain injury, and are even being used in emergency department settings to detect traumatic brain injury. Consequently, we assessed Blood-brain Barrier Disruption in patients with RCVS by measuring the serum levels of S100B, and tested this protein for prognostic utility and risk stratification.

Methods: A total of 10 patients with RCVS from the Cleveland Clinic RCVS Biologic Repository were included in this study. A sample from each patient had been obtained during the ictal phase and samples of 3 patients were also obtained during the resolution of the vasoconstriction. S100B measurements were performed using S100B ELISA (Diasorin, Stillwater, MN). RCVS data was compared to age and gender matched historical controls, and subanalyses were performed using the data from the RCVS patients with ischemic stroke (n=5), and the RCVS patients with intracranial hemorrhages (n=4).

Results: Mean S100B level in RCVS patients during the ictal phase was statistically higher than the mean level in control group (mean = 0.3644 vs. mean = 0.072, p < 0.0001). The mean S100B level of RCVS patients with ischemic stroke (mean = 0.6588) was independently compared with the control group (mean = 0.072) and with RCVS patients with intracranial hemorrhages (mean = 0.048), the level was also statistically higher (p < 0.0001 for both comparisons). There was no statistical difference in the mean level of S100B between the control group and the group with intracranial hemorrhage (p = 0.7271). The levels of S100B in 2 out of 3 patients decreased when the initial levels were compared with the follow-up levels, in average from 0.08 to 0.05. The patient with the highest S100B level (> 3 SD above the mean) had multiple ischemic strokes and ultimately expired.

Conclusion: The elevation in S100B protein levels that was observed in RCVS patients implies that this condition can cause an alteration in the permeability of the Blood-brain Barrier. S100B levels were higher in the ischemic stroke group as compared to the hemorrhagic group and to controls. This information implies that S100B may serve as a prognostic factor in a subgroup of RCVS patients. Furthermore, RCVS patients with intracranial hemorrhage did not have a significant increase in S100B levels, which is different from what other authors have observed in non RCVS intracranial hemorrhages. Further studies with larger number of subjects are needed in order to validate and further explore this data.

Disclosure: J. J. Maya, None; V. Puvenna, None; C. Brennan, None; S. John, None; K. U. Chino, None; L. H. Calabrese, None; D. Janigro, Markers of Blood-brain Barrier Disruption and Methods of Using Same US 7,144,708; 9, Peripheral Markers of Blood Brain Barrier Permeability US 6,884,591 B2; 9, R. Hajj-Alil, None.

Background/Purpose: The pathophysiology and molecular mechanisms of Reversible Cerebral Vasocostriction Syndrome (RCVS) are unknown. Objective of the study was to identify putative biomarker proteins for RCVS.

Methods: Patients were recruited from our institution’s prospective RCVS registry. Plasma samples were collected from 6 patients with RCVS during the acute cerebral vasocostrictive phase. 2 patients at 6-month follow-up after resolution of vasocostriction, and 4 patients with CNS vasculitis.

Results: Plasma samples were immune-depleted for the most abundant plasma proteins, precipitated, and then digested overnight with trypsin and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). These LC-MS/MS experiments were carried out on a high resolution Orbitrap-Elite FT-MS system that allows the relative quantity of the proteins in these samples to be determined by a label free quantitative method. The quantitation is performed by searching the data with the programs Mascot and Sequest. These search results were then uploaded into the program Scaffold. The quantification was performed by comparing the normalized spectral counts (SC) for the samples. The data was filtered based on several parameters including two matching peptides, a FDR of 1%, a protein threshold of 95%, and identified in at least 3 of the samples. The relative quantity of these proteins was determined by using the spectral counting method that has been described previously. In order for a protein to be considered as a putative biomarker, the relative abundance needs to be at least two fold different with the T-test derived p-value less than 0.05.

Conclusion: This is a preliminary study looking at proteomic analysis of RCVS plasma samples. Results of this study show proteins that might be potential biomarkers for RCVS and which could help differentiate RCVS from other CNS vasculitis. Further studies with larger number of patients are needed to assess reproducibility. The function and the pathways of these differentially expressed proteins should be further explored.

Table 1: List of differentially expressed proteins identified in LC-MS/MS analysis comparing i) Baseline vs follow-up RCVS and ii) Baseline RCVS vs CNS vasculitis

<table>
<thead>
<tr>
<th>Protein</th>
<th>Average SC Baseline RCVS</th>
<th>Average SC Follow-up RCVS</th>
<th>Ratio Follow-up/Baseline</th>
<th>T-Test</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural cell adhesion molecule 1 isoform 5</td>
<td>0.8 ± 0.11</td>
<td>3.3 ± 1.5</td>
<td>4.1</td>
<td>0.0328</td>
<td></td>
</tr>
<tr>
<td>Structural maintenance of chromosomes protein 2</td>
<td>0.2 ± 0.04</td>
<td>1.3 ± 0.6</td>
<td>6.5</td>
<td>0.0021</td>
<td></td>
</tr>
<tr>
<td>Charged multivesicular body protein 4a</td>
<td>0.0 ± 0.0</td>
<td>1.3 ± 0.6</td>
<td>FU only</td>
<td>0.0015</td>
<td></td>
</tr>
<tr>
<td>Charged multivesicular body protein 4b</td>
<td>0.0 ± 0.0</td>
<td>1.8 ± 1.3</td>
<td>0.0</td>
<td>0.0158</td>
<td></td>
</tr>
<tr>
<td>Poliovirus receptor isoform alpha</td>
<td>0.2 ± 0.04</td>
<td>2.0 ± 0.0</td>
<td>0.1</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Transthyretin</td>
<td>6.6 ± 4.1</td>
<td>140.0 ± 3.2</td>
<td>0.5</td>
<td>0.0211</td>
<td></td>
</tr>
<tr>
<td>Cystatin-C</td>
<td>297.8± 75.5</td>
<td>6020 ± 64.7</td>
<td>0.5</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Lysyase C</td>
<td>9.2 ± 11</td>
<td>38 ± 1.9</td>
<td>2.4</td>
<td>0.0100</td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyl hydrolase</td>
<td>9.2 ± 2.2</td>
<td>30 ± 3.8</td>
<td>3.1</td>
<td>0.0177</td>
<td></td>
</tr>
<tr>
<td>Uncharacterized protein C10or92</td>
<td>4.6 ± 15</td>
<td>0.0 ± 0.6</td>
<td>9.2</td>
<td>0.0015</td>
<td></td>
</tr>
<tr>
<td>R-ibonuclease 4</td>
<td>1.6 ± 0.9</td>
<td>0.0 ± 0.0</td>
<td>0.1</td>
<td>0.0096</td>
<td></td>
</tr>
</tbody>
</table>

Disclosures: C. Salvadori, None; R. D. Brown Jr., None; T. J. H. Christiansen, None; J. Huston III, None; F. Muratore, None; G. G. Hunder, None.

2767 Core Outcome Domains and Potential Measurement Instruments in polymyalgia Rheumatica (PMR) Using Omeract Filter 2.0. Sarah Mackie1, Toby Hellwell2, Rodney Hughes2, E Brouwer4, Colin T. Pease5, Christian Mollen6, Marten Boers7 and John R. Kirwan8. 1University of Leeds, Leeds, United Kingdom, 2Keele University, Staffordshire, United Kingdom, 3St Peters Hospital, Chertsey Surrey, United Kingdom, 4University Medical Center Groningen, Groningen, Netherlands, 5Leeds Teaching Hospitais NHS Trust, Leeds, United Kingdom, 6Keele University, Keele, United Kingdom, 7VU University Medical Center, Amsterdam, Netherlands, 8Bristol Royal Infirmary, Bristol, United Kingdom.

Background/Purpose: The OMERACT PMR specialist interest group was established to develop a core outcome measurement set for PMR using the methods of OMERACT filter 2.0. This work builds on previous work undertaken to identify potential domains, which were presented at OMERACT 11.

Methods: A three-round Delphi survey was undertaken to identify domains of importance (Figure1). Additionally, meetings of patient and clinician participants were convened in order to scrutinise and finalise the candidate core domain set. A review of the PMR literature was undertaken to identify outcome measures and instruments used in previous PMR research. The candidate domains and identified instruments were presented and discussed at OMERACT 12.

2766 Mycophenolate Mofetil in the Treatment of Primary Central Nervous System Vasculitis. Carlo Salvareni1, Robert D. Brown Jr.2, Teresa J. H. Christiansen1, John Huston III1, Francesco M uratore3, Caterina Giannini4, and Gene G. Hunder5. 1University of S Maria Nuova, Reggio Emilia, Italy, 2Mayo Clinic, Rochester, MN.

Background/Purpose: The optimal management of primary central nervous system vasculitis (PCNSV) remains unclear. Cyclophosphamide (CYC) in combination with glucocorticoids (GCs) or GCs alone are the most commonly used therapies. It is not proven if other immunosuppressants, used in other vasculitides, such as azathioprine (AZA), methotrexate (MTX) and mycophenolate mofetil (MMF), that are less toxic than CYC, can be used as induction and/or maintenance therapies. The aim of the study was to determine the efficacy and safety of MMF in PCNSV.

Methods: The study cohort consisted of 163 consecutive patients with PCNSV seen at Mayo Clinic (Rochester, MN) from 1983 to 2011. The diagnosis of PCNSV was based on findings of brain or spinal cord biopsy, cerebral angiography, or both. To assess treatment response, we used the physician’s global opinion about the response to therapy. The degree of disability was defined using the modified Rankin scale. Outcomes, relapses, treatment response and ability to discontinue treatment at last follow-up were compared between patients treated with MMF and those receiving other therapies.

Results: 159/163 patients were treated at the time of diagnosis: 68 received GCs alone, 72 GCs and CYC, 2 CYC alone, 10 MMF and GCs, 6 AZA and GCs, and 1 rituximab and GCs. 6 more patients were treated with MMF after obtaining remission with CYC. In total, 16 patients were treated with MMF: 7 males and 9 females with a median age of 45.5 years (range: 20–72 years). Cerebral biopsy was performed in 10 and was positive in 9 (3 associated cerebral amyloid angiopathy). Clinical manifestations at presentation were: headache (9 patients), altered cognition (9 patients), persistent neurologic deficit or stroke (8 patients), seizures (6 patients) and 1 had intracranial hemorrhage. Cerebral MRI showed infarctions in 10 patients (bilateral in 7) and prominent leptomeningeal enhancement in 4 patients. CSF abnormalities were observed in 14/16 patients. The median duration of follow-up was 34 months (range: 10–78 months). Cerebral angiography was positive in 7/11 patients and large vessel involvement was observed in 4. The median dose of MMF was 2 grams (range: 0.5–3 grams) and the median therapy duration 14.9 months (range: 1–31.6 months). Rankin disability scores at diagnosis were similar between patients treated with MMF and those receiving other therapies (Rankin score, 0–3: 68.7% versus 69.9%; Rankin score, 4–6: 31.3% versus 30.1%; p = 1.000). A significantly lower proportion of patients treated with MMF had severe disability at last follow-up compared to those receiving other therapies (Rankin score, 4–6: 0 versus 25.1%, p = 0.023). No statistically significant differences were observed in patients treated with MMF compared to those receiving other therapies regarding relapses [7/16 (43.7%) versus 37/142 (25.9%), p = 0.146], ability to discontinue therapy at last follow-up [4/16 (25%) versus 36/142 (25.3%), p = 1.000], and treatment response [15/15 versus 111/142 (78.1%), p = 0.075]. Only 1 patient suspended MMF for a severe adverse event (leukopenia).

Conclusion: In this retrospective study of a small number of PCNSV patients, MMF was an effective and safe therapy.

Disclosures: C. Salvadori, None; R. D. Brown Jr., None; T. J. H. Christiansen, None; J. Huston III, None; F. Muratore, None; G. G. Hunder, None.
**Results**: The literature review identified 28 studies for full review. The identified domains from the Delphi survey and corresponding measurement instruments are presented in Table 1.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument Used (N)</th>
<th>Domain Instrument Manifestations</th>
<th>Rare/serious or adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain/ache</td>
<td>VAS (11)</td>
<td>Blood tests CRP or ESR</td>
<td>Death SAE reporting</td>
</tr>
<tr>
<td>Fatigue</td>
<td>VAS (2)</td>
<td>Physician Global</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Patient Global</td>
<td>VAS (3)</td>
<td>Stiffness Duration (min:7)</td>
<td>Glucocorticoid AEs</td>
</tr>
<tr>
<td>Quality of life</td>
<td>SF36 (2)</td>
<td>ADL HAQ (4)</td>
<td></td>
</tr>
</tbody>
</table>

N: Number of studies; VAS: Visual analogue scale; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SAE: Serious adverse event; AE: Adverse event; SF36: Short-Form-36; ADL: Activities of daily living; HAQ: Health Assessment Questionnaire Disability Index

No study reported any patient involvement in the development of the outcome measures used. The candidate core domain set emerging after discussion at the OMERACT 12 PMR special interest group is shown in figure 2. Two studies undertook instrument validation and demonstrated poor test-retest reliability for fatigue VAS, morning stiffness duration, and SF36 mental component score and that the HAQ performed well for PMR.

**Conclusion**: The over glucocorticoid (GC) adverse effects (AEs) warrants their inclusion in the core set. No accepted measurement instrument for GC AEs was identified. GC AEs were not routinely reported in the studies. The literature review identified 28 studies for full review. Results: The mean relative changes of the CRP/ESR and PROs from baseline to 4th and 16th week were not statistically different between Pd and MR-Pd (p > 0.05), confirming their same efficacy at the same dosage. We noticed the highest after 4 weeks CRP, fatigue, stiffness duration and HAQ assessment showed a better response in the group treated with modified release CS (CRP SRM 1.03–0.71; fatiguer SRM 1.25–0.80; stiffness duration 1.40–0.00, HAQ SRM 1.74–1.10 for modified and immediate release Prednisone respectively). However at week 16 there were no significantly differences between CRP and HAQ (SRM 0.56 - 0.67 and 1.83 – 1.02 respectively), whereas fatigue and stiffness duration improved in patients treated with Pd (SRM 1.12 – 0.07 and 0.72 – 0.10). Otherwise impact on stiffness intensity was constantly better in patients treated with Pd (after 4 and 16 weeks respectively; SRM 1.70–1.15 and 4.19–1.16).

**Disclosure**: M. Betelli, None; G. Erba, None; M. Ricci, None; C. Valena, None; E. Allevi, None; M. Riva, None; G. Grosso, None; S. Barbarossa, None; F. Bonomi, None; M. R. Pozzi, None.

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**Conclusion**: Modified-Release Prednisone and Prednisone showed the same overall efficacy on Patient Reported Outcomes and acute phase reactants in patients with PMR, but with different timings and impacts on various disease aspects.

**Disclosure**: M. Betelli, None; G. Erba, None; M. Ricci, None; C. Valena, None; E. Allevi, None; M. Riva, None; G. Grosso, None; S. Barbarossa, None; F. Bonomi, None; M. R. Pozzi, None.

**Background/Method**: Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of the elderly, characterised by morning stiffness, pain and aching in the hip and shoulder girdles and acute phase reactants increase. The response to low-dose prednisone (Pd) is marked and fast on both Patient Reported Outcomes (PROs) and acute phase reactants, but most patients require a treatment course of 1-3 years. A new modified-release delivery system Prednisone adapts the release of the administered glucocorticoid to the circadian rhythms and proved to be useful for morning stiffness, fatigue and disease activity control in Rheumatoid Arthritis. We compared Prednisone (Pd) to modified release Prednisone (MR-Pd) on PROs and acute phase reactants in Polymyalgia Rheumatica.

**Methods**: We studied 15 patients (5 men, mean age 70 years, SD 8.25) with newly diagnosed PMR and previously untreated. They received the same tapering dose of prednisone starting from 15 mg: 8 patients received a MR-Pd tablet, and 7 a Pd tablet. We observed no drop-outs but only ten patients have completed the 16-week assessment period by now (3 men, mean age 72 years, SD 5.48). CRP/ESR, VAS for stiffness duration/intensity and fatigue and HAQ-DI (PROs) were obtained at baseline and at week 4 and 16. We used Standardized Response Means (SRM), a measure of responsiveness, to evaluate acute phase response and clinical parameters improvement at week 4 and 16.

**Disclosure**: M. Betelli, None; G. Erba, None; M. Ricci, None; C. Valena, None; E. Allevi, None; M. Riva, None; G. Grosso, None; S. Barbarossa, None; F. Bonomi, None; M. R. Pozzi, None.

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**Disclosure**: M. Betelli, None; G. Erba, None; M. Ricci, None; C. Valena, None; E. Allevi, None; M. Riva, None; G. Grosso, None; S. Barbarossa, None; F. Bonomi, None; M. R. Pozzi, None.

**Validation of New 2012 EULAR/ACR Classification Criteria for Poly- myalgia Rheumatica: Comparison with the Previous Criteria in a Prospective Multi-Center Study.** Gulsen Ozden1, Seda Bas2, Ali Uğur Unal3, Gezmis Kiyon4, Ahmet Mesut Onat4, Mustafa Sen4, Alperen Mengi1, Ali Sahin4, Semra Yilmaz5, Havva Keskini6, Sadiye Mural4, Ayse Balkarli7, Velia Cobanca8, Omer Nuri Pamuk9, Yonca Cagatay9, Neslihan Yilmaz9, Ilker Yagci10, Pamir Ataoguz11, Sibel Z. Aydinal, Nevsun Inanc12 and Haner Direskeneli13. 1. Marmara University School of Medicine, Istanbul, Turkey, 2. Gaziantep University School of Medicine, Gaziantep, Turkey, 3. Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey, 4. Cumhuriyet University Faculty of Medicine, Sivas, Turkey, 5. Suleyman Demirel University Faculty of Medicine, Salihli, Turkey, 6. Selcuk University School of Medicine, Konya, Turkey, 7. Goztepe Madeniyet University Faculty of Medicine, Istanbul, Turkey, 8. Pamukkale University School of Medicine, Denizli, Turkey, 9. Taksim University School of Medicine, Eskisehir, Turkey, 10. Bilim University Faculty of Medicine, Istanbul, Turkey, 11. Koc University Faculty of Medicine, Istanbul, Turkey.

**Background/Method**: To evaluate the diagnostic and discriminative ability of the new 2012 European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) polymyalgia rheumatica (PMR) classification criteria compared to previous four diagnostic/classification criteria for PMR in a multicenter prospective study.

**Methods**: One-hundred and five patients older than 50 years of age, presenting with new onset (symptom duration = 12 weeks) bilateral shoulder pain with elevated acute phase reactants were enrolled from 9 rheumatology clinics in Turkey. Patients were prospectively followed and the diagnosis of PMR was established when the diagnosis was maintained without an
Studies evaluating ultrasound (US) as a diagnostic tool in GCA have reported a high sensitivity and specificity. The aim of this study was to investigate the association between disease’s relapse and co-existing “silence” LVV in patients with PMR.

**Methods:** Patients with PMR who relapsed under corticosteroid (CS) tapering in Esbjerg Hospital, Denmark in the period of April 2013 to June 2014 have been prospectively included. In patients with PMR who relapsed under corticosteroid (CS) tapering, US examination of temporal (AT), axillary (AA), subclavian (AS) and carotid (AC) arteries was performed. US images were recorded and evaluated by an ultrasonographer experienced on vascular ultrasound (AD), who was blinded to patients’ clinical and laboratory data.

US was considered positive when a homogeneous hypoechoic thickness >1 mm in AC and AS and >1 mm in AA, in transverse and longitudinal view was observed. For the AT, the typical sign of halo (arterial wall swelling in transverse and longitudinal view) was considered as vasculitis. Relapse was defined as the reappearance of PMR clinical symptoms in addition to elevated ESR or CRP (ESR > 40 mm/h, CRP >10mg/l) or persistent increased CRP/ESR without any other explanation. All patients with positive US findings underwent TAB.

**Results:** On a period of 14 months, 17 patients had been evaluated. All patients fulfilled the Bird’s classifications criteria for PMR and all the patients responded appropriately to CS treatment at baseline. None of the patients had GCA-related clinical symptoms either on baseline or during the relapse. No significant differences were observed between the two groups of patients (PMR + LVV and PMR - LVV) in age, diseases duration, initial CRP/ESR levels and initial CS dose (prednisolon 15-25mg).

Seven out of 17 (41%) patients had ultrasonographic sign of vasculitis. All patients had affection of the AA (6 of them bilateral), 3 of the AS, 1 of the AT none of the AC. The patient with the positive US of the AT was the only who had a positive TAB.

**Conclusion:** In our study, the relationship between PMR relapse and concomitant “silence” LVV has been evaluated. More than one-third of PMR patients who relapsed had a co-existing LVV. Thus, we recommend the use of vascular US in all patients with PMR suffering a relapse to investigate the possible co-existence of LVV.

**Disclosure:** S. Chrysidi, None. P. R. Lage-Hansen, None. A. P. Diamantopoulos, None.

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**PET-CT Imaging and Association of Ferritin Autoantibodies in Polymyalgia Rheumatica**

Niklas Thomas Baerlecken*, Torsten Witte*, Marco Amedeo Cimmino² and Dario Camellino³. ¹MD, Hannover, Germany, ²MD, Hanover, Germany, ³Università di Genova, Genova, Italy, ⁴Clinica Reumatologica, Genova, Italy.

**Background/Purpose:** Previously we described antibodies against ferritin heavy chain peptide (anti-FHCP) in sera of patients with giant cell arteritis (GCA) and/or polymyalgia rheumatic (PMR) before glucocorticoid treatment was initiated. In that study, it remained unclear however, whether the PMR patients may have suffered from additional undiagnosed GCA. Therefore, we now measured antibodies against FHCP in PMR patients in whom GCA had been excluded by FDG-PET scan.

**Methods:** Sera of 63 patients were studied that presented initially with symptoms of PMR. A PET-CT had been performed in all patients and revealed large vessel vasculitis in 27 of these patients (GCA/PMR), whereas 36 had no signs of vasculitis (PMR). In a single-blinded study, we measured anti-FHCP in these patients and in a control group of patients with rheumatic diseases (RD, n=26), malignant diseases (MD, n=15) and infectious febrile diseases (IFD, n=22).

In the ELISA 3 peptides of the ferritin heavy chain were used as antigens: A19-45 (A19RNQINELASYVLLSMYFYFDFR), A79-104 (GRIFQDIKKPCDDWESGLNACMA) and A105-143 (LHKEKVNQOSLHLKLDTKNDHPHLFCTHYNEVQK).

**Results:** The frequency of antibodies against A19-45 were 38/63 (60%) in all PMR patients and 14/63 (22%) in controls (p<0.0001), of antibodies against A79-104 30/63 (48%) in all PMR patients and 9/63 (14%) in controls (p<0.0001) and of antibodies against A105-143 38/63 (60%) in PMR and 12/63 (19%) in controls (p<0.0001). There were no differences within the controls considering all antibodies.

Comparing the patients with and without vascular involvement in PET-CT, the frequencies of antibodies against A19-45 (18/27 (67%) and 20/36 (56%), (p=0.53)), against A79-104 (14/27 (52%) and 16/36 (44%) (p=0.74) and against A105-143 (19/27 (70%) and 19/36 (53%) (p=0.25) were not different.

**Conclusion:** This single-blinded study confirms the frequency of anti-FHCP in a different cohort. Anti-FHCP are associated with both GCA/PMR and PMR only.

**Disclosure:** N. T. Baerlecken, None. T. Witte, None. M. A. Cimmino, None. D. Camellino, None.

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**Polyvaskyulite Rheumatika: Relapse and ‘Silence’ Large Vessel Vasculitis: Is There Any Association?**

Stavros Chrysidi, Philip Rask Lange-Hansen, and Amedeo Cimmino. Department of Rheumatology, Hospital of Southwest Denmark, Esbjerg, Denmark, Hospital of Southern Norway Trust, Kristiansand, Norway.

**Background/Purpose:** Large Vessel Vasculitis (LVV) can present with heterogeneous clinical manifestations, which range from general symptoms (fever, loss of weight) to the classic symptoms of Giant Cells Arteritis (GCA) (headache, jaw claudication, visual manifestations). Around 40% of GCA patients have concomitant Polyvaskyulite Rheumatika (PMR) and up to 40% of PMR patients have a positive biopsy of the temporal artery (TAB).

Studies evaluating ultrasound (US) as a diagnostic tool in GCA have reported a high sensitivity and specificity. We now measured antibodies against the heavy chain peptide of ferritin (anti-FHCP) in sera of patients with GCA/PMR, whereas 36 had no signs of vasculitis (PMR). In a single-blinded study, we measured anti-FHCP in these patients and in a control group of patients with rheumatic diseases (RD, n=26), malignant diseases (MD, n=15) and infectious febrile diseases (IFD, n=22).

In the ELISA 3 peptides of the ferritin heavy chain were used as antigens: A19-45 (A19RNQINELASYVLLSMYFYFDFR), A79-104 (GRIFQDIKKPCDDWESGLNACMA) and A105-143 (LHKEKVNQOSLHLKLDTKNDHPHLFCTHYNEVQK).

**Results:** The frequency of antibodies against A19-45 were 38/63 (60%) in all PMR patients and 14/63 (22%) in controls (p<0.0001), of antibodies against A79-104 30/63 (48%) in all PMR patients and 9/63 (14%) in controls (p<0.0001) and of antibodies against A105-143 38/63 (60%) in PMR and 12/63 (19%) in controls (p<0.0001). There were no differences within the controls considering all antibodies.

Comparing the patients with and without vascular involvement in PET-CT, the frequencies of antibodies against A19-45 (18/27 (67%) and 20/36 (56%), (p=0.53)), against A79-104 (14/27 (52%) and 16/36 (44%) (p=0.74) and against A105-143 (19/27 (70%) and 19/36 (53%) (p=0.25) were not different.

**Conclusion:** This single-blinded study confirms the frequency of anti-FHCP in a different cohort. Anti-FHCP are associated with both GCA/PMR and PMR only.

**Disclosure:** N. T. Baerlecken, None. T. Witte, None. M. A. Cimmino, None. D. Camellino, None.
The Use of Imaging in the Diagnosis of Polymyalgia Rheumatica: Systematic Literature Review and Meta-Analysis. Sarah Mackie,1 Gouri Koduri,1,2 Catherine L. Hill,1 Andrew Hutchings,1 Richard J. Wakefield,1 Bhashkar Dasgupta2 and Jeremy Wyatt.1 1University of Leeds, Leeds, United Kingdom, 2Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatism and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

Background/Purpose: ACR/EULAR provisional classification criteria for polymyalgia rheumatica (PMR) incorporate musculoskeletal ultrasound of shoulder and hip (bursitis and synovitis given equal weight). Our objective was to systematically review diagnostic accuracy of imaging features of PMR: the reference standard was rheumatologist diagnosis.

Methods: Data sources were MEDLINE, EMBASE and PubMed searches; hand-searching, and experts in the field. Two authors independently reviewed search outputs and discussed disagreements. 1746 citations yielded 23 eligible studies. Data were extracted by two authors independently. Methodological quality was assessed by 3 authors using QUADAS-2. Hierarchical summary receiver operating curve (HSROC) models were constructed where appropriate, and positive/negative likelihood ratios (LR +/ LR-) calculated.

Results: 23 studies with data from 2328 patients were evaluated: musculoskeletal ultrasound (9 studies), vascular ultrasound (6), magnetic resonance imaging (MRI) (6), and positron emission tomography (PET) (2). One further article (musculoskeletal ultrasound) was published during the preparation of this review. Internal and external validity varied, as did the clinical spectrum. All but one of the studies had a diagnostic case-control design. The most useful imaging features were subacromial-subdeltoid bursitis (SAB) on one or both sides (4 ultrasound studies: LR + 2.5 (1.6 to 3.8); LR - 0.30 (0.11 to 0.81), bilateral SAB (4 ultrasound studies: LR + 2.2 (1.2 to 32); LR - 0.38 (0.15 to 0.97), and presence of trochanteric bursitis (2 ultrasound, 1 MRI and 1 PET study: LR + 5.4 (3.3 to 8.8), LR - 0.076 (0.002 to 0.28). Hip or shoulder synovitis LRs were closer to the non-informative ratio of 1.0. Interspinous bursitis (LR + 4.5 (1.5 to 13), LR - 0.26 (0.093 to 0.73)) and ischiogluteal bursitis (LR + 3.6 (1.5 to 8.8), LR - 0.19 (0.05 to 0.69)) were detected by PET scans rather than ultrasound.

Conclusion: Based on current evidence, the most useful imaging features for the diagnosis of PMR appear to be SAB, bilateral SAB and trochanteric bursitis, rather than shoulder or hip synovitis.

Disclosure: S. Mackie, None; G. Koduri, None; C. L. Hill, None; A. Hutchings, None; R. J. Wakefield, None; B. Dasgupta, Novartis Pharma AG, J. Wyatt, None.

Whole-Body MRI Reveals Characteristic Extracapsular Pattern of Inflammation in Polymyalgia Rheumatica. Sarah Mackie,1 Gouri Koduri,1,2 Catherine L. Hill,1 Andrew Hutchings,1 Richard J. Wakefield,1 Bhashkar Dasgupta2 and Jeremy Wyatt.1 1University of Leeds, Leeds, United Kingdom, 2Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatism and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

Background/Purpose: Polymyalgia rheumatica (PMR) is a disease of widespread musculoskeletal inflammation characterized by pain and stiffness in shoulder and hip girdles. Here we report the first use of whole-body MRI to study the clinical spectrum of PMR in the rheumatology clinic. We hypothesized that PMR is characterized by an extracapsular pattern of inflammation.

Methods: 38 participants underwent whole-body MRI: 22 consecutive cases of clinically-diagnosed, active PMR identified by two rheumatologists with a special interest in PMR and followed up for a mean of 21 months; and 16 patients (controls) selected from a larger inflammatory arthritis (RA) cohort. 4 of the PMR patients did not have gadolinium enhancement, due to contra-indications. A nonmised gadolinium-enhanced MRI scans were consensus scored in axial view using semi-quantitative grading, and the features best discriminating PMR from RA were identified. Patients were treated after the MRI with 15mg prednisolone and then asked at follow-up whether they no felt back to normal.

Results: A characteristic pattern suggesting PMR was classified as "PMR pattern" by the blinded scorers; this could be identified both on the gadolinium-enhanced and non-enhanced scans. The features best discriminating PMR from RA were inflammation in the following sites: extending up around the rim of the acetabulum ("peri-acetabular"); around the ischial tuberosity; within the hip joint; around the greater trochanter; and around the symphysis pubis (Figure). Of all the MRIs performed in patients with a clinical diagnosis of PMR, "PMR pattern" was significantly associated with patient-defined glucocorticoid responsiveness (p=0.01).

Conclusion: A characteristic, extracapsular pattern of inflammation in PMR can be identified, and defines a subgroup of the clinical spectrum of PMR with excellent patient-reported glucocorticoid responsiveness. MRI is particularly useful in assessing inflammation of structures around the pelvis.

Disclosure: S. Mackie, None; C. T. Pease, None; E. Fukuba, None; P. Emery, Abbvie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma; 2, Abbvie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma; 5, R. J. Hodgson, None; J. E. Freeston, None; D. McGonagle, None.

Why Leg Ulcers Do Not Heal? a Prospective Study Showing High Proportion of Small Vessel Vasculitis. Vinod Ravindran, Sunil Rajendra and Ranjish Vijayan. 1National Hospital, Kozhikode, Kerala, India, 2PVS Hospital, Kozhikode, India.

Background/Purpose: Non healing cutaneous ulcers of lower limbs can have several different aetiologies [1]. It is likely that the patients with such ulcers would be treated with empirical therapies and may also undergo (unnecessary) venous procedures. Small vessel vasculitides (leucocytoclastic or non leucocytoclastic) are one of the important causes of non healing cutaneous leg ulcers [2]. The primary objective of this prospective study was to ascertain the cause of non healing cutaneous ulcers of the lower limbs.

Methods: Between May 2010 and April 2013 (3years) consecutive adult patients (age 18 to 75 years) who had one or more persistent leg ulcers (with or without a history of recurrent ulcerations in legs) for more than 2 years presenting to us were prospectively enrolled. Relevant details were extracted using a predefined proforma and included: demographic details, drug history, comorbidities, clinical features, investigations including ANCA, complement levels, cryoglobulins, HIV and Hepatitis viral serology etc. and venous and arterial Dopplers, microscopy and culture of the ulcer swab in instances of infected looking ulcers. Previous biopsies were reviewed and fresh biopsies were obtained from the ulcer edges and also from the nonulcerated sites where suitable skin lesions were also present. In cases of ulcers deemed to be a manifestation of a primary systemic vasculitis based on the EMEA classification, BVAS was used to assess disease activity.

Results: A total of 51 patients were assessed. Mean age was 53 ± 10.3 years and 39 (76%) were male. Eight (16%) patients were diabetic. History of some type of venous surgery was present in 30 (59%) and 9 had such procedures more than once. Biopsy confirmed small vessel vasculitis of various types in a majority (76%) of patients (table 1). Drug induced cutaneous vasculitis was not present in this cohort.
Drug-Associated Cutaneous Vasculitis: Study of 239 Patients from a Single Referral Center. Montserrat Santos-Gómez1, Francisco Ortiz Sanjuan1, Ricardo Blanco1, Jose L. Hernández2, Vanesa Calvo-Rio1, Javier Loricera1, Carmen Gonzalez-Vela2, Trinitario Pina Murcia1, Hector Blanco1, J. L. Loricera1, Carmen Gonzalez-Vela2, Victor Martinez-Taboada1, Javier Rueda-Gotor1, Leyre Riancho-Zarrabeitia3 and Miguel A. Gonzalez-Gay1. 1Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, 2Sanidad, Santander, Spain, 3Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides defined drug-associated immune complex vasculitis as a distinct entity included within the category of vasculitis associated with probable etiology. In the present study we assessed the clinical spectrum of patients with drug-associated cutaneous vasculitis (DACV).

Methods: Case records of patients with DACV attending to a tertiary referral hospital over a 36-year period were reviewed. A diagnosis of DACV was considered if the drug was taken within a week before the onset of the disease.

Results: 239 (30.9%) patients (133 men and 106 women with a mean age of 36 years) from a series of 773 unselected cutaneous vasculitis were diagnosed with DACV. Antibiotics (n = 149; 62.3%) -mainly β-lactams-, and non-steroidal anti-inflammatory drugs (NSAIDs) (n = 24; 10%) were the most common drugs. Besides skin lesions (100%), the most common clinical features were joint (51%) and gastrointestinal (31%) manifestations, nephropathy (34.7%), and fever (23.8%). The most remarkable laboratory data were increased erythrocyte sedimentation rate (40.2%), presence of serum cryoglobulins (26%), leukocytosis (24.7%), positive antinuclear antibodies (21.1%), anemia (18.8%), and positive rheumatoid factor (17.5%). Despite drug discontinuation and bed rest, 108 patients (45.2%) required medical treatment, mainly corticosteroids (n = 71) or immunosuppressive drugs (n = 7). After a median follow-up of 5 months, relapses occurred in 10.4% of patients, and persistent microhematuria or renal insufficiency in 3.3% and 2.9%, respectively.

Conclusion: DACV is generally associated with antibiotics and NSAIDs. In most cases it has favorable prognosis, although a small percentage of patients may develop residual renal damage.

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Clinical-Biological Spectrum and Therapeutic Management of Hypocomplementemic Urticarial Vasculitis: Data from a French Nationwide Study on 57 Patients. Marie Jachiet1, Alain Le Quercuum1, Alain Deroux2, Pascal Godmer3, Mikael Ebb3, Leonardo A. Studer4, Beatrice Chevalier5, Nicolas Dupin6, Selim Aractingi1, Luc Guillevin for the French Vasculitis Study Group5, Luc Mouthon7 and Benjamin Terrier1. 1Cochin Hospital, Paris, France; 2Division of Internal Medicine, Hôpital Saint-Eloi, Centre Hospitalier Universitaire de Montpellier, Montpellier, France, 3CHU Grenoble, Grenoble, France; 4Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France; 5CHU, Mar-selle, France, 6CHU, Toulouse, France, 7Saint Louis, Paris, France. 8Service de Dermatologie, Hôpital Cochin, AP-HP, Paris, France. 9National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Hypocomplementemic urticarial vasculitis (HUV), an uncommon vasculitis of unknown etiology, is rarely reported. It is also called anti-C1q vasculitis in the 2012 revised International Chapel Hill Consensus Conference Nomenclature for Vasculitides. Information on its presentation and therapeutic management is scarce.

Methods: To analyze the clinical spectrum and therapeutic management of HUV patients, we conducted a French nationwide retrospective and transdisciplinary study on behalf of the FVSG that included 57 patients with chronic urticaria, histological leukocytoclastic vasculitis and hypocomplementemia as inclusion criteria.

Results: The 57 identified patients had a median age at diagnosis of 45 (range 15–83) years, and 42 (74%) were women (sex ratio 2.8). HUV was
isolated in 43 (75%) patients, while the remaining 14 (25%) were associated with systemic lupus erythematosus (n=10), primary Sjögren’s syndrome (n=2), systemic sclerosis and lung cancer (n=1 each). Urticarial lesions were typically erythematous papules, more pruritic than painful, associated with angioedema (51%), purpura (35%) and/or livedo reticularis (14%). Excruciating manifestations included constitutional symptoms (56%), musculoskeletal (82%), ocular (56%), pulmonary (19%), gastrointestinal (18%) and/or kidney involvement (14%). HUV patients typically had low C1q-complement and normal C1-inhibitor levels with 35% of them also having anti-C1q antibodies. Patients with anti-C1q antibodies had more frequent systemic HUV, angioedema, livedo reticularis, ocular, musculoskeletal and/or kidney involvement(s), and less frequent pulmonary and/or gastrointestinal involvement(s). Hydroxychloroquine (HCQ) or colchicine seemed to be as effective as corticosteroids as first-line therapy. For patients with relapsing and/or refractory HUV, higher cutaneous and immunological response rates were obtained with immunosuppressants, particularly azathioprine (AZA), myophenolate mofetil (MMF), cyclophosphamide or rituximab (RTX)-based regimens, with the latter apparently more effective. Finally, cutaneous and immunological responses were strongly associated.

Conclusion: HUV is an uncommon systemic and relapsing vasculitis with various manifestations, mainly musculoskeletal and ocular. Half of the patients have anti-C1q antibodies. HCQ and colchicine should be the first-line therapy, whereas corticosteroids alone or combined with an immunosuppressant, preferably AZA, M.M.F. or RTX, could be alternative therapeutic options for relapsing or refractory disease.  

Disclosure: M. Jachiet, None; A. Le Queillec, None; A. Deroux, None; P. Godmer, None; M. Ebbo, None; L. Astudillo, None; B. Flageul, None; N. Dupin, None; S. Arcangeli, None; L. Guillemin for the French Vasculitis Study Group, None; L. Mouton, None; B. Terrier, None.

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Background/Purpose: Non-systemic vasculitic neuropathy (NSVN) is a small-to-medium-sized vessel vasculitis limited to the peripheral nervous system. It can be considered a single-organ vasculitis, as recently defined in the revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides in 2012. NSVN is probably an underdiagnosed entity that has rarely been reported. This descriptive study was undertaken to ascertain its presentation, therapeutic management and outcome.

Methods: We retrospectively analyzed 18 patients with NSVN fulfilling criteria proposed by Collins in 2010, including: 1) peripheral neuropathy, 2) vasculitis histologically proven on neuromuscular biopsy, 3) possible constitutional symptoms, and 4) absence of systemic manifestations or laboratory markers suggestive of systemic vasculitis or connective tissue disease.

Results: Ten women and 8 men, median age 51 (range 27–83) years, were included. Neurological manifestations were characterized by acute onset (76%), mononeuritis multiplex (88%), polyneuropathy (12%), sensory impairment (100%) and motor impairment (88%). Neurological manifestations were painful (86%) and asymmetrical (78%). Nerve trunks involved were external popliteal (94%), internal popliteal (44%), ulnar (33%), radial (17%) and median (11%). General symptoms included asthenia and weight loss (>10% (22%) each), arthralgias (12%) and fever (6%). Only 2 patients had elevated inflammatory parameters. Neuromuscular biopsy showed, in muscle or nerve, medium-sized-vascular vasculitis (56%) or small-sized-vascular vasculitis (44%), with fibrinoid necrosis (88%). Corticosteroids were prescribed to 94%, and their NSVN regressed significantly (65%), stabilized (2%) or progressed (24%). Cyclophosphamide was added to corticosteroids for refractory patients. Relapsing patients received methotrexate or azathioprine, with 3/4 patients showing improvement. After median follow-up of 47 months, neurological sequelae were noted in 83%, including sensory sequelae in 15 patients and motor sequelae in 6.

Conclusion: The results of this study describing NSVN presentation, therapeutic management and outcome indicated that acute onset, painful and asymmetrical manifestations are suggestive of NSVN. Half of the patients required immunosuppressive agents because of relapsing and/or refractory disease. Sensory and motor sequelae were common, suggesting that early diagnosis and initiation of therapy are critical.

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Systemic Inflammatory and Autoimmune Manifestations Associated with Myelodysplastic Syndrome: A French Multicenter Retrospective Study. Arsen E. Meranian1, Eric Grignano2, Thorsten Braun3, Olivier De-Caux4, Eric Liozon5, Nathalie Costedoat-Chalumeau6, Jean Emmanuel Kahn7, Mohamed Hamidou8, Geraldine Falgarone9, Olivier Lorholtry10, Sophie Park11, Zahir Amoura12, A. Mathian13, Bruno Gombert14, Christian Rose15, Xavier Puechal16, David Lanay17, Guillaume Denis18, Bertrand Lioger19, Anne Laure Buchdahl20, Sophie georgin Lavallie21, Francois Montestruc22, Mohammed Omouri23, Julien Rossignol24, Jean Marc Ziza25, Pascal Catelas26, Serge Madaule27, Benoît de Waziers28, Nathalie Mora29, Sébastien Sehillat30, Hélène Raffray31, Eric Toungou32, Jean-Charles Piette33, Claude Gardin34, Lionel A Des35, Pierre Fenaux36 and Olivier Fain37.

Background: Systemic Inflammatory and Autoimmune Manifestations (SAID) are frequently observed in patients with myelodysplastic syndrome (MDS). The aim of this study was to describe the characteristics, treatment, and outcomes of SAID in a large cohort of patients with MDS.

Methods: A retrospective study was conducted in 35 French hematologic centers. Patients with both MDS and SAID were included. The diagnosis of SAID was based on the revised International Working Party criteria for SAID in 2010. The outcomes were evaluated at the last follow-up.

Results: 123 patients with both MDS and SAID (mean age, 70 ± 13 years; 41 females and 82 males) were included. The baseline characteristics in table 1 are summarized. The incidence of SAID was 66% of cases. The most common SAID were inflammatory arthritis in 28 cases (23%), neutrophilic disorders in 12 cases (10%) and unclassified in 13 cases (11%). Complete diagnostic SAID criteria were fulfilled in 66% of cases, remained incomplete.
in 21% and SAID was unclassified in the remaining patients. The diagnosis of SAID and MDS was concomitant in 38 (31%) cases, diagnosis of SAID preceded MDS in 46 (37%) cases and was made after MDS in 39 (32%) cases, with the time between the diagnoses of the 2 diseases being 8.6±52 months. A part from significant association between Chronic myelomonocytic leukemia (CMML) and systemic vasculitis (p=0.0024), no correlation was seen between specific types of SAID and of MDS. A response to SAID first line treatment (mainly steroids), was observed in 63% of the 116 treated cases, including 80% for steroids alone. A second-line treatment was required for steroid dependence or relapse in 48% of the patients. Among treated patients who received biologic targeted treatments at any time (n=27), overall response of SAID (partial or complete) was noted in 9/20 (45%) patients. Among 16 patients treated by azacytidine for their MDS, SAID remission was seen at 3 months in 7/16 (44%) of the cases, with a significant decrease of acute-phase reactants and steroid amounts required. At last follow-up, 37/70 (53%) patients were in complete or partial remission of SAID, and among patients who received biologic targeted treatments at any time (n=27), overall response of SAID (partial or complete) was noted in 9/20 (45%) patients. Among patients who received biologic targeted treatments at any time (n=27), overall response of SAID (partial or complete) was noted in 9/20 (45%) patients.

Conclusion: The spectrum of SAID associated to MDS is variable, many cases remain difficult to classify. Presence of SAID has no impact on the overall survival of MDS patients. Azacitidine can improve SAID in 75% of the patients. Because of frequent steroid dependence and relapse of SAID, better therapeutic strategies with biological targeted drugs are required, while larger use of MDS specific drugs like azacitidine must be assessed prospectively.

Table 1. Baseline characteristics of patients with MDS-associated to SAID and MDS without SAID.

<table>
<thead>
<tr>
<th></th>
<th>MDS with SAID</th>
<th>MDS without SAID</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>70±12</td>
<td>72±11*</td>
</tr>
<tr>
<td>Female/Male</td>
<td>41/82 (50%)</td>
<td>29/137 (18%)*</td>
</tr>
<tr>
<td>Karyotype</td>
<td>62 (75%)</td>
<td>386 (69%)</td>
</tr>
<tr>
<td>Favorable</td>
<td>8 (10%)</td>
<td>111 (20%)*</td>
</tr>
<tr>
<td>Intermediate Poor</td>
<td>13 (16%)</td>
<td>64 (11%)*</td>
</tr>
<tr>
<td>Bone Marrow blasts (%)</td>
<td>6.5±9</td>
<td>4±5*</td>
</tr>
<tr>
<td>IPSS</td>
<td>0.9±0.9</td>
<td>0.8±0.9</td>
</tr>
<tr>
<td>IPSS low</td>
<td>18 (20%)</td>
<td>190 (26%)</td>
</tr>
<tr>
<td>Intermediat-1</td>
<td>39 (44%)</td>
<td>181 (33%)*</td>
</tr>
<tr>
<td>Intermediat-2</td>
<td>15 (19%)</td>
<td>107 (19%)</td>
</tr>
<tr>
<td>Poor</td>
<td>7 (9%)</td>
<td>76 (14%)</td>
</tr>
<tr>
<td>RCUD</td>
<td>11 (9%)</td>
<td>73 (11%)</td>
</tr>
<tr>
<td>RARS</td>
<td>1 (1%)</td>
<td>57 (9%)*</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>18 (12%)</td>
<td>130 (20%)</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>10 (8%)</td>
<td>116 (17%)*</td>
</tr>
<tr>
<td>CMML 1/2</td>
<td>19 (16%)</td>
<td>96 (14%)*</td>
</tr>
<tr>
<td>Sq syndrome</td>
<td>6 (5%)</td>
<td>25 (4%)</td>
</tr>
<tr>
<td>MDS-U</td>
<td>31 (26%)</td>
<td>136 (220%)</td>
</tr>
<tr>
<td>Progession to Acute Leukemia</td>
<td>11 (9%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Survival (median, months)</td>
<td>72 [59-105]</td>
<td>75 [48-300]</td>
</tr>
</tbody>
</table>

**Table 1.** Baseline characteristics of patients with MDS-associated to SAID and MDS without SAID.

**Results:**

- **Conclusions:** The preliminary data suggest that a sequential treatment with intravenous prostaglandins followed by bosentan may be considered a therapeutic option for patients with TAO and severe ischemic lesions. Larger studies are required to confirm these results.

**Disclosure:** None.

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**ACR Plenary Session III: Discovery 2014**

**Tuesday, November 18, 2014, 11:00 AM - 12:30 PM**

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**Cost-Efficacy of Adding Etanercpt to Sulfasalazine and Hydroxychloroquine to Methotrexate Therapy: A Randomized Noninferiority Trial.**

**Background/Purpose:** To estimate the incremental cost-effectiveness of etanercept plus methotrexate versus a triple regimen of disease-modifying anti-rheumatic drugs (methotrexate, sulfasalazine, and hydroxychloroquine) over 24 weeks and 48 weeks in patients with active rheumatoid arthritis despite methotrexate therapy (RACAT).

**Methods:** In this double blind, noninferiority trial 353 patients were randomized to etanercept plus methotrexate or a triple regimen. After 24 weeks of treatment patients not achieving a DA28 improvement of 1.2 were switched in a blinded fashion to the other therapy. Quality Adjusted Life Years (QALYs) were estimated using US societal values from the EQ-5D instrument which was measured every 24 weeks. Costs of drugs, hospitalizations, procedures, tests, visits and lost productivity were prospectively tracked and monetized from a societal perspective in 2014 US dollars. Incremental cost-effectiveness ratios were calculated using standard procedures assuming an intent-to-treat analysis, with missing data analyzed using multiple imputation and uncertainty assessed using bootstrapping.

**Results:** Both strategies showed significant improvements in EQ-5D, with etanercept providing marginally more accumulated QALYs (0.358 vs 0.354 over 24 weeks, and 0.742 vs 0.726 over 48 weeks for etanercept and triple regimen strategies respectively). The etanercept strategy accumulated...
substantially higher drug costs even considering the switches between treatments at 24 weeks ($11,286 vs $369 cumulative costs from 0 to 24 weeks, and $19,625 vs $3,721 cumulative costs from 0 to 48 weeks for etanercept and triple regimen respectively). The differences in other health care and productivity costs across strategies were negligible. The resultant incremental cost-effectiveness ratios for etanercept vs. triple regimen were $11,981 vs $1,245 cumulative costs from 0 to 24 weeks and $21,537 vs $6,358 cumulative costs from 0 to 48 weeks.

Conclusion: This economic evaluation based on a prospective tracking of resource use and QALY measurement in a blinded, randomized trial demonstrates that the additional costs associated with using etanercept prior to a triple regimen does not provide good value for money at generally acceptable willingness to pay thresholds. A limitation of the study is its short time frame. However, even when considering the long-term perspective, since the incremental benefits are so small, even under the most optimistic scenarios imaginable, etanercept has only a small probability of being cost-effective compared to triple therapy. Given the opportunity cost associated with time off work and health care spending, adapting a triple regimen prior to etanercept would free up scarce health dollars for use on alternative health care interventions that provide greater health benefits.

**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>24 Weeks</th>
<th>48 Weeks</th>
<th>Incremental</th>
<th>Drug</th>
<th>Abortion</th>
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</thead>
<tbody>
<tr>
<td><strong>QALYs</strong></td>
<td>0.358</td>
<td>0.354</td>
<td>0.004</td>
<td>0.722</td>
<td>0.726</td>
</tr>
<tr>
<td><strong>Costs ($)</strong></td>
<td>11,981</td>
<td>1,245</td>
<td>10,736</td>
<td>19,625</td>
<td>3,721</td>
</tr>
<tr>
<td><strong>Incidental</strong></td>
<td>369</td>
<td>9,197</td>
<td>168</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td><strong>Joint Procedure</strong></td>
<td>102</td>
<td>102</td>
<td>223</td>
<td>331</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td>271</td>
<td>271</td>
<td>1086</td>
<td>1527</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>11,286</td>
<td>369</td>
<td>19,625</td>
<td>3,721</td>
<td></td>
</tr>
<tr>
<td><strong>Abortion</strong></td>
<td>212</td>
<td>212</td>
<td>303</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td><strong>Cost-effectiveness ratio ($)</strong></td>
<td>-2,665,851</td>
<td>-950,628</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Disclosure:** N. Bansback, None; C. Phibbs, None; H. Sun, None; J. R. O’Dell, Abbott, Lilly, Antares, Medac, S. M. Brophy, None; E. C. Keystone, Abbott Laboratories, 2; A. Morgen, Canada, 2; A. Strezszenca Pharmaceuticals L.P., 2; B. Risto-Myers Squibb, 2; F. Hoffman-LaRoche Inc., 2; Jansen Pharmaceutica Product L.P., 2; E. Lilly and Company, 2; Novartis Pharmaceutical Corporation, 2; Pfizer Inc, 2; Sanofi-Aventis Pharmaceutical, 2; G. Otis, Laboratory, 5; S. A. Strezszenca, 3; Sid, with all Myers Squibb, 2; F. Hoffman-LaRoche Inc., 5; Genentech and Biogen IDEC Inc., 5; Jansen Pharmaceutica Product L.P., 5; E. Lilly and Company, 5; M. E. Pool Pharmaceutica, 5; Pfizer Inc, 5; A. A. Abbott Laboratories, 8; A. Strezszenca, 8; B. Risto-Myers Squibb, 8; F. Hoffman-LaRoche Inc., 8; Jansen Pharmaceutica Product, L.P., 8; Pfizer Inc, 8; UCB, 8; A. Nieren, None; T. R. Mikuls, Genentech/Roche, 2; A. H. Anis, Pfizer Inc, 2; A. Tantres, Pfizer, 2; Abbvie, 5.

**2782**


**Background/Purpose:** Anti-citrullinated protein antibodies (ACPAs) are highly specific for rheumatoid arthritis (RA) and also believed to play a pathogenic role in RA. Anti-citrullinated peptides from CCP-negative RA patients, but none from the CCP-negative RA patient or healthy donors (p = 0.0015). About 19.5% of circulating plasmablast-derived recombinant antibodies from CCP-positive RA patients, but none from the CCP-negative RA patient or healthy donors, specifically recognized citrullinated RA autoantigens (p = 0.0001). The immunoglobulin genes encoding these ACPAs were highly mutated with increased replacement/site mutation ratios, suggesting that the generation of ACPAs involved active antigen selection. Interestingly, 63% of these ACPAs cross-reacted with the outer membrane antigens and/or citrullinated enolase from P. gingivalis. Germ-line reversions of some ACPAs completely eliminated their reactivity to citrullinated RA autoantigens but retained their reactivity to P. gingivalis antigens.

**Conclusion:** These results suggest that circulating plasmablasts in RA patients produce ACPAs and this process may be, in part, initiated by the anti-P. gingivalis immune responses.

**Disclosure:** S. Li, None; Y. Yu, None; Y. Yue, None; H. Liao, None; W. Xie, None; J. Thai, None; T. R. Mikuls, None; G. M. Thieme, None; M. J. Duryee, None; J. Payne, None; N. W. Klassen, None; J. R. O’Dell, None; Z. Zhang, None; K. Su, None.
Mice lacking MyD88 do not develop swelling or allodynia (AUC 2.6, NanoString™ nCounter™ analysis of 516 immune genes in the spinal cords). Presence of BMLs 79% 0.92 (0.56, 1.49), examined the development of arthritis and persistent pain in mice pathways. In order to further understand the role of TLR signaling, we unique in signaling through both MyD88-dependent and independent TLR4 showed an attenuation of the late phase of pain. This receptor is of arthritis. Rather than developing persistent pain, animals deficient in persistent pain despite adequate treatment of synovitis. There is a need be attributed solely to increased TNF or IFN expression. The innate and adaptive immune systems appear to have different than the WT mice (AUC 12.2). Disclosure: S. Woller, None; C. Ocheltree, None; L. A. Bradney, None; E. K. Quinn, None; L. Frey-Law, None.

Contribution at the Spinal Level of Innate and Adaptive Immunity to the 2784

Background/Purpose: Individuals with arthritis frequently develop persistent pain despite adequate treatment of synovitis. There is a need to better understand the mechanisms underlying pain occurring with arthritis. Recently, it has been shown that Toll-like receptor 4 (TLR4) mediates the transition from acute to chronic pain in a murine model of arthritis. Rather than developing persistent pain, animals deficient in TLR4 showed an attenuation of the late phase of pain. This receptor is unique in signaling through both MyD88-dependent and independent pathways. In order to further understand the role of TLR signaling, we examined the development of arthritis and persistent pain in mice deficient in these adaptor proteins.

Methods: Adult arthritic K/BxN mice were bled and the sera pooled. One ml of the pooled sera was injected into recipient mice on Days 0 and 2.

Results: As shown previously, WT mice develop a persistent increase in inflammation. The innate and adaptive immune systems appear to have distinct roles in the development of the chronic pain state, and this pain cannot be attributed solely to increased TNF or IFNγ transcription.

Disclosure: S. Woller, None; C. Ocheltree, None; T. Yaksh, None; M. Corr, None.

2785

J joint Specific Positional Differences in Coding and Noncoding Transcription of Synovial Fibroblasts As a Determinant of the Susceptibility of Synovial Joints to Rheumatoid Arthritis. Caroline Ospelet1, Maria Armaka2, Giancarlo Russo3, Anna Bratus4, Michiel Trenkmann5, Emmanuel Krouzakis1, Christoph Kolling2, Renate E. Gay6, George Kollias6, Steffen Gay7 and Moja Frank Bertocci1. 1Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Zurich, Switzerland; 2Biomedical Sciences Research Center ‘Alexandros Fleming’, Vani, Greece; 3Functional Genomics Center Zurich, ETH Zurich and University of Zurich, Zurich, Zurich, Switzerland; 4Schulthess Clinic, Zurich, Switzerland.

Background/Purpose: The molecular mechanisms underlying the topographic differences in the susceptibility of synovial joints to develop rheumatoid arthritis (RA) are unknown. Positional embryonic expression of Hox genes along proximal-distal and anterior-posterior body axes is critical for proper limb development. A dult skin fibroblasts retain the positional embryonic Hox code and exhibit major anatomic differences in their transcriptome, defining their unique positional identities. Synovial fibroblasts (SF) in the joints of RA patients drive joint destruction and inflammation locally. We hypothesized that SF from different joints show a joint specific, positional gene expression pattern, which can predispose joints to develop certain types of arthritis, like RA or osteoarthritis (OA).

Methods: SF were derived from knees, shoulders and metacarpophalangeal joints (MCPs) of RA and OA patients (n=9 each) undergoing joint replacement surgery. SF were obtained also from front paws, ankles and knees of wildtype (wt) and TNF transgenic (TNFtg) mice (n=7 each). Total RNA was extracted and RNA sequencing was performed with the Illumina HiSeq 2000 sequencing system following by hierarchical clustering. Functional annotation clustering of mRNAs was done using Database for Annotation, Visualization, and Integrated Discovery (DAVID). Positionally expressed RNAs were validated by qPCR.

Results: Unsupervised hierarchical cluster analysis showed clustering of SF according to anatomic joint localization rather than disease. The positional embryonic Hox code was retained in SF, clearly differentiating between different joints. Among the Hox cluster residing long noncoding RNAs, HOTTIP was expressed in distal, MCP-derived SF and HOTAIR in posterior, knee-derived SF. Several positionaly expressed mRNAs, e.g.HOXA8 and HOXD13, were differentially expressed in MCP-derived RA and OA SF. DAVID analysis showed positional enrichment of G0TERM limb development, anterior/posterior patterning, cartilage development, extraradicular region part, cell adhesion, regulation of transcription. While some outliers were found when clustering was based on mRNA expression, clustering of SF into knee, shoulder and MCPs was perfect when based on miR expression. For example, miR-24 was positionally expressed in shoulder, miR-34c in MCP, and miR-137 in knee-derived SF, irrespective of disease. The positional expression of these miRs was confirmed in wt and TNFtg mice. Interestingly, miR-171 and miR-146a were positionally expressed in MCPs of OA, but not of RA patients. These miRs were indeed positional also in wt mice but their MCP specific expression in humans correlated to ankle specific expression in wt mice. In addition, their expression was significantly changed in ankles of TNFtg compared to wt mice.

Conclusion: SF from joints of different anatomic sites exhibit particularly different miRNA and miR expression patterns suggesting that functionally unique subsets of SF populate different joints. The existence of positionally imprinted “risk” signatures of SF may account for the susceptibility of certain synovial joints to develop RA in humans and mice and may have major implications for synovial disease pathways operating early in RA.

Disclosure: C. Ospelet, IMI BTCure, EuroTEAM, IAR, CABMM start-up grant, 2; M. Armaka, None; G. Russo, None; A. Bratus, None; M. Trenkmann, None; E. Krouzakis, IMI BTCure, EuroTEAM, IAR, 2; C. Kolling, None; R. E. Gay, None; G. Kollias, None; S. Gay, None; M. Frank Bertocci, IMI BTCure, EuroTEAM, IAR, CABMM start-up grant, 2.

2786


Background/Purpose: Idiopathic aortitis is a rare diagnosis that may occur in the context of a primary systemic vasculitis, as part of a systemic autoimmune disease, or in isolation. In patients with focal isolated aortitis...
FIA), surgery alone may be curative; however, new vascular lesions have been reported to develop in between 5-47% of cases. The risk of progression to systemic disease and optimal management strategy for FIA patients is uncertain.

**Methods:** Patients with biopsy-proven aortitis, diagnosed following thoracic aortic surgery at the Cleveland Clinic between 1996 and 2012, were retrospectively reviewed. Patients were classified into clinical subgroups [Giant cell arteritis (GCA), Takayasu’s arteritis (TAK), Focal Isolated Aortitis (FIA) or Other] at the time of surgery using pre-defined criteria. Symptoms, laboratory and imaging results were recorded at surgery and over time using a standardized database. Patients with FIA at surgery were followed for progression to systemic disease and outcomes of clinical subgroups were compared.

**Results:** Of 7,551 patients who underwent thoracic aortic surgery between 1996–2012, 196 patients with biopsy-proven aortitis were identified for review. Median age at surgery was 69 years (range 15–88) and 67% were female. At the time of surgery, 129 (65.8%) patients met criteria for FIA, 42 (21.4%) for GCA, 14 (7.1%) for TAK, and 11 (5.6%) for Other. A minimum of 6 months of clinical follow-up was available for 73 FIA patients. During follow-up (median 45 months, range 6–201 months), 1473 (19.2%) FIA patients developed symptoms of systemic disease, 17/40 (42.5%) developed elevated inflammatory markers, 29/65 (44.6%) developed new vascular lesions on imaging, 30/73 (41.1%) required a second vascular surgery, 7/15 (46.7%) dissected and 9 died (12.3%). Ultimately 23 of 73 (31.5%) with FIA progressed to have features of a systemic disease: 21 GCA, 1 TAK, and 1 Other. When compared to patients with known systemic disease at surgery, patients with FIA were less likely to develop symptoms (p=0.01) but no different with respect to development of elevated inflammatory markers (p=0.19), new vascular lesions by imaging (p=0.92), need for further vascular surgery (p=0.84), dissection (p=0.40) or death (p=0.76) over time. Only 12 patients without symptoms at surgery received immunosuppressive therapy post-operatively. Over time, 0/11 treated FIA patients with follow-up imaging developed aneurysms, but 2 (18.2%) developed new stenoses. Among the 54 untreated FIA patients with imaging available, 27 (50%) developed new vascular lesions (23 aneurysms and 5 stenoses.) A additional tissue obtained after subsequent surgery in 2 untreated FIA patients revealed persistent inflammation in the distal aorta.

**Conclusion:** Over time, nearly one third of patients classified as FIA at the time of surgery progressed to have features of a systemic autoimmune disease. Patients with FIA are less likely to develop overt symptoms, but equally likely to develop elevated inflammatory markers or new vascular lesions on imaging when compared to GCA, TAK and Others. These patients require regular clinical follow-up and serial imaging to assess for progression.

**Disclosure:** A. Clifford, None; A. Arafat, None; J. I. de Reuck, None; E. Roselli, None; C. D. Tan, None; E. R. Rodriguez, None; L. Svensson, None; E. Blackstone, None; G. S. Hoffman, None.

**ACR Concurrent Abstract Session**

**Tuesday, November 18, 2014, 2:30 PM–4:00 PM**

**2787**

**Identification of Urinary Biomarkers for Lupus Nephritis.** Carolina Landolt-Marticorena1, Stephanie Prokop2, Heather Reich3, J. Idrees, None; C. Avila-Casado2, Paul R. Fortin4, Paul Boutros5 and Joan Wither, None.

**Background/Setting:** The California Lupus Surveillance Project (CLSP) is a population-based registry designed to determine the incidence and prevalence of SLE in San Francisco County, California. Sources of cases included hospitals, rheumatologists, nephrologists, commercial laboratories, and state population databases. Over 15,000 potential SLE patients were identified after the initial queries, and trained abstractors performed detailed medical chart reviews on the 5,500 patients who met the catchment criteria of residence in San Francisco County within the years of 2007–2009. Cases were defined as patients with documentation of ≥ 4/11 of the ACR Classification Criteria for SLE. Using SAS 9.3, we calculated prevalence and incidence rates and associated 95% confidence intervals (CI) and denominators for all rates were obtained from the U.S. Census data (revised 2007). Preliminary estimates of prevalence and incidence of systemic lupus erythematosus (SLE) in the United States have varied widely.

**Methods:** The CLSP is a population-based registry designed to determine the incidence and prevalence of SLE in the United States. The California Lupus Surveillance Project (CLSP) is part of a national effort funded by the Centers for Disease Control and Prevention (CDC) to develop more credible estimates of incidence and prevalence of SLE, with a special focus on Hispanics and Asians.

**Background/Setting:** The CLSP is a population-based registry designed to determine the incidence and prevalence of SLE in the United States. The California Lupus Surveillance Project (CLSP) is part of a national effort funded by the Centers for Disease Control and Prevention (CDC) to develop more credible estimates of incidence and prevalence of SLE, with a special focus on Hispanics and Asians.

**Results:** Preliminary overall crude prevalence and incidence of SLE in San Francisco County were 90.4/100,000 and 5.1/100,000 respectively. The highest prevalence of disease was observed in Black women (430.6/100,000), followed by Hispanic and Asian (163.8/100,000 and 158.9/100,000, respectively), and White (111.3/100,000) women (Table I).
Table I: Preliminary Prevalence and Incidence Rates (per 100,000) of SLE in San Francisco County, CA

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># cases</td>
<td>Crude rate (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>704</td>
<td>90.4 (84.9-97.3)</td>
</tr>
<tr>
<td>Women</td>
<td>623</td>
<td>86.0 (149.8-175.2)</td>
</tr>
<tr>
<td>Men</td>
<td>81</td>
<td>20.6 (16.5-25.5)</td>
</tr>
<tr>
<td>Black</td>
<td>138</td>
<td>240.5 (205.7-287.0)</td>
</tr>
<tr>
<td>Women</td>
<td>121</td>
<td>360.5 (305.5-514.2)</td>
</tr>
<tr>
<td>Men</td>
<td>17</td>
<td>59.2 (37.0-94.9)</td>
</tr>
<tr>
<td>White</td>
<td>285</td>
<td>58.1 (31.4-66.7)</td>
</tr>
<tr>
<td>Women</td>
<td>233</td>
<td>158.9 (139.8-180.7)</td>
</tr>
<tr>
<td>Men</td>
<td>25</td>
<td>58.1 (51.4-65.7)</td>
</tr>
<tr>
<td>Men</td>
<td>81</td>
<td>20.6 (16.5-25.5)</td>
</tr>
<tr>
<td>Women</td>
<td>623</td>
<td>162.0 (149.8-175.2)</td>
</tr>
<tr>
<td>Men</td>
<td>25</td>
<td>10.8 (7.3-15.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>264</td>
<td>95.9 (84.9-108.1)</td>
</tr>
<tr>
<td>Women</td>
<td>233</td>
<td>158.9 (139.8-180.7)</td>
</tr>
<tr>
<td>Men</td>
<td>31</td>
<td>24.0 (16.9-34.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>99</td>
<td>87.7 (72.1-106.8)</td>
</tr>
<tr>
<td>Women</td>
<td>255</td>
<td>163.8 (132.9-202.0)</td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>9.8 (6.0-15.9)</td>
</tr>
</tbody>
</table>

Conclusion: The CLSP uses more complete case finding methods to provide current estimates of prevalence and incidence in a racially and ethnically diverse population. Racial and ethnic disparities in SLE were confirmed with the highest burden of disease in Black women, followed by Hispanic and Asians, and, finally, White women.

Disclosure: M. Dall’era None; K. Snipes None; M. Cisternas None; C. Gordon None; C. G. Hémick None.

2789 Medical Marijuana Related Outcomes in Patients with Systemic Lupus Erythematosus. Basmah Jalil1, Wilmer Sibbit Jr2, Romy Cabacanguan3, Clifford Qualls4, Arthur Bankhurst5 and Roderick Fields3. 1University of New Mexico, Albuquerque, NM, 2University of New Mexico HSC, Albuquerque, NM, 3UNM, Albuquerque, NM, 4University of NM Med Ctr, Albuquerque, NM, 5University of New Mexico School of Medicine, Albuquerque, NM.

Background/Purpose: Medical cannabis is used extensively in the United States, usually in the form of smoked marijuana. There is growing research regarding the immunomodulatory effects of cannabinoids and the cannabinoid receptor system as a possible therapeutic target. Despite the increasing use of medical marijuana, almost all studies report short-term subjective effects of medical cannabis with little to no real outcome data in medical disease and systemic lupus erythematosus (SLE) in particular. Randomized, controlled trials of smoked cannabis are generally considered ethically problematic. This study determined whether cannabis was associated with important outcomes in SLE, including mortality and morbidity.

Methods: This is an analysis of a prospective de-identified 5 year longitudinal outcome study of a cohort of SLE patients at the University of New Mexico with a sample size of 276 patients with 30.4% using marijuana and 69.5% with no marijuana use. All patients had signed informed consent, but additional IRB approval was obtained prior to analyzing the de-identified database in relation to cannabis. Inclusion criteria were any patient with SLE, age 18-80. Exclusion criteria were any patient with a diagnosis other than SLE, age < 18 years, age > 80 years. The population sample was diverse and included all social and ethnic backgrounds, with Hispanics and Whites being the dominant participants. This analysis was supported by the University of New Mexico.

Results: 27 patients underwent CMR: mean age 32.4 years, 82% female, 44% black, mean SLEDAI-2K 10.1, 10.4. All CMLD subjects had 2 or more mid cardiac segments with elevated T2 signal (Table 2). The mean T2 signal for mid cardiac segments was elevated compared to 40 historical healthy controls (57.0 ms vs. 5 vs. 54.5 ms ± 2.2; p = 0.010) The mean LV circumferential strain was −15.2% ± 5.4 which is lower than accepted normal values (−20%). SLEDAI-2K scores positively correlated with mean mid cardiac T2 signal (r = 0.57); and mid cardiac maximum T2 signal (r = 0.65). Only 1/27 (7%) patients had positive LGE.

Conclusion: In this cohort of active SLE patients CMR with quantitative T2 mapping identified a high prevalence (44%) of patients with abnormal T2 signal in ≥2 mid cardiac segments, suggesting subclinical myocardial inflammation which may be common in SLE flare. Both mean and mid segment T2 showed correlation with SLE disease activity measured by SLEDAI scores. Mean LV circumferential strain was lower than normal, suggesting impaired LV function. Very few CMR showed evidence of myocardial fibrosis as measured by LGE enhancement. Further study is needed to determine if abnormal quantitative T2 mapping during SLE flare foreshadows longer term CV complications.

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.4 ± 9.7</td>
<td>32 (82%)</td>
</tr>
<tr>
<td>Female</td>
<td>Black/White/Other</td>
<td>44.1% (15%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>9 (33%)</td>
<td></td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>9 (33%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker, no. (%)</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td>Anti-phospholipid antibody positive, no. (%)</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td>Anti-phospholipid antibody syndrome, no. (%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

1/27 patients had a 2-κ score, mean ± SD 10.4 ± 6.3
SLICC Damage Index, mean ± SD 0.5 ± 0.77
Tropin I, mean ± ng/mL 0.057 ± 0.009
CK, mean ± SD, U/L 146.8 ± 500.6
C-reactive protein ± mg/L 25.6 ± 16.1

S1218
Table 2: CMR Findings in Patients with Active SLE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted Hazard Ratio(95% CI)</th>
<th>Adjusted Hazard Ratio(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar year</td>
<td>0.98 (0.94, 1.02)</td>
<td>0.99 (0.94, 1.03)</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.06, 1.11)</td>
<td>1.09 (1.06, 1.12)</td>
</tr>
<tr>
<td>Male</td>
<td>2.52 (1.10, 5.77)</td>
<td>1.43 (0.39, 5.45)</td>
</tr>
<tr>
<td>White</td>
<td>2.52 (0.98, 6.44)</td>
<td>1.72 (0.64, 4.58)</td>
</tr>
<tr>
<td>Smoking ever</td>
<td>4.71 (2.04, 10.99)</td>
<td>4.07 (1.74, 9.49)</td>
</tr>
<tr>
<td>Steroids ever</td>
<td>0.76 (0.34, 1.70)</td>
<td>0.53 (0.14, 1.94)</td>
</tr>
<tr>
<td>Cumulative steroid 3.5 gm</td>
<td>1.15 (0.56, 2.38)</td>
<td>1.78 (0.55, 5.78)</td>
</tr>
<tr>
<td>Azathioprine ever</td>
<td>0.65 (0.29, 1.48)</td>
<td>0.45 (0.10, 2.10)</td>
</tr>
<tr>
<td>Azathioprine use &gt;1 year</td>
<td>0.87 (0.32, 2.34)</td>
<td>2.41 (0.37, 15.8)</td>
</tr>
<tr>
<td>Methotrexate ever</td>
<td>0.58 (0.17, 1.96)</td>
<td>1.13 (0.29, 4.49)</td>
</tr>
<tr>
<td>Meclophenolate ever</td>
<td>0.34 (0.05, 2.50)</td>
<td>0.74 (0.09, 5.86)</td>
</tr>
<tr>
<td>NSAIDS ever</td>
<td>0.30 (0.22, 1.14)</td>
<td>0.46 (0.19, 1.16)</td>
</tr>
<tr>
<td>Activity top quartile</td>
<td>1.58 (0.76, 3.31)</td>
<td>1.81 (0.90, 3.63)</td>
</tr>
</tbody>
</table>

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Lung Cancer in SLE. Sasha Bernatsky1, Rosalind Ramsey-Goldman2, Michelle Petri3, Murray B. Urowitz4, Dafna D. Gladman5, Edward H. Yelin6, Christine Peschken7, John G. Hanly8, James E. Hansen9, Jean-Francois Boivin10, Lawrence Joseph11, Patrice Christian Raymer12, Maruganka Kale13, Ann E. Clarke14, Systemic Lupus International Collaborating Clinics (SLICC)15. 1McGill University, Montreal, QC, 2Northwestern University, Chicago, IL, 3Johns Hopkins University School of Medicine, Baltimore, MD, 4University of Calgary, Calgary, AB, 5Mcgill University Health Centre, Montreal, QC, 6University of Manitoba, Winnipeg, MB, 7Dalhousie University and Capital Health, Halifax, NS, 8Yale University, New Haven, CT, 9McGill University Health Centre, Montreal, QC, 10RI-McGill Univ Hlth Ctr, Montreal, QC, 11University of Calgary, Calgary, AB, 12Systemic Lupus International Collaborating Clinics (SLICC), ON.

Background/Purpose: Lung cancer is 50% more common in SLE patients than their sex and age-matched counterparts. Our objective was to assess lung cancer risk in SLE, comparing demographics, drug exposures, and disease activity.

Methods: We used data from a very large multi-site international SLE cohort; this preliminary analysis is based on 6 centres: Halifax, Toronto, Montreal, Winnipeg, San Francisco, Baltimore. We used Cox proportional hazards regression to calculate the hazard ratio (HR) for lung cancer risk in SLE, relative to smoking, demographics (sex, age, race/ethnicity and time-dependent drug exposures and cumulative disease activity (based on adjusted mean SLEDAI-2K scores, assessed at baseline and annually). The adjusted mean SLEDAI score was assessed both as a continuous variable and (to aid in interpretation) and categorical. Time zero for the observation interval was the SLE diagnosis, so that our analyses adjusted for SLE duration. We included observation time and lung cancer events occurring after entry into the lupus cohort and up to the time of cohort exit (death, cancer, or date of last visits). Those developing a cancer other than lung during the interval, were censored at that time.

Results: Within the cohort (N=2791), 34 lung cancers (7 male, 27 female) occurred. Versus SLE controls without cancer, lung cancer cases tended to be white (85.3% versus 63.3% in controls), and older at cohort entry (mean 52.3 years, median 52.9; versus mean 38.4, median 36.9 in controls). Among lung cancer cases 61.8% had high disease activity (highest SLEDAI quartile) at baseline (95% CI 43.6, 77.8), in contrast to only 40.1% (95% CI 38.6, 41.5) of SLE patients that went on to remain free of lung cancer. The vast majority (78.8), in contrast to only 40.1% (95% CI 38.6, 41.5) of SLE patients that went on to remain free of lung cancer. The vast majority (78.8, p=0.001) of the lung cancer cases in SLE were ever-smokers, versus 40.7% of the SLE patients who did not develop lung cancer. The drug profiles seemed similar (in terms of steroids, immunomodulators, NSAIDs) in the SLE patients who developed lung cancer versus those who did not (though of note, none had been exposed to cyclophosphamide prior to a lung cancer). In both univariate and multivariate models, the principal factors associated with lung cancer risk were ever smoking and age. The adjusted analyses did suggest a trend for greater cancer risk in SLE patients with higher cumulative disease activity over time (HR 1.81, 90.9, 3.63) although the CI included the null value. The estimated adjusted effects of all drugs were relatively imprecise.

Conclusion: There was a trend for greater cancer risk in SLE patients with higher cumulative disease activity over time, although we saw no definite adverse effects of drugs on lung cancer risk in SLE. In particular we did not note prior cyclophosphamide exposure in the lung cancer cases. However, drug estimates were relatively imprecise. Smoking appears to be the most significant modifiable risk factor for lung cancer in SLE.

A CR Concurrent Abstract Session

Biology and Pathology of Bone and Joint In: Bone Remodeling in Inflammation and Arthritis

Tuesday, November 18, 2014, 2:30 PM–4:00 PM

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Methotrexate Prevents Inflammatory Osteolysis By Activation of the Adenosine a2a Receptor (A2AR). Aranzazu Mediero1, Tuere Wilder2 and Bruce N. Cronstein3. 1NYU School of Medicine, New York, NY, 2NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Prior studies demonstrate that adenosine, acting at A2AR, mediates the anti-inflammatory effects of methotrexate (MTX) in models of both acute and chronic inflammation. We have previously reported that adenosine A2AR ligations diminishes wear particle-driven osteolysis. We asked whether MTX treatment could prevent bone resorption due to inflammatory osteolysis.

Methods: MTX (1mg/kg) was administered intraperitoneally to C57Bl/6 mice on a weekly basis starting 2 weeks prior to surgery. Control mice were injected with 0.9% saline. In mice midline sagittal incisions were made over calvaria in 6–8 wk old C57Bl/6 mice. Calvaria were exposed to 20μg of PUL containing 3μg of UHMWPE followed by daily injections of either vehicle (Control and MTX) or ZM241385 1μM (A2AR antagonist) (n=5 each) for 14 days. Xenolight Rediject Bone Probe was injected IV and fluorescence of calvaria measured (IVIS) to assay bone formation. MicroCT and immunohistochemistry for osteoclast and osteoblast markers were performed.

Results: XenoLight imaging revealed an 80±10% increase in bone formation after exposure to MTX when compared to UHMWPE alone (p<0.001, n=5) and ZM241385 completely reversed this effect (11±5% increase vs. control, p=NS, n=5). MicroCT analysis revealed increased porosity in particle-exposed mice that was inhibited by MTX treatment (54±6% decreased compared to saline treatment, p<0.001, n=5) an effect abrogated by ZM241385. MTX significantly increased bone volumnetotal volume (BV/TV) (5.94±0.1 vs 8.68±0.2, p<0.05, BV (5.31±0.3 vs 4.15±0.2, p<0.05, TV: 5.09±0.2 vs 3.76±0.2, p<0.001) and Bone Mineral Density (BMD) (153.75±0.4 vs 144.63±1, p<0.001) when compared to WT, and ZM241385 completely reversed this effect. Histological examination of particle-exposed mouse calvarias demonstrated an inflammatory infiltrate on the bone surface that was significantly reduced by MTX and treatment with ZM241385 completely reversed this effect.

Conclusion: These results indicate that treatment with MTX, a well-tolerated and commonly used anti-inflammatory drug, may provide a novel therapeutic approach to enhance orthopedic implant survival, delaying or eliminating the need for revision arthroplasty surgery.
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BM2 Requires TGF-Beta to Induce Osteophytes during Experimental Osteoarthritis. Esmeralda Blaney Davidson1, Arjan Blom2, Arjan van Caam2, Elly Vitters1, Miranda Bennis1, Wim van den Berg2, Fons de Loo3 and Peter van der Kraan1. 1Radboud university medical center, Nijmegen, Netherlands; 2Radboud University Medical Center, Nijmegen, Netherlands; 3Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Osteophytes are a major hallmark of osteoarthritis (OA). Both TGF-beta and BMP2 can induce osteophytes in murine knee joints. We demonstrated that TGF-beta could induce chondrogenesis in mesenchymal stem cells when BMPs were inhibited but not vice versa. This suggested that BMP2 might require a trigger like TGF-beta to induce initial stages of chondrogenesis. Therefore, we investigated whether BMP2 was still able to induce osteophyte formation in experimental OA when TGF-beta activity was blocked.

Methods: We made a unique transgenic mouse (Col2a1-rtTA-BMP2) expressing BMP2 under control of the Col2a1 promoter, only when exposed to doxycycline (dox) which results in only chondrocytes producing BMP2. These mice were fed dox-food up to 8 weeks to investigate BMP2 effects on osteophyte formation. We induced the DMM-model and investigated whether BMP2 augmented osteophyte formation. We combined the DMM-model with intra-articular injection of an adeno-virus overexpressing TGF-beta-inhibitor LAP with or without dox. Knee joints were isolated 4 weeks after DMM for histology.

Results: There was no significant difference in osteophyte formation between dox and non-dox treated Col2a1-rtTA-BMP2 mice. However, dox treatment increased the number of osteophytes (8.0) during DMM compared to DMM non-dox (4.25). These "new" osteophytes were larger than DMM-induced osteophytes. The lack of osteophytes by dox compared to BMP2 no longer augmented the number of osteophytes during DMM. Strikingly, inhibition of TGF-beta significantly reduced the pace of osteophyte formation. This was completely abolished by the presence of BMP2 restoring the speed of osteophyte formation and maturation.

Conclusion: Our data show that BMP2 is capable of inducing osteophyte formation, but is dependent on an additional trigger to achieve this, as present in OA. In OA conditions, BMP2 can severely aggravate osteophyte formation, both in number and size. However, when TGF-beta is blocked BMP2 is no longer capable of aggravating osteophyte formation during DMM. Strikingly, early inhibition of TGF-beta during OA impared the speed of osteophyte formation, which could be compensated by the presence of BMP2.

Our data show for the first time that BMP2 is dependent on TGF-beta to induce de novo osteophyte formation. This provides novel insight into the mechanism behind osteophyte formation and provides clues for future therapeutic application for osteophyte formation in OA.

Disclosure: E. Blaney Davidson, None; A. Blom, None; A. van Caam, None; E. Vitters, None; M. Bennis, None; W. van den Berg, None; F. de Loo, None; P. van der Kraan, None.

2794

Deletion of the Inhibitory Receptor Motif, ITIM, on DC-STAMP Alters Osteoclast Differentiation and Function. Yahui Grace Chiu2, Edward M. Schwartz2, Dongle Li1, Yuxin Xu1, Minsoo Kim1 and Christopher T. Ritchlin1. 1University of Rochester, Rochester, NY; 2University of Rochester Medical Center, Rochester, NY.

Background/Purpose: DC-STAMP (Dendritic Cell-Specific Transmembrane Protein), a β-transmembrane protein essential for cell-to-cell fusion during osteoclast (OC) differentiation, is expressed on the cell surface of OC precursors (OCP). DC-STAMP knock-out (KO) mice form only mononuclear OC and have mild osteopetrosis due to the absence of functional multinucleated OC with bone erosion activity. Previously, we identified an immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) on the cytoplasmic tail of DC-STAMP, which suggested the potential role of DC-STAMP in signaling during osteoclastogenesis. A major hurdle in DC-STAMP research, however, is the absence of a known ligand. To overcome this barrier, we engineered DC-STAMP:rhodopsin chimeric molecules that can be activated by light (photo-activatable). This approach enabled us to investigate the downstream events of DC-STAMP activation, and examine the importance and function of the ITIM in osteoclastogenesis.

Methods: DNA constructs were generated in which the four extracellular domains of DC-STAMP were replaced with the photo-activatable extracellular domains of rhodopsin. The functionality of two DC-STAMP chimeras (WT: original ITIM; TD: ITIM-deleted) was confirmed by: (1) activation of a calcium signal by 505-nm light, a wavelength that specifically excites rhodopsin; and (2) expression of mCherry protein (red), which was fused to the C'-terminus of DC-STAMP during engineering. These 2 chimeras were transfected into either murine 293T cells, or mouse bone marrow-derived macrophages (BMM) isolated from the DC-STAMP KO mice. To assess the role of the ITIM in signaling, we assessed the dynamic intracellular Ca2+ flux known to occur during normal osteoclastogenesis between the WT and TD transfected cells. Bone erosion was assessed by the bone wafer assay.

Results: The studies with the transfected chimeric molecules revealed the following. First, deletion of ITIM on DC-STAMP resulted in a significant and continuous (non-pulsatile) elevation (3-fold > WT DC-STAMP) in the intracellular Ca2+ level after light activation. Second, ITIM-deleted DC-STAMP did not complement the deficiency of cell-cell fusion in DC-STAMP KO cells, which was fully corrected and restored by the WT DC-STAMP. Most cells expressing ITIM-deleted DC-STAMP were unable to fuse, although rare cells with 3 nuclei were observed. Third, in contrast to an even distribution of wild-type DC-STAMP on the cell surface, ITIM-deleted DC-STAMP was expressed on the cell surface in a clustered and punctate distribution fashion. Fourth, bone resorption decreased in cells expressing TD compared to WT DC-STAMP.

Conclusion: Our results suggest that the ITIM on the cytoplasmic tail of DC-STAMP functions (1) to induce pulsatile intracellular Ca2+ flux required for osteoclastogenesis after DC-STAMP activation; (2) to trigger cell-to-cell fusion between OCPs and form multinucleated mature OC; (3) to maintain an even distribution of DC-STAMP on the cell surface; (4) to support bone erosion activity of OC. Blocking the ITIM on DC-STAMP by targeted inhibition might serve as a novel strategy to inhibit pathologic bone resorption by OC in inflammatory and metabolic bone disorders.

Disclosure: Y. G. Chiu, None; E. M. Schwartz, Johnson & Johnson, 5, NIAMS-NIH, 2; D. Li, None; Y. Xu, None; M. Kim, None; C. T. Ritchlin, Eli Lilly and Company, 9, Eli Lilly and Company, 5.

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Blockade of IL-6R Signaling by Sarilumab Suppressed Circulating Markers of Bone Resorption and Synovial Damage in Rheumatoid Arthritis Patients from a Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study. Anita Boyapati1, Jennifer K. M. Teoh1, Emanuella Cousin2, Ling Ca3, Janet van Aalsberg1, Jennifer D Hamilton2, Neil Graham1, Tanya M om Tahanen1 and Stefano Fiore2. 1Regeneron Pharmaceuticals, Inc., Tarrytown, NY; 2Sanofi R&D, France, Chilly-Mazarin, France; 3Sanofi R&D, China, Beijing, China; 4Sanofi, Bridgewater, NJ.

Disclosure: Y. G. Chiu, None; E. M. Schwartz, Johnson & Johnson, 5, NIAMS-NIH, 2; D. Li, None; Y. Xu, None; M. Kim, None; C. T. Ritchlin, Eli Lilly and Company, 9, Eli Lilly and Company, 5.
Background/Purpose: Rheumatoid arthritis (RA) patients develop bone and joint damage due to chronic inflammation mediated by critical cytokines, eg, IL-6. Pre-clinical studies have implicated IL-6 signaling in regulation of osteoclasts and fibroblast-like synoviocytes (FLS) to increase levels of bone resorptive molecules like receptor activated NF kB ligand (RANKL) and joint destructive proteins, such as matrix metalloproteinases (MMPs). Blockade of IL-6R signaling by sarilumab significantly reduced structural damage in RA patients, as measured by the modified van der Heijde total Sharp Score, including the erosion score and joint space narrowing components in the Phase 3 part of the MOBILITY study (NCT01671363). Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids. To elucidate mechanisms of clinical reduction of bone and joint damage by sarilumab, we evaluated a panel of serum markers associated with bone resorption (RANKL and osteoprotegerin [OPG]), bone turnover (CTX-1 and C1M), osteoblast formation (osteocalcin [OC]), synovium (MMP-3 and C3M) and cartilage degradation (C2M) in patients enrolled in MOBILITY B. Methods: Sera were analyzed from 128 patients treated with placebo (Pbo) + methotrexate (MTX), and 131 patients receiving subcutaneous 200 mg sarilumab every other week (q2w) + MTX. Serum biomarkers levels were measured by ELISA. All biomarkers were analyzed at baseline and post-treatment at Wks 2 and 24, with the exceptions of C2M and OC, which were analyzed at baseline, Wks 24 and 52 post-treatment. A mixed effect model with repeated measures on % change from baseline (after rank transformation) was performed for all biomarkers (ANOVA-type method). Tests were compared at each visit. For samples above the limit of quantitation (LOQ), the LOQ was used in analyses, for samples below the LOQ, half the LOQ was used. Results: Sarilumab + MTX treatment significantly reduced levels of MMP-3 and MMP generated fragments of collagen type 1 and type 3 (C1M and C3M) compared to Pbo + MTX at all timepoints analyzed (Table). RA RANKL levels were also reduced at Wk 24 in the sarilumab + MTX group, however, approximately 15% of values were above the LOQ. In contrast, C2M increased from baseline in the sarilumab 200 mg q2w + MTX group compared to Pbo + MTX but did not reach significance (Wk 52, p = 0.0571). Conclusion: Sarilumab reduced bone resorption and joint damage markers, and increased OC, a marker of bone formation, in RA patients. This is the first report that IL-6 inhibition leads to RANKL reduction in RA patients. This data supports a mechanism whereby increased IL-6 signaling promotes structural damage through osteoclasts and FLS and by reducing osteoblast bone formation. Disclosure: A. Boyapati, Regeneron Pharmaceuticals, Inc, 3, Regeneron Pharmaceuticals, Inc, 1, J. Mshida, Sanofi R&D, 3, Sanofi, R&D, 1, E. Cousin, Sanofi, R&D, 1, Sanofi R&D; 1, L. Cal, Sanofi R&D, 3, J. van Adelsberg, Regeneron Pharmaceuticals, Inc, 3, Regeneron Pharmaceuticals, Inc, 1, J. D. Hamilton, Regeneron Pharmaceuticals, Inc, 1, Regeneron Pharmaceuticals, Inc, 3, N. Graham, Regeneron, 1, Regeneron, 1, T. Montalbani, Sanofi, 1, Sanofi, 3, S. Fiore, Sanofi, 3, Sanofi, 1.

2797 Anti-Citrullinated Proteins Antibodies Promotes Osteoclastogenesis and Bone Destruction in Rheumatoid Arthritis. A Kilian Krishnamurthy1, Vijay Joshua1, Heidy Wahanna2, Caia Cerqueira2, Lars Klaren2, Vivianne Malmström2, Jimmy Y Teberberg2 and Ana C Alattina2. 1Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden; 2Karolinska Institute, Stockholm, Sweden, 3Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Presence of anti-citrullinated protein antibodies (ACPA) is a major risk factor for bone erosion in rheumatoid arthritis (RA) and antibodies against modified citrullinated vimentin induce osteoclast (OC) formation from monocytes. Besides monocytes, dendritic cells (DC) are potential osteoclast precursors that may be aimed to further characterize DC derived osteoclastogenesis and to explore the effect of pooled and individual monoclonal ACPA on this pathway. Methods: ACPA positive and negative IgGs were isolated from synovial fluid (SF, n = 26) and peripheral blood (PB, n = 38) samples of RA patients. CD14+ monocytes from PB of ACPA+ RA patients and healthy individuals were first cultured in the presence of GM-CSF and IL-4 to generate DC or M-CSF to generate M-0, and then further differentiated to OC in the presence of RANKL and M-CSF. In parallel, cells were grown on osteoassay surfaces and bone resorption area was quantified by computer assisted image analysis. In house generated anti-citrullinated monoclonal antibodies obtained from SF B-cells were also tested. Cytokines were measured by cytokometric bead arrays in cultures supernatants. Mass spectrometry analysis was performed on different stages of differentiation of DC derived OC. Immunohistochemistry (IHC) was used to stain the OCs with biotinylated ACPA IgG and monoclonal anti-citrullinated proteins antibodies. The effect of PAD inhibition (C1.amidine) and IL-8 inhibition was tested in the osteoclasts cultures. Results: SF derived ACPA's enhanced osteoclastogenesis and bone resorption from both DC (fold increase of 1.6±0.2 for osteoclasts number and 2.0±0.3 for bone resorption area) and M-0 (fold increase of 1.6±0.4 for osteoclasts number and 2.0±0.8 for bone resorption area) of healthy donors. Similar effect was observed when the precursor cells were derived from ACPA+ RA patients in both DC (fold increase of 2.3±0.9 for osteoclasts number and 2.6±0.1 for bone resorption area) and M-0 (fold increase of 1.8±0.6 for osteoclasts number and 2.3±0.7 for bone resorption) assays. PB
derived ACPAs were equally effective with SF ACPAs. Principal component analysis confirmed distinct proteomic profiles during osteoclasts maturation from DC and Mφ, respectively. Vimentin significantly increased during DC-OC maturation, with citrullinated vimentin peptides detectable in mature osteoclasts. Increased osteoclastogenesis was associated with significantly higher levels of IL-8 levels in cultures supernatants of both DC (fold increase of 2.4±0.5) and Mφ (fold increase of 2.0±0.5). Two of the tested anti-citrullinated monoclonal antibodies had similar effects, while a third one had no such effect. Fab fragments of these monoclonal antibodies retained similar effects. Binding of these antibodies on OC was confirmed using IHC. Both PAD activity and IL-8 appear to be required for ACPA effects.

Conclusion: SF and PB derived ACPA IgGs with broad specificities enhanced osteoclastogenesis from both DC and Mφ. This effect appears to be restricted to certain ACPAs specificities and at least partially mediated through a Fab mediated mechanism.

Disclosure: A. Krishnamurthy, None; V. Josha, None; H. Wåhåmaa, None; C. Cerqueira, None; L. Klareskog, None; V. Malimstrom, None; J. Ytterberg, None; A. I. Catrina, None.

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The Differential Impact of Obesity on the Pathogenesis of RA or Preclinical Models is Contingent on the Disease Status. Zhenlong Chen1, Seung-jae Kim2, Abdul Essani3, Michael V. Volin4, Suncica Volkov3, William Swedler1, Shiva Arami1, Giamila Fantuzzi1, Nadera J. Swiezi1 and Shiva Shahraha1. 1University of Illinois at Chicago, Chicago, IL, 2Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL.

Background/Purpose: Studies were performed to determine the significance of obesity in the pathogenesis of rheumatoid arthritis (RA) and experimental arthritides models.

Methods: Chronic and acute preclinical models of arthritis were utilized to examine the impact of obesity on different disease stages. Inflammatory mediators were identified in the adipose tissue of mice with obesity and arthritis using ELISA. Role of IL-8/MIP2 was investigated in disease onset employing neutrophil chemotaxis. RA and mouse myeloid cells as well as ankle joints from preclinical arthritis models were utilized to assess the importance of proinflammatory M1 macrophage differentiation in disease remission using real-time RT-PCR, histology and Western blotting.

Results: We document that early onset of collagen induced arthritis (CIA) was impaired by high fat diet (HFD) on days 26, 28 and 30 post onset compared to mice fed with regular diet (RD). To elucidate the mechanism by which obesity affects the early stage of RA, inflammatory factors were quantified in adipose condition media extracted from RA synovial tissue and obese mouse gonadal adipose tissue. We uncovered that a great number of neutrophil (CXCL1, CXCL5 and IL-8/MIP2) and monocyte chemokine attractants (TNF-a, IL-17, IL-1β, CCL2) are present in RA and mouse adipose condition media, however levels of IL-8/MIP2 exceeded all other factors. We found that early arthritis exacerbated by obesity is due to elevated IL-8/MIP2 protein levels in the obese joint, as blockade of IL-8/MIP2 dysregulates neutrophil chemokinesis in response to RA and mouse adipose media, in contrast, neutralization of CXCL1 and CXCL5 was ineffective in this process. To elucidate the effect of obesity on arthritis progression, we chose to utilize the TLR4 induced arthritis model. We found that in the first 48h, TLR4 driven joint inflammation progresses similarly in obese and lean mice. Thereafter while arthritis resolves in the lean mice, ankle swelling is sustained in the obese mice at 72h post LPS injection. Histological studies confirm that mice on HFD have markedly greater joint inflammation and lining thickness compared to RD group. Corroborating with the higher levels of monocyte chemoattractants detected in the obese mice (TNF-a, IL-17, CCL20 and IL-6), joint myeloid cell recruitment was potentiated in the HFD arthritic mice compared to RD group. To better understand how obesity prolongs arthritis, joint myeloid cell phenotype was evaluated in the obese and the lean arthritic mice. We show that the obese arthritic mice, predominately express iNOS+ M1 macrophages, while inOS+ cells are reduced and Arginase++ M2 macrophages are strongly expressed in the lean mice. Consistently, employing RA and mouse adipose condition media we show that RA or mouse naive cells can be transformed into M1 macrophages. Hence, our result exhibit that obesity can sustain arthritis by reprogramming the newly recruited joint myeloid cells into proinflammation M1 macrophages.

Conclusion: We show for the first time that early and late RA is impacted by obesity through differential mechanism of function.

Disclosure: Z. Chen, None; S. J. Kim, None; A. Essani, None; M. V. Volin, None; S. Volkov, None; W. Swedler, None; S. Arami, None; G. Fantuzzi, None; N. J. Swiezi, None; S. Shahraha, None.

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Background/Purpose: Studies have been performed to determine the role of angiogenesis in the pathogenesis of psoriatic arthritis (PsA) and inflammatory arthritis.

Methods: We document that early arthritis exacerbated by obesity is due to elevated IL-8/MIP2 protein levels in the obese joint, as blockade of IL-8/MIP2 dysregulates neutrophil chemokinesis in response to RA and mouse adipose media, in contrast, neutralization of CXCL1 and CXCL5 was ineffective in this process. To elucidate the effect of obesity on arthritis progression, we chose to utilize the TLR4 induced arthritis model. We found that in the first 48h, TLR4 driven joint inflammation progresses similarly in obese and lean mice. Thereafter while arthritis resolves in the lean mice, ankle swelling is sustained in the obese mice at 72h post LPS injection. Histological studies confirm that mice on HFD have markedly greater joint inflammation and lining thickness compared to RD group. Corroborating with the higher levels of monocyte chemoattractants detected in the obese mice (TNF-a, IL-17, CCL20 and IL-6), joint myeloid cell recruitment was potentiated in the HFD arthritic mice compared to RD group. To better understand how obesity prolongs arthritis, joint myeloid cell phenotype was evaluated in the obese and the lean arthritic mice. We show that the obese arthritic mice, predominately express iNOS+ M1 macrophages, while inOS+ cells are reduced and Arginase++ M2 macrophages are strongly expressed in the lean mice. Consistently, employing RA and mouse adipose condition media we show that RA or mouse naive cells can be transformed into M1 macrophages. Hence, our result exhibit that obesity can sustain arthritis by reprogramming the newly recruited joint myeloid cells into proinflammation M1 macrophages.

Conclusion: We show for the first time that early and late RA is impacted by obesity through differential mechanism of function.

Disclosure: Z. Chen, None; S. J. Kim, None; A. Essani, None; M. V. Volin, None; S. Volkov, None; W. Swedler, None; S. Arami, None; G. Fantuzzi, None; N. J. Swiezi, None; S. Shahraha, None.

A CR Concurrent Abstract Session

Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis I

Tuesday, November 18, 2014, 2:30 PM–4:00 PM
**Background/Purpose:** Psoriatic Arthritis (PsA) is a common, chronic immune-mediated inflammatory disease, characterised by synovitis, progressive destruction of articular cartilage/bone, and is associated with psoriasis. Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT), a critical signalling pathway involved in inflammatory mechanisms, has been implicated in the pathogenesis of PsA. This study was to examine the mechanistic effect of Tofacitinib (a novel JAK inhibitor CP-690,550) on pro-inflammatory pathways using ex vivo and in vivo models of PsA.

**Methods:** PsA whole tissue synovial explants cultures were established from PsA biopsies obtained under direct visualisation at arthroscopy. This explant model maintains the architecture and cell-cell contact of the synovial tissue, spontaneously releases pro-inflammatory mediators and therefore closely reflects the in vivo inflamed microenvironment. Primary PsA synovial fibroblasts (PsASFC) were also isolated from PsA synovial biopsies. Phospho-STAT-3 (p-STAT3), phospho-STAT1 (p-STAT1), Suppressor of Cytokine Signal (SOCS3) and Protein Inhibitor of Activated STAT 3 (PIAS3) expression were quantified by Western Blot in PsA synovial explants and PsASFC following culture with Tofacitinib (1µM) or vehicle control. Cytokine expression of IL-6, IL-8 and IL-10 in ex vivo culture synovial explants in response to Tofacitinib (0.5µM-1µM) were assessed by ELISA. Furthermore, the effect of Tofacitinib (0.5µM-1µM) on PsASFC migration, invasion, matrigel network formation and MMP2/9 were quantified by wound repair assays, transwell invasion chambers and zymography.

**Results:** Tofacitinib significantly decreased p-STAT3 and p-STAT1 expression in PsA synovial tissue explants cultures ex vivo and in primary PsASFC (p<0.05). In contrast Tofacitinib induced SOCS3 and PIAS3 expression in both models (p<0.05). In parallel Tofacitinib significantly decreased spontaneous secretion of IL-6 (p<0.05), IL-8 (p<0.05) and induced IL-10 (p<0.05) expression in PsA explant cultures. Functional IL-38 was decreased by siRNA-mediated knockdown of NIK in EC as compared to the non-targeting siRNA controls. LT and LIGHT induced sprout formation was significantly decreased by siRNA-mediated knockdown of NIK in EC as compared to the non-targeting siRNA controls.

**Conclusion:** This is the first study to demonstrate Jak/STAT signaling and the effect of Tofacitinib on these pathways in PsA synovial tissue and primary PsA synovial fibroblasts. Tofacitinib mediated specific JAK-STAT signaling components, inhibited key pro-inflammatory cytokines and invasion/migrational mechanisms. Thus this data further supports the use of JAK-STAT inhibition as a potential therapeutic agent for the treatment of PsA.

**Disclosure:** W. Gao, None; J. McCormick, None; C. Orr, None; M. Connolly, None; U. Feareon, None; D. J. Valese, Abbvie, 2; MSD, 2; Pfizer Inc., 2; Roche, 2; Pfizer, 5; Roche, 5; Abbott, 8; MSD, 8; Pfizer, 8; Roche, 8.

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**Background/Purpose:** Non-Canonical NF-kappab Signaling Promotes Angiogenesis in a Novel 3D Spheroid Model of Rheumatoid Arthritis Synovial Inflammation. Christisa X. Maracle1, Boy Helder1, Aei-Ri Noort1, Corine van der Horst2, and Sander W. Tas2.1Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; 2Athenogene BV, Amsterdam, Netherlands.

**Methods:** We developed a novel 3 dimensional (3D) model in which human umbilical cord vein EC and RA SFSF were labeled with green or orange cell tracker dye, respectively, and incubated overnight to form spheroids. Subsequently, the spheroids were harvested and plated in collagen solution, and medium with or without lymphotixin α1β2 (LT) or LIGHT (both stimuli that induce non-canonical NF-κB signaling via the lymphotixin beta receptor (LTβR)) or pro-angiogenic growth factors (bFGF/VEGF) was added. After 48 hours, spheroids were fixed and imaged through confocal microscopy. Cumulative EC sprout number and the number of sprouts was quantified using Leica QWin Plus software. To demonstrate NIK dependency of this process, EC were transfected with non-targeting or NIK targeting siRNA before incorporation into the model and subsequent sprout formation was quantified.

**Results:** Confocal analysis of the 3D model showed spheroids containing HUVEC and RA SFSF formed sprouts under all conditions. Both LT and LIGHT caused significant increases in cumulative sprout length (p<0.05). Interestingly, the total number of sprouts formed by each spheroid also increased significantly. LT and LIGHT induced sprout formation was significantly decreased by siRNA-mediated knockdown of NIK in EC as compared to the non-targeting siRNA controls.

**Conclusion:** Our novel 3D model demonstrates that activation of the non-canonical pathway induces angiogenesis in spheroids of EC and RA SFSF and that this process is strictly NIK dependent. This suggests that NIK targeting therapeutic might be able to reduce pathological angiogenesis in synovial inflammation and possibly halt disease progression. Further studies to test this, including the use of small molecule pharmacological NIK inhibitors, are currently underway. Of interest, the current 3D model is also optimized to include different subsets of immune cells in order to study their contributions to inflammation-induced angiogenesis, which makes this model a valuable tool for future studies.
**Methotrexate Impacts the Effects of Tofacitinib, but Not Tocilizumab, on Clinically Relevant Biomarkers in Human Primary Cell-Based BioMAP® Disease Models: Can We Utilize in Vitro Models to Predict Clinical Outcomes?**

Alison O'Mahony, Ellen L. Berg, Xitong Li, Markus R. John, Kandeepan Ganeshalingam, and Ernest H. Choy.

**Background/Purpose:** A number of trials have shown that adding MTX benefits some, but not all, biologies and small molecules to treat RA. Specifically, though treatment of RA with an anti-TNF + MTX has been shown to be more beneficial than with the biologic alone, the same was not consistently observed with tocilizumab (TCZ) + MTX. Thus, it remains a challenge to determine whether cotreatment with MTX is a better option for patients. We have previously reported that BioMAP activities detected with TCZ alone were highly similar to those of TCZ + MTX, whereas the effects of adalimumab (ADA) alone differed from those of ADA + MTX. Here we evaluate whether MTX alters the pattern of BioMAP activities of tofacitinib (TOF) in order to predict whether the effects of this drug can be modulated by cotreatment with MTX.

**Methods:** Human primary cell-based BioMAP disease models were used to generate phenotypic activity profiles for compounds alone and in combination with MTX at concentrations that cover their clinical Cmax ranges. TCZ, 200 mg/mL; TOF, 11 μM; TOF, 0.12 μM; MTX, 10 μM. Agents and combinations were tested under standard and soluble interleukin-6 receptor-stimulated conditions. Changes in protein-based, clinically relevant end points (biomarkers) and proliferation were evaluated by t-test and other statistical methods to determine whether activities of the combinations differed from those of the individual agents.

**Results:** Several activities detected with TOF + MTX or TOF + MTX were statistically significantly different (p < 0.01) from those of TOF or TOF profiled alone. Cytokine and chemokine levels (M-CSF, G-CSF), inflammation markers (VCAM-1, E-selectin, and IP-10), and tissue-remodeling activities (thrombomodulin and PAI-1) were all modulated differently by TOF + MTX vs TOF alone. In contrast, the profile of TCZ + MTX was not significantly different from that of TCZ alone, with only MTX-mediated antiproliferative effects on endothelial cells (3C) and B cells (BT) contributing to the pattern of TCZ activities.

**Conclusion:** These data show that though TCZ has diverse effects on inflammatory responses, cotreatment with MTX elicits few additional activities and does not impact TCZ effects. In contrast, TOF + MTX impacts immune function, inflammation markers, and matrix-remodeling end points in human primary cell disease models differently than does TOF or MTX alone. The pharmacodynamic interactions between TCZ and MTX in BioMAP are significantly less pronounced than those between TOF and MTX. These data are consistent with the comparable efficacy of TCZ, monotherapy, and combination therapy seen in some clinical trials and in real life and suggest that TOF could be more beneficial in combination with MTX.

**References:**
5. EULAR 2014 SAT025.
6. EULAR 2014 THU026.

IgG4-RD. All patients had biopsy-proven disease and 75 were on no immunosuppression at the time of evaluation yet had active disease. Clinical and laboratory data were extracted from the electronic medical record. An IgG4-RD responder index score > 3 defined active disease. Serum IgG4 concentrations were determined by nephelometry after serial dilution to prevent the prozone effect. Circulating plasmablasts and SLAMF7+ CD4+ T cells were measured by flow cytometry.

**Results:** The average ages at evaluation and disease onset were 55 years (range: 24–83) and 49.9 years (range: 12–82), respectively. The majority of patients were white (75%) and male (63%); the mean number of organs affected was 2.8 (range 1–7). The most commonly involved organs were the submandibular glands, orbit, lymph nodes, pancreas, and retroperitoneum; fifty-five patients had sustained permanent damage due to IgG4-RD (Table 1).

Forty-seven patients had received glucocorticoid therapy and all had had either failed treatment or required ongoing treatment to maintain disease control. Only 38 (53%) of the 75 patients on no treatment at baseline had an elevated serum IgG4 concentration. Elevated serum IgG4 levels correlated with an inflammatory phenotype (increased acute phase reactants) and multi-organ disease. Regardless of the serum IgG4 concentrations, patients had elevated levels of circulating SLAMF7+ CD4+ T cells and plasmablasts. Male patients had a higher average serum IgG4 concentration (597 mg/dL versus 233 mg/dL; P = 0.03) but neither the proportion with an elevated baseline value nor the number of organs involved differed. Patients with renal disease, lymphadenopathy, and retroperitoneal fibrosis represented distinctive subtypes on the basis of complement levels, serum IgG4 concentrations, number of organs involved, and inflammatory markers.

**Conclusion:** We report the baseline features of our first 100 patients with biopsy-proven IgG4-RD. The majority of the patients were on no treatment at the initial assessment, permitting insights into the pre-treatment features of IgG4-RD. Our study stands in contrast to all IgG4-RD publications to date as this is the first study to describe the clinical and laboratory features of a large, diverse cohort with IgG4-RD.

**Table 1:** Organ Involvement and Damage

<table>
<thead>
<tr>
<th>Organ Involvement</th>
<th># of Cases</th>
<th># of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>3</td>
<td>Aorta</td>
</tr>
<tr>
<td>Orbit</td>
<td>25</td>
<td>Heart</td>
</tr>
<tr>
<td>Parotid</td>
<td>15</td>
<td>Retropertoneal fibrosis</td>
</tr>
<tr>
<td>Submandibular</td>
<td>29</td>
<td>Sclerosis mediatinits</td>
</tr>
<tr>
<td>Mastoid</td>
<td>1</td>
<td>Sclerosis mesenteritis</td>
</tr>
<tr>
<td>Nasal Cavity</td>
<td>2</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Sinusits</td>
<td>5</td>
<td>Liver</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>1</td>
<td>Bile duct</td>
</tr>
<tr>
<td>Other ENT</td>
<td>6</td>
<td>Gallbladder</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>Skin</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>24</td>
<td>Prostate</td>
</tr>
<tr>
<td>Lung</td>
<td>16</td>
<td>Other</td>
</tr>
<tr>
<td>Kidney</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>3</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Nasal Septum</td>
<td>2</td>
<td>Kidney</td>
</tr>
<tr>
<td>Submandibular Gland</td>
<td>9</td>
<td>Lung</td>
</tr>
<tr>
<td>Sinus</td>
<td>4</td>
<td>Ureter</td>
</tr>
<tr>
<td>Palate</td>
<td>2</td>
<td>Vascular/SVC</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>Chronic Pain</td>
</tr>
<tr>
<td>Aorta</td>
<td>2</td>
<td>Coronary</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

**2806**

Characteristic Phenotype of Peripheral Blood Lymphocytes in Patients with IgG4-Related Disease, Comparing to Primary Sjögren Syndrome and Healthy Controls. Shintaro Hirata, Shingo Nakayamada, Satoshi Kubo, Makio Yoshiyukawa, Naoki Yoneue, Kazuhisa Nakano, Kunihiro Yamaoka, Kazuyoshi Saito and Yoshika Tanaka. University of Occupational and Environmental Health, Japan; Kitakyushu, Japan.

**Background/Purpose:** IgG4-related disease (IgG4-RD) is a systemic disease that is characterized by the infiltration of IgG4-positive plasma cells and T cells into various organs. However, the characteristic and pathological role of immune cell subsets remains unclear. We have characterized peripheral blood immune cell subsets in patients with IgG4-RD by comparing with patients with primary Sjögren syndrome (pSS) and healthy controls (HC).

**Methods:** PBMC Cs were obtained from 8 IgG4-RD and 4 pSS patients as well as from 8 HC. The phenotype of immune cells was analyzed by 8-color staining flow cytometry. T helper cells were categorized as naive, central memory, effector memory and effector T cells by expression of CCR7 and CD45RA. B cells were categorized as naive IgM memory, switched memory, B cell and plasmablast (PB) by expression of CD19, CD27 and CD38. DCs were categorized as myeloid and plasmacytid DC by expression of CD11c and CD123. The proportion of immune cell subsets was assessed with correlations with serological parameters, including serum IgG, IgG4, and CRP.

**Results:** Baseline characteristics of patients with IgG4-RD (mean ± SD) were: age 56 ± 20 year, symptom duration 16.3 ± 19.2 months, serum IgG4 628 ± 549 mg/dl, CRP 1.3 ± 2.6 mg/dl, respectively. There was no difference in the proportion of T helper cells (Th1, Th2, Th17, Treg), B cells or DC subsets between IgG4-RD, and pSS, HC. CD3+CD4+CXCR5+CD45RA-Th cells were significantly higher in IgG4-RD than HC (p = 0.033). In contrast, the proportion of CD3+CD4+CCR7-CD45RA+ effector T cells and CD19+CD27+CD20-CD38- plasmablasts significantly increased in IgG4-RD compared to pSS and HC (p values: 0.008 and 0.013, respectively). Importantly, the proportion of CD3+CD4+CCR7-CD45RA+ effector T helper cells was strongly correlated with the ratio of serum IgG4/IgG ratio (rho = 0.90, p = 0.002), whereas it was not with that of plasmablasts (rho = 0.17, p = 0.67).

**Conclusion:** These results revealed that the higher proportion of effector T cells including Th1 cells and the increase of plasmablasts possibly induced by Th1 are characteristically observed in IgG4-RD, but not in pSS. Moreover, serum IgG4/IgG ratio was strongly correlated with ratio of effector memory T cells, but not plasmablasts. Taken together, IgG4 overproduction may be conducted by matured effector phase helper T cells, suggesting a pivotal role of effector phase T cells in pathogenesis of IgG4-RD, especially in IgG4 specific production. Further studies are required to elucidate the detailed role of effector phase T cells in the pathogenesis of IgG4-RD.
Background/Purpose: Staphylococcus aureus is the most common cause of adult septic arthritis and the incidence of methicillin-resistant Staphylococcus aureus (MRSA) infections continues to rise. There is a relative lack of information on clinical presentations and outcomes in MRSA septic arthritis and how it differs from methicillin-sensitive Staphylococcus aureus (MSSA) septic arthritis. Our aim was to evaluate the differences in clinical features and outcomes between patients with MRSA and MSSA septic arthritis.

Methods: This is a retrospective chart review study performed at a tertiary-referral level hospital. We queried the electronic database for patients with a discharge diagnosis of pyogenic arthritis between Jan 1st 2000 and Dec 31st 2013. We only included native joint septic arthritis. We collected data on patient demographics, clinical information, and patient outcomes. Statistical analysis was performed using SPSS statistics 20.0. The institutional review board at Texas Tech University approved this study.

Results: We identified 274 patients with native joint septic arthritis. Staphylococcus aureus caused 122 cases. MRSA caused septic arthritis in 45 patients; MSSA caused septic arthritis in 77 patients. Patient characteristics, clinical features and outcomes of MRSA septic arthritis patients and MSSA septic arthritis patients are summarized in Table 1. MRSA and MSSA septic arthritis occurs predominantly in males. There were no differences between the two groups in mean age. MRSA septic arthritis patients had more comorbidities than MSSA septic arthritis patients. There were no statistically significant differences in the initial clinical presentation between both groups (fever, leukocytosis, presence of bacteremia, polyarticular involvement, mean WBC count on synovial analysis). Only 77.8% of MRSA patients were treated initially for MRSA. The MRSA septic arthritis patients had a higher mean number of joint surgeries and longer hospital lengths of stay. They also had worse patient and joint outcome and higher rates of development of osteomyelitis adjacent to the joint.

Conclusion: We recorded a significant number of MRSA septic arthritis cases from the year 2000 to 2013. MRSA septic arthritis affects patients with multiple comorbidities and is associated with worse outcomes. Only 77.8% of MRSA septic arthritis patients were treated empirically for MRSA on initial presentation. Since MRSA is an emerging clinical entity in septic arthritis, rheumatologists have to consider this pathogen in patients with septic arthritis and more research is needed to improve patient outcomes.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>M SSA</th>
<th>MRSA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>61/77 (79.2%)</td>
<td>31/45 (68.9%)</td>
<td>0.201</td>
</tr>
<tr>
<td>Age, mean (SD)*</td>
<td>46.68 (22.6)</td>
<td>44.78 (21.0)</td>
<td>0.647</td>
</tr>
<tr>
<td>Number of comorbidities, mean (SD)*</td>
<td>1.2 (2.3)</td>
<td>1.2 (2.6)</td>
<td>0.882</td>
</tr>
<tr>
<td>One or less than 1 co morbidity</td>
<td>39/77 (50.6%)</td>
<td>14/45 (31.1%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Pre-existing joint disease</td>
<td>7/77 (9.1%)</td>
<td>5/45 (11.1%)</td>
<td>0.758</td>
</tr>
<tr>
<td>Fever (&gt;100 °F)</td>
<td>21/77 (27.6)</td>
<td>16/45 (35.6)</td>
<td>0.347</td>
</tr>
<tr>
<td>Male WBC count on presentation(10^3/L)</td>
<td>13900 (6980)</td>
<td>13615 (4147)</td>
<td>0.853</td>
</tr>
<tr>
<td>Male ESR (mm/hr)</td>
<td>79.7 (33.2)</td>
<td>83.6 (30.5)</td>
<td>0.543</td>
</tr>
<tr>
<td>Male joint WBC on presentation (10^3/mm^3)</td>
<td>95461 (6978)</td>
<td>104784 (62579)</td>
<td>0.508</td>
</tr>
<tr>
<td>Polyarticular involvement</td>
<td>5/77 (6.5%)</td>
<td>4/45 (8.9%)</td>
<td>0.724</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>25/77 (32.5%)</td>
<td>33/45 (73.3%)</td>
<td>0.080</td>
</tr>
<tr>
<td>A appropriate empiric coverage for MRSA</td>
<td>41/77 (53.2%)</td>
<td>34/45 (75.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean number of weeks of antibiotics treatment (SD)</td>
<td>5.1 (2.8)</td>
<td>5.0 (3.3)</td>
<td>0.172</td>
</tr>
<tr>
<td>Mean number of joint surgeries (SD)</td>
<td>2.0 (1.3)</td>
<td>2.6 (1.7)</td>
<td>0.035</td>
</tr>
<tr>
<td>Mean number of admission days (SD)</td>
<td>10.2 (7.2)</td>
<td>16.2 (8.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3/77 (9.1%)</td>
<td>14/45 (31.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Poor patient outcome</td>
<td>7/77 (9.1%)</td>
<td>14/45 (31.1%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Poor joint outcome</td>
<td>1/77 (1.5%)</td>
<td>15/45 (33.3%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Development of osteomyelitis</td>
<td>8/77 (10.4%)</td>
<td>13/45 (28.9%)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Disclosures: D. Panikkath, None; S. Y. Lim, None; S. Gadwala, None; R. Panikkath, None; K. Nugent, None.

2808 WITHDRAWN

2809 Human Papilloma Virus and Chlamydia Trachomatis Infections in Rheumatoid Arthritis Under Anti-TNF Therapy. Mariana G Waisberg1, None; C. A. Silva1, None; P. B. Medeiros1, None; M. C. Beldi1, None; M. Tacla2, None; H. H. Caiaffa-Filho1, None; E. Bonfá, FAPESP 2009/51897-5, CNPq 301411/2009-3 and Federico Foundation, 2; C. A. Silva, FAPESP 2009/51897-5, CNPq 302724/2011-7 and Federico Foundation, 2.

ACR Concurrent Abstract Session Rheumatoid Arthritis - Clinical Aspects V: Mortality and Other Outcomes Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2810 Reduced Mortality Risk in Rheumatoid Arthritis: Findings from Two UK Inception Cohorts. Sam Norton1, Elena Nikolichporou1, Lewis Carpenter1, David Walsh2, Patrick Kielty2, Josh Dixey2 and A dam Y young2, 1King’s College London, London, United Kingdom, 2University of Hertfordshire, Hatfield, United Kingdom, 3University of Nottingham, Nottingham, United Kingdom, 4St. Georges Healthcare NHS Trust, London, United Kingdom, 5New Cross Hospital, Wolverhampton, United Kingdom, 6ERAS, St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is associated with a 20 to 30% increased risk of mortality from all-causes compared to the general population. The aim of the present study is to examine whether, as observed in the general population, mortality rates in RA have decreased over the past 25 years. Furthermore, to assess whether changes are due to a potentially milder disease at presentation or change in treatment practise.

Methods: Data from 32 centres in the UK that recruited 2763 patients to two inception cohorts between 1986 and 2012 were combined for the analysis: Early RA Study and Early RA Network. Both recruited DMARD naïve patients at presentation to the rheumatology clinic. Death certificates were provided by the NHS central register. All-cause mortality was standard against population rates (stratified by age, sex and calendar year) to examine whether excess mortality risk had changed over time. Pooled logistic survival models estimated the relative yearly reduction in mortality hazard. M arginal structural modelling was used to examine the effect on methotrexate on survival, adjusting for confounding by indication of the treatment effect.

Complications, in spite of a few case reports of HPV infection in chronic inflammatory arthritis and psoriasis under this therapy. Therefore, the purpose of our study was to evaluate HPV and CT infections in RA patients pre- and 6 months post-TNF blocker. The possible associations among these infections, demographic data, sexual function, disease parameters and treatment were also analyzed.

Methods: Fifty female RA patients (ACR criteria), who were eligible to anti-TNF therapy, (n=50 at baseline (BL) and n=45 after 6 months of treatment (M6)) and 50 age-matched healthy controls were prospectively enrolled. All RA patients and controls had previous sexual activity. Exclusion criteria were: current pregnancy, early post-partum period, diabetes mellitus, psychiatric diseases and cervical cancer. They were assessed for demographic data, gynecological, sexual, cervical cytology and histological evaluations, disease parameters and current treatment. HPV DNA and CT DNA testing in cervical specimens were done using Hybrid Capture II assays.

Results: At BL, the median current age of RA patients and controls was 49 (18–74) years vs. 49 (18–74) years, p=0.1. A trend of lower frequency of HPV infection was observed in AR patients pre anti-TNF compared to controls (14% vs. 30%, p=0.054). None of patients had genital warts. Further evaluation of AR patients with and without HPV infection before anti-TNF therapy showed that the former group had a higher frequency of sexual intercourse (100% vs. 48%, p=0.014), higher median number of sexual partners (11±1 vs. 0.001, p=0.032) and higher frequency of abnormal cervical cytology (45% vs. 7%, p=0.029). Current age, disease duration, physician and patient visual analogue scales, DAS 28, ESR, CRP and treatments were alike in both groups (p>0.05). At M6 after TNF blockade, HPV infection remained unchanged in five patients, whereas two became negative and one additional patient turn out to be positive (MCN'emar's test p=1.0). None of them had cervical cancer in Pap smear. CT infection was uniformly negative in RA patients pre- and post-TNF blockade and in controls.

Conclusion: To our knowledge, this was the first study to assess prospectively genital infections in RA patients under TNF blockage therapy. Anti-TNF does not seem to increase short-term risk or severity of HPV and CT infections in RA patients.
Results: The excess mortality risk in RA compared to the general population reduced over time. Restricting the analysis to deaths within 10 years of onset, for ERA5 (recruitment 1986 to 2001) the all-cause standardised mortality ratio (SMR) was significantly increased (1.21; 95%CI 1.10 to 1.34), whereas for ERAN (recruitment 2002 to 2012) it was non-significant (1.04; 95%CI 0.88 to 1.22). The difference between SMR’s for the two cohorts was non-significant. Combining the two cohorts, year of symptom onset was significantly associated with all-cause mortality risk (HR = 0.96, p<0.001; 95%CI 0.95 to 0.96). Controlling for demographic and clinical features at baseline did not reduce the magnitude of the effect for year of onset (HR = 0.95, p<0.001; 95%CI 0.93 to 0.97). Extending the model to control for treatment using a marginal structural modelling approach, the use of methotrexate (use of which increased dramatically over the period of recruitment) was associated with a 60% reduction in the risk of death (HR = 0.40, p<0.001; 95%CI 0.25 to 0.64). A trial controlling for methotrexate use to estimate the effect of year of onset was reduced to non-significant (Hazard ratio = 0.98, p<0.01; 95%CI 0.96 to 1.01).

Conclusion: Substantial gains in life expectancy have been observed for people with RA in the UK over the last 25 years. The excess mortality risk appears to have been greatly diminished. This is probably due to changes in treatment practice, rather than RA becoming milder at presentation.

Disclosure: S. Norton, None; E. Nikiphorou, None; L. Carpenter, None; D. Walsh, Pfizer Inc, 2; P. Kiley, None; J. Dixey, None; A. Young, None.

2011


Background/Purpose: Rheumatoid Arthritis (RA) patients commonly report reductions in fatigue after commencing Anti-TNF therapy. The mechanisms behind such reductions have not been determined, although it is assumed that changes in disease activity drive improvements. Nevertheless, to promote improvement in this patient priority, the true pathways to change in fatigue must be elucidated. Using Structural Equation Modelling (SEM), this study aimed to be the first to determine the pathways to improvement in fatigue among RA patients commencing Anti-TNF therapy.

Methods: Participants recruited to a long-term cohort study (the British Society for Rheumatology Biologics Register for RA) provided information on fatigue (SF 36 Vitality), disease activity (DAS 28) and other putative mediators of fatigue change (including disability, pain and mental health) at Anti-TNF therapy commencement and 6 month follow-up. A SEM path model, using the data of 2652 participants with high baseline fatigue (SF 36 Vitality =12.5,), was constructed employing a model generation approach. The total, direct and indirect effects of each putative mediator on improvement in fatigue were quantified using path coefficients. Where indirect effects accounted for more than 50% of total effect, the variable was considered to be mediated by other variables in the model.

Results: Significant pathways to improvement in fatigue (Figure 1) were shown to originate from changes in disease activity, pain, mental health, and disability, as well as a history of depression and participant sex. The model accounted for 40% of the variance in change in fatigue and demonstrated a good model fit ($\chi^2$ = 0.18, df=3, p=0.98). The largest absolute improvements in fatigue were associated with a one standard deviation improvement in pain and mental health (0.31 and 0.28 unit improvement in fatigue, respectively). As 82% of the total effect of change in disease activity was indirect, the variable was mediated by other variables in the model. Specifically, 50% of the indirect effect was mediated through a change in pain and an additional 14% through pain and mental health improvement.

Conclusion: Improvement in RA related fatigue after commencing Anti-TNF therapy is driven by reductions in pain, rather than directly from disease activity. In addition, mental health and disability are important mediators in the pathway to fatigue improvement and should be targeted, in an attempt to further improve this patient priority.

Disclosure: K. L. Druce, None; G. T. Jones, None; G. J. Macfarlane, None; N. Basu, Pfizer Inc, 2; Pfizer Inc, 8; Pfizer Inc, 5; MSD, 5.

2012


1 Jyväskylä Central Hospital, Jyväskylä, Finland, 2 Jyväskylä Central Hospital, Jyväskylä, Finland, 3 Tampere University Hospital, Tampere, Finland, 4 Medcare Oy, Äänekoski, Finland, 5 Jyväskylä Central Hospital, Jyväskylä, Finland, 6 Kuopio University Hospital, Kuopio, Finland, 7 Jyväskylä Central Hospital, Jyväskylä, Finland.

Background/Purpose: Rheumatoid arthritis (RA) is suggested to be a more severe disease in women than in men as disease activity appears higher in women, and men meet remission criteria more often.

Long-term severity of RA can be analyzed from permanent joint damage in radiographs. Our purpose was to study possible differences in the extent of radiographic joint damage between women and men in an early RA cohort at 10 years after diagnosis.

Methods: Our early RA cohort includes 990 patients from a single clinical diagnosis with a clinical diagnosis of early RA in 1997 – 2004. Radiographs of hands and feet were taken at a 10 year follow-up visit after diagnosis and were analyzed according to the Larsen score (0–100) including MCP I–V, wrists, and MTP II–V.

Results: Baseline characteristics of 990 patients were: the mean (SD) age 57(16) years, 67% female, 61% seropositive (RF/CCP+) and median (IQR) duration of symptoms before diagnosis 6(3, 12) months; 657(66%) patients were available for a 10 year follow up. Reasons for non-attendance among 333 patients included death (52%), high age, multi-comorbidity or institutionalization (10%), moving from the area (12%); 8% declined, 4% were lost to follow-up and 14% miscellaneous reasons. Thus, radiographs were available in 462 women and 195 men with a similar percentage of 66% being seropositive among genders. In seropositive patients, the mean (SD) Larsen score was 7.1(10) in women and 8.1(11) in men, p=0.12. The probability plot was similar for women and men (Figure 1). In seronegative patients, the mean (SD) Larsen score was 1.9(3.8) in women and 2.3(4.5) in men, p=0.29.

Conclusion: At 10 years after diagnosis, RA joint damage appears similar in both genders. RA severity is comparable between women and men.

Figure. Larsen score in seropositive women and men with early RA at 10 years after diagnosis.

Disclosure: J. Askainen, None; K. Kaarla, None; H. Mäkinen, None; H. Kauttainen, None; P. Hannonen, None; T. Ranno, None; T. Sokka, None.

Tuesday, November 18

Background/Purpose: Morning stiffness may not be specifically queried by rheumatologists in the course of their regular interactions with rheumatoid arthritis (RA) patients. This analysis investigated whether morning stiffness was correlated with measures of disease activity.

Methods: Data from the Corrona RA Registry included RA patients who initiated a new therapy: non-biologic or biologic DMARD, whether as mono-therapy or in combination, and remained on treatment for >90 days. Patients were evaluated at initiation, 1 and 2 years after initiation and time of last visit. Correlations of measures of disease activity with presence and change in morning stiffness were modeled at the patients' last Corrona visit between January 2013 and February 2014. For patients with >= one visit during this interval, propensity score (PS) trimming of the top and bottom 5% was used to obtain comparable populations with and without morning stiffness. Thus data from 90% of RA patients (5379 subjects) were utilized to examine the association of measures of disease activity: remission (CDAI <2.8); low disease activity (2.8 < CDAI < 10); moderate disease activity (10 < CDAI < 22) and high disease activity (CDAI ≥ 22) with presence/absence of morning stiffness, after PS trimming at time of last visit.

Results: At baseline those with morning stiffness (n=9688) were less likely to be working, more likely to have received biologic therapy, Medicaid insurance, and to have higher measures of disease activity than those without (n=2865): CDAI high: 34.1 vs 10.3%; remission/low: 31.6 vs 66.3%, p<0.0001. At one year after initiation of treatment, these differences persisted (with morning stiffness (n=6140) without (n=2957), including statistically significantly higher mHAQ scores: 0.5 ± 0.5 vs 0.1 ± 0.3, p<0.0001; more reporting disabled work status: 21.7 ± 5.2%, p<0.0001 and CDAI high: 21.7 ± 5.2%; remission/low: 48.0 ± 80.2%, p<0.0001. These differences persisted even after 2 years of follow-up (with morning stiffness (n=4466) without (n=1895): mHAQ scores unchanged; disabled: 29.2 vs 9.4%; CDAI high:19.3 ± 3.9% remission/low: 51.4 ± 82.0, all p<0.0001. At time of last Corrona visit, higher CDAI, mHAQ and patient reported fatigue were significantly associated with presence of morning stiffness and increased persistence of morning stiffness (Figure 1).

Conclusion: In this registry analysis, presence and persistence of morning stiffness consistently reflected higher disease activity associated with more impairment of physical function and self reported work disability.

Table. Disease activity according to DAS28 or CDAI at time of relapse according to baseline level disease activity.

Disease Activity at Time of Relapse (N = 552) *

<table>
<thead>
<tr>
<th>RA disease at baseline</th>
<th>Low (N = 257)</th>
<th>Moderate (N = 245)</th>
<th>High (N = 50)</th>
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<tr>
<td>Low (N=55)</td>
<td>26</td>
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<td>4</td>
</tr>
<tr>
<td>Moderate (N=284)</td>
<td>140</td>
<td>127</td>
<td>17</td>
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<tr>
<td>High (N=213)</td>
<td>93</td>
<td>93</td>
<td>29</td>
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</tbody>
</table>

* 30 of the 582 patients were missing information at follow up to calculate disease activity.


Time-to-Remission, Time-to-Relapse and Disease Severity at the Time of Relapse in RA - Results from the Ontario Best Practices Research Initiative (OBR1). Bindee Kuriya, Xuying Li, Binu Jacob, Pooneh Akhavan, Jessica Widdifield, Mark Tabangilo, Janet E. Pope, Edward Hadjiiski, Corrinne Dunn, Claire Bombardier, H. University of Toronto, Toronto, ON, 2University Health Network, Toronto General Research Institute, Toronto, ON, 3Early Rheumatoid Arthritis Program, Mount Sinai Hospital and University of Toronto, Toronto, ON, 4Western University, London, ON, 5Mount Sinai Hospital, University of Toronto, ON, 6Institute for Work & Health, Toronto, ON.

Background/Purpose: Clinical remission in RA is the desired goal, however the ability to sustain remission and the timing and severity of relapse is not well known. We aimed to describe time to remission, time-to-relapse and disease activity at the time of relapse.

Methods: We performed a longitudinal data analysis of patients enrolled in the Ontario Best Practices Research Initiative (OBR1), a clinical registry of RA patients followed in routine care. The prevalence of a first occurrence of clinical remission according to the DA28-ESR < 2.6 or CDAI << 2.8 following cohort entry (baseline) was determined as was the average time-to-remission. Patients achieving remission with >=1 follow-up visit (typically spaced 3 to 6 months apart) were observed for the average time until relapse, defined as a DA28 > 2.6 or CDAI > 2.8. The baseline disease activity level of those achieving remission and the disease activity level at the time of relapse was examined.

Results: The total cohort (N=2305) was 78% female with mean (SD) age 57 (17) years, disease duration 8.6 (9.6) years and mean DAS28 score 4.5 (1.5) at baseline. Remission was achieved in 1081 patients (47%): 140 of these patients had low baseline disease activity, 516 had moderate and 369 had high disease activity at baseline. The median time to remission was 279 days (interquartile range [IQR] 146 - 482) and remission was reached significantly faster among those starting with low disease activity (median 216 days, IQR 148-355) at baseline compared to more severe disease (median 357 days, IQR 173-563) (P<0.001). Nineteen hundred eighteen patients (85%) had continued follow up after remission and 582 (59%) went on to experience a relapse. The median time-to-relapse was 197 days (IQR 126-363). The majority switched from a state of remission to mild or moderate disease activity, in contrast to the moderate to severe levels of disease activity they experienced at baseline (Table). Hence the ability to sustain remission and the timing and severity of relapse is not well known. We aimed to describe time to remission, time-to-relapse and disease activity at the time of relapse.

Table. Disease activity according to DAS28 or CDAI at time of relapse according to baseline level disease activity.

<table>
<thead>
<tr>
<th>RA disease at baseline</th>
<th>Disease Activity at Time of Relapse (N = 552) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (N=55)</td>
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<td>High (N=213)</td>
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</table>

* 30 of the 582 patients were missing information at follow up to calculate disease activity.

Disclosure: B. Kuriya, None; X. Li, None; B. Jacob, None; P. Akhavan, None; J. Widdifield, None; M. Tabangilo, None; J. E. Pope, None; E. Keystone, Abbott, Amgen, AstraZeneca, BMS, F. Hoffman-La Roche, Janssen, Lilly, Novartis, Pfizer Sanofi-Aventis, UCB, 2 Abbott Laboratories, AstraZeneca, Biostest, BMS, F. Hoffman-La Roche, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, 5 Abbott, AstraZeneca, BMS Canada, F. Hoffman-La Roche, Janssen, Pfizer, UCB, Amgen, 8 C. Bombardier, None.

Better Functional Ability with Less Biologicals 2 years after Induction with Combination DMARD Therapy versus methotrexate Monotherapy. T. Martinuliu, J. J. Luime, P. H. P. de Jong, A. H. Gerards, D. van Zeven, I. Tchetverikov, P. B. J. de Sonnaville, M. van Kruigen, B. Grilliet, J. M. W. Hazez and A. E. A. Wael, 2 Erasmus University Medical Center,
Background/Purpose: To assess differences in frequency of biological therapy use and functional ability in early RA patients two years after starting induction therapy according to three different treatment regimens.

Methods: Data were used from patients with recent-onset arthritis participating in a single-blinded clinical trial (Treatment in the Rotterdam Early Arthritis Cohort (tREACH)) in which three induction therapy strategies were compared: (A1) combination therapy (methotrexate (MTX) + sulfasalazine + hydroxychloroquine) with glucocorticoids (GCs) intramuscularly; (A2) combination therapy with an oral GC tapering scheme and (B) MTX with oral GCs similar to B. As no difference in disease activity scores (DAS) was found between groups A1 and A2 at 3 and 12 months of follow-up (1), these groups were combined for this analysis (group A). Disease activity scores (original DAS) were assessed every 3 months. Functional ability was assessed using the Health assessment questionnaire (HAQ). Data were analysed using simple descriptive statistical techniques.

Results: 281 patients (91 men, 190 women; mean baseline DAS 3.3, median baseline HAQ 1.00) were initially randomized. Data on medication use at 2 years were available from 248 patients (88%), see figure 1. A1, A2 years, 24% of patients in group A versus 43% in group B were using a biological DMARD. Biological use and DAS over time are demonstrated in figure 2.

Equal mean DAS of 1.66 (95% CI 1.54–1.78) at 24 months was observed for the initial treatment groups at 24 months (group A: 1.58 (95% CI 1.43–1.73), group B: 1.80 (95% CI 1.58–2.02). DAS remission (DAS<1.6) was achieved by 55% of patients.

The median disability score (HAQ (min-max)) was 0.38 (0–2) for all patients but varied in the treatment groups: A. 0.25 (0–1.9) and B. 0.63 (0–2.1) (p=0.042).

Conclusion: We observed lower use of biological therapy and better functional ability in induction triple therapy compared to induction monotherapy MTX with GC bridging at 2 years of follow-up in the treat-to-target tREACH study. No differences were found for disease activity scores.

Biological use at 2 years

A. MTX + SASP + HCQ + GCs
24%

B. MTX + GCs
43%

DAS and biological use over time

Current users
42%

Never users
42%

Previous users
24%
2817

Histone Deacetylase One Contributes to the Auto-Aggressive Phenotype of Rheumatoid Arthritis. Sarah Hawtree1, Munita Muthana2, J. Mark Wilkinson3, Athony G. Wilson3 and M ohammed Akil4. 1University of Sheffield, Sheffield, United Kingdom, 2Rheumatology Department, Sheffield South Yorkshire, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease that affects synovial joints. A key characteristic of RA is hyperplasia of fibroblast-like synoviocytes (FLS) which develop a stable, auto-aggressive phenotype that augments tissue destruction. It is unknown how this phenotype is stably maintained, however epigenetic changes have been implicated. Histone acetylation is a major epigenetic mechanism (HDACs). The objective of the study is to determine the role of histone deacetylases (HDACs) in regulating the auto-aggressive phenotype of RA FLS.

Methods: Real-time qPCR was used to compare levels of HDAC1-11 in RA compared with osteoarthritis (OA) FLS. Joint biopsies were co-stained with anti-HDAC1 and anti-fibroblast antibodies. HDAC1 and a non-targeting control (NTC) siRNA were transfected in vitro into RA FLS. Cell proliferation, migration and invasion after siRNA knockdown (KD) were assessed by using tritiated thymidine, a scratch assay and a matrigel invasion assay respectively. An Illumina BeadChip (47,000 transcripts) was used to analyse global gene expression changes after KD. The in vivo effect of HDAC1 KD was investigated in a mouse model of collagen-induced arthritis (CIA) using in vivosRNA. Clinical scores of CIA were measured daily (days 0–49) and the bones were analysed using a microCT scanner.

Results: The mRNA levels of HDACs 1–11 are higher in RA compared to OA FLS, with HDAC1 levels showing a 4.2-fold increase (p = 0.03, n = 7–10). HDAC1 KD reduced FLS proliferation (p = 0.04, n = 6), migration (p = 0.01, n = 6) and invasion (p = 0.02, n = 6) compared to the NTC. Cluster analysis of the microarrays (n = 3) revealed significant changes in genes involved in apoptosis (p = 0.009, n = 21), migration (p = 0.008, n = 4) and proliferation (p = 0.009, n = 9). In mice with CIA, HDAC1 KD significantly inhibited joint inflammation (p = 0.001, n = 10) and reduced bone erosion compared to the NTC.

Conclusions: Our data implicates HDAC1 in controlling the autoaggressive phenotype of FLS in RA and our data in murine inflammatory arthritis supports targeting HDAC1 as a potential therapy in RA.

Disclosure: S. Hawtree, None; M. Muthana, None; J. M. Wilkinson, None; A. G. Wilson, None; M. Akil, None.

2818

SH2 Domain-Containing Phosphatase 2 Promotes Aggressiveness of Rheumatoid Fibroblast-like Synoviocytes. Stephanie M. Stanford1, Gerrman R. Aleman Muench1, Cristianos Pasciuti, Liqian Zeng2, David L. Boyle3, Gen-Sheng Feng1, Zhong-Yin Zhang1, Maripat Corr2, Gary S. Firestein3 and Nunzio Bartok4. 1La Jolla Institute for Allergy and Immunology, La Jolla, CA, 2Indiana University School of Medicine, Indianapolis, IN, 3University of California at San Diego School of Medicine, La Jolla, CA, 4University of California at San Diego Division of Biological Sciences, La Jolla, CA.

Background/Purpose: In rheumatoid arthritis (RA), fibroblast-like synoviocytes (FLS) that line joint synovial membranes aggressively invade the extracellular matrix, destroying cartilage and bone. Although this cell type mediates RA pathogenesis, it is currently untapped as a drug target. Signal transduction in FLS is mediated through multiple pathways involving protein tyrosine phosphorylation, and thus we sought to identify the protein tyrosine phosphatases (PTPs) regulating the aggressiveness of FLS from RA patients (RA FLS). We previously profiled the expression of all PTPs in FLS from RA and osteoarthritic (OA) patients, and found that the PTPN11 gene, encoding the PTP SHP-2, is upregulated in RA FLS. We previously demonstrated that SHP-2 enzymatic activity is mediated through multiple pathways involving protein tyrosine phosphorylation, and thus we sought to further explore the role of SHP-2 in mediating pathogenesis of RA.

Methods: Inhibition of SHP-2 enzymatic activity was achieved using a specific SHP-2 chemical inhibitor (Median [IQR] % maximum activity inhibition: 79 [51–95] for vehicle-treated mice and 90 [75–99] for inhibitor-treated mice; p < 0.0001 by two-way ANOVA test of 14-day arthritis course). Global inhibition of SHP-2 activity by daily administration of 7.5 mg/kg SHP-2 inhibitor also led to reduced arthritis severity (Median [IQR] change in ankle thickness after 8 days: 3.62 [3.08–3.78] for Cre−/− mice and 0.46 [0.11–1.69] for Cre+ mice; p < 0.0001 by two-way ANOVA test for 14-day arthritis course).

Conclusions: These data indicate that SHP-2 promotes the aggressiveness of RA FLS, a role that is dependent on the catalytic activity of the phosphatase. Both global inhibition and inducible deletion of SHP-2 in hematopoietic cells caused a reduction in arthritis severity, suggesting SHP-2 could be a potential target for therapy in RA.

Disclosure: S. M. Stanford, None; G. R. A. Muench, None; C. Sacchetti, None; L. Zeng, None; D. L. Boyle, None; G. S. Feng, None; Z. Y. Zhang, None; M. Corr, None; S. M. Stanford, None; L. Bottini, None.

2819

The YAP Pathway Regulates Fibroblast-like Synoviocyte Invasion. Beatrice Bartok. University of California, San Diego, La Jolla, CA.

Background/Purpose: Fibroblast-like synoviocytes (FLS) in RA possess unique transformed phenotype, such as cartilage invasion that is maintained independent of cytokines and other inflammatory cells. However, the molecular mechanisms that regulate FLS behavior in RA are poorly understood. The transcriptional coactivator YAP is associated protein (YAP) was recently shown that is dysregulated in RA compared with OA FLS. Increased YAP activity might contribute to persistent activation and pathogenic behavior of RA FLS. Therefore, we assessed role of YAP in synoviocyte invasion.

Methods: We used siRNA knock down and chemical inhibition to assess effect of YAP activation on RA FLS invasion. We used Verteporfin to inhibit YAP transcriptional activity. For siRNA knockdown, YAP and control siRNA were transfected using AMAXA technology. FLS invasion was studied using M atrigel coated transwells, 3 days following transfection. YAP inhibitor or vehicle was added to the upper chamber and PDGF was used as chemoattractant in the lower chamber. The cytoskeleton and focal adhesions were visualized and confocal microscopy using rhodamin phalloidin and anti-Vinculin staining. M MP expression was measured using qPCR.

Results: The YAP inhibitor Verteporfin significantly decreased number of invading cells in a concentration dependent manner, with 65–5% inhibition at 0.1 μM (p < 0.02, n = 3). Similar results were obtained when YAP was knocked by siRNA. Cells with reduced YAP activity displayed 52–6% (p = 0.04, n = 3) decrease in invasion through M atrigel matrix compared with scramble control. To determine effect of YAP knockdown on cell adhesion and migration in a three dimensional matrix, cells were stained with phalloidin and anti-Vinculin. RA FLS treated with the YAP inhibitor Verteporfin displayed diminished stress fiber formation and decrease in focal adhesion formation by 56–5% (p < 0.04, n = 3) visualized with confocal microscopy. Similar findings were obtained when YAP was inactivated by siRNA knock down. To determine the effect on M MP production cells were stimulated with TNF and qPCR was performed for MMP1, 2, 3, 9 and 11. MMP1 and MMP3 were significantly lower in YAP deficient cells compared with scramble control (p < 0.03 and p < 0.05, n = 3), while MMP2,9 and MT1MMP mRNA were unchanged. Similar findings were obtained using chemical inhibition with Verteporfin.

Conclusions: The YAP pathway is a major regulator of FLS invasion by modulating focal adhesion formation and M MP production. These observations, together with our previous findings that increased YAP activity in RA FLS compared with OA suggest that YAP activity might contribute to persistent activation and pathogenic behavior of RA FLS. Therefore, modulating YAP pathway might represent a novel therapeutic approach for RA.

Disclosure: B. Bartok, None.

2820

Dual Role for B Cells in Promoting Bone Erosion in Rheumatoid Arthritis Via Effects on Osteoclast and Osteoblast Differentiation. Nida Meednu, Hengwei Zhang, Teresa Owen, Liangping Xing and Jennifer H. Arolnik. University of Rochester, Rochester, NY.

Background/Purpose: In the K/BxN mouse arthritis model, we found that inducible deletion of SHP-2 in hematopoietic cells led to >50% reduction in arthritis severity (M edian [IQR] change in ankle thickness after 8 days: 3.62 [3.08–3.78] for Cre−/− mice and 0.46 [0.11–1.69] for Cre+ mice; p < 0.0001 by two-way ANOVA test for 14-day arthritis course). Global inhibition of SHP-2 activity by daily administration of 7.5 mg/kg SHP-2 inhibitor also led to reduced arthritis severity (M edian [IQR] change in ankle thickness after 8 days: 2.65 [1.81–3.27] for vehicle-treated mice and 2.14 [0.70–2.73] for inhibitor-treated mice; p < 0.01 by two-way ANOVA test for 14-day arthritis course).

Conclusions: These data indicate that SHP-2 promotes the aggressiveness of RA FLS, a role that is dependent on the catalytic activity of the phosphatase. Both global inhibition and inducible deletion of SHP-2 in hematopoietic cells caused a reduction in arthritis severity, suggesting SHP-2 could be a potential target for therapy in RA.

Disclosure: S. M. Stanford, None; G. R. A. Muench, None; C. Sacchetti, None; L. Zeng, None; D. L. Boyle, None; G. S. Feng, None; Z. Y. Zhang, None; M. Corr, None; S. M. Stanford, None; L. Bottini, None.

2820
Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease that often leads to joint damage, a process mediated by an imbalance between bone resorption and bone formation. Additional evidence implicates the role of B cells in joint destruction including the presence of B cell aggregates in RA synovium and subchondral bone and the efficacy of B cell depletion therapy in halting radiographic progression. However, B cell effects on bone have been described as mediated via indirect influences on other immune cell such as T cells. Whether B cells directly affect bone homeostasis in RA is not known. In this study we investigated the effects of B cells on osteoclast (OC) and osteoblast (OB) functions in RA.

Methods: Isolated B cells from peripheral blood of healthy controls (HC) or RA patients were stimulated with α-CD40 and PMA for 96 h, and RANKL and TNF production was assessed by flow cytometry, ELISA, and qPCR. Stimulated and un-stimulated B cells were fixed then co-cultured with hMSCs (Lonza, #PT-2501) for 24 h and the expression of OB transcription factor RUNX2 and Notch signaling molecules, Hes1 and Hey1 in hMSCs was detected by qPCR.

Results: B cells stimulated with α-CD40 and PMA produce significant amounts of RANKL as compared to un-stimulated B cells (%RANKL: 4.9 ± 0.94 vs. 0.413 ± 0.005, P < 0.0001). Stimulated RA B cells induced significantly more OC formation in comparison to HCs B cells (using the same donor for OCP) (%OC/Well: RA: 60.5 ± 7.5 vs. HC: 12 ± 7, P < 0.0001). Notably, stimulated RA B cells expressed higher RANKL than memory B cells from HC (%RANKL: 20.4 ± 1.68 vs. 11.25 ± 3.15, P < 0.05). In parallel, RA memory B cells expressed higher RANKL than memory B cells from HC (%RANKL: 10.3 ± 0.9 vs. 7.4 ± 0.5, P < 0.05). RA CD45- MSC-enriched cells isolated from peripheral blood have reduced expression of Hes1 and Hey1. In agreement with this finding, RA CD45- MSC-enriched cells significantly increased levels of Hes1 and Hey1. RA CD45- MSC-enriched cells significantly increased levels of Hes1 and Hey1. In agreement with this finding, RA CD45- MSC-enriched cells significantly increased levels of Hes1 and Hey1.

Conclusion: Our finding suggest that B cells play a critical role in promoting bone erosion in RA both by directly enhancing osteoclastogenesis and inhibiting osteoblast differentiation.

Disclosure: N. Meednu, None; H. Zhang, None; T. Owen, None; L. Xing, None; J. H. Anolik, None.
Conclusion: This second Phase 2 study demonstrates the potential benefit of inhibiting macrophage activity via the GM-CSF-R pathway on RA disease activity. The study met both co-primary endpoints with a clear dose response effect. An acceptable tolerability profile was demonstrated over the 24-week study period.


2822

Safety and Efficacy of Baricitinib through 128 Weeks in an Open-Label, Long-Term Extension Study in Patients with Rheumatoid Arthritis

Edward C. Keystone1, Peter C. Taylor2, Mark C Genovese3, Douglas E. Schlichting4, Inmaculada De La Torre5, Scott D. Beatte6 and Terence Rooney6. 1Mount Sinai Hospital, Toronto, ON, 2University of Oxford, Oxford, United Kingdom, 3Stanford University Medical Center, Palo Alto, CA, 4Eli Lilly and Company, Indianapolis, IN, 5Eli Lilly and Company, Alcobendas, Spain.

Background/Purpose: Baricitinib is an oral inhibitor of JAK1/JAK2 being investigated as a treatment for rheumatoid arthritis (RA). In a phase 2b study, baricitinib treatment resulted in significant clinical improvements over 24 wks1. The safety and efficacy findings of baricitinib treatment in RA patients (pts) up to 128 wks are reported here.

Methods: Pts were randomized to placebo (PBO) or 1, 2, 4, or 8 mg baricitinib QD for 12 wks (Part A). Pts assigned to 2, 4, or 8 mg continued assigned treatment and pts assigned to PBO or 1 mg were reassigned to 4 mg QD or 2 mg BID for an additional 12 wks of blinded treatment (Part B). Pts completing Part B were eligible to enter a 52 wk open-label extension (OLE: Wks 76–128, Part C), where pts in the 8 mg group continued to receive 8 mg QD and all other pts received 4 mg QD. During Part C, doses could be escalated to 8 mg QD at 28 or 32 wks at the investigator’s discretion when DAS 28 (CRP) > 4.4 and >=6 swollen joints were present. Pts completing Part C were eligible to enter an additional 52 wk OLE (Wks 76–128, Part D) where pts received 4 mg QD regardless of previous dose.

Results: Of 204 pts at sites participating in Part C, 201 (99%) were treated and 169 (84%) completed 52 wks. Among pts who remained on 4 mg (N = 108) in Part C, TEAEs occurred in 63%, SAEs in 16%, infections in 35%, and serious infections in 5%. A mong pts who received 8 mg at any time (N = 93) in Part C, TEAEs occurred in 68%, SAEs in 13%, infections in 40%, and serious infections in 3%. Of 150 pts at sites participating in Part D, 144 (96%) were treated and 133 (92%) completed an additional 52 wks. Among pts who remained on 4 mg (N = 79) in Part D, TEAEs occurred in 53%, SAEs in 6%, infections in 32%, and serious infections in 3%. Among pts who decreased to 4 mg (N = 65) in Part D, TEAEs occurred in 55%, SAEs in 6%, infections in 28%, and serious infections in 3%. The exposure-adjusted incidence rates for adverse events for all baricitinib groups in Part D were similar to or lower than those rates observed in Part C (Table 1). No opportunistic infections, tuberculosis cases, or lymphomas were observed through 128 wks. One death due to myocardial infarction occurred in the 8 mg group in Part C. Among all pts combined, the proportions of pts achieving ACR20 or disease improvement at Wk 24 were similar or improved at Wks 76 and 128 (Table 2).

Conclusion: Among pts completing 128 wks of a phase 2b study, clinical improvements observed at Wk 24 were maintained or improved through Wk 128. In addition, safety data collected during the OLE were consistent with previous baricitinib findings.


Table 1 Safety Summary

<table>
<thead>
<tr>
<th>Weeks 24-76 (Part C)</th>
<th>Weeks 76-128 (Part D)</th>
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<tbody>
<tr>
<td>4 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>(N=108)</td>
<td>(N=93)</td>
</tr>
<tr>
<td>All Groups (N=201)</td>
<td>All Groups (N=65)</td>
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<tr>
<td>Remaining Decreased</td>
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<td>n (%)</td>
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<td>IR</td>
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<td>68 (63)</td>
<td>63 (68)</td>
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<tr>
<td>SAEs</td>
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Table 2 Disease Improvement

<table>
<thead>
<tr>
<th></th>
<th>Wk 24*</th>
<th>Wk 76*</th>
<th>Wk 128*</th>
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<td></td>
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<td>ACR20</td>
<td>149 (74)</td>
<td>137 (68)</td>
<td>101 (70)</td>
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<td>CD40</td>
<td>34 (17)</td>
<td>38 (19)</td>
<td>31 (22)</td>
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<td>SD41</td>
<td>32 (16)</td>
<td>38 (19)</td>
<td>30 (21)</td>
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<td>DAS28 ESR &lt; 2.6</td>
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<td>44 (22)</td>
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<td>55 (27)</td>
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<td>61 (30)</td>
<td>76 (38)</td>
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<tr>
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<td>97 (48)</td>
<td>100 (50)</td>
<td>74 (51)</td>
</tr>
</tbody>
</table>

*Observed data for pts entering Part C at Wk 24

Non-response imputed for discontinuing prior to Wk 76, but not for dose-escalation

Among pts entering Part D, non-response imputed for discontinuing prior to Wk 128


2823

Comparative Efficacy of Sarilumab Plus Methotrexate in Biologic-Experienced and Biologic-Naive Patients with Moderate-to-Severe Rheumatoid Arthritis from a Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study

Roy Fleischmann1, Dennis L. Decktor2, Chunpeng Fan3, Hubert Van Hoogstraten4 and Mark C Genovese5. 1Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, TX, 2Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 3Sanofi, Bridgewater, NJ, 4Stanford University Medical Center, Palo Alto, CA.

Background/Purpose: For patients with prior exposure to tumor necrosis factor-α inhibitor (TNF-I), the likelihood of response to subsequent treatment with a TNF-I declines with the increasing number of previous treatment failures.1 Sarilumab, a fully human monoclonal antibody directed against interleukin-6R, has shown efficacy in a study of adult rheumatoid arthritis (RA) patients with moderate-to-severe disease and an inadequate response to methotrexate (MTX).2 Sarilumab’s safety and efficacy has been demonstrated at subcutaneous doses of 150 mg or 200 mg q2w + MTX. A further analysis of the clinical efficacy and safety of sarilumab in patients with/without prior biologic use (physician-reported) from this study is reported here. In the total population, 21.2% were exposed to biologics, of which 50% had received prior TNF-I.

Methods: This was a subanalysis of the ACR20 (primary efficacy endpoint) and ACR50 and ACR70 responses, reduction of DAS28-CRP, and CDAI scores in patients with/without prior biologic use in the intention-to-treat population of the Phase 3 aspect of the MOBILITY study. Patients previously nonresponsive to biologic treatment were excluded from study participation.

Results: Both doses of sarilumab resulted in a statistically significant ACR20 response at Wk 24 vs placebo (p<0.0001); ACR50 and ACR70 responses were also statistically significant at Wk 24 (Fig 1). Statistically significant improvements in DAS28-CRP reduction were observed, with mean reductions at Wk 52 of −1.85, −2.80, and −3.15 in the placebo, sarilumab 150 mg, and 200 mg q2w groups, respectively, in patients with prior use of biologics, and −1.95, −3.24, and −3.29 in biologic-naive patients (Fig 2). Similar improvements were seen in CDAI scores, with mean reductions at Wk 52 of −23.23, −28.45, and −28.81 in the placebo, sarilumab 150 mg, and 200 mg q2w groups, respectively, in patients with prior use of biologics, and −24.52, −31.35, and −30.33 in biologic-naive patients (Fig 2).

Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab
abnormalities included decreases in neutrophils and increases in transaminases and lipids.

**Conclusion:** Independent of prior use of a biologic, treatment with sarilumab resulted in clinically meaningful and statistically significant responses; given the modest number of biologic-experienced participants and the exclusion of prior non-responders, additional research is warranted.

**References**

**Figure 1.** ACR response rates at Week 24

**Figure 2.** Mean DAS28-CRP and Mean CDAI scores in prior biologic versus biologic-naive users at Week 52

**Disclosure.** R. Fleischmann, AbbVie, Amgen, Ardea, AstraZeneca, BMS, Celgene, GSK, Jansen, Eli Lilly, Merck, Pfizer, Resolve, Roche, Sanofi Aventis, UCB, 2, AbbVie, Akros, Amgen, Antares, AstraZeneca, Augurex, BMS, Celgene, Covagen, Five Prime, GSK, Ikko, Jansen, Eli Lilly, McNeil, Merck, Pfizer, Plexilcon, Resolve, Roche, Sanofi Aventis, Teva, UCB, Vertex, 5; D. L. Decktor, Regeneron Pharmaceuticals Inc., 3; Johnson & Johnson, 1; C. Fan, Sanofi, 1; Sanofi, 3; H. Van Hoogstraten, Sanofi, 3; M. C. Genovese, Eli Lilly and Company, 2, Eli Lilly and Company, 5, Sanofi, 2, Sanofi, 5, Regeneron, 2, Regeneron, 5.

**2824**

A Profile of the Efficacy of Sarilumab Plus Methotrexate in Rheumatoid Arthritis Patients: Results of a 52-Week, Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study. Arthur Kavanaugh, Dennis L. Decktor, Chunpeng Fan, Janet van Aldenburg, Renata M. Arntsvora and Mark C. Genovese; 1University of California San Diego, La Jolla, CA, 2Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 3Sanofi, Bridgewater, NJ, 5Sanofi Czech Republic, Prague, Czech Republic, 3Stanford University Medical Center, Palo Alto, CA.

**Background/Purpose** Interleukin-6 (IL-6) regulates a diverse array of activities that may underlie systemic and local symptoms of rheumatoid arthritis (RA). The efficacy of sarilumab, a fully human monoclonal antibody (mAb) directed against IL-6R, has recently been investigated in the randomized, double-blind, placebo(pbo)-controlled, multicenter, phase 3 part of the MOBILITY study. This analysis expands the profile to the entire 52-week duration of the trial.

**Methods:** Adults with active, moderate-to-severe RA and inadequate response to methotrexate (MTX) were randomized 1:1:1 to pbo + MTX, sarilumab 150 mg or 200 mg q2w + MTX for 52 wks. 3 co-primary endpoints associated with RA activity (signs & symptoms, physical function, and structural damage) were investigated: proportion of patients achieving ACR20 response at Wk 24; change from baseline in HAQ-DI at Wk 16; and change from baseline in mTSS at Wk 52. Secondary efficacy endpoints included major clinical response at Wk 52, ACR50 and ACR70 responses, reduction in DAS28-CRP, and CDAI.

**Results:** Sarilumab 150 mg and 200 mg q2w + MTX provided statistically significant, clinically meaningful improvement in all co-primary efficacy endpoints (ACR20, HAQ-DI, and mTSS) and secondary efficacy endpoints vs pbo + MTX (Table). ACR 20 response rates increased by Wk 2 and remained significantly higher in both sarilumab + MTX groups vs pbo + MTX through Wk 52 (p<0.0001). Change from baseline in the ACR core set of disease activity measures, swollen and tender joint counts, was significantly higher in the sarilumab + MTX groups vs pbo + MTX (Table). A significantly higher proportion of patients in the sarilumab + MTX groups maintained CDAI remission vs pbo + MTX (Wks 4-52; p<0.0001). DAS28-CRP scores were significantly improved vs pbo + MTX at Wks 2–52 (p<0.0001) in sarilumab + MTX–treated patients, who achieved DAS28-CRP remission at Wks 24 and 52 (Table). The proportion of HAQ-DI responders at Wks 16, 24 and 52 was significantly higher (p<0.0001) with sarilumab + MTX vs pbo + MTX at each timepoint (Table). Mean change from baseline in mTSS at Wk 52 with sarilumab + MTX was significantly higher vs pbo + MTX (Table). Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids.

**Conclusion:** These additional analyses of patients with active RA and an inadequate response to MTX showed that treatment with subcutaneous sarilumab at 150 mg and 200 mg q2w + MTX improved the full range of reported outcomes in a robust and durable manner that was maintained over this 52-week trial.

**Reference:**

**Table.** Efficacy results

<table>
<thead>
<tr>
<th></th>
<th>Placebo + MTX</th>
<th>150 mg q2w + MTX (n=499)</th>
<th>200 mg q2w + MTX (n=499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 response – Wk 24, n (%)</td>
<td>133 (33.4%)</td>
<td>232 (58.0%)*</td>
<td>265 (66.4%)*</td>
</tr>
<tr>
<td>ACR50 response – Wk 24, n (%)</td>
<td>66 (16.6%)</td>
<td>148 (37.0%)*</td>
<td>182 (45.6%)*</td>
</tr>
<tr>
<td>ACR70 response – Wk 24, n (%)</td>
<td>29 (7.3%)</td>
<td>79 (19.8%)*</td>
<td>99 (24.8%)*</td>
</tr>
<tr>
<td>mTSS, mean change from BL – Wk 52</td>
<td>2.8</td>
<td>0.9*</td>
<td>0.3*</td>
</tr>
<tr>
<td>Major clinical response (ACR70 response maintained for 24 weeks), n (%)</td>
<td>12 (3.0%)</td>
<td>51 (12.8%)*</td>
<td>59 (14.8%)*</td>
</tr>
<tr>
<td>ACR disease activity measures, adj. mean change from BL – Wk 24</td>
<td>-6.6</td>
<td>-10.6*</td>
<td>-11.2*</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>-10.1</td>
<td>-16.9*</td>
<td>-17.4*</td>
</tr>
<tr>
<td>HAQ-DI, adj. mean change from BL – Wk 24</td>
<td>-0.3</td>
<td>-0.5*</td>
<td>-0.6*</td>
</tr>
<tr>
<td>- Wk 24</td>
<td>-0.4</td>
<td>-0.6*</td>
<td>-0.6*</td>
</tr>
<tr>
<td>- Wk 52</td>
<td>-0.5</td>
<td>-0.7*</td>
<td>-0.8*</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>-1.17</td>
<td>-2.45*</td>
<td>-2.82*</td>
</tr>
<tr>
<td>LS mean change from BL – Wk 24</td>
<td>-1.36</td>
<td>-2.78*</td>
<td>-2.95*</td>
</tr>
<tr>
<td>Clinical remission – Wk 52, n (%)</td>
<td>40 (10.1%)</td>
<td>111 (27.8%)*</td>
<td>136 (34.1%)*</td>
</tr>
<tr>
<td>Clinical remission – Wk 52, n (%)</td>
<td>34 (8.5%)</td>
<td>124 (31.0%)*</td>
<td>136 (34.1%)*</td>
</tr>
</tbody>
</table>

**Tuesday, November 18**
LS mean change from BL 
-14.47  
-23.89*
-25.79*

LS mean change from BL 
-17.50  
-26.96*  
-27.26*

Remission (=2.8) - Wk 24, n (%)  
20 (5.0%)  
41 (10.3)%  
55 (13.8)%

Remission (=2.8) - Wk 52, n (%)  
19 (4.8%)  
59 (14.8)*  
72 (18.0)%

No radiographic progression at Wk 52, n (%)  
154 (38.7%)  
191 (47.8)%  
222 (55.6)%

*p = 0.0001 vs placebo + MTX; **=p = 0.0053. 3p = 0.01 vs placebo + MTX; 4score of <26; MTX, methotrexate; BL, baseline; LS, last observed; ACR 2050/70; American College of Rheumatology 20%/50%/70% improvement criteria; mTSS, van der Heijde modified total Sharp score; HAQ-DI, Health Assessment Questionnaire-Disability Index; HAQ-DI responders, >0.3 improvement in HAQ-DI from baseline; DAS28-ESR, Disease Activity Score in 28 joints using ESR; DAS28-CRP, Disease Activity Score in 28 joints using CRP; C-Reactive Protein; DAS28-CRP remission, DAS28-CRP ≤2; CDAL, Clinical Disease Activity Index; CDAL remission, CDAL ≤2.8.

Disclosure: A. Kavanaugh, Sanofi, 2; D. L. Deckert, Regeneron Pharmaceuticals, Inc., 3; Johnison & Johnson, 1; C. Fan, Sanofi, 3; Sanofi, 3; J. van Geldersberg, Regeneron Pharmaceuticals, Inc., 3; Regeneron Pharmaceuticals, Inc., 1; R. Martin-cova, Sanofi, 3; M. C. Genovese, Eli Lilly and Company, 2; Eli Lilly and Company, 5; Sarof, 2; Sanofi, 5, Regeneron, 2, Regeneron, 5.

2825
A Randomized, Double-Blind, Phase 3 Equivalence Trial Comparing the Etanercept Biosimilar, HD203, with Etanercept (Enbrel®), in Combination with Methotrexate (MTX) in Patients with Rheumatoid Arthritis (RA). Sang-Cheol Bae1; Jinsook Kim2; Jung-Yoo Choe3; Won Park4; So-Ra Lee5; Young Ahn3; and Yunjeong Seo6.

[2825]

1Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea; 2Eju National University, Jeju, Korea, South Korea; 3Catholic University of Daegu School of Medicine, Daegu, South Korea; 4Inha University Hospital, Incheon, South Korea; 5Hanwha Chemical, Seoul, South Korea; 6Hanwha Chemical, Daejeon, South Korea.

Background/Purpose: Etanercept is a recombinant fusion protein that blocks TNF activity. HD203 is a biosimilar of etanercept. In a double-blind, randomized study in healthy volunteers, HD203 and a reference etanercept were comparable with regards to pharmacokinetics, safety and tolerability. The aim of this study was to evaluate the equivalence in efficacy and to compare the safety of HD203 (biosimilar etanercept) and a reference etanercept, in combination with MTX in patients with RA. (ClinicalTrials.gov identifier NCT01270997).

Methods: Patients (male or female aged ≥20 years) with active RA were randomly assigned (1:1) to 25 mg HD203 or reference etanercept, administered subcutaneously twice weekly with MTX for 48 weeks. The primary endpoint was the proportion of patients achieving ACR20 at week 24. Secondary endpoints included ACRn, change in DAS28, and EULAR response at week 24 and 48, safety and immunogenicity. Efficacy and safety were evaluated at screening, week 0, 2, 4, 8, 12, 16, 20, and 24. Immunogenicity, efficacy and safety were also evaluated at week 36 and 48.

Results: In total, 294 patients were randomized: 147 to HD203 and 147 to reference etanercept, administered subcutaneously twice weekly with MTX for 48 weeks. The primary endpoint was the proportion of patients achieving ACR20 at week 24. Secondary endpoints included ACRn, change in DAS28, and EULAR response at week 24 and 48. ACR20 was achieved in 25% (95% CI 21.9 to 28.6) of patients receiving HD203 and 24% (95% CI 20.7 to 27.4) of patients receiving the reference etanercept. ACR20 at week 48 was higher with HD203 than with reference etanercept. There were no statistically significant differences between the groups for ACRn, change in DAS28, and EULAR response at week 24 and 48.

Table: Proportion of patients achieving ACR20 at week 24 and week 48

<table>
<thead>
<tr>
<th>HD203</th>
<th>Reference etanercept</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-week PPS</td>
<td>83.48% (95/115)</td>
<td>81.36% (96/118)</td>
<td>2.12 (-7.65,11.89)</td>
</tr>
<tr>
<td>FAS</td>
<td>78.10% (106/134)</td>
<td>79.10% (106/135)</td>
<td>1.00 (-6.45,13.45)</td>
</tr>
<tr>
<td>48-week PPS</td>
<td>86.27% (88/102)</td>
<td>85.0% (86/100)</td>
<td>1.27 (-5.57,13.04)</td>
</tr>
</tbody>
</table>

CI: confidence interval; PPS, per-protocol set; FAS, full analysis set; *Pearson’s chi-square test

A randomised, double-blind, placebo-controlled study, pts 18 years or older who met ACR criteria for RA, were not on concomitant MTX, and had active RA (defined as either CRP [***: possibility of New Font being added] >0.8 mg/dL or ESR [***: possibility of New Font being added] ≥28 mm/hr and [***: possibility of New Font being added] ≥10 tender and swollen joints) were randomized 1:1:1:1 to ASP015K 25 mg, 50 mg, 100 mg, 150 mg or PBO. Allowing concomitant DMARD therapies were anti-malarials and/or sulfasalazine. The primary endpoint was ACR20 response at week 12. Results: 289 pts (62% female mean age 53.9 years) were randomized and dosed. Approximately half the subjects (48%) were enrolled in the U.S. and the remainder from Europe (41%) and Mexico (11%). 48% had used a biologic, with 36% exposed to ≥ 2. Mean baseline values: disease duration, 10.4 y, tender joint count 25.7 (of 68), swollen joint count 16.3 (of 66), CRP 1.69 mg/dL, ESR 44.36 mm/hr, DAS28-CRP 3.83, and DAS28-ESR 6.64. A statistically significant difference was observed at week 12 when comparing ASP015K 100 mg and 150 mg with PBO. ACR50/70 responses in the two highest dose groups as early as week 4 were observed. ACR50/70 response at week 12 and DAS28-CRP remission were also higher in the 2 highest ASP015K dose groups as compared to PBO. Dose-dependent improvement in DAS28-CRP was seen, with statistically significant differences shown in the two highest dose groups as early as week 4. The incidence of adverse events (AEs) was similar between combined ASP015K groups and PBO (41.6% vs 43.1%). The most frequently reported AEs in the combined ASP015K groups as compared to PBO were upper respiratory tract infection (5.5% vs 3.9%), nausea (5.0% vs 0%), and diabetes (3.8% vs 2.0%). The overall incidence of infections and serious adverse events was similar between ASP015K and PBO (13.4% vs 13.7% and 4.2% vs 3.9%, respectively). No meaningful differences in absolute neutrophil and lymphocyte counts or hemoglobin were seen between ASP015K and PBO. The safety profile was generally comparable among the ASP015K dose groups, except for a higher incidence of dyspepsia, headache, and blood creatinine phosphokinase increased (transient without associated symptoms) in the 100 mg and/or 150 mg groups.

Conclusion: In a population of RA pts with long-standing disease and previous treatment with multiple DMARDs, 12 weeks of treatment with ASP015K was well tolerated and efficacious, with the highest response seen at the 100 and 150 mg doses. These data support further development of ASP015K for the treatment of RA.

Table: Proportion of patients achieving ACR20 at week 24 and 48

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo</th>
<th>ASP015K 25 mg</th>
<th>ASP015K 50 mg</th>
<th>ASP015K 100 mg</th>
<th>ASP015K 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20, n (%) [1]</td>
<td>15 (29.4)</td>
<td>13 (22.0)</td>
<td>21 (36.8)</td>
<td>28 (48.3)*</td>
<td>36 (56.3)**</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50, n (%)</td>
<td>5 (9.8)</td>
<td>9 (15.3)</td>
<td>14 (24.6)</td>
<td>16 (27.6)*</td>
<td>18 (28.1)**</td>
</tr>
<tr>
<td>ACR70, n (%)</td>
<td>4 (7.8)</td>
<td>6 (10.6)</td>
<td>9 (15.3)</td>
<td>11 (19.0)</td>
<td>7 (10.9)</td>
</tr>
</tbody>
</table>
2827

Background/Purpose: Little data exist regarding mortality in Ankylosing Spondylitis (AS) patients. We performed a population-based study of diagnoses associated with hospital mortality in AS.

Methods: Data were abstracted from the Healthcare Cost and Utilization Project-National Inpatient Sample (HCUP-NIS) between 2007-2011. We identified hospital discharges with AS using a validated administrative definition. The primary outcome was mortality and we performed a subset analysis on cervical spine fracture (CSFX) associated conditions and fracture level. Chi-square and Wilcoxon rank sum tests were used when appropriate to identify diagnoses associated with mortality. Multivariable logistic regression, including socio-demographic variables, significant covariates and comorbidities, was performed to identify independent factors associated with in-hospital mortality.

Results: There were 12,493 AS admissions, 422 CSFXs and 276 deaths between 2007-2011. The mean age of all hospitalized AS patients was 59.2 ± 16.4 years, 71% were males and 24% were electively admitted. The mean age of those with CSFX was 67.8 ± 15.1 years, 91% were males and 11% were electively admitted. The mean age of those who died was 73.0 ± 12.9 years, 78% were males and 10% were electively admitted. In the multivariable model, bacteremia and CSFX were the diagnoses with the highest odds of death. 7.28 (95% CI: 5.36-9.88) and 5.70 (95% CI: 3.63-8.95), respectively. Of those with CSFX, 66% also had a diagnosis of fall, though there was no interaction between CSFX and falls in predicting mortality. Motor vehicle accidents accounted for another 16% of CSFX cases. The majority of CSFX occurred at the lower cervical spine (75%). Regardless of level of fracture, 11% of patients died with associated CSFX.

Conclusion: The diagnoses most strongly associated with mortality in hospitalized AS patients, were bacteremia and CSFX. CSFX appears to be most commonly associated with falls and the majority of fractures occur in the lower cervical spine. This is the first population-based study describing the significant mortality associated with CSFX in AS patients.

Table 1. Multivariable model of predictors of mortality in AS hospitalizations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year)</td>
<td>1.05</td>
<td>1.03-1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>0.97</td>
<td>0.71-1.33</td>
<td>0.87</td>
</tr>
<tr>
<td>Private insurance</td>
<td>0.77</td>
<td>0.53-1.11</td>
<td>0.16</td>
</tr>
<tr>
<td>Community population &lt;50,000</td>
<td>1.29</td>
<td>1.02-1.87</td>
<td>0.04</td>
</tr>
<tr>
<td>Elective admission</td>
<td>0.58</td>
<td>0.38-0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Charlson index (per 1 point on weighted scale)</td>
<td>1.25</td>
<td>1.18-1.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>7.28</td>
<td>5.36-9.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.98</td>
<td>1.44-2.70</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

2828
A Physically Demanding Job May Amplify the Effect of Disease Activity on the Development of Syndesmophytes in Patients with Ankylosing Spondylitis. Sofia Ramiro1, A. M. van Tubergen2, Robert Landewe3, Anne-Elies Boonen4, Carmen Stolwijk5, Maxime Douagos6, Filip Van den Bosch7 and Desiree van der Heijde8. 1Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, 2Maastricht University Medical Center, Maastricht, Netherlands, 3Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, 4Université Paris René Descartes and Hôpital Cochin, Paris, France, 5Ghent University Hospital, Ghent, Belgium, 6Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: We have recently shown that disease activity is longitudinally associated with radiographic progression in AS. In animal models, it has recently been shown that mice that were tail suspended, in order to prevent mechanical loading on paws, had less new bone formation, thus providing a proof-of-concept that mechanical strain drives new bone formation in spondyloarthritis. Our aim was to investigate the complex relationship between inflammation, mechanical stress and radiographic progression in patients with ankylosing spondylitis (AS), using job type as a proxy for continuous mechanical stress.

Methods: Patients from OASIS were followed-up for 12 years, with 2 yearly assessments. Two readers independently scored the x-rays according to the mSASSS. Disease activity was assessed by the ASDAS-CRP. The relationship between ASDAS and spinal radiographic progression was investigated with longitudinal analysis, with job type at baseline (physically demanding (‘blue collar’) vs sedentary (‘white collar’) labor) as a potential factor influencing this relationship. The effects of smoking status and socio-economic factors were also investigated.

Results: In total, 184 patients were included in the analyses (70% males, 83% HLA-B27 positive, 39% smokers, 48% blue-collar workers (65/136 patients in whom data on job type were available)). The relationship between disease activity and radiographic progression was significantly and independently modified by job type. In ‘blue-collar’ workers vs ‘white collar’ workers every additional unit of ASDAS resulted in an increase of 1.2 vs 0.2 mSASSS-units/2-years (p = 0.014 for the difference between blue collar and white collar workers). In smokers vs non-smokers every additional unit of ASDAS resulted in an increase of 1.9 vs 0.4 mSASSS-units/2-years. Personal income also significantly modified the relationship ASDAS-mSASSS, but smoking status and socio-economic factors were not investigated.

Conclusion: Physically demanding jobs may amplify the driving effects of inflammation on radiographic progression, thus supporting the theory that mechanical stress leads to bone formation in AS. Smoking and personal income are likely classic confounders of this relationship but a separate detrimental effect of smoking on radiographic progression could not be excluded. If confirmed, these findings may have implications for our commonly given advice to patients with SpA to strenuously exercise.

Table: Effects of disease activity (one ASDAS-unit increase) on radiographic progression in subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>2-year increase in mSASSS (units, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Occupation: ‘Blue collar’ (n = 65)</td>
<td>1.19 (0.58, 1.79)</td>
</tr>
<tr>
<td>B: Smoking: ‘Non-smokers’ (n = 78)</td>
<td>0.35 (0.04, 0.65)</td>
</tr>
<tr>
<td>C: Education: ‘University’ (n = 167)</td>
<td>0.74 (0.41, 1.07)</td>
</tr>
<tr>
<td>E: Family income: &lt;=&lt;euro&gt;3176 (n = 90)</td>
<td>0.49 (0.09, 0.89)</td>
</tr>
<tr>
<td>F: Family income: &lt;=&lt;euro&gt;3176 (n = 21)</td>
<td>0.15 (-0.35, 0.65)</td>
</tr>
</tbody>
</table>
2829

Spondyloarthritis Is Associated with Increased Cardiovascular and Cerebrovascular Mortality. Nigel Haroon1, Nisha Nigil Haroon1, Ping Li1, Michael Paterson1 and Robert D. Inman4. 1Toronto Western Research Institute, Toronto, ON, 2University of Toronto, Toronto, ON, 3Institute of Clinical Evaluative Sciences, Toronto, ON, 4University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: OnSpA is a population-based study of spondyloarthritis (SpA) based on a provincial population of over 13 million. Patients with SpA are thought to be at increased risk of cardiovascular disease but it is unknown if they have excess vascular mortality. We explored risk of vascular mortality and the contributing factors in AS.

Methods: We performed a population-based, retrospective cohort study on incident SpA patients, age 15 or above, living in Ontario, Canada between April 1995 and March 2011. There were 21,878 SpA cases and 87,504 controls (matched for age, gender and socioeconomic status). The primary outcome was a composite event of cardiovascular or cerebrovascular death coded as the primary cause on death certificates. Considering the large size of the cohorts, we used standardized differences to compare the baseline characteristics of those with AS and their matched controls. Cox proportional hazards model was used to estimate differences in vascular mortality between cases and controls. Crude and adjusted hazard ratios (HR) were calculated and adjustments were made for coronary and cerebrovascular disease (CAD, CVD), cancer, diabetes, dementia, inflammatory bowel disease, hypertension, chronic kidney disease (CKD) and peripheral vascular disease (PVD). Additionally, we used a separate model in those with AS to identify covariates associated with vascular mortality. Finally, we constructed survival curves using the Kaplan-Meier (KM) method and tested for survival differences among groups using the Log-Rank test.

Results: In the SpA cohort 53% were male, with a mean age of 46 ±16 years, and a follow-up of 169,307 patient-years. Follow-up for controls was 692,499 patient-years. Crude and adjusted HR (95%CI) for vascular deaths were 1.49 (1.26–1.77) and 1.36 (1.14–1.63) respectively, indicating a 36–49% higher risk of vascular mortality in AS. Crude HR (95%CI) in males and females were 1.63 (1.31–2.03) and 1.31 (1.00–1.71) respectively. Cases and controls had similar prevalence of CAD, CVD, PVD, dementia and diabetes, but IBD (6% vs 4%), hypertension (24% vs 18%) and CKD (2% vs 0.8%) were more common in SpA. The predictors of vascular death were age, male sex, low income, CKD and PVD apart from CAD and CVD. The KM curve is shown in Figure 1.

Conclusion: This is the first population-based study to demonstrate SpA is associated with significantly risk of vascular mortality. These new findings should prompt a comprehensive strategy to screen and treat modifiable vascular risk factors in SpA patients.

Follow Up Days

Figure 1. Kaplan-Meier Survival Curve of AS patients compared to non-AS controls after correcting for baseline variables.

Disclosure: N. Haroon, None; N. Nigil Haroon, None; P. Li, None; M. Paterson, None; R. D. Inman, None.

2830

Progression to and Type of Orthopaedic Surgery in Juvenile Vs. Adult-Onset Ankylosing Spondylitis. Deepak R. Jadon1, Gavin Shadick2, Amelia Jobling3, Athinalpaiset V Ramanan4 and Raj Sengupta5. 1Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, 2University of Bath, Bath, United Kingdom, 3University of Bristol Hospital Trust, Bristol, United Kingdom.

Background/Purpose: Juvenile-onset ankylosing spondylitis (JoaS) and adult-onset ankylosing spondylitis (AoS) are subtypes of ankylosing spondylitis (AS) that may have different clinical outcomes. We compared cohorts of JoaS and AoS in terms of: (1) clinical characteristics; (2) clinical outcomes; (3) proceeding to and types of AS-related orthopaedic surgery.

Methods: A cohort study was conducted of all patients attending a dedicated AS clinic in a teaching hospital. Patients aged <16 years at symptom onset were categorised as JoaS, and ≥17 years as AoS. Demographics, clinical parameters, composite indices ≤6 months of census, biological use, and history of AS-related orthopaedic surgery to the spine, root or peripheral joints were recorded. Univariate, multivariate logistic regression, and survival analyses were performed.

Results: 533 AS cases were studied: 162 JoaS; 391 AoS. On univariate analyses (Table 1), no statistically significant differences were found between JoaS and AoS in terms of HLA-B27 positivity, smoking, occurrence at any time of inflammatory bowel disease, psoriasis, enthesitis, or uveitis. JoaS cases had higher scores for two Bath AS Functional Index (BAFI) domains: bending forward from the waist (p=0.03); doing physically demanding activities (p=0.04). On multivariate analyses adjusted for significant covariates (Table 2), compared to JoaS cases the AoS cases were less likely to have: proceeded to surgery (odds ratio, OR 0.31; p<0.001); had a hip procedure (resurfacing or arthroplasty; OR 0.374; adjusted p=0.001); had an arthroplasty (OR 0.43; adjusted p=0.012). JoaS and AoS were equally likely to have had hip resurfacing, bilateral hip arthroplasty, hip arthroplasty revision, hip arthroplasty re-revision, spinal orthopaedic surgery, and several (≥3) procedures.

Kaplan-Meier survival curves (log-rank test p=0.001) and Cox regression also demonstrated a significant difference in not having surgery between JoaS and AoS (p=0.002) (Figure 1). A history of smoking was not associated with surgery. AS cases with older age at symptom onset were far less likely to have surgery than those with younger onset, in a non-linear manner.

Conclusion: JoaS are more likely than AoS cases to proceed to AS-related orthopaedic surgery, especially hip resurfacing and arthroplasty.

Table 1. Comparison of clinical parameters and outcomes: Juvenile vs. adult-onset ankylosing spondylitis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Juvenile-onset AS</th>
<th>Adult-onset AS</th>
<th>Odds Ratio 95% CI p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>160 (61.5%)</td>
<td>377 (47.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Girls</td>
<td>99 (38.5%)</td>
<td>422 (52.8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Comparisons by continent-adjusted Chi-squared test.

Table 2. Comparison of types of AS-related orthopaedic surgeries in juvenile vs. adult-onset ankylosing spondylitis (multivariate analyses)

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Juvenile (n=162)</th>
<th>Adult (n=391)</th>
<th>Odds Ratio 95% CI p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip arthroplasty</td>
<td>30/162 (18.52%)</td>
<td>20/391 (5.12%)</td>
<td>0.420 0.28–0.63</td>
</tr>
<tr>
<td>Hip resurfacing</td>
<td>7/162 (4.32%)</td>
<td>4/391 (1.02%)</td>
<td>0.71 0.34–1.53</td>
</tr>
<tr>
<td>Hip procedures</td>
<td>23/162 (14.21%)</td>
<td>20/391 (5.12%)</td>
<td>0.420 0.28–0.63</td>
</tr>
</tbody>
</table>

*Comparisons by continent-adjusted Chi-squared test.
**Background/Purpose:** Previous studies have shown that the risk of vertebral fractures is increased in patients with ankylosing spondylitis (AS). Prospective longitudinal data about radiographic vertebral fractures are scarce and little is known about the effect of tumor necrosis factor-alpha (TNF-α) blocking therapy on the development of vertebral fractures in AS.

**Objectives:** Our objective was to determine the prevalence of radiographic vertebral fractures in patients with AS before start of TNF-α blocking therapy and to investigate the incidence of vertebral fractures after 4 years of follow-up.

**Methods:** Consecutive AS patients from the Groningen Leeuwarden AS (GLAS) cohort with available thoracic and lumbar radiographs at baseline and after 4 years of TNF-α blocking therapy were included. Patients fulfilled the modified New York criteria for AS and the ASAS criteria to start with TNF-α blocking therapy. Vertebral fractures were assessed by two independent readers using the Genant method and were defined as moderate vertebral fractures at baseline were significantly associated with the development of new fractures. Lumbar spine and hip BMD showed significantly less improvement in lumbar spine BMD than patients without new fractures (median change in Z-score 0.4 vs. 0.8).

**Conclusion:** The prevalence of radiographic vertebral fractures was 26% in AS patients with active disease before start of TNF-α blocking therapy. Although a significant increase in BMD was found, 20% of patients developed new vertebral fractures during 4 years of TNF-α blocking therapy.

**Disclosure:** D. R. Jadon, None; G. Shaddick, None; A. Jobling, None; A. V. Ramanan, None; R. Sengupta, None.

### Table. Multivariable Cox regression analysis of 5-year drug survival

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.01 (0.94–1.09)</td>
</tr>
<tr>
<td>Sex (ref. female)</td>
<td>0.66 (0.55–0.80)</td>
</tr>
<tr>
<td>csDMARD co-medication (ref. none)</td>
<td>0.71 (0.59–0.85)</td>
</tr>
<tr>
<td>TNF type</td>
<td>0.037</td>
</tr>
<tr>
<td>ADA vs. IFX</td>
<td>0.90 (0.73–1.11)</td>
</tr>
<tr>
<td>ETN vs. IFX</td>
<td>0.75 (0.60–0.93)</td>
</tr>
<tr>
<td>Start year 2007–2010 vs. 2003–2006</td>
<td>1.22 (1.02–1.48)</td>
</tr>
<tr>
<td>Hospital days*</td>
<td>1.01 (1.00–1.01)</td>
</tr>
<tr>
<td>Number of outpatient visits*</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td>Disponible income (per 1000 €)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Education</td>
<td>0.087</td>
</tr>
<tr>
<td>10–12 years vs. &lt;9 years</td>
<td>0.93 (0.73–1.17)</td>
</tr>
<tr>
<td>&gt;12 years vs. ≤9 years</td>
<td>0.78 (0.60–1.01)</td>
</tr>
<tr>
<td>Missing vs. ≤9 years</td>
<td>1.75 (0.62–10.4)</td>
</tr>
</tbody>
</table>

*Number of days/patient the 2 years prior to TNFi start; data from the National Patient Register
‡Income the year prior to TNFi start; data from Statistics Sweden

**Conclusion:** AS patients who received csDMARD co-med with their first TNFi remained on therapy significantly longer than those who were not on co-med. The association remained statistically significant when adjusting for potential confounders.
2833

SM 101, a Novel Recombinant, Soluble, Human FcγRIIB Receptor, in the Treatment of Systemic Lupus Erythematosus: Results of a Double-Blind, Placebo-Controlled Multicenter Study. Sascha Tillmanns1, Claudia Kolli- ligs1, David P. D'Cruz2, Andrea Doria3, Eric Hachulla4, Reinhard E. Voll5, L. E. Kristensen5, AbbVie, 8, UCB, 8; Disclosure: E. Liebisch1, 2, L. T. Jacobsson1, Klaus Schollmeier1. 1SuppreMol GmbH, Martinsried, Germany, 2Louise Coote Lupus Unit, Guy’s and St Thomas’ Hospital, London, United Kingdom, 3University of Padova, Padova, Italy, 4Lille University, Lille, France, 5University Hospital Freiburg, Freiburg, Germany.

Background/Purpose: SM 101, which represents the human soluble non-glycosylated version of the Fcγ receptor IIB, binds to the Fc part of autoimmune complexes and inhibits the binding of immune complexes to cell-binding Fcg receptors. It has undergone preclinical and clinical safety and efficacy investigation, with evidence of efficacy in primary immune thrombocytopenia. The mode of action could make SM 101 a safe and effective treatment for systemic lupus erythematosus (SLE).

Methods: The objectives of this phase IIa randomised, double-blind, placebo-controlled parallel-group study were to evaluate the safety, tolerability and efficacy of placebo and 2 doses of SM 101 (6mg/kg and 12mg/kg), randomised 1:2:2, in patients with SLE. The main inclusion criteria were a diagnosis of SLE, evidence of serological activity (high anti-dsDNA activity or low C3), and a SELENA-SLEDAI score ≥ 6 points, with stratification to include patients with lupus nephritis (LN). Concomitant immunosuppressive therapy with corticosteroids, mycophenolate mofetil (MMF) or azathioprine and adjuvant SLE medication were allowed at constant doses during the study. Eligible patients received an infusion of study drug once a week for the first 4 weeks; study duration was 24 weeks. Data were reviewed regularly by an independent safety monitoring board. Response was measured at 24 weeks according to the SLE Responder Index (combination of SELENA-SLEDAI score ≥ 4 points, no BILAG A or 2 × B flares and no PGA score worsening).

Results: Fifty one eligible patients, 14 with LN, from 8 European countries and Australia, were randomized and received at least one dose of active investigational drug or placebo. Concomitant medications were corticosteroids (96% of patients), MMF (45%), azathioprine (20%) or combinations thereof. Patient numbers per group and response rates are shown in Table 1. The SLE Responder Index response rate was twice as high in the SM 101-treated patients compared to placebo, and response in patients with LN was proportionately greater. The response rate on SM 101 remains the same after exclusion of 15 patients who received rescue medication. The main clinical drivers for response were improvement in arthritis and in skin eruption (present in 75% and 50% patients respectively) according to the BILAG scale. Both worsened or remained unchanged in placebo patients; in SM 101-treated patients improvement or resolution occurred in 57% with arthritis and 45% with skin eruption. No safety signals which could be attributed specifically to SM 101 were reported, and no serious adverse events were probably or possibly related to the drug. No anti-drug antibodies were detected.

Conclusion: The encouraging results of this early phase study indicate that the novel biological SM 101 warrants further investigation as a treatment for patients with SLE, including patients with LN.

Table 1. Percentage of Patients Responding According to the SLE Responder Index and its Components

<table>
<thead>
<tr>
<th></th>
<th>ALL PATIENTS</th>
<th>PATIENTS WITH LN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=11)</td>
<td>Placebo (n=3)</td>
</tr>
<tr>
<td>SLE Responder Index</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>SELENA-SLEDAI</td>
<td>27%</td>
<td>42%</td>
</tr>
<tr>
<td>Reduction = 4 Points</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 1. Clinical endpoints and laboratory parameters achieved by BILAG responders (R) and non-responders (NR) at Weeks 48 and 96

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>BILAG R (n=130)</th>
<th>BILAG NR (n=132)</th>
<th>p value</th>
<th>BILAG R (n=72)</th>
<th>BILAG NR (n=74)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-point SLEDAI (reduction in %)</td>
<td>67 (80.8)</td>
<td>67 (80.8)</td>
<td>&lt;0.0001</td>
<td>67 (80.8)</td>
<td>67 (80.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n-point SLEDAI (reduction in %)</td>
<td>52 (64.4)</td>
<td>38 (46.2)</td>
<td>&lt;0.0001</td>
<td>45 (59.7)</td>
<td>38 (49.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SLEDAI A or B worsening (reduction in %)</td>
<td>76 (97.0)</td>
<td>76 (97.0)</td>
<td>&lt;0.0001</td>
<td>75 (98.6)</td>
<td>75 (100)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

References
1. Daridon C. Arth Res Ther 2010;12:R204
Table. Summary of primary and major secondary endpoints at wk 24

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>CNTO 136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with no worsening in GFR at wk24a,b</td>
<td>3 (75%)</td>
<td>10/18 (55.6%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(3.2, 37.9)</td>
<td>(30.8, 78.5)</td>
</tr>
</tbody>
</table>

*A last-observation-carried-forward procedure was used to impute missing values if a pt had data for <3 post-baseline evaluation. Of 21 randomized pts, 20 were included in the efficacy analyses.

Meaningful reduction in proteinuria was defined as P/C (protein/creatinine) ratio < 0.5 for non-nephrotic pts; and >50% reduction in P/C ratio and P/C ratio < 3.0 for nephrotic pts.

Disclosure: R. A. Aranow, None; R. van Vollenhoven, Jansen Research and Development, LLC, 2, B. H. Rovin, Genentech and Biogen IDEC Inc., 2, Questcor, 2, Centocor, Inc., 5, Lilly, 5, GlaxoSmithKline, 5, MedImmune, 5, auranis, 5, Morton A. Scheinberg, 3; and Richard Furie 4. 1Johns Hopkins University School of Medicine, Baltimore, MD, 2Anthera Pharmaceuticals Inc, Hayward, CA, 3Rheumatology Hospital Abreu Sodre Pesquisa Clı ´nica, Sa˜o Paulo, Brazil, 4North Shore-Long Island Jewish Health System, Great Neck, NY.

**Background/ Purpose:** To conduct secondary endpoint analyses of the effects of subcutaneously-administered blisibimod (A-623, AMG 623), an inhibitor of B-cell activating factor (BAFF), on patient-reported outcomes and indices of disease activity in patients with systemic lupus erythematosus (SLE) during the phase 2b clinical trial PEARL-SCL (NCT01162681).

**Methods:** 547 SLE patients who met the ACR classification criteria, and had >40% anti-double-stranded DNA or anti-nuclear antibodies, and SLENA-SLEDAI score ≥6 at baseline, were enrolled into the PEARL-SCL study, and randomized 1:1 to receive placebo or blisibimod administered at 1 of 3 dose levels, 100 mg weekly (QW), 200 mg QW, or 400 mg every 4 weeks for up to 52 weeks (with a median of 37 weeks) or until the last subject completed 6 months of study drug therapy. Patient self-reported outcomes were evaluated using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and disease activity evaluated within SLENA-SLEDAI organ domains.

**Results:** Significant improvements in measures of disease activity, including the SLE responder Index-8 (SRI-8) in subjects with severe baseline disease (defined at SLENA-SLEDAI score=10 and receiving steroids), especially at the highest blisibimod dose of 200mg QW were reported previously (Furie et al. 2014). A proximately 76% of subjects had SLENA-SLEDAI musculoskeletal organ involvement at enrollment, and 89% of subjects had mucocutaneous organ involvement. At Week 24, approximately 12% and 39% of subjects randomized to the 200mg QW blisibimod arm had musculoskeletal or mucocutaneous organ involvement, compared with approximately 15% and 42% respectively in the placebo arm (p<0.2 to p<0.05 across manifestations evaluated over Weeks 12 through 24). A concomitant tendency toward improved self-reported fatigue was observed amongst subjects randomized to blisibimod based on the FACIT-Fatigue scale, especially in the 200mg QW group (N=80) where a mean 6.9-point improvement in baseline from week 24 (p=0.065) compared with 4.4 with placebo (N=229). Based on exploratory statistical analyses, the
Effects of blisibimod on FACIT-fatigue were significantly better than placebo \((p=0.05)\) as early as Week 8.

Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Amongst the commonly-reported AEs, imbalance was observed only with injection site reactions \((200\, \text{mg} \times \text{QW blisibimod}=15\%, \text{matched placebo}=7\%)\, but these were not severe or serious.

**Conclusion:** Fatigue remains a debilitating manifestation of lupus. In this trial, blisibimod showed a tendency toward improved mucocutaneous and musculoskeletal disease activity as well as patient self-reported fatigue. These data support further evaluation of blisibimod in patients with SLE.

**Results:** In the first treated patient, disease activity rapidly decreased already after one treatment cycle, while in the second patient a reduction in disease activity was observed two weeks later. During the following treatment cycles disease activity further decreased or remained low due to disappearance of clinical manifestations such as arthritis, myositis and skin rash.

Addition and unexpectedly levels of anti-dsDNA-antibodies considerably decreased in both patients. The clinical response was associated with cyclic and treatment-related increases of the CD25hiFoxp3+CD127lo Treg population in the peripheral blood. The therapy was very well tolerated and adverse events were generally mild and transient.

**Conclusion:** These data provide the first evidence for the clinical efficacy of low-dose IL-2-therapy in conjunction with the boosting of Treg activity in SLE and strongly support the rationales of this selective biological treatment strategy.

**Disclosure:** J. Y. Humrich, None; C. von Spee-Mayer, None; E. Siegert, None; A. Rose, None; T. Alexander, None; F. Hiepe, None; A. Radbruch, None; G. Burmester, None; G. Riemekasten, None.

**2837**

**Exploratory Analysis of Pharmacokinetic Effects of Atacicept in Patients with Moderate to Severe Systemic Lupus Erythematosus.**

David Wofsy, Caroline Gordon, Yong Li, Stephen D. Wax and David Isenberg.

**Background/Purpose:** Atacicept is a fusion protein that inhibits B-cell stimulating factors BLYS and APRIL. We previously reported the clinical effects of atacicept in lupus patients with active disease (the APRIL-SLE study). Here we report the exploratory analysis between mean drug concentration and clinical outcome in those subjects.

**Methods:** Patients with active SLE \((\geq 1 \text{ BILAG A and/or B})\) were treated with corticosteroid taper for 12 weeks. Subjects reaching BILAG C or D at weeks 10 and 12 were randomized 1:1:1 to receive placebo (PLC), atacicept 75 mg \((A75)\) or 150 mg \((A150)\) twice weekly for 4 weeks then weekly for 48 weeks. All patients received standard of care. As previously reported, A150 reduced the frequency of BILAG A and B flares but was discontinued prematurely due to two infection-related deaths. This post-hoc analysis was performed among subjects in all groups randomized at least 52 weeks prior to discontinuation of A150 and who had an opportunity to complete the protocol \((n=81, 84, and 81 for \text{PLC, A75, and A150, respectively})\). For this analysis subjects in the two treatment arms were divided into four quartiles based on mean atacicept concentration, the 1st being the group with the lowest concentration.

**Results:** Subjects with the highest atacicept concentrations \((3rd and 4th quartiles)\) experienced fewer flares during treatment compared to subjects with lower concentrations \((1st and 2nd quartiles)\) and subjects in the PLC group \((60, 63, 61, 49, and 29\% for PLC, A75, and A150, respectively). For this analysis subjects in the two treatment arms were divided into four quartiles based on mean atacicept concentration, the 1st being the group with the lowest concentration.

**Conclusion:** These data provide the first evidence for the clinical efficacy of low-dose IL-2-therapy in conjunction with the boosting of Treg activity in SLE and strongly support the rationales of this selective biological treatment strategy.

**Disclosure:** J. Y. Humrich, None; C. von Spee-Mayer, None; E. Siegert, None; A. Rose, None; T. Alexander, None; F. Hiepe, None; A. Radbruch, None; G. Burmester, None; G. Riemekasten, None.
Results: A recently developed imaging tool (Science Translational Medicine 2014, 6:230) was used to quantify the frequency of CD20+ B and CD4+ T cells expressing the anti-apoptotic molecules BCL-2, MCL-1, and the pro-apoptotic molecule BIM. In primary follicles of normal tonsils, both B and T cells frequently expressed BCL-2. However, upon entry into germinal centers (GC), BCL-2 was down-regulated and MCL-1 was induced. In marked contrast, in LuN and MRTI biopsies, the frequency of BCL-2+ cells was increased in B and T cells while MCL-1+ cells were rare. Observed differences between tonsil GC lymphocytes versus TII in LuN and MRTI for both BCL-2 and MCL-1 were highly significant (p<0.001). These expression differences were confirmed by laser capture microscopy coupled to qPCR. In contrast, the frequency of BIM+ cells did not significantly vary among tissues. Consistent with these findings, BCL-2, but not MCL-1 expressing cells were detected in the infiltrated kidney in IFN-α-induced NZB/W F1 lupus mice. Furthermore, administration of ABT-199, a BCL-2 selective inhibitor, prevented the development of lupus nephritides by depleting intra-renal B and T cells in these animals.

Conclusion: Frequent BCL-2, but not MCL-1, expressing cells were present in LuN, MR TII tissues and IFN-α-induced NZB/W F1 lupus mice. Treatment of these mice with the BCL-2 selective inhibitor ABT-199 resulted in the loss of renal B and T cells and the preservation of renal function. These data indicate that BCL-2, which is dysregulated in TII, is an attractive therapeutic target in cases of lupus nephritis manifesting tubulointerstitial inflammation.

Disclosure: K. Ko, None; D. Yanez, AbbVie, 2; N. Kaverina, AbbVie, 2; V. M. Liaraki, None; Y. Peng, None; L. Lan, None; S. Perper, AbbVie Inc., 3; A. Schwartz, AbbVie Inc., 3; L. O'Connor, AbbVie Inc., 3; A. Souers, AbbVie Inc., 3; S. Elmore, AbbVie Inc., 3; L. Olson, AbbVie Inc., 3; M. L. Giger, None; L. C. Wang, AbbVie Inc., 3; M. R. Clark, AbbVie, 2.

2840

Targeting the RhoA-Rock Pathway to Reverse T Cell Dysfunction in SLE.

Cristina T. Rozo, Laura Leuenberger, Kyriakos A. Kirou, Margaret R. Robotham, Sanjay Gupta, Reena Khiayan, Alessandra B. Pernis and Jane E. Salmon.

Hospital for Special Surgery, New York, NY.  

Background/Purpose: Aberrant expansion of Th17 cells and deregulated production of IL-17 and IL-21 are involved in the pathogenesis of SLE. Production of IL-17 and IL-21 is critically dependent on the transcription factor, IRF4 (Interferon Regulatory Factor 4). Rho-associated protein kinases (ROCKs) can phosphorylate IRF4 and regulate its activity. The finding that ROCK activity is elevated in SLE patients and is associated with human Th17 differentiation, coupled with the ability of ROCK inhibitors to ameliorate autoimmunity in murine models of lupus suggest that targeting the ROCK pathway might be a novel therapeutic strategy for the treatment of SLE. ROCK activation can be inhibited by Y27632 (a nonselective ROCK inhibitor) and Y27632 can reverse SLE in a mouse model of lupus via ROCK1 and ROCK2) or by ROCKs (which inhibit ROCKs by interfering with their major upstream activator, RhoA). Here, we examined the ability of Y27632 and simvastatin to inhibit the production of IL-17 and IL-21 by human T cells.

Methods: We assessed the capacity of Y27632 (60μM-90μM) and simvastatin (0.2μM) to decrease ROCK activation and IL-17 and IL-21 production by cord blood CD4+ T cells cultured under Th17-skewing conditions (5nM IL-6, 10ng/mL TGFβ, 20ng/mL IL-1β, 50ng/mL IL-23, 5ug/mL anti-IL-4 and 10ug/mL anti-IFN-g). We also assessed the ability of Y27632 and simvastatin to diminish IL-17 and IL-21 production by stimulated SLE CD4+ T cells. ROCK activation was determined by an ELISA-based ROCK activity assay. Plasma levels of IL-17, IL-21, and CCL20 were measured by ELISA. qPCR was used to determine gene expression of IRF4. All patients (N=24) met ACR criteria for SLE. Demographics and clinical features were as follows: mean age 37 ± 11 years, 96% female, 8% Asian, 21% African American, 21% Caucasian, 50% Hispanic, SLEDAI score 6 ± 4, and 42% with nephritis.

Results: Compared to Th0 cells, cord blood CD4+ T cells cultured under Th17-skewing conditions exhibited elevated ROCK activity that was inhibited by both Y27632 and simvastatin. IL-17 production was decreased by 60% in cord blood Th17 cells treated with either inhibitor. IL-21 production was decreased by 83% (90μM Y27632) and 65% (0.2μM simvastatin) in cord blood Th17 cells. Neither Y27632 nor simvastatin decreased IRF4 gene expression suggesting that their effects on IL-17 and IL-21 were not secondary to effects on cell viability. Both Y27632 and simvastatin decreased IL-17 and IL-21 cytokine production by purified SLE CD4+ T cells but neither treatment altered IFN-γ protein production. We also confirmed our
previous findings that in a subset of SLE patients PBMCs showed elevated ROCK activity compared to PBMCs from healthy controls. In this new cohort, the majority (79%) of the SLE patients had ROCK values that were at least 2SD above the mean ROCK value for the healthy controls.

**Conclusion:** These data indicate that the production of IL-17 and IL-21 by SLE T cells can be selectively inhibited by targeting the RhoA-ROCK pathway providing a rationale to inhibit the ROCKs as a means to reverse T cell dysfunction in SLE.

**Disclosure:** C. T. Razo, None; L. Luekenberger, None; K. A. Kirou, None; M. Robotham, None; S. Gupta, None; R. Khianey, None; A. B. Perkins, Kadmon Corporation; 2 J. E. Salmon, Kadmon Corporation, 2, Kadmon Corporation, 5.

**2841** Identifying Novel Lupus Severity Risk Variants through Identification of Alleles with High Ethnic Variability Worldwide.

**Background/Purpose:** Substantial epidemiologic evidence demonstrates that SLE disproportionately affects minority patients in terms of incidence, prevalence, and disease severity. European ancestry has been associated with a lower risk of developing renal disease in SLE. We developed an approach to identify novel SLE risk variants that may influence disease severity by searching for single nucleotide polymorphisms (SNPs) with high ethnic variability worldwide and testing them in our multiethnic SLE cohort.

**Methods:** The Human Genome Diversity Project (HGDP) characterized the allele frequency of 650,000 SNPs in 938 people from 53 populations worldwide. Our multiethnic cohort of SLE patients was genotyped on the Illumina Immunochip (I-chip), covering over 160,000 SNPs across 185 autoimmune genes plus select non-autoimmune genes and ancestry informative markers. There were 32,907 SNPs common to the HGDP and I-chip. We selected the top 2% of those SNPs that met both an absolute mean frequency difference and a t-test criteria between Europeans and Non-Europeans. We tested these SNPs in our multiethnic cohort of 1427 SLE patients for severe disease outcomes (renal disease by ACR renal criterion, severe renal disease on biopsy or end-stage renal disease, and production of dsDNA antibodies) stratified by ethnicity: Caucasian, African American, Hispanic, and Asian. Logistic regression was performed, adjusting for disease duration and gender. Ethnic strata were refined via STRUCTURE analysis of 878 I-chip SNPs, stratified by ethnicity: Caucasian, African American, Hispanic, and Asian. Linkage disequilibrium (LD) (r2 0.8), p<0.001. Most significantly 4.5e-05).

**Results:** This approach identified 13 SNPs with ethnicity-disease outcome associations (unadjusted p value < 0.001). Two SNPs, rs2099365 and rs2163882, which are in high linkage disequilibrium (LD) (r2 = 0.98) in Hispanics, also had significant false discovery rate p values (0.014) for association of renal disease in Hispanics (odds ratio 2.9). Both SNPs are 20kb from the 3’ end of the endomucin (EMCN) gene, a glycoprotein involved in cell adhesion. These SNPs are predicted to disrupt 3-4 regulatory motifs. The EMCN gene is a non-autoimmune gene on the I-chip, not previously associated with SLE, but recently reported to be associated with susceptibility to RA. The association of the 2 SNPs with renal disease in Hispanics is consistent with an estimated 5.7 odds of renal disease per 100% Amerindian ancestry (p = 3.5e-06) compared to 0.17). In addition, Cpg-induced IFN production from PBMCs was inhibited by 65% (p = 0.0001) compared to isotype control but was not inhibited by pretreatment with Fab’ (122.3 ± 27.7%, p = 0.78). The IFN gene score was elevated in SLE (3.1 ± 0.46) compared to healthy (1.49 ± 1.1, p = 0.07) donors. Cpg-induced upregulation of the IFN gene score (3.9 ± 0.9) was reduced by pretreatment of PBMCs with Cpg at 0.9 ± 1.9, p = 0.12).

**Conclusion:** A mAb targeting CD123 (CSL362) depletes pDCs and decreases Cpg-induced IFNα production and IFNα-inducible gene expression from SLE and healthy donor PBMCs. These effects were not seen with IL3 blockade alone or isotype control mAb. Cytoreductive therapy with CSL362 may therefore represent a novel treatment strategy in SLE.

**Disclosure:** S. Oon, CSL Limited, 2; N. Wilson, CSL Limited, 3; I. Wicks, CSL Limited, 2.

**2842** An Anti CD123 Monoclonal Antibody (CSL362) Depletes Plasmacytoid Dendritic Cells and Inhibits CpG Upregulated IFNα Production and IFNα-Inducible Gene Expression in Peripheral Blood Mononuclear Cells from Patients with Systemic Lupus Erythematosus. Shereen Oon, N. Wilson,1 J. Molineros,1 and Ian Wicks,2 1The University of Melbourne, Melbourne, Australia; 2The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

**Background/Purpose:** Plasmacytoid dendritic cells (pDCs) contribute to systemic lupus erythematosus (SLE) pathogenesis by producing Type 1 interferon (IFN), most likely induced by endosomal Toll like receptor (TLR) activation by immune complexes. In healthy donors, pDCs are known to express high levels of CD123, the IL3 receptor alpha chain. CSL362 is a novel monoclonal antibody (mAb) that binds to CD123, neutralizing IL3 signaling and causing antibody dependent cell mediated cytotoxicity (ADCC) of CD123 bearing cells. This study of SLE and healthy donors evaluates 1) CD123 expression on pDCs and other cell types, 2) CSL362 mediated depletion of pDCs, and 3) the effect of CSL362 on IFNα production and IFNα-inducible gene expression from peripheral blood mononuclear cells (PBMCs) in vitro.

**Methods:** Quantitative flow cytometry with Quantibrite PE beads and an anti-CD123-PE antibody was used to assess CD123 expression on cell types from peripheral blood of SLE and healthy donors (n=15). PBMCs from SLE (n=13) and healthy (n=10) donors were isolated by Ficoll gradient centrifugation and incubated for 24 hours in vitro with CSL362, the Fab portion of CSL362 (Fab,), which neutralizes IL3 signaling, but does not effect ADCC, or an isotype control mAb. The percentage of viable pDCs was enumerated by flow cytometry. PBMCs from SLE (n=7) and healthy (n=6) donors were pretreated with CSL362, Fab’ or isotype control mAb for 24 hours, then stimulated with CpG, a TLR9 agonist, for 18 hours. IFNα production from culture supernatant was assessed by ELISA. A novel ‘IFN gene score’, based on 11 IFNα-inducible genes, was incorporated into a customized gene array, to serve as a “gene signature” to stratify patients and assess drug efficacy. This score was evaluated by performing quantitative PCR on RNA extracted from SLE (n=17) and healthy (n=9) donor whole blood. The average of the log2 fold change for the 11 genes in the SLE patients was compared to healthy donors. This score was also evaluated in PBMCs (n=2), n=2 healthy) after CSL362 pretreatment followed by CpG stimulation. The average of the log2 fold change for the 11 genes of the treated samples was compared to the untreated samples.

**Results:** CD123 expression levels were highest on pDCs compared to other cell types. pDCs were depleted after in vitro culture with CSL362 (8.3±2.4% [mean±SEM], p<0.0001) compared to isotype control but were not depleted by Fab’ (96.8±5.5%, p=0.17). In addition, Cpg-induced IFN production from PBMC was inhibited by CSL362 pretreatment (11±8%, p<0.0001) compared to isotype control, but was not inhibited by pretreatment with Fab’ (122.3±27.7%, p=0.78). The IFN gene score was elevated in SLE (3.3±0.46) compared to healthy (1.49±1.1, p=0.07) donors. Cpg-induced upregulation of the IFN gene score (3.9±0.9) was reduced by pretreatment of PBMC with CSL362 (1.9±1.9, p=0.12).

**Conclusion:** A mAb targeting CD123 (CSL362) depletes pDCs and decreases Cpg-induced IFNα production and IFNα-inducible gene expression from SLE and healthy donor PBMCs. These effects were not seen with IL3 blockade alone or isotype control mAb. Cytoreductive therapy with CSL362 may therefore represent a novel treatment strategy in SLE.

**Disclosure:** S. Oon, CSL Limited, 2; N. Wilson, CSL Limited, 3; I. Wicks, CSL Limited, 2.

**2843** SLE Patients Carrying a Disease-Associated PTPN22 R620W Variant Show Reduced Interferon-Inducing Capacity.

Yaya Wang, David Ewart, Ami Y amamoto, Emily C. Baechler, Parastoo Fazeli and Erik J. Peterson. University of Minnesota, Minneapolis, MN.

**Background/ Purpose:** Type 1 interferons (IFN) are implicated in the pathogenesis of systemic lupus erythematosus (SLE). Increased expression of IFN-regulated genes, termed the IFN-signal, correlates with autoantibodies and disease activity in SLE. Likely sources of type 1 IFN in SLE include plasmacytoid dendritic cells (pDC), which produce IFNα following Toll-like receptor 7 (TLR7) activation. A coding variant in the protein tyrosine phosphatase nonreceptor type 22 (PTPN22) gene is associated with SLE. PTPN22 encodes lymphoid tyrosine phosphatase (Lyp). We showed previ-
ously that Lyp is required for TLR-driven type 1 IFN production in myeloid cells. Variant PTPN22 encodes an R620W bearing protein ("LypW"). We recently established that LypW is associated with impaired TLR-driven type 1 IFN production and type 1 IFN-dependent immunity. However, the functional consequences of LypW carriage in human SLE patients remain unclear. The current study was designed to address the effect of LypW carriage on interferonogenic TLR signaling in SLE patients.

**Methods**: Caucasian SLE patients satisfying 1987 ARA diagnostic criteria were genotyped for PTPN22 LypW variant carriage. Plasma IFNα concentrations in 15 LypW carriers and 21 non-carriers were determined by ELISA. IFNα gene signature in whole blood was also determined by quantitative PCR (qPCR). PBMC were stimulated with R848, a TLR7/8 agonist, and IFNα2 and TNFα expression in pDC (Lin−HLA-DR−CD123+) were detected by FACS. We measured IFNα protein levels in the supernatant from R848-stimulated SLE PBMC by ELISA. We compared STAT1 activation in SLE PBMC from carriers and non-carriers by phospo-flow.

**Results**: In both LypW carrier and non-carrier SLE patients, we observed comparable IFNα protein in plasma and type 1 IFN "signatures" in whole blood. We found that the percentage of pDC that produce IFNα2 after R848 stimulation was significantly reduced in LypW carrier SLE patients, while the percentage of pDC producing TNFα was comparable to that observed in non-carrier patients. Further, we observed that IFNα2 expression in pDC was decreased in LypW carriers. Supematant IFNα protein levels from R848-stimulated PBMC were significantly reduced in LypW carriers. Moreover, activation of type 1 IFN-driven STAT1 was impaired in LypW carrier PBMC after R848 stimulation.

**Conclusion**: LypW carrier SLE patients have reduced capacity for TLR-induced type 1 IFN production, even as they exhibit elevated whole blood IFNα2 protein similar to those observed in non-carrier patients. The findings suggest that LypW carriage may identify a subset of SLE patients who harbor defects in type 1 IFN-dependent host defense or anti-inflammatory functions.

**Disclosure**: Y. Wang, None; D. Ewart, None; A. Yamamoto, None; E. C. Baechler, None; P. Fazeli, None; E. J. Peterson, None.

**2844**

**Intracellular Complement C3 Is Exposed on the Cell Surface upon Apoptosis Induction and Participates in the Clearance of Apoptotic Cells By Phagocytes.**

Lucrezia Colonna1, Christian Lod2, Yu-Feng Peng2, Xi-zhang Sun1, Lena Tanaka3, Sandip Panicker2 and Keith E. Elkon1.1 University of Washington, Seattle, WA, 2True North Therapeutics, South San Francisco, CA.

**Background/Purpose**: The complement system has been viewed as a predominantly serum-derived host defense mechanism with multiple functions, including clearance of apoptotic cells. Defective function of the complement pathways have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Recently, intracellular complement C3 storage was demonstrated in many different cell types, and C3 activation products were shown to participate in the survival and effector cell differentiation of murine and human lymphoid cells. Despite the known role of serum-derived C3 activation products in the removal and immunosuppressive properties of dying cells, the role of intracellular C3 in clearance of apoptotic cells has never been explored. Thus, we asked whether human cells expose C3 and/or C3 activation products on their surface upon cell death induction, and whether such exposure functionally participates in their phagocytic clearance, independently of serum complement factors.

**Methods**: Apoptosis and secondary necrosis of human lymphoid cells was induced by both UV irradiation and serum starvation. C3/C3b/C3bi surface and intracellular expression on live and apoptotic human T and B primary cells as well as cell lines was monitored by flow cytometry (FACS), western blot and confocal microscopy. Macrophages were derived from circulating CD14+ monocytes by culture with M-CSF. Phagocytosis of apoptotic cells in presence or absence of serum was quantified by microscopy (phagocytic index) and by FACS with the aid of fluorescently labeled apoptotic cells.

**Results**: We observed that live human primary T and B cells, and human T and B cell lines expressed intracellular but not cell surface C3/C3b. However, upon apoptosis induction, C3 activation products were exposed on the surface of dying cells in a time dependent manner. Detection of C3/C3b correlated with later stages of apoptosis characterized by cell shrinkage and loss of membrane integrity (Annexin V+ PI+ cells). Confocal microscopy of unfixed cells revealed detection of C3/C3b in a granular distribution, possibly in blebs and/or other endosomal compartments. To determine whether surface-exposed C3/C3b had functional relevance, we blocked the macrophage C3bi receptors CR3 and CR4 with antibodies, and compared phagocytosis of apoptotic cells in the absence of serum. Strikingly, functional blockade of CR3 and CR4 on human macrophages in the absence of serum specifically reduced the uptake of C3bi+ late apoptotic cells, and not that of latex beads (with an inhibition of 19.3% for CR3, 21.4% for CR4, and 48% for CR3+CR4 blockade; p = 0.182, 0.066 and 0.043, respectively).

**Conclusion**: Our results suggest that we have uncovered a novel function of intracellular complement C3 activation products in the removal of dying cells. C3 is a very large protein of 185,000 molecular mass and penetration into tissues is likely to be limited. Cell intrinsic, serum-independent, C3-mediated clearance of apoptotic cells may therefore be of particular relevance in tissues where there is accumulation of dead cells as observed in patients with SLE, as well as under other conditions such as hypoxia reperfusion injury and stroke.

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CaMK4 Inhibition Ameliorates the Development of Th17 Driven Inflammatory Disease through an IL-17-dependent mechanism.

Background/Purpose: IL-17 producing T helper (Th17) cells have been closely associated with the development of organ damage in inflammatory and autoimmune diseases. We have previously shown that Calcium/calmodulin-dependent protein kinase IV (CaMK4) plays a crucial role in Th17 cell differentiation in vitro and in vivo and suggested that CaMK4 inhibition ameliorates clinical and pathological findings in experimental autoimmune encephalomyelitis (EAE) and MRL/lpr mice (1). We have also shown that iNOS-1 is important in the expression of anti-glomerular basement membrane Ab-induced glomerulonephritis (AIGN) (2). However, the effect of CaMK4 on recruitment of pathogenic T cells to target tissues in inflammatory settings has not been studied.

Methods: To determine the role of CaMK4 in the infiltration of inflammatory cells to target tissues, we induced experimental AIGN in CaMK4 sufficient or deficient mice and compared the kidney injury including the number of IL-17 producing cells in both groups. We also evaluated the effect of KN-93, a compound of CaMK4 antagonist in this AIGN model.

Results: CaMK4 deficient mice displayed less glomerular injury and less protoporphyrin IX (PPIX) at day 34 and at day 21 after induction of AIGN. Kidney infiltration by Th17 producing CD4 T cells was decreased significantly in CaMK4 deficient mice, suggesting that CaMK4 facilitated AIGN damage by promoting local inflammatory cells accumulation. In line with these observations, KN-93 treatment improved clinical and pathological findings in mice induced AIGN at dose dependent manner.

Conclusion: Collectively, our results indicate that CaMK4 inhibition might be a novel therapeutic strategy of Th17 cells-mediated inflammatory diseases.

References:
1. CaMK4-dependent activation of AKT/tmTOR and CREM-α underlies autoimmunity-associated Th17 imbalance.

Disclosure: T. Koga, None; K. Otomo, None; M. Mizui, None; Y. Yoshida, None; J. C. Crispin, None; A. Kawakami, None; G. C. Tsokos, None.

Survivin Co-Ordinates Formation of Follicular T-Cells in Rheumatoid Arthritis.

Survivin is a proto-oncogene that regulates cell division and apoptosis. Recently, survivin has emerged as a biomarker of persistently active and joint destructive rheumatoid arthritis (RA). High serum levels of survivin are frequently associated with antibodies against cyclic citrullinated epitopes (ACPA). Here we study the role of survivin in the formation of follicular T-cells and in the antibody production in RA.

Methods: The intracellular expression of survivin and Bcl-6 was studied in RA patients (age 21-71 years, disease duration 1-49 years) by flow cytometry and qPCR. DNA binding of survivin and Bcl-6 was studied in in RA patients (age 21–71 years, disease duration 1–49 years) by flow cytometry and qPCR. DNA binding of survivin and Bcl-6 was studied in the antibody production in RA.

Results: The sSurv-RA group (n=76) was characterized by higher frequency of RF+ and ACPA+ patients, as well as by higher levels of ACPA compared to sSurv-RA (n=68). Intracellular survivin was present in the effectors (CD45RA+CD27+) CD4+ T cells. Survivin co-expressed with Bcl-6 on lymphocytes of arthritic mice and in RA patients. Bcl-6+ subset comprised 7-38% of surv-CD4+ T-cells and was also CXCR5+. Bcl6+ Surv+ subset of CD4 T cells and mRNA levels of Bcl-6 were lower in blood of sSurv+ patients.

Conclusion: Follicular (CXCR5+PD-1+) CD4 population in spleen and lymph nodes of arthritic DBA1 mice were mostly surv-Bcl6+. Mice treated with survivin-derived peptides developed the phenotype similar to sSurv+ RA patients and had high serum levels of survivin and higher levels of aCII and RF antibodies. Surv- vaccinated mice had significantly increased survivin expression and the subset of surv-Bcl6+ within CXCR5+CD4+ cells in LN. shSurv-treated mice had reduced CD4+surv+ and CD19+surv+ populations in spleens, and smaller CXCR5+CD4+ and CXCR5+B220+ populations. While Bcl-6 gene transcription was increased, inhibiting survivin led to reduced levels of anti-CII antibodies and lower RF, suggesting insufficient Bcl-6 and poor Th17 development. Chromatin immunoprecipitation showed that survivin binds within Bcl-6 responsive element of Blimp-1 promoter potentially controlling transcriptional activity of Bcl-6.

Disclosure: M. Bokarewa, None; K. Andersson, None; M. Erlandsson, None; M. Svensson, None; N. Cavallini, None; M. Brisslert, None.

T-Cell Signaling Defects Can Be Corrected By Manipulating ‘TCR Signal Fine Tuning’ Molecules That Are Altered Due to Increased Ubiquitination in Systemic Autoimmune Disease.

Background/Purpose: T-cell selection in the thymus is primarily determined by the avidity of T cell receptor (TCR) for self-ligand-MHC. Since this process is dependent on the somatically generated receptors against the internal antigenic environment, all T cells are inherently self-reactive to some degree. Hence, a signaling threshold must be established whereby overtly high self-avidity, potentially pathogenic, T cells are removed, while allowing other lower self-avidity T-cells to survive. Using a avidity-based TCR transgenic model system, we found that besides the TCR, there are other signal regulating molecules that play a role in establishing signal threshold during thymic selection known as TCR tuning, which controls the intensity of TCR signaling (Pinkhasov et al, manuscript in preparation). Here, we determined the expression of potential TCR signal fine-tuning (TFT) molecules in a model of multi-system autoimmune disease, and investigated their role in T-cell signaling defects and mechanisms of their alteration.

Methods: The availability of murine strains that develop autoimmune disease resembling human SLE enables one to study the preclinical events in the pathogenesis. Here, we used MRL/MpJ-Fas-/- (MRL/+/-) mice that develop SLE at 8–10-months of age, congenic MRL/MpJ-Fasgrgpr (MRL/ppr) mice that develop accelerated SLE due to a mutation of the fas gene, and MHC-matched C3H control mice. To analyze TFTs in antigen-specific T cells, studies were repeated in MRL/ppr, MRL/+/- and healthy B10.BR mice carrying the AND TCR transgene.

Results: We found the altered expression patterns of a battery of TFTs on thymocytes from MRL/ppr and MRL/+/- mice compared to C3H controls; specifically, negative regulator TFTs were reduced, while positive regulator was increased. Thymocytes from young MRL/+/- and MRL/ppr mice showed increased activation and phosphokinase signal upon ex vivo stimulation, which were restored to near normal levels in the presence of a CDS agonistic antibody. Unexpectedly, we observed a drastic reduction of TFTs in activated peripheral T-cells after disease onset. The reduced levels of negative TFTs correlated with increased responsiveness to TCR stimulation and to weak antigenic ligands. The reduced expression of TFTs in periphery was not due to their decreased transcripts, but rather, to activation-induced post-translational modification due to increased ubiquitination leading to targeted protein degradation. This was associated with an altered expression of E3 ubiquitin ligases CIITA, Tra1-81, and Hc1 in MRL mice.

Conclusion: These results suggest that T-cells are able to tune the expression levels of TFTs post-development, likely by targeted protein degradation using the ubiquitin cycling pathway. We propose that the ability of T-cells to alter their internal signal threshold by altering TFP expression is a novel mechanism for
T-cells to escape peripheral tolerance and perpetuate autoimmune disease. Restoration of TCR signals to normal upon increased signaling through a TFF raises hope for a new avenue of treating systemic autoimmune diseases.

Disclosure: J. Pinkhasov, None; R. R. Singh, None.

2849

Involvement of CD8⁺ T Cells in the Pathogenesis of Giant Cell Arteritis and Polymyalgia Rheumatica. Maxime Samson¹, Sylvain Audia², M. Alika Trad¹, Marion Ciudad³, Hervé Devilliers¹, Alexandre Gautheron², Valérie Quipourt¹, François Maurier¹, Nadine Mœaux Ruault¹, Patrick Manckoundia¹, Paul Ornetti¹, Jean-François Maillefer³, Jean-François Besancenot¹, Christophe Ferrand³, Philippe Saïs³, Laurent Martin⁴, Nona Jankishvili⁵, and Bernard Bonnotte⁶. ¹INSERM UMR 1098, Besançon ; ²University of Burgundy, Faculty of Medicine, IFR100 ; ³Department of Internal Medicine and Clinical Immunology, Dijon, France; ⁴INSERM UMR 1098, Besançon, Dijon, France; ⁵Department of internal medicine and systemic diseases, Dijon, France; ⁶Department of Geriatric Internal Medicine, Dijon, France.

Background/Purpose: Previous studies have demonstrated the implication of CD4⁺ T cells, especially T helper (Th1) and Th17 cells, in the pathogenesis of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). However, very little is known concerning CD8⁺ T cells. This study aimed to investigate their implication in the pathogenesis of GCA and PMR.

Methods: Thirty patients suffering from GCA (n = 23) or PMR (n = 7) and 21 age-matched healthy volunteers were enrolled. Blood samples were collected at diagnosis and after 3 months of glucocorticoid (GC) treatment. Percentages of circulating cytotoxic T lymphocytes (CTL) (CD3⁺CD8⁺ Perforin⁺ GranzymeB⁺), Tc1 cells (CD3⁺CD8⁺ IFN-γ⁺), Tc17 cells (CD3⁺CD8⁺ IL-17⁺) and the expression of CXCL9, HLA-D, CR5, CR6, CR7, CD26L and CXCR3 by CD8⁺ T cells of GCA and PMR patients were determined by flow cytometry analysis. Levels of soluble Granzyme A, Granzyme B, CCL2, CCL20, CCL9, CXCL10 and CXCL11 were determined by ELISA or LumineX® technology. Temporal artery biopsies (TAB) were stained for CD3, CD4, and CD8. Data are expressed by mean±SEM and P value is the result of the Mann Whitney U test or Wilcoxon matched-pairs signed rank test, when appropriate.

Results: Percentages of circulating CTL and Tc17 in total CD8⁺ T cells were significantly higher in controls: 36.6±4.1% vs. 16.3±3.1% (P = 0.0004) and 5.9±0.11 vs. 0.15±0.03% (P < 0.0001), respectively. The level of Tc1 cells was not different between two groups. CD63 expression, which is expressed at the membrane once CTL have degranulated, was higher in patients than in controls (29.3±3.5 vs. 14.8±2.9%; P = 0.003). Levels of Granzyme A and B were also significantly increased in the serum of patients when compared to controls: 20.6±4.4 vs. 11.6±2.7 µg/mL (P = 0.02) and 3.2±1.3 vs. 0.95±0.49 µg/mL (P = 0.044), respectively. After 3 months of GC treatment, percentages of circulating CTL and Tc17 and soluble levels of Granzyme A and B were significantly decreased, whereas the percentages of Tc1 and CD3⁺CD8⁺ cells in total CD8⁺ T lymphocytes remained stable. Expression of chemokine receptors was comparable between patients and controls except for CXCR3 that was expressed at a higher level by CD8⁺ T cells from patients: 48.1±3.6 vs. 28.5±3.5% (P = 0.0004). Levels of CXCR3 ligands were increased in the serum of patients compared to controls: 629.8±194.7 vs. 92.8±132.2 pg/mL (P = 0.0001) for CXCL9, 31.4±6.9 vs. 9.2±1.5 pg/mL (P = 0.0001) for CXCL10 and 120.±0.1 vs. 35.7±2.7 pg/mL (P = 0.009) for CXCL11. Importantly, the levels of these 3 chemokines were decreased after 3 months of GC treatment. Immunohistochemical analyses of TAB (5 GCA patients) revealed a strong infiltration by CD4⁺ and CD8⁺ T cells in all the layers of the artery.

Conclusion: This study provides the first data that demonstrate an implication of CD8⁺ T cells in the pathogenesis of GCA and PMR. In untreated patients, CD8⁺ T cells, that infiltrate lesions of vasculitides, have an activated phenotype that is partly corrected by GC treatment. CXCR3 is upregulated on CD8⁺ T cells from GCA and PMR patients while levels of CCL9, -10 and -11 are increased in the serum of patients, which argues for the implication of CXCR3 in the homing of CD8⁺ T cells in the lesions of GCA.

Disclosure: M. Samson, None; S. Audia, None; M. Trad, None; M. Ciudad, None; H. Devilliers, None; A. Gautheron, None; V. Quipourt, None; F. Maurier, None; N. Mœaux Ruault, None; P. Manckoundia, None; P. Ornetti, None; J. F. Maillefer, None; J. F. Besancenot, None; C. Ferrand, None; P. Saas, None; L. Martin, None; N. Jankishvili, None; B. Bonnotte, None.
Background/Purpose: Patients with age-related macular degeneration (AMD), a leading cause of irreversible blindness, have a 10-fold increased prevalence of abdominal aortic aneurysms. Single nucleotide polymorphisms (SNPs) in a number of genes, including Complement Factor H (CFH) on chromosome 1 and age-related macular susceptibility protein 2 (ARMS2) and HTRA Serine Peptidase 1 (HTRA1) on chromosome 10, are strongly associated with increased risk for developing AMD. These AMD-associated loci are also strongly associated with vasculopathies, including choroidal neovascularization, EGPA, and Takayasu’s arteritis. The aim of this study was to test the hypothesis that AMD-associated gene variants may also be involved in the development of vasculitis, especially the large-vessel vasculitides (LVV) and Takayasu’s arteritis (TAK).

Methods: A candidate gene study was performed to investigate the association between variants in AMD and LVV (TAK) gene. In these subjects, presence of the killing activity was determined for 1799 of the controls and 1710 of the cases. In these subjects, presence of the killing activity was determined for 1799 of the controls and 1710 of the cases. The study included patients with LVV and 1248 healthy controls matched for age, sex, race, and ethnicity. Additive p-values were calculated for each subtype of vasculitis.

Results: The main results of the study are reported in the Table. The controls had a minor allele frequency (MAF) of 21% for rs10490924. Overall, there was a significant association of all vasculitis types with rs10490924.

Type of vasculitis

<table>
<thead>
<tr>
<th>Type of vasculitis</th>
<th>Cases, n</th>
<th>MAF in cases</th>
<th>MAF in controls</th>
<th>Additive OR (95% CI)</th>
<th>Additive p-value</th>
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<td>0.21</td>
<td>1.15 (1.00–1.32)</td>
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</table>

Conclusion: This candidate gene study demonstrated a significant association between variants in ARMS2 and idiopathic forms of vasculitis, including large-vessel vasculitides. Further validation is needed, this study suggests the possibility of a common pathogenesis between arteriopathology in AMD and large-vessel vasculitis.

Association of rs10490924 with Vasculitis

2852 Evaluation of KIR3DL1/KIR3DS1 Association with Behcet’s Disease in Turkish Individuals.

Background/Purpose: Behcet’s disease (BD)-associated HLA-B type, HLA-B*51 (B*51), is a ligand for a pair of allotype killer immunoglobulin-like receptors (KIR) present on cytotoxic cells — KIR3DL1, which inhibits their cytotoxicity, and KIR3DS1, which activates their cytotoxic activity. KIRs are inherited in evolutionarily conserved haplotypes in which KIR3DL1 and KIR3DS1 are mutually exclusive. We therefore tested the hypothesis that KIR-regulated cytotoxic mechanisms contribute to BD by testing for association between the presence of KIR3DL1 and KIR3DS1 alleles in Turkish individuals.

Methods: Turkish BD patients (n = 1,900) and controls (n = 1,779) were genotyped for the KIR3DL1 and KIR3DS1 alleles with two sequence-specific PCR assays. Genotypes of 6,994 SNPs from the HLA region were determined with the Illumina bead array and used to impute the individuals’ HLA types using SNP2HLA and a reference panel of 5,225 European individuals. A chi-squared test for association was used to evaluate the contribution of KIR3DL1 and KIR3DS1 to BD. A P-value less than 0.05 was considered significant.

Results: Classical HLA types were determined by imputation in all samples and types with posterior probability greater than 0.9 were included in analyses. KIR3DL1 and KIR3DS1 genotypes were determined for 1799 of the controls and 1710 of the cases. In these subjects, presence of the killing activity was determined for 1799 of the controls and 1710 of the cases. The activating allele did not appear to interact with HLA-B alleles. It was present at similar frequencies in B*51-positive cases and controls (43.0% vs 43.0%, P = 0.63), in Bw4-positive cases and controls (43.0% vs 41.1%, P = 0.31), and in cases and controls bearing the Bw4 motif with isoleucine at position 80 (43.7% vs 41.4%, P = 0.32). Similarly, no disease association was found for the inhibitory KIR3DL1 allele in all the samples or any in the HLA-B subsets.

Conclusion: We found no association of BD with the presence of the KIR3D activating (KIR3DS1) or inhibitory (KIR3DL1) receptors, which together regulate cytotoxic cell activity through binding of a subset of HLA class I molecules, including the BD-associated HLA-B*51. Due to the complexity of this locus (i.e., sequence variation, copy number variation), lack of association between BD and the presence/absence of KIR3DS1 or KIR3DL1 does not exclude a role for KIRs in the pathogenesis of BD. Further studies of KIR3DL1/KIR3DS1 types and copy number variants, as well as other KIRs, are warranted.

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2853 Comparative Study of Inflimab Versus Adalimumab in Patients with Refractory Uveitis Due to Behcet’s Disease. Multicenter Study of 125 Cases.

Results:

- Inflimab was well tolerated by all patients.
- Adalimumab was well tolerated by all patients.

Conclusion: The study found no significant difference between the two treatments in terms of efficacy and safety.
1 year of therapy ADA and IFX do not show differences in the visual outcome of patients with refractory ulcers due to BD.

Conclusion: After 1 year of therapy ADA and IFX do not show differences in the visual outcome of patients with refractory ulcers due to BD.

Table: Treatment results at 1 year of therapy: Differences between ADA and IFX

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ADA/IFX</th>
<th>Crude Odds ratio (95% confidence interval) Adjusted Odds ratio* (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity improvement (differences)</td>
<td>66.7%/88.2% 2.148 (0.879–5.250)</td>
<td>0.094 1.84 0.214</td>
</tr>
<tr>
<td>Inactive anterior chamber inflammation</td>
<td>67.6%/82.1% 1.324 (0.528–3.323)</td>
<td>0.550 1.66 0.346</td>
</tr>
<tr>
<td>Inactive Vitritis</td>
<td>60.5%/66.7% 0.767 (0.330–1.782)</td>
<td>0.537 0.86 0.765</td>
</tr>
<tr>
<td>Inactive retinal vasculitis</td>
<td>85.2%/93% 0.431 (0.089–2.099)</td>
<td>0.298 0.30 0.217</td>
</tr>
<tr>
<td>Macular thickness &lt; 250 microns</td>
<td>36.8%/21.3% 2.100 (0.539–8.185)</td>
<td>0.285 1.447 0.620</td>
</tr>
</tbody>
</table>

* adjusted for age, sex, and disease duration.

Disclosure: L. Riano-Zarrabellota, None; Y. Calvo-Rio, None; R. Blanco, None; P. Rodriguez-Cundin, None; E. Beltran, None; J. Sanchez Burson Sr., None; M. Mesquida, None; A. Adan, None; M. V. Hernandez, None; M. Hernandez Graffel, None; E. Valis Pascual, None; L. Martinez-Costa, None; A. Selgas-Fernandez, None; M. Cordero-Coma, None; M. Diaz-Llopis, None; R. Gallego, None; J. L. Garcia Serrano, None; N. Ortego-Centeno, None; J. M. Herreras, None; A. Fonollosa, None; A. M. Garcia-Aparicio, None; O. Maiz Alonso, None; A. Blanco, None; I. Torre Salabelli, None; C. Fernandez Espatero, None; V. Jovani, None; D. Pelaeo, None; E. Pato, None; J. Cruz, None; C. Fernandez, None; E. Andreu Franca, None; M. A. Munoz Fernandez, None; C. A. Montilla Morales, None; F. Francisco, None; S. Insua, None; S. Gonzalez-Suarez, None; M. A. Sanchez Andrade, None; F. Gameo, None; L. F. Linares Ferrando, None; F. Romero, None; A. J. Garcia-Gonzalez, None; R. Almeoador Gonzalez, None; E. Miguez, None; C. Carrasco Cubero, None; A. Blanco, None; J. Vazquez, None; O. Ruiz Moreno, None; F. J. Jimenez-Zorzo, None; J. Manero, None; S. Munoz Fernandez, None; J. Rueda-Gotor, None; T. Pina, None; M. Santos-Gomez, None; M. A. Gonzalez-Gay, None.

2854

Effect of Apremilast on Quality of Life and Physical Function in Patients with Behcet's Syndrome. Gulen Hatemi1, Melike Melikoglu2, Recep Tunc2, Cengiz Korkmaz2, Barun Turgit Ozturk2, Cem Mat2, Peter A. Merkel2, Kenneth Calamia2, Lilia Pineda3, Ziqi Liu4, Randall M. Stevens5, Hasim Y azici6 and Yusuf Y azici6.

Wednesday, November 18

Background/Purpose: The oral ulcers in Behcet's syndrome (BS) can be painful, causing difficulty in eating and speaking, and can impair the quality of life. Apremilast is an oral phosphodiesterase 4 inhibitor that modulates inflammatory pathways. A clinical trial demonstrated a beneficial effect on oral ulcers with this agent. For this study, we aimed to assess whether apremilast is effective in improving quality of life in patients with BS.

Methods: This was a phase 2, multicenter, controlled study of 111 patients with BS, without major organ involvement but with ≥2 oral ulcers, who were randomized to apremilast 30 mg BID or placebo for 12 weeks, followed by a 12-week active-treatment period for all patients. The primary outcome, which was the number of oral ulcers at Week 12, and secondary outcomes at Week 12, including oral ulcer pain, number of genital ulcers, number of patients with a complete or partial response, number of genital ulcers, and disease activity assessed by the BS activity scale (BAS) and Behcet’s disease current activity form, have already been reported. We now report the results of health related quality of life measurements from the trial (using the BSQoL questionnaire). We used the BSQoL questionnaire and the SF-36v2 questionnaire to assess quality of life at baseline and at Week 12.

Results: The mean ± SD BASQoL score showed a significantly greater improvement from baseline at Week 12 with apremilast vs. placebo (4.5 ± 7.61 vs. –1.6 ± 5.30; p = 0.0397). The mean ± SD SF-36v2 physical

S1247
Efficacy and Safety of Rituximab Retreatment Regimen at Clinical Relapse in Severe Cryoglobulinemic Vasculitis. Luca Quaruccio1, Francesca Zuliani2, Patrizia Scaini1, Marco Lenzi1, Antonio Tavoni1, Marco Sebastiani1, Teresa Urraro1, Francesco Saccardo1, Costanza Sbrigella2, Pietro Pioletti1, Paolo Fraticelli1, Davide Filippini1, Salvatore Scarpato1, Onesti Perrella1, Armando Gabrielli14, Dario Roccatello15, Anna Linda Zignego2, Clodoveo Feri2, Stefano Bombardieri7, Maurizio Pietrogrande8, Massimo Gali3, Giuseppe Monti9 and Salvatore De Vita10.

Background/Purpose: Two independent controlled randomized trials recently reported the efficacy and safety of rituximab (RTX) monotherapy in severe cryoglobulinemic vasculitis (CV) (1, 2), with one reporting a follow-up lasting two years (1). The aim of this study is to report the very long term efficacy and safety of a retreatment regimen with RTX administered at clinical relapse after the end of the abovementioned trial (1).

Methods: Long term follow up data of a trial of RTX in severe CV (1) were analysed, by considering patients managed with retreatment with RTX at clinical relapse. During this follow-up, only RTX monotherapy was used. Number of retreatments, disease activity at last follow up, adverse events and causes of deaths were registered. Clinical response was evaluated at the last follow-up visit, as follows: i) complete response (remission), partial response (response < 50% of at least one manifestation among glomerulonephritis, severe neuropathy or skin ulcers) (1), and active disease despite treatment.

Results: After the end of the 24-month controlled trial (1), follow-up data were analysed in 30 patients, all positive for hepatitis C virus infection. The mean follow up after beginning of RTX therapy (1) was 72.6±20.4 months, including 24 (80%) patients followed for more than 4 years and 6 (20%) patients followed for 2.4–4 years. Of them, 21 patients were still under an active follow up, 3 patients were lost from follow-up shortly after the end of the trial, and 6 patients died. Survival of RTX regimen was 7.6±0.3 yrs (mean±standard error). Seventeen out of 30 (56.7%) patients needed a retreatment for relapse of their disease after 6 months. 6/30 were retreated during the first 9 months only after the end of the trial and 1/30 during both follow-up periods, accounting for 25 retreatments in total, the first one at a mean of 22.3±12.1 months from last RTX cycle during the trial. Patients were retreated for nephritis (7/25), neuropathy (12/25), skin ulcers (6/25) or widespread purpura (6/25). Of the 17 patients retreated, 6/17 (35.3%) showed complete response at the last follow-up, 5/17 (29.4%) a partial response, while 6/17 (35.3%) had an active disease. Interestingly, of the remaining 13/30 patients undergoing only one single course of RTX during the follow-up, 6/13 were still in active follow-up and in clinical remission at the last follow-up. Recurrent infections occurred in three patients (10%; urinary and upper respiratory), related to severe hypogammaglobulinemia (IgG < 3 g/l) in 2/3. Death occurred in 6 patients. However, only 2/6 deaths were linked to relapsed vasculitis, with new onset of intestinal vasculitis.

Conclusion: A long-term RTX monotherapy with a retreatment at relapse regimen is effective and safe in cryoglobulinemic vasculitis, with low rate of severe hypogammaglobulinemia. Clinicians should be aware to promptly recognize and treat clinical relapse, as well as concomitant infections. Relapses with life-threatening manifestations (i.e. intestinal vasculitis) were uncommon. Further investigation may be required to select patients where maintenance RTX therapy may be the best choice.

References:

Disclosure: L. Quaruccio, None; F. Zuliani, None; P. Scaini, None; M. Lenzi, None; A. Tavoni, None; M. Sebastiani, None; T. Urraro, None; F. Saccardo, None; C. Sbrigella, None; P. Pioletti, None; P. Fraticelli, None; D. Filippini, None; S. Scarpato, None; O. Perrella, None; A. Gabrielli, None; D. Roccatello, None; A. L. Zignego, None; C. Feri, None; S. Bombardieri, None; M. Pietrogrande, None; M. Gali, None; G. Monti, None; S. De Vita, None.
Restricting Back Pain Is Strongly Associated with Disability in Community-Living Older Persons over the Course of 13 Years. Una Makris, Lisa Fraenkel, Ling Han, Linda Leo-Summers and Thomas M. Gill. 1Department of Medicine, University of California, Los Angeles, CA; 2Department of Medicine, New Haven, CT, 3Department of Medicine, New Haven, CT, 4Yale University, New Haven, CT.

Background/Purpose: Although back pain is common and costly, few longitudinal studies have evaluated the association between back pain severe enough to restrict activity and the development of disability. The objective of this study is to evaluate the association between RBP and subsequent episodes of disability in basic, instrumental, and mobility activities, respectively.

Methods: Participants included the 754 members of the Precipitating Events Project (median age 78 y, 64.6% women), a prospective study of community-living persons, aged 70+ years, who completed monthly telephone assessments of RBP and disability, and who were at risk for developing new and recurrent disability episodes for up to 159 months. RBP was defined as staying in bed for at least 1/2 day and/or cutting down on one's usual activities due to back pain. Disability was defined as needing help with/inability to complete ≥1 of the activities, listed in the Table, in any given month for each of the three outcome categories. The event rates for the three disability outcomes were estimated using a GEE Poisson model. A recurrent events Cox model was used to evaluate the association between RBP and each of the three disability outcomes. The model was adjusted for fixed-in-time (sex, education, ethnicity) and time-varying covariates (listed in Table) (age, chronic conditions, BMI, depressive symptoms, cognitive impairment, physical frailty) that were updated every 18 months.

Results: For the basic, instrumental and mobility activities, the disability event rates were: 3.6 per 100-person months (95% CI 3.37, 3.89), 8.5 per 100-person months (95% CI 8.05, 8.98), and 9.38 per 100-person months (95% CI 8.98, 9.81), respectively, with a median duration of 2 months per disability episode for each of the three outcomes. The unadjusted and adjusted associations of restricting back pain with the 3 disability outcomes are listed in the Table.

Conclusion: In this longitudinal study, RBP was independently associated with disability in basic, instrumental and mobility activities among older persons. Interventions directed at preventing or decreasing RBP may reduce the likelihood of disability in activities across three key domains of function.

### Table 1. ANOVA with OES as Dependent Variable (p<0.003)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>OES Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High School or less</td>
<td>50</td>
<td>3.66</td>
<td>0.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Some College/Trade School</td>
<td>91</td>
<td>3.96</td>
<td>0.88</td>
<td>0.06</td>
</tr>
<tr>
<td>College Degree</td>
<td>51</td>
<td>4.13</td>
<td>0.50</td>
<td>0.75</td>
</tr>
<tr>
<td>Graduate School</td>
<td>64</td>
<td>4.24</td>
<td>0.55</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

Disclosure: T. Gamache, None; L. L. Price, None; J. B. Driban, None; W. F. Harvey, None; C. Wang, None.

Randomized Controlled Trial of Postoperative Care Navigation in Total Knee Arthroplasty Patients: Does One Size Fit All? Elena Losina, Jamie E. Collins, John Wright, Meghan E. Daigle, Laurel Donnell-Fink, Doris Strnad, Vladislav Lerner, Stanley Abrams and Jeffrey N. Katz. Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: A number of TKA recipients have suboptimal improvements after surgery. Our objective was to establish the efficacy of a motivational-interviewing (M)-based telephone intervention aimed at improving functional outcomes post-TKA and to identify subgroups especially likely (or unlikely) to benefit from the intervention.

Methods: We conducted the RCT to compare functional status in TKA recipients randomized to one of two strategies: 1) enhanced postoperative care with frequent follow-up by a care navigator; 2) usual postoperative care. Those who were randomized into the care navigation arm received ten calls from a trained non-clinician care navigator over the first 6 months post-TKA. The trained navigator used theory-driven M to engage TKA recipients in discussions about their rehabilitation goals, including plans for confidence in achieving those goals. Patients in the usual care arm received standard postoperative care. Patients in both arms were assessed at baseline, 3 and 6 months post-TKA. The study enrolled subjects 40+ years of age with OA who were scheduled for TKA. Primary outcome was the difference between the arms in WOMAC function score change, over the 6 months post-TKA.
We defined a satisfactory functional improvement as either achieving WOMAC function scores $< 15$ or reducing pre-operative functional score by $19$+ points, suggested as MCID in TKA patients (Escobar, 2007). We examined whether sex, obesity and pain catastrophizing affected the efficacy of the care navigator intervention.

**Results:** We enrolled 309 TKA recipients, average age 67 years; 60% female. 84% Kelgren-Lawrence Grade 4, 50% obese (BMI $> 30$ kg/m$^2$). Mean pre-operative WOMAC function score was $40$ (18), on a 0-100 scale; 100-worst. Baseline characteristics did not differ between study arms. At 6 months, participants in care navigation arm improved by 29.4 (16.1) points compared to 26.1 (18.3) in control arm ($p = 0.1126$). Overall, 21% of study participants did not achieve satisfactory functional improvements, with similar rates across arms. Greater pain catastrophizing led to less improvement over and its association with poor outcome was more prominent among females compared to males ($p$ value for interaction $= 0.0022$). Further analysis revealed that females showed that greater pain catastrophizing modified the impact of the intervention: females with a low degree of pain catastrophizing improved by 8 points more (33 vs. 25) in the navigation arm than in the control arm, while females with a high degree of pain catastrophizing improved by five points less in the navigation arm than in the control arm ($p$-value for interaction $= 0.0233$).

**Conclusion:** The results of this RCT did not show benefits of the MI based enhanced postoperative care navigation in functional improvements in TKA recipients. The negative overall result could be explained by differential effect of intervention among females with high and low levels of pain catastrophizing. Greater focus on understanding the determinants of and effective therapies for reducing pain catastrophizing could improve the efficacy of interventions focused on better functional outcomes in TKA recipients.

**Disclosure:** E. Losina, None; J. E. Collins, None; J. Wright, DePuy, A Jhonson & Johnson Company, 5, DePuy, A Jhonson & Johnson Company, 7; M. E. Daigle, None; L. Donnäll-Fink, None; D. Strnad, None; V. Lerner, None; S. Abrams, None; J. N. Katz, None.

**2860**

**Randomised Comparison of the Effectiveness of a Non-Pharmacological Multidisciplinary Face-to-Face Group-Based Treatment Program Vs a Telephone-Delivered Treatment Program on Knee Function in Patients with Generalized Osteoarthritis.** Nienke Cuperus$^1$, Thomas Hoogeboom$^2$, Clarinda Kersten$^3$, Leonie Rietveld$^4$, Aïfons den Broeder$^5$, Thea Vliet Vlieland$^6$ and Cornelia H.M. van den Ende$^6$. 1Sint Maartenskliniek, Nijmegen, Netherlands, 2CAPRI school for public health and primary care, CCTR centre for Care Technology Research, Maastricht University, Maastricht, Netherlands, 3Leiden University Medical Center, Leiden, Netherlands.

**Background/Purpose:** Generalized osteoarthritis (GOA) is a widely accepted and prevalent OA phenotype characterized by the involvement of multiple joints. However, current research and clinical practice mostly examine OA populations for a specific OA localization. The effectiveness of non-pharmacological interventions for GOA is therefore largely unknown. In addition, there is no evidence concerning the optimal mode of care delivery. Therefore, we compared the effectiveness of a non-pharmacological multidisciplinary face-to-face group-based treatment program versus a telephone-delivered treatment program on daily function for patients with GOA, until one year after treatment.

**Methods:** In this single blind randomized clinical superiority trial, individuals clinically diagnosed with GOA were randomly allocated to either a six week multidisciplinary face-to-face group-based treatment program or a six week telephone-delivered treatment program. Both programs aimed to improve daily function and to enhance self-efficacy to control the disease. The programs had comparable content but critically differed in mode of delivery and intensity. Primary (daily functioning; HAQ-DI) and secondary outcome measures were assessed at baseline, 6, 26 and 52 weeks. The 6-week time point was used to assess the short-term effects of both interventions. The average score obtained from the 6, 26 and 52 time points was used to assess the long-term effects. Directly after finishing the treatment patient satisfaction was measured. Multiple imputation was used to estimate missing values. Differences in effectiveness between both treatment programs were analysed using linear regressions adjusted for baseline, sex and age.

**Results:** Of 158 randomized patients (mean (SD) age 60 (8); female 85%), 147 (93%) completed at least the baseline measurement and were included in the intention to treat analysis. Of these patients, 75 were allocated to the face-to-face-treatment program and 72 to the telephone-delivered treatment program. No difference in effectiveness between both treatment groups was found on the HAQ-DI at both the short (p = 0.59) and long-term (p = 0.65). Moreover, no differences in effectiveness between the two modes of care delivery on the secondary outcomes were found (p > 0.05). Patient satisfaction was significantly higher in the face-to-face treatment program than in the telephone-delivered treatment program.

**Conclusion:** In this trial we found no differences in effectiveness between two modes of delivery of non-pharmacological care for patients with GOA. Therefore, our results imply that the choice of mode of treatment delivery i.e. face-to-face versus telephone-delivered could be based on patients’ preferences and/or costs.

**Disclosure:** N. Cuperus, None; T. Hoogeboom, None; C. Kersten, None; L. Rietveld, None; A. den Broeder, None; T. Vliet Vlieland, None; C. H. M. van den Ende, None.

**2861**

**Changes in Knee Kinematics from a 6-Week Hip and Trunk Strengthening Program for Persons with Patellofemoral Osteoarthritis.** Lisa Hoglund$^1$, Laura Pontiggia$^1$, John Kelly IV$^2$, Mark Arnott$^1$, Olumide Babalola$^1$, Andrew Gushen$^1$ and James Carey$^1$. 1University of the Sciences, Philadelphia, PA, 2University of Pennsylvania, Philadelphia, PA.

**Background/Purpose:** Patellofemoral (PF) osteoarthritis (OA) is prevalent in middle-aged adults. Ablation lower extremity (LE) biomechanics is one etiology of knee OA. Reduced peak knee flexion angles and increased peak tibial abduction angles were reported during sit-to-stand (STS) in persons with general knee OA and with PF OA, respectively. Additionally, reduced strength of the hip abductor, hip extensor, and knee extensor muscles was reported in PF OA, which may impact LE biomechanics. Studies have reported improved knee and hip biomechanics in persons with PF pain when treated with proximal LE strengthening. It is unknown if a proximal LE strengthening program with pelvic/abdominal stabilization training will alter LE kinematics, improve symptoms, and improve function in persons with PF OA. This study examined the impact of a 6-week hip and trunk muscle strengthening and stabilization program on knee and hip kinematics during STS and a step-down (SDn) task and self-reported symptoms and function in persons with PF OA.

**Methods:** Six female subjects with PF OA and anterior knee pain, median age (interquartile range [IQR]): 52 years (48-56 years) participated in the study. Subjects attended a biomechanical evaluation, 10 supervised exercise treatment sessions, and a reevaluation. Biomechanics of the most painful LE were examined during STS from a stool and SDn on a 3-step staircase. Subjects were treated with hip and abdominal/trunk strengthening exercises. In addition, subjects were instructed in proper LE position and pelvic stability. Outcome measures included triplanar knee and hip joint peak angles and the Knee Injury and Osteoarthritis Outcome Score (KOOS). Data analysis included group medians (IQR) and Wilcoxon Signed Rank tests.

**Results:** Peak knee flexion angle during STS increased: Initial: 76° (67, 86), Final: 93° (87, 97), $p = 0.03$. Peak knee extension angle during STS decreased: Initial: 2° (0.4, 9), Final: -7° (-11, -4), $p = 0.03$. Peak knee extension angle during SDn decreased: Initial: -0.2° (-5, 0.5), Final: -11° (-16, -6), $p = 0.03$. KOOS-Symptoms score improved: Initial: 62 (54, 68), Final: 75 (68, 89), $p = 0.03$. KOOS-Function score improved: Initial: 69 (47, 76), Final: 84 (79, 85), $p = 0.03$.

**Conclusion:** A hip and trunk strengthening program with education in proper LE alignment and pelvic stability resulted in increased knee flexion angles and reduced knee extension angles during two tasks that increase PF joint stress. In addition, subjects reported significant improvement in symptoms and function. The intervention may have improved subjects’ ability to tolerate loading the PF compartment in activities requiring knee flexion. This may be one method to improve symptoms and function in persons with PF OA.

**Disclosure:** L. Hoglund, None; L. Pontiggia, None; J. Kelly IV, None; M. Arnott, None; O. Babalola, None; A. Gushen, None; J. Carey, None.

**2862**

**Satisfaction Following Total Knee Replacement: Journey or Destination?** Jeffrey N. Katz$^1$, Yian Dong$^1$, Jamie E. Collins$^1$, John Wright$^1$, David Dalury$^2$, Kirk Kinnsfater$^1$ and Elena Losina$^1$. 1Brigham and Women’s Hospital, Boston, MA, 2Townson Orthopedics, Maryland, Baltimore, MD, Orthopedic Center for the Rockies, Ft. Collins, CO.

**Background/Purpose:** Total knee replacement (TKR) outcome is often assessed with measures of pain and function (fxn), but there is no consensus on whether surgery should be evaluated as extent of improvement on these scores (“journey”) or final score (“destination”). We addressed this question.
by evaluating whether improvement (journey) or final score (destination) is more closely associated with patient satisfaction with TKR.

Methods: We analyzed data from a prospective, multicenter cohort undergoing TKR. Subjects completed the WOMAC Pain and Fxn scales (0–100, 100 worst) preoperatively and 6 months postoperatively. At 6 months patients also completed a question on satisfaction with results of TKR. We defined the journey criterion as improvement by the minimal clinically important difference following TKR, ≥23 points on the WOMAC Pain or ≥31 on WOMAC Fxn Scale (Escobar et al). The destination criterion was the Patient Acceptable Symptom State following TKR, <31 on WOMAC Fxn (Tubach et al). We calculated the number of subjects who achieved the journey criterion, the destination criterion, both or neither. In each group, we calculated the proportion who reported being dissatisfied, somewhat satisfied and very satisfied with surgery. We used ordinal logistic regression to examine independent effects of achieving journey or of achieving destination criteria on satisfaction with TKR.

Results: 329 subjects were included, mean age 66, 57% female. Mean preoperative WOMAC Pain and Fxn scores were 40 (sd 18) and 42 (sd 17) respectively. 238 subjects (72%) met both journey and destination criteria for success while 10 (3%) met neither criterion. 63 subjects (19%) achieved the destination criterion but not journey, while 18 patients (5%) achieved the journey criterion but not destination. Among subjects who achieved the destination but not the journey criterion, 59% were satisfied and only 6% were dissatisfied (Figure). Among those who achieved the journey but not the destination criteria, 44% were very satisfied and 33% were dissatisfied. In ordinal logistic regression models that adjusted for age, sex and baseline WOMAC Fxn, achieving the destination criterion had a stronger association with satisfaction (OR 7.7, 95% CI 3.2, 18) than the journey (OR 2.2, 95% CI 1.0, 4.7). This finding was essentially unchanged when we excluded the 30 subjects with preoperative WOMAC Fxn scores < 19, who were not eligible to achieve the journey criterion.

Conclusion: Improvement in outcome score (journey) and final score (destination) are distinct metrics for assessing results of surgery. In this TKR cohort, both metrics were associated with patient satisfaction with the results of TKR, with destination having a stronger association than journey. These data suggest that both journey and destination criteria should be integrated into patient-centered assessment of TKR.

Disclosure: J. N. Katz, None; Y. Dong, None; J. E. Collins, None; J. Wright, None; D. Dalury, None; K. Kindfater, None; E. Losina, None.
**Methods:** This study comprised 411 patients with autoimmune diseases who visited Hokkaido University Hospital Rheumatology Clinic between 2002 and 2003. Demographic, clinical data and cardiovascular risk factors were obtained from the medical charts. Lupus anticoagulant (LAC) assays and IgG/M anticardiolipin antibodies, IgG/M anti-β2-glycoprotein I antibodies and IgG/M phosphatidylserine dependent anti-thrombin antibodies were performed in all subjects. Among all the patients, 257 (62.5%) patients with follow-up period of more than 5 years (median follow-up periods: 126(IQR 92.5,33) months) were eligible. The demographic and clinical characteristics of these patients are as follows: 17(7%) primary APS, 25(10%) APS with systemic lupus erythematosus(SLE), 84(33%) SLE (without APS), 45(18%) rheumatoid arthritis and 85 patients with other autoimmune diseases.

To evaluate the diagnostic powers for GAPPS and aPL-S, area under the curve (AUC) of receiver operating characteristic (ROC) curves were calculated. To evaluate the powers of the two scores for thrombosis prediction, Cox proportional hazard regression analyses were performed separately for each score with the cut off derived on the ROC curve. Each risk factor for the multivariate Cox analyses were assessed through separate univariate Cox regression test. To evaluate and compare the predictive powers of the two scores, Somer’s d coefficient was calculated.

**Results:** Thirty-seven patients newly developed thrombosis during the observation period; 23 arterial thrombosis and 23 venous thrombosis. The ROC curve of GAPPS showed higher AUC than that of aPL-S (0.693 vs 0.656, p<0.05) indicating that GAPPS have better ability of diagnosing APS (GAPPS vs aPL-S: 0.693 vs 0.656, p<0.05 ). The cut off values of GAPPS and aPL-S for predicting future thrombosis were 10 and 31, respectively. The Cox multivariate proportional hazard regression analyses revealed that both scores, with appropriate cut off levels, accurately reflected the risks of future thrombosis with statistic significance (GAPPS – 10 p=0.01, aPL-S – 31 p=0.0001). The aPL-S showed higher Somer’s d coefficient than GAPPS (0.497 vs 0.412, respectively, p<0.05).

**Conclusion:** The aPL-S and GAPPS accurately reflected the diagnosis of APS and the risk for future thrombotic events in patients with autoimmune diseases in our cohort. GAPPS may have relatively high potential for APS diagnosis and aPL-S might be superior to GAPPS in predicting future thrombosis.

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**2866**

**External Validation of the Global Anti-Phospholipid Syndrome Score in Comparison to IgG Antibodies Directed Against Domain I of β2-Glycoprotein I. A Prospective Multicentre Cohort Study.**

**Background/Purpose:** The aim of this study was to externally validate the GAPPS score against other IgG antibodies directed against Domain I of β2-Glycoprotein I (aPL-I). To this end, we performed a prospective multicentre cohort study of patients with APS.

**Methods:** A total of 411 patients with APS were recruited from 12 centres in 9 European countries. Inclusion criteria were: clinical APS according to ACR criteria, presence of lupus anticoagulant (LA), or aPL-I in patients with APS. Exclusion criteria were: patients with systemic lupus erythematosus (SLE), or rheumatoid arthritis. The score was validated in the external cohort; 176 patients (43%) with APS and 235 control patients (57%). The primary outcome was the occurrence of a primary APS-related event. Patients were followed up for a median of 5 years (interquartile range 4-6 years).

**Results:** Of the 411 patients, 176 (43%) were included in the external validation cohort. The external validation cohort was similar to the development cohort with respect to several clinical characteristics, except that the proportion of women was lower in the external validation cohort. The externally validated GAPPS score had a strong predictive value for APS-related events (area under the ROC curve = 0.79, 95% confidence interval 0.74-0.84). The discriminatory power of the GAPPS score was similar to that of the aPL-I titre (area under the ROC curve = 0.76, 95% confidence interval 0.71-0.81). The externally validated GAPPS score remained a strong predictor of APS-related events after adjusting for age, sex, and cardiovascular risk factors (hazard ratio 1.04 per 1 point increase in GAPPS score, 95% confidence interval 1.02-1.06, p=0.003). The externally validated GAPPS score was highly predictive of both arterial and venous APS-related events (arterial: area under the ROC curve = 0.71, 95% confidence interval 0.64-0.79, p=0.007; venous: area under the ROC curve = 0.78, 95% confidence interval 0.71-0.85, p<0.001).

**Conclusion:** The externally validated GAPPS score was highly predictive of both arterial and venous APS-related events. The externally validated GAPPS score remained a strong predictor of APS-related events after adjusting for age, sex, and cardiovascular risk factors. The externally validated GAPPS score was highly predictive of both arterial and venous APS-related events. The externally validated GAPPS score remained a strong predictor of APS-related events after adjusting for age, sex, and cardiovascular risk factors.

**Disclosures:** B. Artim-Esen: None; N. Smoktunowicz: None; V. M. Ripoll: None; C. Pericles: None; R. Chambers: None; I. Mackie: None; D. Isenberg: None; A. Rahman: None; Y. Ioannou: None; I. Giles: None.
anticardiolipin and anti-\(\beta_2\)-glycoprotein I antibodies). GAPPS was computed for each patient.

**Results:** One hundred and thirty eight patients (median age 43.5±15.3 years; 108 women) were followed-up for a mean duration of 43±20.7 months (493.9 patient-years). Thrombosis during follow-up occurred in 16 patients (3 strokes, 1 myocardial infarction, 1 splanchic arterial thrombosis, 3 pulmonary embolisms, 3 deep veins, 5 small vessels thromboses). Higher values of GAPPS were seen in patients who experienced thrombosis compared to those without (10.9±4.8 vs 7.9±5.4, p=0.03). While triple positivity (HR = 3.38 [CI95%; 0.83–6.80], p=0.01) and GAPPS above 10 (HR = 1.56 [CI95%; 0.55–4.47], p=0.41) were not predictive of further incident thrombotic events, GAPPS above 16 (HR = 5.27 [CI95%; 1.16–23.39], p=0.03) and high levels of antiDI above the 90th percentile of patients (HR = 0.55–4.47, p=0.014) were highly predictive of incident thrombotic events.

**Conclusion:** GAPPS and high levels of antiDI are significant predictors of thrombosis in aPL/SLE patients. These antibodies seem to add a substantial improvement in risk prediction of thrombosis independently of clinical variables assessed by GAPPS’ components.

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### 2867

**Antiphospholipid Antibodies Promote the Release of Neutrophil Extracellular Traps: a New Mechanism of Thrombosis in the Antiphospholipid Syndrome**

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**Background/Purpose:** Antiphospholipid antibodies (aPL), especially those targeting beta-2-glycoprotein I, are known to activate endothelial cells, monocytes, and platelets, with prothrombotic implications. However, the interaction of aPL with neutrophils and leukocyte in human blood, the neutrophil, has only rarely been considered. Neutrophil extracellular trap (NET) release—a form of neutrophil cell death that results in the externalization of decondensed chromatin decorated with granular proteins—has recently been recognized as an important activator of the coagulation cascade, as well as an integral component of deep vein thrombi in both humans and animals. Here, we hypothesized that aPL activate neutrophils to release NETs, thereby predisposing to thrombosis.

**Methods:** Neutrophils, sera, and plasma were prepared from patients meeting criteria for primary antiphospholipid syndrome (APS) by the revised Sapporo classification criteria (n=50), or from healthy volunteers. Circulating NETs were quantified in sera and plasma by a myeloperoxidase-DNA quantification assay. NETs from aPL-positive patients were scored for their ability to release NETs by both immunofluorescence microscopy and fluorescence-based quantification of extracellular DNA. Neutrophils from healthy volunteers were stimulated with APS patient sera, purified IgG, or aPL monoclonal antibodies, and NET release was quantified; dependence on generation of reactive oxygen species was also determined. Expression of known aPL receptors, beta-2-glycoprotein I and annexin A2, was measured on the neutrophil surface.

**Results:** Sera and plasma from APS patients have elevated levels of NETs as compared to healthy volunteers (2.7-fold increase when comparing means; p=0.0279). Neutrophils isolated from patients with primary APS are predisposed to spontaneous NET release when compared to healthy volunteers (p=0.0143). Importantly, APS-patient sera and IgG purified from patients with aPL, stimulate NET release from healthy-volunteer neutrophils (p=0.004 and 0.0187, respectively). Human aPL monoclonal antibodies, especially those that target beta-2-glycoprotein I, also enhance NET release; this enhancement can be abrogated by blockade of reactive oxygen species production (histologically and/or at registry entry) as well as the association between the aPL-related events and the aPL profile (triple, double, or single positivity based on inclusion tests). The results did not change when the single aPL group was restricted to LA-positive patients only (data not shown). The percentages of patients tested for aPL, aCL, and a2GPI were 93%, 100%, and 76%, respectively in the double aPL-positive group; 97%, 99%, and 77% in the single aPL-positive group. The percentages of the patients with positive LA, aCL, and a2GPI were 65%, 89%, and 39%, respectively in the double aPL-positive group; and 72%, 23%, and 5% in the single aPL-positive group.

**Conclusion:** Serum and plasma from patients with primary APS have more circulating NETs than healthy controls. Sera and plasma from APS patients have elevated levels of NETs as compared to healthy controls. Neutrophil netting warrants further investigation as a novel therapeutic target in APS patients.

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### 2868

**Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION)**

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**Background/Purpose:** APS ACTION International Clinical Database and Repository (“Registry”) was created to study the natural course of disease over 10 years in persistently aPL-positive patients with/without other systemic autoimmune diseases. The objective of this preliminary analysis is to report the baseline characteristics of currently enrolled patients.

**Methods:** A secure web-based data capture system is used to store patient information including demographics, aPL/APS history, and aPL data. The inclusion criteria are positive lupus anticoagulant (LA) test based on the ISTH recommendations, medium-to-high titer (> 40U and/or > 99th percentile) anticardiolipin antibody (aCL) IgG/M/A, and/or medium-to-high titer anti-\(\beta_2\)-Glycoprotein-I (a2GPI) IgG/M/A tested at least twice within one year prior to enrollment. Clinical and blood collection (for core laboratory aPL confirmation and mechanistic studies) are performed once a year, or when patients develop new events. We used chi-square or Fisher’s exact test for group comparison, and linear-by-linear association test to analyze for trend.

**Results:** As of June 2014, 408 patients have been recruited from 17 centers globally (mean age at entry: 43.7±12.8y; female: 310 [76%]; white: 261 [69%]; and other systemic autoimmune diseases: 130 [32%]). Table shows the distribution of the aPL-related events (historically and/or at registry entry) as well as the association between the aPL-related events and the aPL profile (triple, double, or single positivity based on inclusion tests). The results did not change when the single aPL group was restricted to LA-positive patients only (data not shown). The percentages of patients tested for aPL, aCL, and a2GPI were 93%, 100%, and 76%, respectively in the double aPL-positive group; 97%, 99%, and 77% in the single aPL-positive group. The percentages of the patients with positive LA, aCL, and a2GPI were 65%, 89%, and 39%, respectively in the double aPL-positive group; and 72%, 23%, and 5% in the single aPL-positive group.

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**Disclosure of Grants:** None; None; None; None.
Autoimmune Hemolytic Anemia (n:23) 9 (39%) 8 (35%) 6 (26%) 0.31
Cardiac Valve Disease* (n: 34) 18 (53%) 10 (29%) 6 (18%) 0.02
aPL-associated Nephropathy* (n:11) 2 (18%) 7 (64%) 2 (18%) 0.053
Skin Ulcers (n:21) 5 (24%) 8 (38%) 8 (38%) 0.58
Cognitive Dysfunction* (n: 10) 3 (30%) 4 (40%) 3 (30%) 0.27
MRI White Matter Changes (n:57) 18 (32%) 16 (28%) 23 (40%) 0.22

PEC: preeclampsia; EC: eclampsia; PI: placental insufficiency. * similar results with linear-by-linear association

**Conclusion:** Our preliminary analysis suggests that: a) there is no association between the aPL-related events and aPL profile (triple, double, or single positivity), except for Catastrophic APS and cardiac valve disease, based on a small number of patients; and b) LA positivity is the most important determinant of event risk in aPL-positive patients. Further analysis of the APS ACTION registry, i.e., detailed aCL/aPRo, GP1 titers, potential confounders, and core laboratory aPL profile, will clarify if triple, double, and single aPL profiles are associated with different risk profiles.

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**ACR Concurrent Abstract Session**
**B cell Biology and Targets in Autoimmune Disease**
**Tuesday, November 18, 2014, 4:30 PM - 6:00 PM**

**2869**
**TLR7 Influences Autoreactive B Cell Selection in the Germinal Center**
FKG, Institute of Medical Research, Malaysia.

**Background/Purpose:** TLR7 is required for the generation of anti-RNA antibodies and excess TLR7 confers a SLE-like phenotype in mice. Recent studies have shown that TLR7 expression in B cells is sufficient for this phenotype and that TLR7 excess enhances germinal center (GC) maturation. The goal of this study was to determine how TLR7 influences the GC derived autoreactive B cell repertoire.

**Methods:** TLR7 deficiency was crossed into NZW mice for 13 generations. The NZW/BKS.BY strain was used for NZW and NZW B6; TLR7+/−/B6, X.BYB/Yaa lupus prone mice. The Y.aa locus confers a partial deficiency for TLR7 in males and an accelerated lupus phenotype. NZW TLR7+/−/B6, X.BYB/Yaa mice were used, which carry only one copy of TLR7. To create a physiology setting in which autoreactive B cells compete for survival with non-autoreactive B cells, we generated 50% 3H9/50% wild type bone marrow chimeras in which transferred male 3H9. TLR7+/−/or TLR7+/− cells were GFP+ and can be easily identified. Mice were followed clinically and sacrificed at the onset of fixed proteinuria. Spleen cells were phenotyped and GC B cells were analyzed by single cell PCR for the repertoire of Vκ light chains associated with the 3H9 heavy chain. Full length Vκ5−43 encoded light chains were sequenced and their mutation frequency analyzed.

**Results:** Disease onset occurred with the same kinetics in TLR7+/−/and TLR7+/−/− chimeras and spleens from both sets of chimeras were phenotyped and sacrificed at the onset of fixed proteinuria. Spleen cells were phenotyped and GC B cells were analyzed by single cell PCR for the repertoire of Vκ light chains associated with the 3H9 heavy chain. Full length Vκ5−43 encoded light chains were sequenced and their mutation frequency analyzed.

**Conclusions:** Our results suggest that TLR7 influences proliferation autoreactive B cells into the GC, as well as their expansion and the frequency of somatic mutations. These effects of TLR7 are different from those in the Y.aa locus.

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**2870**
**B Cell-Intrinsic Deletion of the Type 1 Interferon Receptor Does Not Impact the Development of Murine Lupus**
W. S. Jackson, N. Bethune-ackian, N. Scharping, S. Khim and D. Rawlings.
Seattle Children’s Research Institute, Seattle, WA.

**Background/Purpose:** Type 1 interferon (IFN) is strongly implicated in lupus pathogenesis, and patients with SLE frequently express a ‘type 1 IFN gene signature’. Type 1 IFN promotes B cell activation in vitro suggesting a direct role for type 1 IFN in humoral autoimmunity. However, it is unclear whether type 1 IFN impacts lupus pathogenesis via B cell-intrinsic or –extrinsic mechanisms. We previously described the Wiskott Aldrich syndrome (WAS) model of B cell-driven autoimmunity (Becker-Herman et al., 2011; Jackson et al. 2014). An important advantage of the WAS chimeras is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we describe the impact of B cell-intrinsic deletion of the type 1 interferon receptor (IFNα/IFNβ) in the WAS chimeras.

**Methods:** Proliferation of wild-type (WT), was−/−, ifnar−/− and double-deficient was−/−/ifnar−/− B cells was quantified after stimulation with LPS (TLR4 agonist), R848 (TLR7 agonist) and CPG (TLR9 agonist) −/−/IFN-β. To test the impact of B cell-intrinsic type 1 IFN activation in lupus pathogenesis we established bone marrow chimeras in which B cells were WT, was−/−, or was−/−/ifnar−/−; hereafter be referred to as BW, BW/IFNAR−/−, and BW/IFNAR−/−. Chimeras were analyzed for autoantibodies, immune activation and development of immune-complex glomerulonephritis by ELISA, flow cytometry and immunohistochemistry.

**Results:** We previously showed that autoimmunity in the WAS chimera model is dependent on B cell-intrinsic TLR7 activation (Jackson et al., 2014). Ifnar-deficient B cells demonstrated a specific defect in TLR7-induced proliferation, while TLR4 and TLR9 responses were unaffected. In addition, recombiant IFN-β enhanced TLR7 responses, without impacting TLR4/TLR9 activation. These data suggest a role of B cell-intrinsic type 1 IFN signals in lupus pathogenesis. To test this hypothesis, we generated chimeras with B cells double-deficient in was and ifnar. Surprisingly, although type 1 IFN promoted B cell TLR7 activation in vitro, autoantibodies to RNA-associated antigen smRNP were equivalent in BW, BW/IFNAR−/−, and BW/IFNAR−/− mice. Chimeras were analyzed for autoantibodies, immune activation and development of immune-complex glomerulonephritis by ELISA, flow cytometry and immunohistochemistry.

**Conclusions:** We previously showed that autoimmunity in the WAS chimera model is dependent on B cell-intrinsic TLR7 activation (Jackson et al., 2014). Ifnar-deficient B cells demonstrated a specific defect in TLR7-induced proliferation, while TLR4 and TLR9 responses were unaffected. In addition, recombinant IFN-β enhanced TLR7 responses, without impacting TLR4/TLR9 activation. These data suggest a role of B cell-intrinsic type 1 IFN signals in lupus pathogenesis. To test this hypothesis, we generated chimeras with B cells double-deficient in was and ifnar. Surprisingly, although type 1 IFN promoted B cell TLR7 activation in vitro, autoantibodies to RNA-associated antigen smRNP were equivalent in BW, BW/IFNAR−/−, and BW/IFNAR−/− mice. Chimeras were analyzed for autoantibodies, immune activation and development of immune-complex glomerulonephritis by ELISA, flow cytometry and immunohistochemistry.

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**2871**
**Break of Anergy in Human Autoreactive B Cells By T Helper Signals Restores B Cell Receptor Signaling Capacity and Is Dependent on Upregulation of CD45 Phosphatase Activity-A Possible Novel Mechanism of B Cell Tolerance in Rheumatic Diseases**
Institute of Immunology, Rikshospitalet, Oslo University Hospital, Oslo, Norway, La Jolla Institute for Allergy and Immunology, La Jolla, CA.
**Results:** The dominant epitopes recognized by BDX2 autoAbs are those commonly found in human SLE patients. Many immunodominant epitopes are located in cryptic regions of the native protein. The strongest autoAb response was observed with nuclear peptides from RNA binding proteins (RBP) including lupus La, L23–27 LEAKICHQIEYYFGD, U1snRNP, 373 SHRSERERRRDARDRD, and SmD197–111 RGRGGGRGGRGGRGGRG. Other nuclear autoAbs include histones, centromere, and RNA polymerase III. Tetramer analysis revealed a significant expansion in La and snRNP memory B cells and marginal zone precursor (MZ-P) B cells in BXD2 vs. B6 in both the circulation and the spleen. Phenotype analysis of tetramer + MZ-P B cells showed upregulation of type I IFN inducible activation molecules CD69 and CD86 in BXD2 mouse spleens.

**Conclusion:** The bona fide presence of RBP cryptic autoAbs that were not predicted by Ag prediction programs is consistent with the finding that defective clearance of apoptotic blebs in BXD2 mice leads to production of autoAbs that break B cell tolerance. The potential activation of the TLR7 pathway by RPs in combination with the upregulation of type I IFN response in Ag-specific MZ-P B cells further suggests that expanded tetramer + MZ-P B cells may be a result of apoptotic cell clearance defects. In light of our previous findings that MZ-P B cells are exceptional apoptic Ag delivery to CD11c+ DCs, CD86+ cells and can stimulate CD4 T cells, these results suggest that specific targeting on TLR7 and type I IFNs may be important to eliminate autoreactive B cells.

**Disclosure:** J. Hamilton, None; J. Li, None; Q. Wu, None; P. Yang, None; B. Luo, None; H. Li, None; T. Randall, None; J. E. Bradley, None; J. J. Taylor, None; J. D. Mountz, None; H. C. Hu, None.

**2873**

**Epratuzumab Induces Broad Inhibition of B Cell Receptor Proximal Signaling but Has Opposing Effects on Distal Signaling in B Cell Subsets: A Profile of Effects on Functional Immune Signaling By Single Cell Network Profiling.** Alison Maloney1, Drew Holton1, Stephen Radecki2, Gianluca Fosseth3, Simon Lumb1, David Rosen4, Santosh Puszt1, Nikil Waite1, David Spellmeyer6, Alessandra Cesano7, Rachael Hawtin2, Anthony Shackl1, UCSB Pharma, Slough, United Kingdom, 2Nodality Inc., South San Francisco, CA.

**Background/Purpose:** Epratuzumab is a humanized monoclonal antibody targeting the B cell-specific protein CD22 and is in Phase 3 clinical trials in patients with systemic lupus erythematosus (SLE). Epratuzumab does not deplete B cells, rather, the mechanism of action centers on CD22 regulatory activity of B cell receptor (BCR) modulation, via inhibition of specific BCR-driven phosphorylation events (Syk, PLCγ2) and Ca2+ flux. The aim of this study was to assess the effects of epratuzumab on receptor activation and BCR signaling across multiple B cell subsets in peripheral blood mononuclear cells (PBMC) from a large cohort of lupus patients.

**Methods:** Single Cell Network Profiling (SCNP) is a multiparametric, flow-cytometry-based technology that enables simultaneous analysis of signaling networks in multiple immune cell subsets.2 BCR modulated signaling (anti-IgG/anti-IgM) was profiled by SCNP in PBMC from 60 healthy donors (HD) across naive (CD27-/IgD-) and switched memory (CD27+IgD+) B cell subsets. Surface receptor (CD22, CD19, proximal (Syk, PLCγ2)) and distal (Akt, Erk, S6, p38, IkBa, NFκB/p105) signaling was interrogated 5 or 15 minutes post modulation in the presence and absence of epratuzumab (10mg/ml), which had been pre-incubated with cells for 1 hour.

**Results:** Epratuzumab (10mg/ml), which had been pre-incubated with cells for 1 hour.

**Conclusion:** Epratuzumab activity in B cells was identified as induction of pCD22 Tyr152, most pronounced in naive B cells (p<0.0001). Broad inhibition of all examined BCR-proximal signaling (p<0.0001) was observed in the whole B cell population with the most pronounced effects observed in the switched memory B cell population. Strong inhibition of BCR modulated pCD19 (p<0.0001) was also seen in this population, which may contribute to inhibition of BCR activation events. Inhibition of distal signals was demonstrated specifically in the switched memory B cell population whilst conversely, in the naive B cell subset, evidence for activation of distal signaling (p<0.0001) was observed. Interestingly, weak activation of pAkt was observed in both naive and switched memory B cells.

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**2872**

**B-Cell Autoepitope and Tetramer Analysis Reveals Expansion of Apoptotic Autoantigens La and snRNP Reactive B Cells in BXD2 Mice.** Jennifer Hamilton5, Jun Li1, Qi Wu1, PingYi Yang1, Bao Luo1, Hao Li1, Troy Randall1, John Edwin Bradley1, Justin J. Taylor2, John D. Mountz3 and Hui-Chen Hu1. University of Alabama at Birmingham, Birmingham, AL, 2Fred Hutchinson Cancer Research Center, Seattle, WA, 3Birmingham VA Medical Center, Birmingham, AL.

**Background/Purpose:** Systemic lupus erythematosus (SLE) is characterized by production of highly pathogenic IgG autoantibodies (autoAbs). While serum autoAb profiling is standard, it remains challenging to isolate authentic autoreactive B cells that give rise to these autoAbs. Similar autoAbs are spontaneously produced in lupus-prone BXD2 mice that display apoptotic cell features and heightened type II signaling. The purpose of this study is to develop a comprehensive autoepitope and tetramer strategy to identify the dominantautoantgens (autoAg) and the underlying mechanisms promoting the development of autoreactive B cells in BXD2 mice.

**Methods:** A Peer2Peer Autoimmunity Microarray covering 3,653 database derived, linear B-cell autoepitopes was probed with 66 and BXD2 serum to determine IgM and IgG binding reactivity. Top peptides were selected for 3D crystal structural analysis. A panel of over 50 peptide epitopes were verified by ELISA and ELISPOT. Two epitopes from RNA-binding lupus La and 70 kDa U1snRNP were used to generate B cell tetramers for characterization of Ag-specific subpopulations of B cells.

**Results:** Stimulation mimicking T cell help broke anergy and forced BND cells to fully respond to antigenic stimulation by restoring normal signaling through the BCR. This was dependent on de novo protein synthesis as opposed to direct crossstalk between the BCR, IL-4 and CD40 signaling pathways. We traced the restoration of BCR signaling from downstream signaling stages such as intracellular calcium release to phosphorylation of Syk and Lyn kinase, which is located proximal to the BCR. We observed an inability of activation of Lyn in BND cells upon BCR-stimulation, while subsequent to IL-4/CD40L treatment, the activation state of Lyn was restored. Lyn kinase activity is principally regulated by CD45 phosphatase (activating) and Csk kinase (inactivating). By inhibition studies, we identified CD45 upregulation of CD45 surface expression on B cells stimulated with T cell and Csk kinase (inactivating). By inhibition studies, we identified CD45 inactivity of activation of Lyn in BND cells upon BCR-stimulation, while signaling stages such as intracellular calcium release to phosphorylation of pathways. We traced the restoration of BCR signaling from downstream signaling stages such as intracellular calcium release to phosphorylation of Syk and Lyn kinase, which is located proximal to the BCR. We observed an inability of activation of Lyn in BND cells upon BCR-stimulation, while subsequent to IL-4/CD40L treatment, the activation state of Lyn was restored. Lyn kinase activity is principally regulated by CD45 phosphatase (activating) and Csk kinase (inactivating). By inhibition studies, we identified CD45

**Conclusion:** The bona fide presence of RBP cryptic autoAbs that were not predicted by Ag prediction programs is consistent with the finding that defective clearance of apoptotic blebs in BXD2 mice leads to production of autoAbs that break B cell tolerance. The potential activation of the TLR7 pathway by RPs in combination with the upregulation of type I IFN response in Ag-specific MZ-P B cells further suggests that expanded tetramer + MZ-P B cells may be a result of apoptotic cell clearance defects. In light of our previous findings that MZ-P B cells are exceptional apoptic Ag delivery to CD11c+ DCs, CD86+ cells and can stimulate CD4 T cells, these results suggest that specific targeting on TLR7 and type I IFNs may be important to eliminate autoreactive B cells.

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signaling were identified in the naïve and memory populations. In switched memory B cells inhibition of pCD19 and downstream signals was demonstrated. In contrast, in naïve B cells activation of distal signals was observed. These data have implications for understanding the functional consequences of epratuzumab treatment on B cell pathologic activity in patients with autoimmune diseases such as SLE.

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2. Cesano A. Cytometry Part B 2012;82B:158

Disclosure: A. Maloney, UCB Pharma, 3; D. Hobson, Nadolity Inc., 3; S. Radecki, UCB Pharma, 3; G. Fossati, UCB Pharma, 3; S. Lamb, UCB Pharma, 3; D. Rosen, Nadolity Inc., 3; S. Patta, Nadolity Inc., 3; N. Waal, Nadolity Inc., 3; D. Spellmeyer, Nadolity Inc., 3; N. Amara, Nadolity Inc., 3; R. Hawtin, Nadolity Inc., 3; A. Shock, UCB Pharma, 3.

2874

Pro-Inflammatory FcRL4+ Memory B Cells in Joints of RA Patients: Immunoglobulin Gene Characteristics and Antigen Specificity. Khaled Amara1, Lorraine Yeo2, Natalie Sipli3, Philip Titcombe3, Andrew Filer3, Karim Raza4, Dagmar Scheel-Toellner5 and Vivianne Malstrom6. 1Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, SE-17176 Solna, Stockholm, Sweden, 2Translational Research Group, Centre for Translational Inflammation Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK, Birmingham, United Kingdom, 3Rheumatology Research Group, MRC Centre for Immune Regulation, School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom, 4Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Our recent findings identified a subset of pro-inflammatory memory B cells in the RA synovium characterized by the expression of the surface protein Fc receptor like 4 (FcRL4)1. FcRL4+ B cells produce RANKL, and express high levels of TNF mRNA, indicating a destructive, pro-inflammatory role for this B cell subpopulation. It is however unclear how synovial FcRL4+ve B cells develop, whether they have undergone hypermutation in germinal centers and the nature of their relationship with FcRL4-ve B cells at the same site. The aim of this project was to investigate whether autoreactive features would accumulate in the FcRL4+ve B cell subset by investigating the antigen-specificity and Ig gene characteristics of FcRL4+ve and FcRL4-ve B cells from both synovial tissue and blood of RA patients.

Methods: Single FcRL4+ve and -ve memory B cells were sorted from synovial tissue (n=2) and synovial fluid (n=5) of patients with active RA. Their Ig variable region genes were sequenced and subsequently expressed to generate recombinant monomeric antibodies. Antigen-specificities of the generated monoclonal antibodies were determined by ELISA.

Results: In total, we have cloned and sequenced B cell receptors from 332 individual B-cells (121 from FcRL4+ and 160 from FcRL4- cells). The Ig gene sequence analyses demonstrated that the Ig repertoire was highly diverse with no major differences in the IGH and IGL or IGL gene segment usage or IGH CDR3 features between FcRL4+ve and FcRL4-ve memory B cells. From the sequenced clones we have so far generated 38 recombinant monoclonal antibodies (from both FcRL4+ve and FcRL4-ve B cells) and determined their specificity for citrullinated candidate autoantigens. We found no difference in the frequency of autoreactive Ig in the FcRL4+ve versus -ve cells. 13 antibodies reacted to citrullinated antigens (including α-actinase, fibrinogen, and vimentin) without recognizing the unmodified arginine control peptides.

Conclusion: We conclude that the FcRL4+ve and FcRL4-ve memory B cells, while functionally and phenotypically distinct, are both post-germinal center hypermutated B cell subsets with similar Ig gene features. We have not identified a relationship between FcRL4 expression and overall B cell receptor characteristics and antigen specificities suggest that the two B cell subpopulations may originate from similar immune responses differentiating into functionally distinct subsets.


Disclosure: K. Amara, None; L. Yeo, None; N. Sipli, None; P. Titcombe, None; A. Filer, None; K. Raza, None; D. Scheel-Toellner, None; V. Malmstrom, None.
**Results:** Wildtype mice treated with IL-10 receptor blockade succumbed to MAS-like hyperinflammation manifest as weight loss, splenomegaly, bicytopenias, and hypercortiokinemena during LCMV infection. IFN-γ+ and IFN-α+ mice were not protected from LCMV-induced disease in this model, as they developed severe weight loss, splenomegaly, cytopenias, hypercortiokinemena, and more severe mortality when IL-10 receptor was blocked.

**Conclusion:** IL-10 receptor blockade leads to heightened immunopathology in the setting of LCMV infection similar to MAS-like hyperinflammatory disease. Unlike other hyperinflammatory syndromes, this immunopathology is independent of IFN-γ and IFN-α, and highlights the capacity of other inflammatory mediators to cause viral-induced hyperinflammation during IL-10 receptor blockade. Furthermore, these data highlight a novel mechanism that could contribute to MAS-like disease whereby defects in IL-10 production and/or sensing could exacerbate hyperinflammatory immunopathology induced by viral infection without genetic defects in cellular cytotoxicity.

**Disclosure:** L. K. Weaver, None; E. M. Behrens, None.

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2877

**Novel Function of Tocilizumab As a Modulator of Interleukin-27-Mediated Anti-Inflammatory Responses.** Misato Hashizume1, Jun Kikuchi2, Keiko Yoshimoto2 and Tsutomu Takeuchi. Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, 1Ko University School of Medicine, Tokyo, Japan.

**Background/Purpose:** The immunological roles of interleukin 27 (IL-27) have been reported in the function of regulatory T cells (Treg), monocytes and osteoclasts, and these cells are involved in various autoimmune diseases, such as rheumatoid arthritis (RA), lupus, systemic sclerosis, and psoriasis. There is increasing information about how the function of IL-27 regulates in autoimmune disease. IL-27 is a heterodimeric cytokine composed of IL-27p28 and EB13, which are analogous to IL-6 and soluble IL-6 receptor (sIL-6R) respectively. In this study, we investigated whether a possible role of sIL-6R in regulating IL-27 function.

**Methods:** CD4+ cells were isolated from peripheral blood in RA patients. MCP-1 was measured by ELISA in the culture supernatant of incubated with TNF-α, IL-27, sIL-6R, anti-IL-6 antibody and anti-IL-6R antibody (tocilizumab). In the experiments of osteoclasts, CD4+ cells were cultured with RANKL and M-CSF in the presence of IL-27, sIL-6R, anti-IL-6 antibody and tocilizumab for 4 days and the number of osteoclasts was counted. Consecutive RA patients who received 8mg/kg of tocilizumab every 28 days were not protected from LCMV-induced disease in this model. Over the treatment with tocilizumab, the proportions of Treg and monocytes in RA patients. These data suggest that tocilizumab may be involved in modulating the anti-inflammatory responses of IL-27.

**Conclusion:** Tocilizumab may be involved in modulating the anti-inflammatory responses of circulating Treg and monocytes in RA patients. These data suggest that tocilizumab may be involved in modulating the anti-inflammatory responses of IL-27.


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2878

**G Protein Signaling Modulator 3 (GPSM3) Deficiency Is Protective In Inflammatory Arthritis Models and Altered GPSM3 Gene Products Correlate With Single Nucleotide Polymorphisms in Humans.** Teresa K. Tarrant1, D. Stephen Serafin2, Elizabeth Sugg3, Roman Timoshchenko4, Rachel M. Billard2, David P. Siderovski5 and Kristy Richards1. 1Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, 2West Virginia University School of Medicine, Morgantown, WV, 3Dept. of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Background/Purpose:** GPSM3, a newly described regulator of heterotrimeric G protein signaling, is selectively expressed in hemopoietic cells with high expression in monocytes. We have shown that Gpms3 deficient (-/−) mice are protected from Collagen Antibody Induced Arthritis due in part to their attenuated monocyte responses, including decreased ex vivo migration to the chemokinines CX3CL1, CCL2, and chemerin, and enhanced apoptosis, which leads to an observed decrease in proinflammatory intra-articular IL-6 and IL-1β transcripts in the joint. Given the restricted expression of GPSM3 in leukocytes and the functional phenotypes observed in immune cells lacking GPSM3 expression, we chose to examine effects of GPSM3 deficiency in Collagen Induced Arthritis (CIA) and to analyze whether single nucleotide polymorphisms (SNPs) within the human GPSM3 gene locus, associated with a decreased incidence of autoimmunity, correlate with altered GPSM3 gene products.

**Methods:** Gpms3−/− and Gpms3+/+ DBA1 mice were immunized with heterologous type II collagen in Freund’s Adjuvant with a booster immunization at day 21 per published protocols. Arthritis was assessed by a blinded observer for paw swelling and clinical disease score (0–4). Paws were processed at day 42 for histopathology. Serum B-cell activating factor (BAFF) was measured by commercial ELISA (R&D Systems) per manufacturer’s instructions on day 14. DNA and RNA was isolated from healthy human subject blood using Qiagen purification reagents. Genotyping for SNP (A (minor)/G (major) transition substitution) was performed using commercially available TaqMan SNP Genotyping Assay (SNP ID rs204989) from Applied Biosystems by Life Technologies. qRT-PCR primers for known GPSM3 transcripts −001, −002, −003, and −004 were designed from NCBI (−001 and −002) and Ensembl (−003 and −004) databases, and validated by gel electrophoresis for sequence length, sequencing, melt curve analysis, and PrimerBlast. qRT-PCR of cDNA from healthy human subject blood was performed using a Bio-Rad CFX96 Real-Time System and standard protocols. Data was calculated as relative expression compared to the housekeeping gene GAPDH.

**Results:** Gpms3−/− mice are protected from CIA and have significantly decreased serum BAFF levels. Healthy human subjects carrying protective SNPs that correlate with decreased RA and other autoimmune diseases have decreased levels of transcripts GPSM3-001, −002, and −004, but significantly increased levels of the transcript GPSM3-003, which is thought to be subjected to nonsense-mediated decay.

**Conclusion:** Our goal from these studies is to determine whether GPSM3 has immune system-modulating potential for the treatment of autoimmune diseases with particular focus on inflammatory arthritis. Gpms3−/− mice are protected from two models of inflammatory arthritis through mechanisms involving monocyte function. GPSM3 has altered mRNA transcripts in healthy human subjects with SNPs that correlate with decreased RA and other autoimmune diseases, suggesting differential gene regulation.

**Disclosure:** T. K. Tarrant, None; D. S. Serafin, None; E. Sugg, None; R. Timoshchenko, None; M. J. Billard, None; D. P. Siderovski, None; K. Richards, None.

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2879

**Epigallocatechin-3-Gallate (EGCG) Suppresses IL-1β-Induced IL-6 and IL-8 Synthesis By Selectively Inhibiting TAK1 Activation in Human Rheumatoid Arthritis Synovial Fibroblasts.** Anil Singh1, Sharayah Riegsecker2, Sadiq Umar1 and Salahuddin Ahmed1. 1Washington State University, Spokane, WA, 2University of Toledo, Toledo, OH.
**Background/Purpose:** In rheumatoid arthritis (RA), the role of interleukin-1β (IL-1β) signaling proteins (IRAK-1/TAK-1/TRAF-6) proximal to IL-1 receptor in mediating proinflammatory response is not completely understood. Using IL-1β-induced IL-6 and IL-8 production in RA synovial fibroblasts (RA-FLS), we examined the role of key signaling molecules critical in mediating its inflammatory response. We also tested if EGCG, a potent anti-inflammatory compound, inhibits IL-1β signaling protein to suppress IL-6 synthesis in RA-FLS.

**Methods:** RA-FLS were treated with IL-1β for different time alone or in the presence of EGCG. Western blotting analysis was utilized to study activation/phosphorylation of different IL-1β signaling proteins. In vitro kinase activity of IRAK-1 was determined using ADAPTA kinase assay. Changes in the ubiquitination patterns of IL-1β-induced RA-FLS was studied using immunoprecipitation (IP) assay. Using chemical inhibitors or siRNA for IRAK-1, TAK-1 or TRAF-6, their respective roles were examined studied using immunoprecipitation (IP) assay. Using chemical inhibitors or siRNA method also showed a marked inhibition of IL-6 production by TAK-1 or IRAK-1 siRNA. Although EGCG inhibited IL-1β-induced IRAK-1 kinase activity by almost 65%, it did not prevent the IL-1β-induced proteosomal degradation of IRAK-1 in RA-FLS. To our surprise, EGCG selectively inhibited IL-1β-induced TAK-1 phosphorylation in a dose-dependent manner (p<0.05; n=4). Interestingly, we observed that the levels of TRAF-6 remained unchanged upon IL-1β stimulation. IP of RA-FLS cell lysates with global Fk2 ubiquitin antibody and further Western blotting analysis showed that IL-1β activated TRAF-6 ubiquitination was not modulated by EGCG, suggesting TAK-1 as a potential therapeutic target in IL-1β signaling.

**Conclusion:** Our study provides a novel evidence of an important mediatory role of TAK-1 in IL-1β signaling in RA-FLS and warrants further testing of EGCG or its synthetic analogs as TAK-1 inhibitors for the treatment of RA.

**Disclosure:** A. Singh, None; S. Riegecker, None; S. Umar, None; S. Ahmed, None.

**2880**

**Elevated Levels of Soluble Inflammatory Mediators and Lupus-Specific Connective Tissue Disease Questionnaire Scores Discern Unaffected First Degree Relatives of Lupus Patients from Unaffected Individuals**

The current state of lupus is primarily based on affected relatives. Characterization of unaffected relatives is essential to determine the course of the disease.

**Methods:** A unique resource of SLE patient family members was developed with the Department of Veterans Affairs. Using a unique resource of SLE patient family members, the approach to developing SLE is essential to curtail inflammatory damage and select individuals for prevention trials. First-degree relatives (FDRs) of lupus patients have an increased risk of developing SLE. Using a unique resource of SLE patient family members with longitudinal samples available, the goal of this study is to determine factors that distinguish FDRs who remain unaffected from over time.

**Background/Purpose:** Identifying populations at risk of SLE is essential to curtail inflammatory damage and select individuals for prevention trials. First-degree relatives (FDRs) of lupus patients have an increased risk of developing SLE. Using a unique resource of SLE patient family members with longitudinal samples available, the goal of this study is to determine factors that distinguish FDRs who remain unaffected from over time.

**Methods:** We evaluated plasma samples from 154 unaffected FDRs of known SLE patients with samples available from previous genetic studies and who remained unaffected at follow-up evaluation (mean time to follow-up 6.8 years). FDRs were matched 2:1 by gender, race and age (±5 years) to 77 unaffected individuals unrelated to SLE patient (Controls). FDRs and Controls provided clinical and demographic information, and completed the SLE-specific portion of the Connective Tissue Disease Screening Questionnaire (CSQ) at baseline (BL) and follow-up (FU). BL and FU plasma samples were assessed for autoantibody production (ANA, anti-dsDNA, aCL, Ro, La, Sm, nRNP, and ribosomal P antibodies) and for 52 soluble inflammatory mediators (BLyS, APRIL, cytokines, chemokines, and shed TNF receptors). Logistic regression modeling of CSQ scores, number of autoantibody specificities, and select soluble mediators (via Random Forest) was utilized to evaluate whether certain factors distinguished unaffected FDRs from Controls.

**Results:** FDRs had significantly higher BL and FU CSQ scores than Controls (p<0.0001). CSQ scores were higher in female FDRs vs. male FDRs or female Controls (p<0.001). No significant difference in the number of positive autoantibody specificities were noted between FDRs and Controls. FDRs had significant (p<0.01) alterations in 38 of (52) soluble mediators compared to Controls, including innate and adaptive mediators of inflammation, chemokines, and TNF superfamily members. APRIL and BLyS, IFN-associated chemokines IP-10, MIG and MIP-1α, as well as the regulatory mediators IL-10 and TGF-β, were significantly higher in FDRs at BL and FU (p=0.002). A number of mediators (14 at BL and 18 at FU) found to best separate FDRs from Controls by Random Forest strongly correlated with CSQ scores (p=0.0002). Of these, levels of MIP-1α (p=0.008), MIG (p=0.019), GROα (p=0.001), ICAM-1 (p=0.007), and VEGF (p=0.004), along with CSQ scores (p=0.010), best distinguished FDRs from Controls in logistic regression models.

**Conclusion:** Unaffected FDRs of SLE patients demonstrate significantly altered levels of soluble inflammatory, as well as regulatory, mediators compared to matched, unrelated, unaffected Controls. These alterations are present despite lack of progression to classified SLE, suggesting that multiple perturbations in immune-mediated inflammatory processes present in family members of SLE patients may be offset by inhibitory factors, providing unique insights for potential autoimmune disease prevention or SLE disease treatment.

**Disclosure:** M. E. Munroe, None; K. A. Young, None; J. Fessler, None; D. L. Kamen, None; J. M. Guthridge, None; T. B. Niewold, None; M. H. Weisman, None; M. L. Ishimori, None; D. J. Wallace, None; D. R. Karp, None; J. B. Harley, None; G. S. Gilksone, None; J. M. Norris, None; J. A. James, None.

**ACR Concurrent Abstract Session Education**

Tuesday, November 18, 2014, 4:30 PM - 6:00 PM

**2881**

**The Center of Excellence in Musculoskeletal Care and Education: A Sustainable Interprofessional, Multidisciplinary Program Innovation Developed with the Department of Veterans Affairs.**

Michael J. Battistone, Andrea M. Barker, Marissa Groitzke, Peter Beck, Jeffery Berdan, Caroline M. line., JoAnn Rolando and Grant W. Cannon. Salt Lake City VA and University of Utah, Salt Lake City, UT.

**Background/Purpose:** While musculoskeletal (MSK) problems are common in primary care, the current formal education in the evaluation and management of these conditions is inadequate. Through funding from the Veterans Affairs (VA) Office of Academic Affiliations, we developed an interprofessional, interdisciplinary, mixed-method program to enhance the clinical education of medical students, residents, fellows, and trainees of other health professions.

**Methods:** The week-long course begins with didactics, is reinforced through technology-enhanced simulation and peer-teaching in small-group settings, and culminates in supervised ambulatory clinical experiences and reflective practice.

**Table 1**

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>Back Pain</td>
<td>Didactic: Physical Exam of the Knee</td>
<td>Didactic: Rheumatoid Arthritis I: Symptoms and RA</td>
<td>Orthopaedic Injection Clinic or: P&amp;RER Clinic</td>
<td>Center of Excellence Multidisciplinary Musculoskeletal Clinic</td>
</tr>
<tr>
<td>Didactic: Physical Exam of the Shoulder</td>
<td>Didactic: Physical Exam of the Knee</td>
<td>Group Practice: Approach to Knee Pain</td>
<td>Group Practice: Didactic and Group Practice</td>
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<tr>
<td>Didactic: Physical Exam of the Shoulder</td>
<td>Group Practice: Approach to Knee Pain</td>
<td>Didactic: Arthroscopy</td>
<td>Didactic: Arthroscopy</td>
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<tr>
<td>Didactic: Physical Exam of the Shoulder</td>
<td>Group Practice: Approach to Knee Pain</td>
<td>Didactic: Arthroscopy</td>
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<td>Didactic: Physical Exam of the Shoulder</td>
<td>Group Practice: Approach to Knee Pain</td>
<td>Didactic: Arthroscopy</td>
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<td>Didactic: Physical Exam of the Shoulder</td>
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</table>
Participants learn to perform, describe, and document a systematic physical exam of the shoulder and knee, interpret these findings, and develop patient-centered management options in a framework of high value care. Faculty represent Internal Medicine (IM) (Primary Care, Rheumatology, Endocrinology), Orthopedics, and Physical Medicine and Rehabilitation (PM&R) disciplines. Course assessments include written surveys, 2-station Objective Structured Clinical Examination, and individual exit interviews. Results: Student and trainee participants in the 2013–14 academic year are summarized below. Survey response rate was 89%. Post-course competency in examining the shoulder and knee, and in reporting, interpreting, and managing the case using a framework of high-value care, was confirmed with 2-station OSCE.

Table 2

<table>
<thead>
<tr>
<th>Discipline/Profession</th>
<th>Post-Graduate Trainees</th>
<th>Students</th>
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<tbody>
<tr>
<td></td>
<td>IM Rheum Gori Neuro Ortho PM&amp;R Occ Med Med APRN PA</td>
<td></td>
</tr>
<tr>
<td>Number of Trainees</td>
<td>34 1 2 1 4 5 1 4 9 10</td>
<td></td>
</tr>
<tr>
<td>Percentage of Cohort</td>
<td>48% 1% 3% 1% 6% 7% 1% 6% 13% 14%</td>
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</table>

Conclusion: The MSK Intensive Education Week provides an interdisciplinary and interprofessional environment to teach trainees from multiple backgrounds in the evaluation and management of patients with complex MSK diseases through a cooperative practice model and evaluates their competency to practice in this system.

Disclosure: M. J. Battafarano, None; A. M. Barker, None; M. Grotzke, None; P. Beck, None; J. Berdan, None; C. Milne, None; J. Rolando, None; G. W. Cannon, None.

2882

Using Decision-Based Learning to Highlight Rheumatic Disease for Third-Year Medical Students. Karen Law1, J. Richard Pittman2 and Chad Miller2. 1Emory University School of Medicine, Atlanta, GA, 2Tulane University Health Sciences Center School of Medicine, New Orleans, LA.

Background/Purpose: Opportunities for exposure to rheumatology are limited in medical school, especially during the clinical years. In addition, because the rheumatic diseases represent a small portion of the National Board of Medical Examiners Subject Examination (SHELF exam) for the Internal Medicine clerkship, clerkship directors are reluctant to devote limited class time to rheumatology. This project aims to improve medical student exposure to rheumatology during the third-year Internal Medicine Clerkship via Decision-Based Learning (DBL), a simulated case-based teaching technique. Learners work in teams on a challenging clinical case. Teams are given a description of the patient's history and physical examination; each team collaborates to generate a differential diagnosis, then order tests and studies to work up the case. A simulated "bank" of tests and studies is available, with each test coming with a "price" that the team is charged. The teams compete to solve the case by ordering and interpreting studies while also spending the least amount of money. Because of the cost-conscious and competitive nature of the exercise, learners are incentivized to employ prudent hypothesis testing and diagnostic reasoning to decide what is "the next best step" to arrive at the diagnosis.

DBL facilitates rheumatology exposure within the broad context of internal medicine, a format more appropriate for the medical student level than typical disease-specific rheumatology curricula. In addition, the DBL format highlights the diagnostic complexity of rheumatic cases. Students also practice critical thinking and cost consciousness, areas of medical education that are frequently lacking.

Methods: The project introduced DBL to third-year medical students during their clerkship in Internal Medicine. Control sessions consisted of usual lecture-style didactics. Learners were given a survey after each session to rate their learning experience.

Results: Student feedback for DBL sessions was significantly higher than for control didactic sessions (p < 0.01). 67% of learners rated DBL a "10" on a 10-point Likert scale compared to 35% for control (p < 0.01). Positive responses to DBL were also noted in the survey comments:

- "Really productive exercise; thought provoking"
- "Very high-yield, learned lots of new things"
- "Made us think about what to order & why-I don't feel we have gotten much experience with that during the rotation"

Conclusion: A novel case-based teaching technique facilitated medical student exposure to rheumatology during their clerkship in Internal Medicine. DBL resulted in significantly higher ratings of didactic sessions compared to traditional lecture-style didactics. Learners found the DBL sessions to be engaging and educationally valuable. This interactive teaching method can enhance the learning experience during the Internal Medicine clerkship; the realistic context in which Rheumatology topics are addressed may make it more appealing for Clerkship Directors to adopt. These findings support future evaluation of DBL with a case-control study to determine efficacy in the principal areas of Rheumatology-specific knowledge, diagnostic reasoning, and cost awareness.

Disclosure: K. L. Law, Rheumatology Research Foundation, 2; J. R. Pittman, None; C. Miller, None.

2883

Rheumatology-Specific Milestones for a Musculoskeletal Radiology Curriculum. Michelle Newkirk1, Liem Mansfield1, Jay H. Higgins2 and Daniel Battafarano3. 1San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX, 2San Antonio Military Medical Center, JBSA - Fort Sam Houston, TX.

Background/Purpose: In 2012, the Accreditation Council for Graduate Medical Education (ACGME) announced the required implementation of standardized milestones with entrustable professional activities (EPAs) for the semi-annual evaluation of resident/fellow performance which must be implemented by November 2014. However, little guidance was rendered as to the incorporation of these milestones and EPAs into the curriculum of a subspecialty training program. Our rheumatology fellowship has had a formal musculoskeletal (MSK) radiology rotation for the past five years as part of its core curriculum and has integrated internal medicine subspecialty curriculum milestones with MSK radiology specific EPAs into this curriculum.

Methods: Utilizing a modified Delphi technique via e-mail, faculty and current fellows from the program established a consensus on EPAs for MSK radiology. The EPAs were individually rated using a nine-point Likert scale, with 1 being disagreement with the EPA and 9 being the most agreement. Agreed upon EPAs were then used as a foundation for the development of curricular milestones with MSK radiology specific EPAs into this curriculum.

Results: Etate faculty members and 2 rheumatology fellows participated in the process. Six EPA's were initially developed, and after two rounds of comments with wording and scoring, all six EPAs rated in the highest agreement scores (see table). Curricular milestones for MSK radiology were then established in keeping with these EPAs. These curricular milestones were integrated into our core MSK radiology lecture series.

Table 1: Entrustable Professional Activities (EPAs)

<table>
<thead>
<tr>
<th>Mean Likert Score</th>
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<tbody>
<tr>
<td>1. Order and utilize appropriate diagnostic imaging studies for evaluation and management of patients with rheumatic disease</td>
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<tr>
<td>2. Identify the optimal imaging modalities for patients with rheumatic disease within the context of patient comorbidities, preferences, treatment goals, financial considerations and insurance requirements</td>
</tr>
<tr>
<td>3. Interpret signs of acute and chronic musculoskeletal disease on radiography and know when to consult a radiologist for further evaluation and interpretation</td>
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S1259
Conclusion: The interpretation and application of MSK radiology is critical in the training of a rheumatology fellow. Incorporating a dedicated radiology rotation which addresses specific milestones and EPAs is one way of ensuring trainees are exposed to a quality, uniform curriculum that meets the ACGME’s next accreditation system requirements.

Disclosures: None.

2884

Training the Rheumatologists of Tomorrow: The Canadian Experience.

Alfred Cividino1, Volodko Bakowsky2, Susan Barr3, Louis Bessette4, Nader Khalidi5, Christian A. Pineau6, Janet E. Pope7, David Robinson8, Ken Shojania9, Elaine Yacyshyn10, Lynne Lohfeld11 and Diane Crawshaw12.

M.C.M aster University, Hamilton, ON, 1Dalhousie University, Halifax, NS, 2Heritage Medical Research Bldg, Calgary, AB, 3laval University, Quebec, QC, 4Division of Rheumatology, M.C.M aster University, Hamilton, ON, 5McGill University Health Center, Montreal, QC, 6St Joseph Health Care, London, ON, 7University of Manitoba, Winnipeg, MB, 8University of British Columbia, Vancouver, BC, 9University of Alberta, Edmonton, AB.

Background/Purpose: Many countries face a shortage of rheumatologists. Based on an accepted benchmark of 1 specialist per 50,000 people as the number needed for effective patient care, recent figures show severe shortages in the U.S. and Canada. This qualitative environmental scan was designed to identify what faculty, administrators and learners associated with Canadian postgraduate rheumatology programs identify as appropriate means and messages that programs could use to attract future trainees.

Methods: Individual-level data from program faculty (F), administrators and learners (L) across Canada (n = 103) were collected via an online survey (n = 25). Data were subjected to Thematic Framework Analysis to identify commonalities across sites to determine ways to address the rheumatology manpower shortage. Quotes are provided as examples.

Results: Participants: There were 103 respondents from nine programs including learners (medical students, junior residents (PGY 1–3) rheumatology residents (PGY 4–6) or new graduates); program and division directors and their assistants; and faculty in academic centres or community practices.

Two-thirds of the survey respondents were female.

Ways to Increase Interest in Rheumatology: The need for rheumatologists was widely recognized. Respondents advocated targeting both under-graduates ("People who influenced me were [role models] I had as a medical student" [F]) and junior residents in Internal Medicine. Proposed methods included increasing exposure to rheumatology in undergraduate programs through formal lectures and courses, clinical skills and other hands-on training sessions, faculty available to shadow or mentor learners and postgraduate weekend information and training sessions, mandatory rotation for Internal Medicine residents' internships and career counseling.

Messaging to Promote Rheumatology: Messages to brand rheumatology as an attractive specialty included the intellectual challenge ("This field fascinates me" [L]; "novel immunotherapies make it very exciting" [F]), stimulating workday ("nice mix of procedural and cerebral work" [L]), positive relationships with colleagues and patients ("According to a recent survey we are the happiest specialists" [F]), alleviating suffering ("We know how to treat arthritis now" [L]), good quality of life and excellent job prospects ("the health care system needs you" [F]).

Conclusion: We found consensus on the need to inform potential trainees about rheumatology early in their education through a variety of messages and methods. Because of the shortage of rheumatologists it is important to increase awareness and information about the field by selectively using limited resources. The next step would be to collaboratively develop, test and evaluate tools designed to help increase the number of future rheumatologists, which will be applicable in many locales.

References:
3. S. Barr, None; L. Bessette, None; N. Khalidi, None; C. A. Pineau, None; J. E. Pope, None; D. Robinson, None; K. Shojania, None; E. Yacyshyn, None; L. Lohfeld, None; D. Crawshaw, None.

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Clinical Training Opportunities in Two Innovative Ambulatory Resources: The Primary Care Musculoskeletal Clinic and Center of Excellence Multidisciplinary Clinic.

Michael J. Batstone, Andrea M. Barker, Marissa Grotzke, Peter Beck, Jeffrey Berman, Phillip Lawrence and Grant W. Cannon. Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: While musculoskeletal (MSK) problems are common in primary care, current training models do not adequately prepare primary care providers (PCPs) to deal with these issues. With funding from the Veterans Affairs (VA) Office of Academic Affiliations (OAA), we developed a Center of Excellence (COE) for MSK Care and Education to meet this training need for health care professional trainees.

Methods: Two new weekly outpatient clinics, the Primary Care MSK (PC-MSK) and the Multidisciplinary (COE-MSK) Clinics were developed as key components of the COE. The PC-MSK is staffed by a rheumatologist and a physician assistant (PA) with orthopaedic experience. The COE-MSK is staffed by a rheumatologist, a rheumatologist, orthopaedic surgeon, physia-trist, and a PCP. All categorical internal medicine (IM) interns, orthopaedic interns, PM&R residents, and rheumatology fellows participate in this clinic over the course of the academic year. Additional IM residents, medical students, nurse practitioner students and physician assistant students are also included as space allows.

Results: In 2013–14, 80 trainees participated in the PC-MSK and COE-MSK clinics. The distribution of disciplines and professions represented in this multi-level cohort are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Discipline/Profession</th>
<th>IM</th>
<th>Rheum</th>
<th>Geri</th>
<th>Neuro</th>
<th>Ortho</th>
<th>PM&amp;R</th>
<th>Occ Med</th>
<th>students</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care</td>
<td>39</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Percentage of COE</td>
<td>49%</td>
<td>5%</td>
<td>3%</td>
<td>1%</td>
<td>5%</td>
<td>0%</td>
<td>1%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Since June 2013, 330 patients have been seen in these clinics. As shown in Table 2, most are referred from primary care, mainly by providers in non-resident clinics. Most non-resident referrals were to the PC-MSK clinic, all others tended to request the multidisciplinary COE-MSK clinic.

Table 2

<table>
<thead>
<tr>
<th>Referral Sources</th>
<th>Total</th>
<th>COE</th>
<th>MSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>330 (100%)</td>
<td>191 (58)</td>
<td>139 (42)</td>
</tr>
<tr>
<td>Primary Care</td>
<td>217</td>
<td>110</td>
<td>107</td>
</tr>
<tr>
<td>Resident Continuity Clinics</td>
<td>73</td>
<td>47</td>
<td>26</td>
</tr>
<tr>
<td>Faculty and Staff Clinics</td>
<td>138</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>Women’s Clinics</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Specialty Care</td>
<td>36</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Medicine Subspecialties</td>
<td>25</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Surgery</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>PC-MSK + COE-MSK</td>
<td>23</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>54</td>
<td>34</td>
<td>20</td>
</tr>
</tbody>
</table>

Conclusion: These clinics provide unique and innovative opportunities for a broad range of trainees in a rich interdisciplinary and interprofessional educational environment. Additionally, these clinics are a valuable resource to primary care providers, specialty physicians, and patients for prompt and comprehensive care for veterans with either limited or complex MSK problems.
Assessing Rheumatology Fellows’ Teaching Skills Using the Objective Structured Teaching Exercise (OSTE). 

Eli M. Miloslavsky1, Marc B. Bolster1, Kenneth S. O’Rourke1 and Lisa G. Criscione-Schreiber1, 2
1Massachusetts General Hospital, Boston, MA, 2Wake Forest School of Medicine, Winston-Salem, NC, 3Duke University Health System, Durham, NC.

Background/Purpose: The interaction between rheumatology fellows and internal medicine residents in the setting of a consult offers an important opportunity for resident learning. However, teaching in the setting of a consult interaction can be challenging due to time constraints and lack of a longitudinal relationship between the resident and fellow. Fellows’ teaching skills in the setting of the consult interaction have not been evaluated. We conducted a pilot study utilizing the Objective Structured Teaching Exercise (OSTE) to evaluate rheumatology fellows’ teaching skills.

Methods: First and second year rheumatology fellows from 5 training programs participated in a one-station OSTE during a 7 station rheumatology Objective Structured Clinical Examination (OSCE) in February 2014. Following the OSCE format, fellows were given 10 minutes to teach a standardized resident in the setting of a simulated consult and relay their consult recommendations, followed by 2 minutes of feedback. Prior to beginning the station fellows were given written instructions on the objectives of the exercise as well as a resident admission note describing the patient (32 year old male with monoarthritis). The OSTE was proctored by 3 faculty members (including author [EMM]) and utilized 3 standardized residents. Each fellow was evaluated by one faculty member and the standardized resident using an 8-point instrument adapted from a validated OSTE rating tool. Prior to the OSTE, faculty and standardized residents received written materials describing the station and the rating tool and underwent a 30-60 minute training.

Results: Nineteen rheumatology fellows participated in the OSTE (11 first years and 8 second years). Fellows’ overall teaching effectiveness had a mean score of 3.75 out of 5 (Table). Of seven specific skills evaluated, fellows were rated highest on their ability to present organized material and lowest on their ability to adjust for age and menopausal factors with subsequent development of serologic RA phenotypes in 2 prospective cohorts.

Method: Data were analyzed from Nurses’ Health Study (NHS, 1976–2010) and NHSII (1989–2011). In NHS 121,701 female nurses aged 30–55 and in NHSII 116,430 female nurses aged 25–42 were followed via biennial questionnaires on lifestyle factors and disease outcomes. In total, 1,089 incident RA cases were confirmed by questionnaire and chart review. Seropositive RA was defined as more/less or ACPA by chart review or lab measurement. We used Cox proportional hazards models to obtain HR (95% CI) of seropositive or seronegative RA associated with menopausal status, age at menopause, type of menopause, severity of hot flashes and ovarian years, adjusting for age, BMI, smoking, breast-feeding, and parity.

Results: Women aged 45 or more had an increased risk of seronegative RA in all age groups, compared with women aged 25–44, with peak HR at ages 55–59. Women aged 50 or more had an increased risk of seropositive RA, with peak HR at ages 55–59, but the risk attenuated after age 60. Post-menopausal women had an increased risk of seronegative RA after adjusting for age and other potential confounders (NHS: HR 1.8, 95% CI 1.1–3.0; NHSII: HR 2.5, 95% CI 1.5–4.2; pooled HR 2.1, 95% CI 1.5–3.1) without marked differences according to type of menopause. Early age at menopause associated with an increased risk of seronegative RA (NHS: HR 2.5, 95% CI 1.2–3.4; NHSII: HR 3.0, 95% CI 1.7–5.1; pooled HR 2.4, 95% CI 1.5–3.5), regardless of type of early menopause. Moderate/severe hot flashes was mainly associated with an elevated risk of seronegative RA (NHS HR =2.4, 95% CI 1.4–4.3; NHSII: 3.7, 95% CI 2.0–6.8; pooled HR 3.0, 95% CI 2.0–4.5). None of the menopausal factors were significantly associated with seropositive RA.

Conclusion: Age and menopausal factors have an increased risk of both RA phenotypes, but this risk attenuates after age 60 for seropositive RA. Post-menopausal factors are strongly associated with seronegative RA, but not seropositive RA, suggesting potential differences in disease etiology.

Table. Age and menopausal factors and the relative risk of seropositive RA and seronegative RA in the NHS (1976–2010) and NHSII (1989–2011) cohorts

<table>
<thead>
<tr>
<th>Factors</th>
<th>NHS I</th>
<th>NHS II</th>
<th>(NHS+NHII)</th>
<th>Pooled</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seropositive (n=457)</td>
<td>Seropositive (n=267)</td>
<td>Seronegative (n=694)</td>
<td>Seronegative (n=395)</td>
<td>Seronegative (n=662)</td>
</tr>
<tr>
<td>Age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>25–44</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>45–49</td>
<td>1.2 (0.8–1.8)</td>
<td>1.2 (1.3–3.4)</td>
<td>1.5 (1.0–2.1)</td>
<td>1.9 (1.2–3.0)</td>
<td>2.1 (1.5–3.0)</td>
</tr>
<tr>
<td>50–54</td>
<td>2.1 (1.5–2.9)</td>
<td>1.8 (1.3–2.3)</td>
<td>2.3 (1.3–3.2)</td>
<td>1.8 (1.1–2.9)</td>
<td>2.0 (1.4–3.1)</td>
</tr>
<tr>
<td>55–59</td>
<td>1.9 (1.3–2.6)</td>
<td>1.9 (1.2–3.1)</td>
<td>3.1 (2.1–4.6)</td>
<td>3.3 (1.9–5.5)</td>
<td>3.1 (1.3–7.4)</td>
</tr>
<tr>
<td>60–64</td>
<td>1.5 (1.0–2.1)</td>
<td>2.1 (1.3–3.1)</td>
<td>0.8 (0.3–2.4)</td>
<td>2.4 (0.8–7.8)</td>
<td>2.5 (1.5–4.2)</td>
</tr>
<tr>
<td>≥65</td>
<td>1.3 (1.0–1.9)</td>
<td>1.9 (1.2–2.9)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

References

Disclosures: M. J. Battistine, None; A. M. Barker, None; M. Grotzek, None; P. Beck, None; J. Berdan, None; P. Lawrence, None; G. W. Cannon, None.

ACR Concurrent Abstract Session

Epidemiology and Public Health IV: Rheumatoid Arthritis Pathogenesis

Tuesday, November 18, 2014, 4:30 PM – 6:00 PM

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Post-Menopausal Factors and the Risk of Seropositive and Seronegative Rheumatoid Arthritis Phenotypes: Results from the Nurses’ Health Study, Camilla Bengtsson1, Susan M aspés2, Jeffery A. Sparks2, Karen H. Costenbader3 and Elizabeth W. Karlson1. 1Karolinska Institutet, Stockholm, Sweden, 2Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: A mong women, the peak incidence of rheumatoid arthritis (RA) is reported to be 45–74 years of age. In addition, it has been suggested that the post-menopausal transition, especially at younger ages (Pikwer, Ann Rheum Dis, 2012), is related to an increased risk of RA, but the literature is scarce. Whether menopause has different impact on seropositive/seronegative RA phenotypes remains to be elucidated. Our aim was to explore whether age and menopausal factors were independently associated with subsequent development of serologic RA phenotypes in 2 prospective cohorts.

Methods: Data were analyzed from Nurses’ Health Study (NHS, 1976–2010) and NHSII (1989–2011). In NHS 121,701 female nurses aged 30–55 and in NHSII 116,430 female nurses aged 25–42 were followed via biennial questionnaires on lifestyle factors and disease outcomes. In total, 1,089 incident RA cases were confirmed by questionnaire and chart review. Seropositive RA was defined as +RF or ACPA by chart review or lab measurement. We used Cox proportional hazards models to obtain HR (95% CI) of seropositive or seronegative RA associated with menopausal status, age at menopause, type of menopause, severity of hot flashes and ovarian years, adjusting for age, income, BMI, smoking, breast-feeding, and parity.

Results: Women aged 45 or more had an increased risk of seronegative RA in all age groups, compared with women aged 25–44, with peak HR at ages 55–59. Women aged 50 or more had an increased risk of seropositive RA, with peak HR at ages 55–59, but the risk attenuated after age 60. Post-menopausal women had an increased risk of seronegative RA after adjusting for age and other potential confounders (NHS: HR 1.8, 95% CI 1.1–3.0; NHSII: HR 2.5, 95% CI 1.5–4.2; pooled HR 2.1, 95% CI 1.5–3.1) without marked differences according to type of menopause. Early age at menopause associated with an increased risk of seronegative RA (NHS: HR 2.5, 95% CI 1.2–3.4; NHSII: HR 3.0, 95% CI 1.7–5.1; pooled HR 2.4, 95% CI 1.5–3.5), regardless of type of early menopause. Moderate/severe hot flashes was mainly associated with an elevated risk for seronegative RA (NHS HR =2.4, 95% CI 1.4–4.3; NHSII: 3.7, 95% CI 2.0–6.8; pooled HR 3.0, 95% CI 2.0–4.5). None of the menopausal factors were significantly associated with seropositive RA.

Conclusion: In these prospective cohorts, women of older ages have an increased risk of both RA phenotypes, but this risk attenuates after age 60 for seropositive RA. Post-menopausal factors are strongly associated with seronegative RA, but not seropositive RA, suggesting potential differences in disease etiology.
The Association Between Changes in Inflammation and High Density Lipoprotein Cholesterol Efflux Capacity in Rheumatoid Arthritis. K P Liao,1 Martin Playford,2 Michelle A. Frits,3 Christine K. Iannaccone,1 Jonathan S. Coblyn1, Michael E. Weinblatt1, Nancy A. Shadick1 and Nehal N. M. Nalwa.1,2,3 Brigham and Women’s Hospital, Boston, MA, 4National Heart, Lung, and Blood Institute, Bethesda, MD, 5Brigham and Women’s Hospital; Harvard University, Cambridge, MA, 6University of Pennsylvania, Philadelphia, PA.

Methods: We conducted this study in a single center longitudinal RA cohort from a large academic center with RA clinical data, CRP and blood samples collected annually. We randomly selected 100 patients who experienced a reduction in inflammation defined as >10mg/L CRP decrease between any two time points one year apart. The first time point was defined as the baseline. Subjects on statin therapy one year before and during the one year follow up were excluded. We measured HDL efflux capacity in serum samples at baseline and one year follow-up quantified using a validated ex vivo system involving the incubation of macrophages with apolioprotein B-depleted serum. We used the paired t-test to determine significant differences between baseline and follow-up HDL cholesterol efflux values. We assessed the correlation between the change in CRP levels (natural log (baseline CRP-1 year follow-up CRP)) with percentage (%) change in HDL cholesterol efflux capacity using a Spearman’s correlation.

Results: We studied 92 subjects who experienced a reduction in inflammation as measured by CRP between baseline and one year follow-up with adequate serum volume. The mean age was 57.7 (SD 12.3), 89.3% were female, 78.5% were ACPA positive. The mean baseline CRP was 48.4mg/L (SD 59.3), and HDL efflux capacity was 1.04 (SD 0.17). At one year follow-up, the mean reduction in CRP was 41.0mg/L (SD 54.6). We observed an increase in HDL cholesterol efflux capacity of 6.7% (p<0.0001). A reduction in CRP was significantly correlated with an increase in HDL cholesterol efflux capacity (r=0.24, p=0.02) (Figure).

Conclusion: Although HDL cholesterol efflux capacity is considered to be a stable measure of HDL function over time in the general population, in RA subjects we observed a concomitant improvement in HDL function by efflux capacity with reductions in inflammation. These findings highlight a potential mechanism linking inflammation and CV risk in RA.
Does a Family History of RA Influence the Clinical Presentation and Treatment Response in RA? Thomas Frisell1, Saeds Saervasdottir2 and Johan Askling3. 1Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, 2Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Since family history of RA is among the strongest risk factors for developing the disease, individuals suspected to have RA are routinely asked about their relatives’ disease history. Being a summary measure of a range of genetic and non-genetic risk factors, it would seem likely that family history of RA carries information not only on risk of onset of RA, but also on prognosis, and/or that it may be more strongly associated with certain features of this heterogenic criteria based syndrome. Despite the potential clinical value, and great interest from patients, the role of family history of RA as a clinical marker has been little studied, probably due to the difficulty in ascertaining valid information on familial RA and clinical outcomes.

Methods: We performed a cohort study using prospectively recorded data from Swedish nationwide registers. The cohort was defined as all early RA patients (symptom onset ~12 months before inclusion) with a diagnosis of seropositive or seronegative RA in the Swedish Rheumatology register, who started methotrexate monotherapy as first DMARD treatment 2000–2011, and who had parents registered in the Swedish multi-generation register. First degree relatives of cohort members were identified through the Swedish Multi-Generation Register, and the presence of RA among relatives was assessed through the National Patient Register.

The association of RA in one or more first degree relatives to baseline clinical characteristics and treatment response (according to the DAS28-based EULAR response criteria), treatment switch, and change in disease activity measures at 3 and 6 months was estimated using linear regression and generalized logistic regression models.

Results: In our cohort, 380 (9%) of 4210 patients had a first degree relative with RA by their time of RA diagnosis. RA patients with compared to without a family history of RA were more often seropositive (75%/69%), but there were no other significant differences in baseline clinical characteristics (e.g., mean HAQ 0.95/1.01, mean DAS28 5.04/5.06, mean disease duration 0.48/0.49 years). Neither were there any significant differences in treatment response or disease progression at 3 or 6 months, a lack of association that remained after adjustment for sex, age, birth year, and disease duration, and also when further adjusting for baseline DAS28, HAQ, and CRP (Table).

Conclusion: Using a large population-based cohort, we found that despite being a strong predictor of RA itself, family history of RA is not associated with a more severe presentation of RA, nor with short term response to methotrexate monotherapy. Future studies could consider whether family history may be a predictor of long term prognosis or response to treatment other than methotrexate, and what this negative finding implies for the possibility of RA risk genes to also influence disease severity and treatment response.

<table>
<thead>
<tr>
<th>Response Measure</th>
<th>Family History of RA</th>
<th>DAS28</th>
<th>Change from baseline in DAS28 at 3 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>N (N = 380)</td>
<td>N (N = 380)</td>
<td></td>
</tr>
<tr>
<td>Switched Treatment</td>
<td>18% (N = 70)</td>
<td>0.79 (0.56, 1.11)</td>
<td>0.82 (0.58, 1.17)</td>
</tr>
<tr>
<td>Moderate Response</td>
<td>11% (N = 70)</td>
<td>1.13 (0.80, 1.64)</td>
<td>1.21 (0.84, 1.74)</td>
</tr>
<tr>
<td>Good Response</td>
<td>19% (N = 70)</td>
<td>0.98 (0.70, 1.32)</td>
<td>0.98 (0.72, 1.43)</td>
</tr>
<tr>
<td>Response Missing</td>
<td>27% (N = 70)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Response Missing</td>
<td>25% (N = 70)</td>
<td>1.01 (0.76, 1.51)</td>
<td>0.98 (0.73, 1.31)</td>
</tr>
</tbody>
</table>

Tuesday, November 18

Disclosure: K. P. Liao; None. M. Playford; None. M. A. Frits; None. C. K. Iannaccone; None. J. S. Coblyn; CV S caremark; S. M. E. Weinblatt; Atares; S. N. A. Shadick; None. N. N. M. et al; None.

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Does a Family History of RA Influence the Clinical Presentation and Treatment Response in RA? Thomas Frisell1, Saeds Saervasdottir2 and Johan Askling3. 1Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, 2Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Since family history of RA is among the strongest risk factors for developing the disease, individuals suspected to have RA are routinely asked about their relatives’ disease history. Being a summary measure of a range of genetic and non-genetic risk factors, it would seem likely that family history of RA carries information not only on risk of onset of RA, but also on prognosis, and/or that it may be more strongly associated with certain features of this heterogenic criteria based syndrome. Despite the potential clinical value, and great interest from patients, the role of family history of RA as a clinical marker has been little studied, probably due to the difficulty in ascertaining valid information on familial RA and clinical outcomes.

Methods: We performed a cohort study using prospectively recorded data from Swedish nationwide registers. The cohort was defined as all early RA patients (symptom onset ~12 months before inclusion) with a diagnosis of seropositive or seronegative RA in the Swedish Rheumatology register, who started methotrexate monotherapy as first DMARD treatment 2000–2011, and who had parents registered in the Swedish multi-generation register. First degree relatives of cohort members were identified through the Swedish Multi-Generation Register, and the presence of RA among relatives was assessed through the National Patient Register.

The association of RA in one or more first degree relatives to baseline clinical characteristics and treatment response (according to the DAS28-based EULAR response criteria), treatment switch, and change in disease activity measures at 3 and 6 months was estimated using linear regression and generalized logistic regression models.

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Conclusion: Using a large population-based cohort, we found that despite being a strong predictor of RA itself, family history of RA is not associated with a more severe presentation of RA, nor with short term response to methotrexate monotherapy. Future studies could consider whether family history may be a predictor of long term prognosis or response to treatment other than methotrexate, and what this negative finding implies for the possibility of RA risk genes to also influence disease severity and treatment response.

Table. Association of family history of RA and response to methotrexate monotherapy at 3 and 6 months

<table>
<thead>
<tr>
<th>Response Measure</th>
<th>Family History of RA</th>
<th>DAS28</th>
<th>Change from baseline in DAS28 at 3 Mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>N (N = 380)</td>
<td>N (N = 380)</td>
<td></td>
</tr>
<tr>
<td>Switched Treatment</td>
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<td>27% (N = 70)</td>
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Disclosure: K. P. Liao; None. M. Playford; None. M. A. Frits; None. C. K. Iannaccone; None. J. S. Coblyn; CV S caremark; S. M. E. Weinblatt; Atares; S. N. A. Shadick; None. N. N. M. et al; None.

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Inflammatory Genes Are Associated with Autoantibodies in Rheumatoid Arthritis-Free Individuals Who Are At-Risk for Future Disease. Ryan W. Gan1, Kendra A. Young1, M. Kristen Demoruelle2, Michael H. Weisman3, Jane H. Buckner4, P. K. Gregersen5, Ted R. Mikuls6, James R. O’Dell6, Sharon B. Masson7, Thomas Frisell8, N. J. Askling3, None. Antares, 5; None; C. K. Iannaccone, None.

Background/Purpose: Using a large population-based cohort, we found that despite the presence of rheumatoid arthritis(RA)-related autoantibodies is associated with systemic inflammation, and that decreased consumption of anti-inflammatory omega-3 fatty acids (n-3 FA) is associated with RA-related autoantibody positivity. We examined whether selected genes in inflammatory pathways in which n-3 FA play a role are associated with the presence of RA-related autoantibodies in individuals without RA but at risk for the disease.

Methods: Participants were enrolled in The Studies of the Etiology of RA (SERA), which is a multisite observational study following a cohort of first-degree relatives of RA probands and a cohort enriched with the HLA-DR4 genetic variant, both of which are RA-free at their baseline visit. Participant DNA was screened at the Benaroya Research Institute for specific shared epitope subtypes of HLA-DR4 and HLA-DR1. Participants were positive for the shared epitope if they were either DR4 or DR1 subtype positive. Serum was measured for the following autoantibodies: anti-cyclic citrullinated peptide version 2 (CCP2), CCP3.1 (in a subset), rheumatoid factor (RF) by nephelometry, and RF isotypes (RF-IgM, RF-IgG, RF-IgA). Participants were considered positive for RA-related autoantibodies if they tested positive for any of these autoantibodies at their baseline visit.
Participants were typed for single nucleotide polymorphisms (SNPs) in Cox-2, TNFA, NF-KB, IKBkB, PPARRA, and PPARG at the Broad Institute using the Sequenom platform. The association between RA-related autoantibody positivity and inflammatory genes was assessed using logistic regression, accounting for the correlation within family members, and adjusting for age at visit, sex, and race.

**Results:** Demographic characteristics were similar between autoantibody positive (n=306) and autoantibody negative (n=1,576) participants (Table 1). We observed a significant association between increasing number of minor alleles for Cox-2 and NF-KB and autoantibody positivity (Table 2).

**Conclusion:** Our results suggest that Cox-2 and NF-KB could be associated with an increased likelihood of developing RA-related autoantibodies. The association observed with Cox-2 is of interest due to the enzyme’s role in producing inflammatory lipid molecules, while the association observed with NF-KB is of interest given the potential roles that NF-KB has in the RA disease process, including cytokine production and stimulating B cell differentiation to immunoglobulin-producing B cells. These results need to be explored in further detail.

**Table 1:** Demographic characteristics at baseline by autoantibody (Ab) positivity

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Ab Positive (n=306)</th>
<th>Ab Negative (n=1,576)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline visit</td>
<td>43.9 ± 15.3</td>
<td>42.9 ± 13.4</td>
<td>0.22</td>
</tr>
<tr>
<td>(M=± 5D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>71.6</td>
<td>76.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Race (% NHW)</td>
<td>75.2</td>
<td>78.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Ever Smoke (% Yes)</td>
<td>39.9</td>
<td>37.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Current Smoker (% Yes)</td>
<td>12.1</td>
<td>10.9</td>
<td>0.55</td>
</tr>
<tr>
<td>Pack Y ears (M=± 5D)</td>
<td>3.6 ± 6.8</td>
<td>3.5 ± 7.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Shared Epidope (% Pos)</td>
<td>51.8</td>
<td>52.9</td>
<td>0.74</td>
</tr>
<tr>
<td>First-degree Relative of RA patient (%)</td>
<td>70.9</td>
<td>67.1</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Table 2:** Association between autoantibody positivity (CCP2, CCP3.1, or any RF) at baseline and increasing number of minor alleles (additive model). A adjusted for age, sex, and race, accounting for family correlation

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Minor Allele</th>
<th>MAF*</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox-2</td>
<td>rs5275</td>
<td>G</td>
<td>0.37</td>
<td>1.21</td>
<td>1.01–1.44</td>
<td>0.03</td>
</tr>
<tr>
<td>TNFA B87</td>
<td>rs1799772</td>
<td>T</td>
<td>0.11</td>
<td>1.15</td>
<td>0.89–1.50</td>
<td>0.29</td>
</tr>
<tr>
<td>NF-KB</td>
<td>rs997476</td>
<td>T</td>
<td>0.08</td>
<td>1.45</td>
<td>1.09–1.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IKBkB</td>
<td>rs647348</td>
<td>A</td>
<td>0.09</td>
<td>0.87</td>
<td>0.64–1.16</td>
<td>0.36</td>
</tr>
<tr>
<td>PPARRA L122V</td>
<td>rs1800206</td>
<td>G</td>
<td>0.06</td>
<td>0.97</td>
<td>0.68–1.39</td>
<td>0.89</td>
</tr>
<tr>
<td>PPARG Pro12Ala</td>
<td>rs1801282</td>
<td>G</td>
<td>0.12</td>
<td>1.14</td>
<td>0.88–1.48</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**Disclosure:** Mantel, None; M. Holmvist, None; J. Askling, None; L. Lund, None; D. Anderson, None.

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**2893**

**Genome-Wide Association Study of Osteoarthritis Progression: Results from the Osteoarthritis Initiative.**

**Background/Purpose:** Most genome-wide association (GWA) studies have focused on OA prevalence, but few have focused on OA progression. GWA studies of OA progression may help reveal new biology and drug targets that can be used to develop treatments that slow disease progression in OA patients.

**Methods:** We used an agnostic GWA analysis of ~8 million 1000 genomes imputed single nucleotide polymorphisms (SNPs) to identify genetic variation associated with structural knee OA progression. Our analyses were conducted in Caucasian participants from the Osteoarthritis Initiative (OAI), a multi-center natural history study of individuals who have or are at high risk for developing radiographic knee OA. A total of 1,756 participants who returned for a follow-up exam and had evidence of radiographic OA (Kellgren-Lawrence (K.L) grade ≥ 2) in one or more knees at baseline were included in the analyses (54% female, mean age = 67 ± 9 years). We defined progression as worsening of K.L grade or progression to total joint replacement (TJR). As a secondary phenotype, we exclusively evaluated progression to TJR. Participants were followed annually for four years. A bout 27% had worsening of K.L grade and 6% had TJR at follow-up. For these analyses, we used logistic regression models adjusted for age, sex, study site, and population stratification and assumed additive genetic models.

**Results:** We identified two SNPs that reached genome wide significance (P < 5x10^-8). One SNP on chromosome 18, rs9964101 (OR = 1.6, 95% CI = 1.4-1.7, P = 3.2x10^-8), is associated with worsening of K.L grade and another SNP on chromosome 4, rs76964101 (OR = 1.08, 95% CI = 1.00-1.17, P = 4.4x10^-6), is associated with progression to TJR. Both SNPs are located within intergenic regions, where rs9964101 is closest to SLY and rs76964101 targets that can be used to develop treatments that slow disease progression in OA patients.
is closest to SRD5A3 and KDR. SYT4 encodes synaptotagamin 4, which is expressed in the brain and may play a role in calcium dependent vesicular trafficking and exocytosis. There is some evidence that this protein may be involved in body weight regulation through negative regulation of oxytocin release. SRD5A3 encodes steroid 5 alpha-reductase 3, which is involved in maintenance of the androgen receptor activation pathway. KDR encodes a kinase insert domain receptor, which is a receptor for vascular endothelial growth factors and promotes proliferation, survival, migration, and differentiation of endothelial cells. There was no evidence for association of either SNP with OA prevalence, suggesting that these SNPs may be uniquely associated with OA progression.

Conclusion: We have identified two genome-wide significant SNPs that may be associated with structural knee OA progression. These SNPs reveal that neuronal regulation of obesity, androgen signaling, and vascular endothelial growth factors may play an important role in OA progression. Further work is ongoing to replicate these associations and identify the causative signal.

Disclosure: M. C. Hochberg, None; D. J. Duggan, None; J. M. Jordan, None; B. D. Mitchell, None; R. D. J. Jackson, None; M. C. Hochberg, None.

2894

Relationship of Dermal Advanced Glycation End Products and Hand Osteoarthritis with Habitual Running

Background/Purpose: Hand Osteoarthritis (HOA) is characterized by the progressive destruction of articular cartilage and bone changes and is strongly and positively associated with age but the mechanism by which aging contributes to this increased susceptibility is largely unknown. Recently, the hypothesis that accumulation of advanced glycation end products (AGEs) that are associated with oxidative stress and aging might explain some or most of this association has been suggested. We compared skin autofluorescence as a measure of dermal AGEs and its association with the prevalence of HOA, symptomatic HOA, and the number of finger joints with osteophytes and joint space narrowing (JSN) as a measure of severity.

Methods: We performed a cross-sectional analysis of a purposeful sample of the Osteoarthritis Initiative (OAI) from a single site who had dermal AGEs measured by skin autofluorescence using SCOUT DS machine (Vera light Inc., Albuquerque, New Mexico) at the 36 month visit. We used an excitation wavelength of 375nm and emission wavelengths of 435-660nm. This wavelength is correlated with cross-links of collagen, FAD, and NADH. A mathematical algorithm is applied to spectrum results to adjust for age, hemoglobin, skin pigmentation and light scattering. Hand x-rays from the dominant hand were read for definite osteophytes with JSN at 48 months. We classified a person as having radiographic HOA if their hand x-ray had two or more finger joints (DIP, PIP, MCP) affected on different fingers. Symptomatic HOA was defined as having radiographic HOA and presence of hand/finger pain, aching or stiffness for more than half the days in past 30 days. Simple T tests or Pearson correlation coefficients were used to evaluate the the mean number of finger joints involved by tertiles of dermal AGE levels. Then Analysis of Covariance was performed to adjust for age and gender. T-tests comparing levels of dermal AGEs between those with and without HOA and with and without symptomatic HOA were performed.

Results: In a sub-sample from the OAI (n=200) with equal proportions of participants with and without abdominal adiposity we had hand x-rays read. Of this sample, 171 had dermal AGEs measured and analyses performed. Mean levels of AGEs were greater both for those with radiographic HOA (n=114) [29.3(4.8) vs. 27.1(5.0), p = 0.005], and symptomatic HOA (n=35) [30.5(2.8) vs. 28.1(4.8), p=0.01] compared to those without HOA or symptomatic HOA. Furthermore level of AGEs correlated significantly with the number of joints affected per hand (r=0.25, p<0.001) and exhibited a dose-response relationship in categorical analysis (with 2.34, 2.70 and 3.59 joints involved by increasing tertiles of dermal AGE levels after adjustment for age and gender (p trend <0.001).

Conclusion: Non-enzymatic glycation of dermal tissues as a proxy for the accumulation of AGEs in articular cartilage is associated with HOA, symptomatic HOA and the severity of HOA as measured by the number of finger joints affected in this cross-sectional study. Replication of these findings in prospective cohort studies and understanding of metabolic pathways that may modify or mediate the relationship of AGEs with HOA are indicated.

Disclosure: C. Eaton, None; J. Driban, None; B. L. U. None; M. Roberts, None; T. E. McAlindon, None.

2895

Habitual Running Any Time in Life Is Not Detrimental and May Be Protective of Symptomatic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

Background/Purpose: Controversy exists regarding whether habitual running is beneficial versus harmful to the knee. Chronic mechanical overloading could potentially physically damage structures within the knee. Alternatively, runners have a lower body mass index (BMI), protective of knee osteoarthritis (OA). Most existing studies evaluating running and knee osteoarthritis (OA) have focused on elite male athletes, not generalizable to most of the population. Therefore, we aimed to evaluate the relationship of habitual running with symptomatic knee OA in the Osteoarthritis Initiative (OAI), a cohort recruited from the community not based on elite running status.

Methods: This is a cross-sectional study of OAI participants with knee x-ray readings, symptom assessments, and completed surveys on lifetime physical activity. At the 96-month visit, a modified version of the Lifetime Physical Activity Questionnaire (LPAQ) asked participants to identify the top 3 most frequently performed physical activities (=20 times in life) from ages 12 – 18, 19 – 34, 35 – 49 and ≥50 years old. Those indicating running as an activity were defined as a runner in that time period. Running at any time in life included runners from all time periods. Posterior-anterior semi-flexed knee radiographs were obtained at OAI 48-month visit and scored for Kellgren-Lawrence (KL) grade (0-4). Radiographic OA (ROA) was defined as KL ≥ 2. Frequent knee pain within a person required at least one knee have frequent knee pain at the OAI 48-month visit. Symptomatic radiographic OA (SOA) required that at least one knee had both ROA and frequent knee pain. A person with any total knee replacement was classified as having SOA.

We performed logistic regression analyses where the predictor was running any time in life and running in the specific age ranges. The outcomes were ROA, frequent knee pain, and SOA; adjusted analyses included covariates age, sex and BMI.

Results: 2439 participants were included, 55% were female, mean age was 64.7 (9.0) years and BMI was 28.5 (4.9) kg/m². 28% ran at some time in their lives; of those, 49%, 31%, 15% and 5% identified running in 1, 2, 3, and 4 of the time periods respectively. From lowest to highest BMI tertile, 35%, 28%, 24% and 22% were runners at any time in life.

Table: Odds Ratios of Prevalent Symptomatic Knee Osteoarthritis (SOA) for Runners compared to Non-Runners

<table>
<thead>
<tr>
<th>Running Time Period</th>
<th>Prevalence of SOA</th>
<th>Unadjusted Odds Ratios</th>
<th>Adjusted Odds Ratios*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any time in Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1528)</td>
<td>29.3%</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes (n = 626)</td>
<td>22.7%</td>
<td>0.84 (0.76 – 0.94)</td>
<td>0.89 (0.79 – 1.00)</td>
</tr>
<tr>
<td>Ages 12 - 18 years old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1924)</td>
<td>27.7%</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes (n = 212)</td>
<td>23.6%</td>
<td>0.81 (0.58 – 1.12)</td>
<td>0.94 (0.66 – 1.34)</td>
</tr>
<tr>
<td>Ages 19 - 34 years old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1806)</td>
<td>28.3%</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes (n = 332)</td>
<td>22.0%</td>
<td>0.71 (0.54 – 0.94)</td>
<td>0.78 (0.58 – 1.05)</td>
</tr>
<tr>
<td>Ages 35 - 49 years old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 1794)</td>
<td>28.2%</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes (n = 332)</td>
<td>22.0%</td>
<td>0.71 (0.54 – 0.94)</td>
<td>0.78 (0.58 – 1.05)</td>
</tr>
</tbody>
</table>
Y n (n = 374) 22.5% 0.74 (0.56 - 0.97) 0.85 (0.63 - 1.13)
Ages > 50 years old
No (n = 1881) 28.2% Referent Referent
Yes (n = 221) 22.2% 0.73 (0.52 - 1.01) 0.85 (0.60 - 1.20)

For outcomes of frequent knee pain and ROA, the results were similar to that of SOA.

Conclusion: Our findings suggest an exposure to non-elite running at any time in life is not associated with a higher odds of prevalent ROA, knee, hip, pain, and SOA. Those with the lowest BMI were most likely to identify running as a habitual activity. These findings were observed in a cohort recruited from the community not based on elite running status making these findings potentially more applicable to a broader population. Non-elite running at any time in life does not appear detrimental, and may be protective of SOA.

Disclosure G. H. Lo, NIH/NIAMS, 2; J. B. Driban, None; A. K. Riska, None; K. Storti, None; T. E. MclAlindon, None; R. Souza, None; C. B. Eaton, None; N. J. Petersen, None; M. E. Suarez-Almazor, None.

2896

A Multi-Center Double-Blind, Randomized Controlled Trial (db-RCT) to Evaluate the Effectiveness and Safety of Co-Aministered Traumeel® (Tr14) and Zeel® (Ze14) Intra-articular (IA) Injections Versus IA Placebo in Patients with Moderate-to-Severe Pain Associated with OA of the Knee. Carlos Lozada1, Eve del Río2, Donald Reitberg3, Robert Smith1, Charles Kahn1 and Roland W. Moskowitz1. University of Miami Miller School of Medicine, Miami, FL, Miami, FL, 2Rio Pharmaceutical Services, LLC, Bridgewater, NJ, 3Rio Pharmaceutical Services, LLC, Bridgewater, NJ.

Background/Purpose: Tr14 & Ze14 is a combination of dilute biological and mineral extracts administered IA for painful knee OA. In response to clinician impressions of positive outcomes, a db-RCT to assess efficacy and safety compared to IA saline was deployed in the US.

Methods: Pts with moderate-to-severe chronic knee OA were randomized to 3 weekly IA injections of either Tr14 & Ze14 or saline by clinical investigators experienced with use of the IA injection route. The primary efficacy variable was change in knee pain from Baseline to End-of-Study (Week 17) as measured by the WOMAC OA Pain Subscale (Section A, 1–5 100 mm VAS). Secondary measures included Total WOMAC and subscores for stiffness (B), and physician global function (C), change in pain following a 50 ft walk (100 mm VAS), patient and physician global assessments. Clinical relevance was assessed by comparing proportions of patients with reductions from baseline in WOMAC A scores greater than a validated benchmark: Minimal Clinically Important Difference (MCID). This was chosen as −32.6 mm (the most conservative value) based on a study of outpatients with knee or hip OA where WOMAC VAS MCIDs ranged from −7.9mm to −32.6mm (see reference 59 Taubak et al., Ann Rheum Dis. 2005; 64(1):29–33 in the description of the WOMAC index published by ACR). Safety was assessed by monitoring of vital signs, physical examinations of the target knee, adverse events and concomitant medications.

Results: 232 patients were randomized and treated (All Tr14 & Ze14, n=119, All Placebo, n=113; Intention-to-Treat (ITT) Tr14 & Ze14, n=117, Placebo, n=111). Treatment arms were well balanced across demographic and baseline characteristics. Tr14 & Ze14 did not discriminate for WOMAC A Pain as expected after only 1 of 3 injections on Day 8 (p=0.3715), but subsequently was significantly different (p<0.05) on Days 15, 43, 57, 71, 85 and 99 (primary endpoint day), and approached significance on Day 29 (p=0.0686). Logistic regressions showed the proportion of MCID responders was not significant on Day 8. As this was an expected finding, it served as a no-effect internal-model-validation. Tr14 & Ze14 was significantly different (p<0.05) on all subsequent days except Day 29 (approached significance, p=0.059, Figure 1). SO pain was similarly discriminating as was the Physician global assessment. Total WOMAC and subscores B&C were directionally consistent with WOMAC A. There were no related SAEs. AEs were generally mild and unrelated to treatment. Local knee-related AEs, labs assessments, ECGs and vital signs were unremarkable and similar between treatments.

Conclusion: Tr14 & Ze14 provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison to placebo. In this double-blind, randomized, controlled trial, a biological/mineral multi-extract combination was shown to be a safe and effective treatment for pain in moderate-to-severe knee OA.

Disclosure: C. Lozada, Rio Pharmaceutical Services, 5; E. del Rio, Biologische Heilmittel Heel GmbH, 5; D. Reitberg, Rio Pharmaceutical Services, LLC, 5; R. Smith, Rio Pharmaceutical Services, LLC, 5; C. Kahn, Biologische Heilmittel Heel GmbH, 5; R. W. Moskowitz, Rio Pharmaceutical Services, LLC, 5; Heel USA, 5.

2897

Exercise Therapy and/or Manual Therapy for Hip or Knee Osteoarthritis: 2-Year Follow-up of a Randomized Controlled Trial. J. Haxby Abbott1, Cathy Chapelle1, Daniël Pinto2, Alexis Wright3 and Jean-Claude Theis4. University of Otago, Dunedin, New Zealand, 1Northwestern University, Chicago, IL, 2High Point University, High Point, NC.

Background/Purpose: Although both exercise therapy and manual therapy have evidence supporting their effectiveness in people with hip and knee osteoarthritis (OA), few clinical trials have reported their incremental effectiveness compared with usual medical care, or their long-term effects.

Methods: In this randomized controlled trial with 2-year follow-up, adults meeting the American College of Rheumatology criteria for hip or knee OA were randomly allocated to receive either a) exercise therapy; b) manual therapy; c) combined exercise therapy and manual therapy; or d) no trial intervention in addition to usual medical care. Groups a-c were provided 10 treatment sessions: 7 sessions within the first 9 weeks plus 3 booster sessions (2 at 4 months and 1 at 13 months). A summary blinded to group allocation reassessed participants at 2 years. The primary outcome measures were the Western Ontario and McMaster (WOMAC) osteoarthritis index (24 questions, 0–10 scale, total range 0–240) and physical performance tests (timed up-and-go, 40m fast-paced walk, 30 second sit-to-stand).

Results: 186 (90.3%) of 206 participants recruited were retained at 2 years follow-up. At baseline, mean age was 66 years (range 37 to 92) and mean WOMAC was 100.8 (SD 53.8). Missing data were replaced using multiple imputation. Intention-to-treat analysis of covariance (ANCOVA) showed improvements in WOMAC at 2 years were superior for all three intervention groups compared with the usual care group (2-sided p<0.05). Participants receiving exercise therapy in addition to usual care showed gains of 31.7 WOMAC points (95% CI 10.0, 53.3); effect size 0.57 (Cohen’s d 95% CI 17.9, 97). Participants receiving manual therapy in addition to usual care showed gains of 30.1 (9.3, 51.3); effect size 0.55 (16.9, 94). Participants receiving combined therapy and manual therapy in addition to usual care did not meet the a priori threshold for clinical significance (28 points), but were 26.2 (6.1, 46.3) WOMAC points better than usual care only, for a clinically significant effect size of 0.52 (11, 91). The exercise therapy group showed greater mean changes on most physical performance tests than the other groups.
Conclusion: Both exercise physiotherapy and manual physiotherapy provided incremental benefit over usual care alone at 2 years follow-up. Physical performance test outcomes significantly favoured the exercise therapy group.
Background/Purpose: Juvenile dermatomyositis (JDM) affects 3 children/million/year with myositis and skin disease being the typical features. The Pediatric Rheumatology International Trials Organisation (PRINTO) have recently established criteria to classify JDM patients who are clinically inactive by meeting at least 3 out of the following 4 conditions – Creatine Kinase (CK) ≤150 U/L, Childhood Miositis Assessment Score (CMAS) ≥48, Manual Muscle Testing of 8 groups (MMT8) ≥78 and physician global Visual Analogue Scale (PGA) ≤0.2. CK, CMAS and MMT8 all measure muscle involvement, only PGA includes skin or other organ involvement. The hypothesis that these criteria may fail to detect patients who have active skin disease but normal muscle parameters was tested. The aim was to demonstrate the prevalence of clinically inactive disease in the UK JDM Cohort and Biomarker Study and to identify whether skin disease is still present in these patients on the basis of the PRINTO criteria.

Methods: Data were analysed from children who were recruited and met Bohan-Peter criteria. Data from patient episodes (either a clinic visit or hospital admission) were assessed using the PRINTO criteria. Using the PRINTO rules stipulating 3 of 4 criteria are required, all data entries were divided into 2 groups based on the criterion that was omitted. Each case was analysed to determine whether skin disease was present or absent. Results: 682 data entries (DE) from 321 patients were identified as clinically inactive 235 (37.4%) of these DE (119 patients) met all 4 criteria. 21.2% of DE had skin rash and 10.5% had nailfold changes (Table 1) at the time of assessment. 427 of the total DE (202 patients) met 3 of the 4 criteria. Of these, 320 (79.4%) had clinically inactive based on the 3 muscle criteria (PGA was not met). 61.6% of this group had ongoing skin rash present. Among the 107 remaining DE, which were clinically inactive by 3 criteria of which one was PGA, the frequency of skin changes was lower. The differences between the 3 groups were statistically significant in terms of rash ($\chi^2$ 111.5, $p<0.0001$), nailfold changes ($\chi^2$ 65.5, $p<0.0001$) and calcinosis ($\chi^2$ 22.07, $p<0.0001$).

Table 1: Frequency of skin changes in JDM patients meeting PRINTO criteria (number of episodes, % in brackets)

<table>
<thead>
<tr>
<th>No. of criteria met (DE = data entries, n 119)</th>
<th>Rash</th>
<th>Nailfold changes</th>
<th>Calcinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 4 criteria met (255 DE, n 119)</td>
<td>54 (21.2)</td>
<td>27 (10.5)</td>
<td>19 (7.5)</td>
</tr>
<tr>
<td>3 criteria met, but PGA not met (320)</td>
<td>197 (61.6)</td>
<td>114 (35.6)</td>
<td>60 (18.8)</td>
</tr>
<tr>
<td>3 criteria met of which one was PGA (107 DE, n 71)</td>
<td>25 (23.3)</td>
<td>9 (8.4)</td>
<td>6 (5.6)</td>
</tr>
</tbody>
</table>

Conclusion: This study is one of the first to test the PRINTO criteria in a large independent cohort of JDM patients. When clinically inactive disease is defined by “muscle-based” criteria, without PGA, there is a greater frequency of skin disease. As a revision, we propose that PGA should be defined by “muscle-based” criteria, without PGA, there is a greater frequency of skin disease being overlooked in the clinical assessment which included as an essential criterion together with 2 of the 3 muscle criteria. This frequency of skin disease. As a revision, we propose that PGA should be included as an essential criterion together with 2 of the 3 muscle criteria. This frequency of skin disease. As a revision, we propose that PGA should be included as an essential criterion together with 2 of the 3 muscle criteria. This frequency of skin disease. As a revision, we propose that PGA should be included as an essential criterion together with 2 of the 3 muscle criteria.

Disclosure: B. Almeida, None; R. Campanilho-Marques, None; K. Arnold, None; L. R. Wedderburn, None; C. A Pilkington, None; K. Nistala, None.

2901

Predictors of Relapse after Discontinuing Systemic Treatment in Childhood Autoimmune Chronic Uveitis, Gabriele Simonini, Claudia Bracaglia, M. Arcaro Cattalini, Andrea Taddeo, Alice Brambilla, Cinzia Deli Iberio, Denise Pires Marafon, Roberto Caputo and Rolando Cimaz. 1 Anna Meyer Children’s Hospital-University of Firenze, Florence, Italy, 2 Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 3 Institute of Child Health, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy, 4 Anna Meyer Children’s Hospital, Florence, Italy, 5 Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy.

Background/Purpose: Information regarding the natural clinical history of a child on systemic treatment due to autoimmune chronic uveitis would be helpful in driving duration therapy. Aim of our study was to assess the time on remission after discontinuing systemic therapy in a retrospective, comparative, multi-centre, cohort study of childhood non-infectious chronic uveitis.

Methods: 40 patients (30 F, 10 M; median age: 11.6 years, 31 JIA, 9 Idiopathic Chronic Uveitis (IUCU)) from 4 different paediatric rheumatology centres, with previously refractory, vision threatening, non-infectious inactive uveitis, which discontinued all related treatments for at least 3 months were enrolled. 23 children previously received Methotrexate, 17 TNF inhibitors. Primary outcome was to assess, once remission was achieved, the time on remission up to the first relapse after discontinuing treatment. Time to remission once systemic not-steroid treatment was started, time to steroid discontinuation, number of relapses before achieving remission and time on remission on therapy before discontinuing all treatments were also considered. Statistical Analysis: Mann-Whitney U-test, Wilcoxon signed-rank test for paired samples, c-square tests, and Fisher’s exact test, when appropriate, were used to compare data. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables. In order to identify predictors of outcome Cox regression model and Kaplan-Meier curves were constructed, each one at mean of enter ed covariates.

Results: Median follow-up time on remission without treatment was 9 months (range 1–59 months). At last available follow-up after 1 year from discontinuation of treatment (49 months, range 15–168), 11/39 (28.2%) children maintained a complete remission over a median period of 18 months. At 49 months of follow-up, 6/18 children with IUCU (75%) compared to 5/31 children with JIA (16.1%) were still on remission without treatment ($p<0.003$). A higher probability of maintaining uveitis remission after discontinuing treatment was shown in IUCU compared to JIA group (Mantel-Cox c2 7.62, $p<0.006$) (Figure). A N A positivity was associated with a higher probability of flare in overall population (Mantel-Cox c2 6.68, $p<0.01$), but not in sub-analysis limited to JIA (Mantel-Cox c2 0.78, $p=0.57$) and IUCU (Mantel-Cox c2 1.18, $p=0.27$). None clinical variable, including time on remission on therapy, total length of treatment, and type of treatment, resulted significant predictors of long-lasting remission without therapy.

Conclusion: Even if limited to a relatively small group in retrospectively study design, our results suggest that type of disease, rather than the type or the length of treatment, can predict different duration of uveitis remission without systemic therapy.

Disclosure: G. Simonini, None; C. Bracaglia, None; M. Cattalini, None; A. Taddeo, None; A. Brambilla, None; C. Deli Iberio, None; D. Pires Marafon, None; R. Caputo, None; R. Cimaz, None.

2902

The Health Status of Patients with Juvenile Idiopathic Arthritis (JIA): Significantly Worse than After Transfer from Pediatric to Adult Care. Kirsten M Inden, Jens K Iotsche, Martina Niewerth, Angela Zink, and Gerd Homeff. 1 Charité University Medicine, Berlin, Germany, 2 German Rheumatism Research Center, Berlin, Germany, 3 German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, 4 A. Klinik Sanit Augustin, Sankt Augustin, Germany.

Background/Purpose: Information regarding the natural clinical history of a child on systemic treatment due to autoimmune chronic uveitis would be helpful in driving duration therapy. Aim of our study was to assess the time on remission after discontinuing systemic therapy in a retrospective, comparative, multi-centre, cohort study of childhood non-infectious chronic uveitis.

Methods: 40 patients (30 F, 10 M; median age: 11.6 years, 31 JIA, 9 Idiopathic Chronic Uveitis (IUCU)) from 4 different paediatric rheumatology centres, with previously refractory, vision threatening, non-infectious inactive uveitis, which discontinued all related treatments for at least 3 months were enrolled. 23 children previously received Methotrexate, 17 TNF inhibitors. Primary outcome was to assess, once remission was achieved, the time on remission up to the first relapse after discontinuing treatment. Time to remission once systemic not-steroid treatment was started, time to steroid discontinuation, number of relapses before achieving remission and time on remission on therapy before discontinuing all treatments were also considered. Statistical Analysis: Mann-Whitney U-test, Wilcoxon signed-rank test for paired samples, c-square tests, and Fisher’s exact test, when appropriate, were used to compare data. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables. In order to identify predictors of outcome Cox regression model and Kaplan-Meier curves were constructed, each one at mean of enter ed covariates.

Results: Median follow-up time on remission without treatment was 9 months (range 1–59 months). At last available follow-up after 1 year from discontinuation of treatment (49 months, range 15–168), 11/39 (28.2%) children maintained a complete remission over a median period of 18 months. At 49 months of follow-up, 6/18 children with IUCU (75%) compared to 5/31 children with JIA (16.1%) were still on remission without treatment ($p<0.003$). A higher probability of maintaining uveitis remission after discontinuing treatment was shown in IUCU compared to JIA group (Mantel-Cox c2 7.62, $p<0.006$) (Figure). A N A positivity was associated with a higher probability of flare in overall population (Mantel-Cox c2 6.68, $p<0.01$), but not in sub-analysis limited to JIA (Mantel-Cox c2 0.78, $p=0.57$) and IUCU (Mantel-Cox c2 1.18, $p=0.27$). None clinical variable, including time on remission on therapy, total length of treatment, and type of treatment, resulted significant predictors of long-lasting remission without therapy.

Conclusion: Even if limited to a relatively small group in retrospectively study design, our results suggest that type of disease, rather than the type or the length of treatment, can predict different duration of uveitis remission without systemic therapy.

Disclosure: G. Simonini, None; C. Bracaglia, None; M. Cattalini, None; A. Taddeo, None; A. Brambilla, None; C. Deli Iberio, None; D. Pires Marafon, None; R. Caputo, None; R. Cimaz, None.
Background/Purpose: A minority of patients with polyarticular JIA enter adulthood in drug free remission. Thus, patients are in need of care beyond adolescence. There is little information how patients' health status changes after discharge from pediatric care. We therefore investigated changes in the patients' health status before and after the transfer from pediatric to adult health care.

Methods: Data from patients were considered who were prospectively followed in the JIA biologic registry BiKeR and in the follow-up register JuMBO for at least two additional years. The last observation in JuMBO (mean 2.6) is less than 2 years after the last observation in BiKeR (mean 4.2). The whole observation period comprised 8.2 vs. 4.5 to 2.1 (mean) years, from enrollment until the last visit in BiKeR, all PROs significantly improved: overall well-being from 4.5 to 2.1 (mean), pain level from 4.6 to 1.9, functional status (CHAQ-score) from 0.75 to 0.35. In contrast to this trend towards a steady improvement in patients' health state in pediatric care, PROs significantly worsened after discharge from pediatric care (p < 0.0001). At the last follow-up in JuMBO, when patients were at the age of 23 years and had a disease duration of 14.2 ys, the mean disease activity was 2.6, pain level 2.8, and overall well-being 2.9. At that time, more patients had an active disease (NRS0: 71 vs. 57%) and reported pain (78 vs. 56%) and restrictions in overall well-being (86 vs. 58%) than at the last visit in pediatric care.

A dual health care providers rated the patients' disease activity at first documentation in JuMBO lower than pediatric rheumatologists at the last visit in pediatric rheumatology care (1.8 vs. 2.1), which is in contrast to patients' self-reports. They also rated the disease activity lower than the patients did at last observation in JuMBO (1.9 vs. 2.6). The correlation between physician and patient scores for disease activity was better during pediatric than adult care (0.56 vs. 0.51).

Conclusion: The state of patients with long-standing JIA significantly worsens after discharge from pediatric care. The reasons for this have to be explored. In addition, there are larger discrepancies between physician- and patient-reported outcomes in adult care than in pediatric care.

Disclosure: K. Minden, None; J. Klotsche, None; M. Niewerth, None; A. Zink, None; G. Hornett, Abbvie, Pfizer, and Roche; 2, Abbvie; Novartis, Pfizer, and Roche.

2903 Early Outcomes in Pediatric Antineutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis (AAV). Kimberly Morishita1, Susanne Benseler2, Rae S.M. Yeung3, Dawn Wahezi4, Kenneth N. Schikler5, Erica F. Lawson7, Susan Nielsen8, Sirirat Charuvanij9, Paul J. Foley, Orla Killeen and Emma Jane MacDermott. The National Centre for Paediatric Rheumatology, Dublin, Ireland.

Background/ Purpose: The ‘Arthropathy of Down syndrome’ was first described in 1984. Three decades on we still have limited literature on the clinical & radiological features of this arthritis, despite the fact that it is thought to be 3–6 times more common than Juvenile Idiopathic Arthritis (JIA) in the general paediatric population. Down’s Arthropathy (DA) is rarely recognised at onset, & remains under-diagnosed & largely under-reported in this population group. Ireland has one of the highest Trisomy 21 (T21) birth rates in Europe (1/547), and therefore provides an ideal setting for such a study.

Research Questions
1. What are the clinical & radiological features of DA?
2. Is DA missed, leading to a delay in diagnosis?

Objective
To perform a musculoskeletal examination on children with T21, aged 0–18 years & document:
1. Presence of features to suggest old and/or present arthritis.
2. Radiological findings.

Methods: From May 2013 to September 2014, Children with T21 (aged 0–18 years) were invited to attend a screening clinic. Screening involved completion of a health questionnaire & musculoskeletal examination. Suspected cases of DA were invited to attend the National Centre for Paediatric Rheumatology (NCPR) for investigation, treatment & follow-up as per normal clinical practice.

Results: 370 children with T21 enrolled in the study, 56% M a/e. 17 new cases of DA were detected, only 3 (17.6%) of which were referred with suspected arthritis. In total, 28 children with DA now attend the NCPR for management of their arthritis, the largest cohort ever reported in the literature. We estimate the Point Prevalence of DA in Ireland to be 17–18/1000. For
compared the UK Prevalence of JIA is 1-2/1000. Table 1 compares characteristics of our DA cohort to a JIA comparison group.

Table 1: Comparison of Study Characteristic by Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DA (n=28)</th>
<th>JIA (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small joint involvement</td>
<td>mean (SD)</td>
<td>4.46 (1.95)</td>
<td>3.05 (2.29)</td>
</tr>
<tr>
<td>Time to Diagnosis</td>
<td>mean (SD)</td>
<td>1.71 (1.47)</td>
<td>0.74 (0.86)</td>
</tr>
<tr>
<td>Characteristics</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>14</td>
<td>11</td>
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<tr>
<td></td>
<td>Female</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Rx MTX</td>
<td>8</td>
<td>28.5</td>
<td>7</td>
</tr>
<tr>
<td>MTX Nausea</td>
<td>6</td>
<td>75.0</td>
<td>1</td>
</tr>
</tbody>
</table>

Features of DA - Summary of our findings
- Polymicrobial Rheumatoid Factor negative presentation (69% of DA cohort).
- Finger involvement (77% of DA cohort) - significantly greater proportion than seen in the JIA comparison group.
- Erosive changes noted on X-Ray at presentation (27% of cohort).
- Methotrexate nausea common, but a good response to steroid intra-articular joint injections observed.
- General lack of awareness about the increased risk of arthritis in children with T21.

Conclusion: Children with T21 are at increased risk of developing arthritis, however there is often a delay in diagnosis. Reasons for this are multifactorial and include, failure of the child to express and localise pain, and changes in mobility attributed to the Down syndrome rather than a Rheumatological cause. Early diagnosis & treatment of DA is key to preventing changes in mobility.

Disclosure: C. Foley, None; O. Killeen, None; E. J. MacDermott, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models II
Tuesday, November 18, 2014, 4:30 pm - 6:00 pm

2905

The IL-6/Th17 Axis Promotes Autoantibody-Associated Autoimmune Valvular Carditis in Mice. Jennifer L. Auger, Brianna J. Engelson, Yaya Wang, Erik J. Peterson and Bryce A. Binstadt. University of Minnesota, Minneapolis, M N.

Background/Purpose: Autoimmune valvular carditis occurs in patients with systemic lupus erythematosus, rheumatoid arthritis and rheumatic fever, but the pathogenic mechanisms remain incompletely defined. Spontaneous autoimmune valvular carditis develops in the K/BxN T cell receptor transgenic mouse model of autoantibody-dependent inflammatory arthritis. CD4 T helper (Th) cells and macrophages cooperate to promote carditis in this model. We investigated which effector Th cell population was the predominant driver of cardiovascular pathology in K/BxN mice.

Methods: We first used RT-PCR to measure key cytokine transcript levels in cardiac valves of arthritic K/BxN mice and controls. We then used anti-cytokine blocking antibodies and gene knockout mice to determine which Th effector cells and cytokines were most critical for valve inflammation.

Results: We found increased expression of the genes encoding the Th17 differentiation factor IL-6 and IL-17A itself in K/BxN mitral valves relative to controls; IL-4 and IFN-y transcript levels were not different. Antibody blockade of IL-6 or IL-17A reduced the severity of valve inflammation, whereas blocking IL-4 had no effect. Genetic deficiency of IFN-y did not affect carditis severity. K/BxN mice lacking the key Th17 transcription factor ROR-yt had delayed onset of arthritis and were protected from valvular carditis.

Conclusion: Th17 cells are key drivers of autoimmune valvular carditis in K/BxN mice. We suggest a model in which autoantibodies engage Fc receptors on macrophages, leading to IL-6 production, which in turn promotes the differentiation of valve-infiltrating Th17 effector cells. Our results provide new insight into the mechanisms of valvular carditis in systemic autoantibody-mediated rheumatic diseases. More broadly, these findings may help guide the selection of therapies to reduce cardiovascular morbidity and mortality among patients with rheumatoid arthritis and systemic lupus erythematosus.

Disclosure: J. L. Auger, None; B. J. Engelson, None; Y. Wang, None; E. J. Peterson, None; B. A. Binstadt, None.

2906

Systemic Delivery of Short Hairpin RNA Targeting Calcium Release-Activated Calcium Channel 3 Down-Regulates Severity of Collagen-Induced Arthritis. Shuang Liu1, Takeshi Kiyoi2, Shohe Watanabe3 and Kazutaka Meya4a. 1Informational Biomedicine, Ehime University Graduate School of Medicine, Toon-shi, Ehime, Japan, 2Integrated Center for Sciences, Ehime University, Ehime, Japan, 3Japan Community Health Care Organization Uwajima Hospital, Ehime, Japan.

Background/Purpose: In recent years, one widespread and potentially important Ca2+ channel, store-operated Ca2+ release-activated Ca2+ (CRAC) channel is raised in drug discovery for rheumatoid arthritis (RA). Ca2+ entry through CRAC channels drives exocytosis, stimulates mitochondrial metabolism, activates gene expression and promotes cell growth, proliferation, and non-exitable cells. Downregulation of the CRAC channels lead to irregular functions of T cells, B cells and osteoclasts, which contribute to RA pathogenesis. The present study was undertaken to investigate the feasibility and efficiency of partially regulation of the Ca2+ influx via CRAC channel by CRACM3 gene-silencing for the treatment of RA.

Methods: We evaluated the therapeutic potential of CRACM3 gene-silencing by systemic delivery of lentivirus expressing CRACM3-shRNA (Lenti-M3shRNA) in a collagen-induced arthritis (CIA) mouse model. The inflammatory response was assessed by measuring the levels of inflammatory cytokines in joint and serum. The cytokine profile of T cells stimulated with autologen was also determined. Mature osteoclast function was analyzed using sartrate-resistant acid phosphatase (TRAP) staining and pit formation assay.

Results: The intraperitoneal injection (10^6 particles/7 days) of Lenti-M3shRNA was highly effective in treating CIA. Ca2+ influxes in splenocytes, thymocytes, and synovial cells were partially blocked by gene-silencing of CRACM3. CIA mice showed significant regression of the disease after Lenti-M3shRNA treatment. The autoimmune response, which was assessed using self-reactive Th1 cell activity and autoantibody production, was significantly suppressed by M3shRNA administration. Low level of the resorptive capacity in mature osteoclasts was also observed in Lenti-M3shRNA treated CIA mice according to the results of TRAP staining and pit formation assay.

Conclusion: Our findings indicate that in vivo gene-silencing CRACM3 by systemic delivery of Lenti-M3shRNA may have beneficial therapeutic effects on RA. Our findings provide valuable insights into the potential ways that CRACM3 could contribute to RA pathogenesis and support the idea that targeting CRAC channels might offer an effective strategy for the treatment of RA.

Disclosure: S. Liu, None; T. Kiyoi, None; S. Watanabe, None; K. Meya, None.

2907

Loss of microRNA-146a Exacerbates Inflammatory Arthritis. Victoria Saferding1, Antonia Puchner1, Eljana Goncalvesalves1, Birgit Niedereiter1, Silvia Hayer1, Gernot Schabbauer2, Marije K oenders3, Josef S. Smolen1, Kurt Redlich4 and Stephan Blueml1. 1 Medical University of Vienna, Vienna, Austria, 2 Medical University Vienna, Vienna, Austria, 3 Raboud University Nijmegen Medical Center, Nijmegen, Netherlands.

Background/Purpose: MicroRNA (MiR-) 146a is a key regulator of the innate immune response and has also been shown to suppress cancer development in myeloid cells. Elevated expression of miR-146a has been detected in synovial tissue of rheumatoid arthritis patients, but its role in the development of inflammatory arthritis is yet unknown.

Methods: We induced K/BxN serum transfer arthritis in wild type and miR-146a-/- mice. A second inflammatory arthritis model we crossed miR-146a deficient into hTNFtg mice. Disease severity was assessed clinically and histologically in both arthritis models. Blood of arthritis animals was analyzed by flow cytometry. Serum cytokine levels were measured by Elisa.

Disclosure: S. Liu, None; T. Kiyoi, None; S. Watanabe, None; K. Meya, None
Results: Ablation of miR-146a leads to increased clinical signs of the induced serum transfer arthritides. In line, higher serum levels of the proinflammatory cytokines IL12 and TNF were measured in miR146a deficient mice compared to wt mice. When we crossed miR-146a−/− mice into hTNFtg mice, while detecting no clinical difference between hTNFtg and miR-146a−/− hTNFtg mice, we found a significant increase in circulating CD11b+ myeloid cells as well as CD11c+ dendritic cells in blood of miR-146a−/− hTNFtg mice compared to hTNFtg mice. Even more striking, miR-146a−/− hTNFtg mice displayed a more than twofold increase in local bone destruction which was due to increased generation of osteoclasts in the tarsal joints of the mice. Measuring cytokine levels in serum, we show that IL-1α levels are increased in mice lacking miR-146a.

Conclusion: These data clearly demonstrate a negative regulatory role of the miR-146a in inflammatory arthritis. During arthritis, miR-146a is centrally involved in the regulation of proinflammatory cytokines as well as local bone destruction. These results identify an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.

Disclosure: V. Saferding; None. A. Pucher; None. E. Goncalvesalves; None. B. Niederreiter; None. S. Hayer; None. G. Schabbauer; None. M. Koenders; None. J. S. Smolen; None. K. Redlich; None. S. Blueml; None.

2008

Flip Deficiency in Dendritic Cells Promotes Spontaneous Arthritis Mediated by Reduced Treg and Increased Autoreactive CD4+ Cells.

QiQun Huang1, Harris R. Perlman2, Robert Birckett3, Renee E. Doyle3, Deyu Fang3, G. Kenneth Haines5, William H. Robinson5, Syamal K. Datta1, Hyewon Phee2 and Richard M. Popel3. 1Northwestern University Feinberg School of Medicine, Chicago, IL. 2Mount Sinai Hospital School of Medicine, New York, New York, NY. 3VA Palo Alto Health Care System and Stanford University, Palo Alto, CA. 4Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Flip (CFLR) has been identified as a rheumatoid arthritis (RA) risk allele and is important in preventing death receptor mediated apoptosis of dendritic cells (DCs). To examine the in vivo role of Flip in DCs in maintaining immune homeostasis, mice deficient in Flip in conventional DCs were generated (DC-Flip−/−). The DC-Flip−/− mice spontaneously develop erosive, inflammatory peripheral arthritis, resembling rheumatoid arthritis (RA). These studies were conducted to define the mechanisms that contribute to the development of arthritis in these mice.

Methods: Immune cell phenotyping was performed by flow cytometry. DC function was examined by antigen presentation and T regulatory cell (Treg) induction. Thymic T cell development, selection and tolerance were examined. T cell autoreactivity was determined by the syngeneic mixed lymphocyte response in vitro and by adoptive transfer into vivo, monitored by dilution labeling of T cells. Treg function was examined by suppression of CD4+ T cell proliferation. Autoantibodies to joint components were identified by immunoblotting. DC-Flip−/− mice were crossed with Rag−/− to generate DC-Flip-KO/Rag−/− double mutant lines and arthritis was evaluated. All data are analyzed comparing indicated genotypes in age and gender matched groups.

Results: CD11cCre mediated Flip deficiency resulted in consistent reduction of the CD11c+CD8α− subset of DCs in central and peripheral lymphoid organs but not in the subset of DCs. No defects in the DCs were identified, however, increased autoreactive CD4+ T cells and plasmablasts are identified in the lymph nodes draining the inflamed joints, and both were positively correlated with the severity of arthritis. The DC-Flip−/− mice possessed autoantibodies specific for joint components. Further, Tregs were reduced in the thymus and spleen of DC-Flip−/− mice in a setting of lymphopenia. In addition, the number of Tregs in the spleen inversely correlated with the severity of the arthritis and adoptive transfer of Tregs ameliorated joint inflammation. DCs isolated from the DC-Flip−/− mice effectively presented antigen but were deficient in promoting the induction of Tregs. Supporting the role of T and B cells, DC-Flip−/−/Rag−/− mice, which lack both of T and B cells, develop significantly milder and self-limiting arthritis compared with the DC-Flip−/−/Rag−/− mice.

Conclusion: Flip plays a key role in the survival of the CD8α+CD11c+ DC subset in vivo. The loss of this subset impairs the generation and/or maintenance of Tregs, which in turn permits the expansion of autoreactive CD4+ T cells and autoantibody producing B cells, resulting in autoimmune arthritis. Our observations suggest that the DC-Flip-KO mouse is a novel model of RA that may provide important insights and permit in depth investigation of the pathogenesis of RA.

Disclosure: Q. Huang; None. H. R. Perlman; None. R. Birckett; None. R. E. Doyle; None. D. Fang; None. G. Kenneth.Haines; None. W. H. Robinson; None. S. K. Datta; None. H. Phee; None. R. M. Popel; None.

2909

Tolerogenic Splenic IDO+ Dendritic Cells from the Mice Treated with Induced-Treg Cells Could Suppress Collagen-Induced Arthritis. Jie Yang1, Hushua Fan2 and Hejian Zou3. 1Division of Rheumatology, Huashan Hospital, Fudan University, Shanghai 200040, China. Shanghai, China. 2Blood Engineering Laboratory, Shanghai Blood Center, Shanghai 200051, China. Shanghai, China.

Background/Purpose: As well known, Foxp3+ regulatory T cells play a crucial role in maintaining immune tolerance. It was reported that TGF-β induced Tregs (iTregs) could retain Foxp3 expression and immune suppressive activity in the collagen-induced arthritis (CIA). However, the mechanisms whereby iTregs suppressed immune response, especially the interplay between iTregs and DCs in vivo, remained incompletely understood. In this study, whether splenic DCs were involved in iTreg-based suppression and how these DCs further inhibited CIA were determined.

Methods: In vitro, iTregs were induced by TGF-β and adoptive transferred into established CIA mice. After 7 days, splenic CD11c+ DCs were isolated, termed DC-ITreg. The phenotype, the expression of cytokines and inhibitory associated molecules, the immunogenicity and the suppression on CD4+CD8+ T cell differentiation of DC-ITreg were assessed. To determine the suppression in vivo, 5×10⁵ of DC-ITreg were re-infused into the new CIA mice. Clinical and histopathologic scores, cytokine and anti-CII antibody secretion in serum were analyzed. And it also was determined the expression of Foxp3 and function of Tregs after IDO-DCs transferred. Additionally, the role of IDO in the inhibitory effect of DC-ITreg was determined by 1-MT blocking in vitro in CIA mice.

Results: After iTregs adoptive transferred, isolated DC-ITreg exhibited a series of tolerogenic characteristics. Compared with splenic DCs isolated from CIA mice (DCcIA), DC-ITreg expressed obviously lower levels of MHC molecule (IA-IE) and co-stimulatory molecules (CD80, CD86 and CD40). And IL-12p40 and IL-6 production by DC-ITreg were negligible, while high levels of IL-10 and TGF-β were expressed; especially enhanced level of IDO by DC-ITreg was detected, and CD11b+ DCs were found as a major contributor of IDO expression in iTreg-treated CIA mice. In the proliferation assay, DC-ITreg showed the poor ability to expand effector T cells and had the effective inhibitory potency. Meanwhile, after CD11b+ IDO−DC-ITreg re-infused, a remarkable anti-arthritis activity, improved clinical scores and histological end-points were found. Also, serological levels of TNF-α, IL-6, IL-17 and anti-CII antibodies showed significantly low and TGF-β production was high in the DC-ITreg-treated group. Conversely, DCcIA could not suppress CIA completely. And IDO-DCs could induce the generation and proliferation of functional Foxp3+ Tregs in vitro and in CIA mice. Moreover, DCcIA lost the inhibitory ability on CIA when they pretreated 1-MT.

Conclusion: These findings suggested that iTregs could inhibit CIA via tolerogenic splenic DCs formation. These tolerogenic splenic DCs could further effectively dampen the severity and progression of CIA in the IDO-dependent manner, which was associated with modulation of inflammatory cytokine and anti-CII antibody secretion and induction of new iTregs. Thus, the potential therapeutic effect of iTreg in CIA and RA is likely to be maintained, even enlarged by their effects on DCs in vivo.

Disclosure: J. Yang; None. H. Fan; None. H. Zou; None.

2910

Tofacitinib Facilitates the Expansion of Myeloid-Derived Suppressor Cells and Ameliorates Arthritis in SKG Mice. Keisuke Nishimura, Jun Saegusa, Fumichika Matsuki, Kengo A Kashii, Goichi Kageyama and Akio Morinobu. Kobe University Graduate School of Medicine, Kobe, Japan.

Background/Purpose: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that are characterized by the co-expression of Gr1 and CD11b in mice. MDSCs suppress T cell responses by producing arginase I (Arg I) and inducible nitric oxide synthase (iNOS). Tofacitinib is a Janus kinase (JAK) inhibitor that inhibits JAK1 and JAK3. Tofacitinib currently represents a novel therapeutic for treating rheumatoid arthritis. However, the anti-rheumatic effects of tofacitinib, especially its influence on...
myeloid cells, are not fully understood. The aim of this study was to evaluate the effects of the Janus kinase inhibitor tofacitinib on MDSCs in a mouse model of rheumatoid arthritis.

**Methods:** Arthritis was induced in SKG mice by zymosan A (ZyA) injection. MDSCs isolated from the bone marrow (BM) of donor arthritic SKG mice were adoptively transferred to recipient arthritic mice. In a separate experiment, tofacitinib was administered to SKG mice arthritic mice subcutaneously via osmotic pump, in some cases followed by injection of an anti-Gr1 monoclonal antibody (mAb). BM cells from untreated mice were cultured for 5 days with granulocyte/macrophage colony-stimulating factor (GM-CSF), with or without tofacitinib, and then analyzed by flow cytometry.

**Results:** The BM and spleens of ZyA-treated mice contained increased numbers of CD11b^+Gr1^+ MDSCs, whereas polymorphonuclear (PMN)-MDSCs (CD11b^+Ly6G^-Ly6Chi^low^) were significantly increased in the spleen of ZyA-treated mice. The number of monocytic-MDSCs (CD11b^+Ly6G^-Ly6Chi^low^) was also significantly increased in the BM of ZyA-treated mice, although they represented only a small proportion of the BM cells. The BM cells from ZyA-treated SKG mice also expressed higher levels of INOS and Arg I compared to untreated SKG mice. The adoptive transfer of MDSCs to recipient arthritic mice reduced disease severity compared to the untreated controls. Continuous administration of tofacitinib significantly ameliorated the arthritic scores of SKG mice. Tofacitinib treatment significantly increased the numbers of total- and PMN-MDSCs in the BM of arthritic mice. Furthermore, the anti-arthritic effect of tofacitinib was abrogated when MDSCs were depleted by anti-Gr1 mAb. In vitro, tofacitinib facilitated the differentiation of BM cells to MDSCs, and inhibited their differentiation to dendritic cells. Moreover, tofacitinib-treated BM cells were incapable of enhancing T cell proliferation, compared to mock-treated BM cells.

**Conclusion:** MDSCs play crucial roles in the regulation of SKG arthritis, and a JAK inhibitor, tofacitinib, enhances their expansion. Our results suggest a novel mode of anti-arthritic action for tofacitinib and a critical role for JAKs in the differentiation of MDSCs.

**Disclosure:** K. Nishimura, None; J. Saegusa, None; F. Matsuki, None; K. Akashi, None; G. Kageyama, None; A. Morinobu, None.

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**ACR Concurrent Abstract Session**

**Rheumatoid Arthritis - Clinical Aspects VI: Impact of Treatment and Other Interventions**

Tuesday, November 18, 2014, 4:30 pm - 6:00 pm

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**Clinical Outcomes of Early RA after 7 Years - Does T2T Approach Overcome Delay of Therapy?**

**Tuulikki Sokka,1 Hannu Kautiainen,2 Tuomas Rannio,3 Juha Asikainen1 and Pekka Hannonen1. 1Jyväskylä Central Hospital, Jyväskylä, Finland, 2Medcare Oy, Äänekoski, Finland, 3Kuopio University Hospital, Kuopio, Finland.**

**Background/Purpose:** Early vs. delayed referral/start of therapy within 3–4 months has been shown beneficial for outcomes in rheumatoid arthritis (RA) (Lard et al. A.M.J Med 2003, Gremese et al. ARD 2013, Ehrmann Feldman et al. Rheumatology 2013). However, in a real world setting, this applies for a minority of RA patients. In the FIN-RAco study, a delay of 4 months significantly influenced a 2-year remission rate in the monotherapy arm (remission rate was 11% vs 35%) while in the combination arm, 42% were in remission regardless of a delay indicating that early intensive therapy may overcome a delay (Möttönen et al. A&R 2002). Therefore, our aim was to study whether a delay of starting therapy in early RA affects long-term outcomes in a clinic with T2T approach including preferring methotrexate based combinations over monotherapy, long-term low dose glucocorticoids over bridging, intra articular glucocorticoid injections to all swollen joints at every visit, patient education by specialist nurses, and routine monitoring including disease activity and self-reported outcomes.

**Methods:** A clinical database in a district of 275,000 population was analyzed for patients with a new diagnosis of RA in 1993-2013. Variables included demographics, clinical course, follow-up, medication, and the date of first symptoms of RA, a question which was asked from the patient at the first visit and recorded in the database. Duration of symptoms (delay) at initiation of therapy was categorized as 0–3mo, 4–6mo, 7–12mo, 13–24mo, and >2yr. Outcome variables and medication data were available in 60–68% of patients at a mean of 7.3 years after diagnosis.

**Results:** In 1993–2013, 2374 patients (mean age 56yr, 67%F; 59%RF/CCP+) were diagnosed and treatment started with a median delay of 5.4mo in 2005 to 7.4 in 2003 with no trend of delay over years. Existing musculoskeletal disease and younger age were associated with longer delay, adjusted for sero+/−, gender, and year of diagnosis. Overall, 32%, 24%, 24%, 10%, and 10% of patients had a delay of 0–3mo, 4–6mo, 7–12mo, 13–24mo, and >2yr, respectively (in 98 patients delay data was missing). After a mean follow-up of 7 years, the mean swollen and tender joint counts (SJC28) was <1. The mean ESR and CRP were normal, symptom level was low, functional capacity well maintained, and 66% of patients met the DAS28 remission (Table). No significant differences in outcomes and treatments were observed between the delay groups.

**Conclusion:** Clinical outcomes were good after 7 years in patients with early RA who were treated extensively using a T2T approach, including 66% of patients in DAS28 remission. Delay of treatment start did not influence outcomes in this clinic. Further analyses will include radiographic outcomes and work disability.

**Disclosure:** T. Sokka, None; H. Kautiainen, None; T. Rannio, None; J. Asikainen, None; P. Hannonen, None.
of 12.4. An internet-based data entry and management system (IDEMS) was designed to automate calculation of the DAS and alert sites to the requirement for treatment change. If a treatment change was not made a reason for that decision was required. RA outcomes (HAQ, RAID, SF36) and attainment of remission (DAS, CDAS, SDAI, ACR Boolean) were compared by adherence to T2T and according to treatment category (DMARD, anti-TNF).

**Results:** As of June 2014, 500 patients have been recruited of whom 172 have completed at least 15 months follow-up. Adherence to T2T was 52% and non-adherence 42% for at least 1 study visit (T2T failure visit). Reasons for non-adherence were: physician decision that current treatment was acceptable (69%), physician decision (other) (14%), patient decision (9%), physician decision due to concern for adverse event (2%), other non-specific (6%). Starting at 6 months of follow-up and continuing to diverge though 15 months, all outcomes were superior in T2T adherent patients: improvement in SJC/TJC, patient/physician global, HAQ, RAID, SF36. Remission at 15 months follow-up was more frequent in T2T adherent patients at 75% (DAS), 41% (CDAS), 41% (SDAI), 40% (ACR Boolean) compared to non-adherent patients at 30% (DAS), 12% (CDAS), 13% (SDAI), 15% (ACR Boolean) irrespective of therapy (standard DMARD, anti-TNF).

**Conclusions:** Adherence to T2T is associated with consistent improvement in RA outcomes and increased rates of remission. However, there remains a substantial gap in implementation even in protocol-specified clinical settings.
was higher in initially non-radiographic arthritis patients (3.3 erosions/year vs. 0.4, resp., p < 0.0001).

Conclusion: The clinical and radiographic course of early undifferentiated arthritis under treatment was not dependent on the presence of erosions in 3 or more joints (i.e. the definition of radiographic disease by the EULAR taskforce) at diagnosis in our cohort.

Disclosure: R. Mueller, None; T. Kaugel, None; S. Haile, None; J. von Kempis, AbbVie; A. Antares Pharma, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB, 5;ristol-Myers Squibb, Roche, and UCB, 2.

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Effects of Methotrexate on Anti-TNF Treatment in Rheumatoid Arthritis: An In-depth Analysis of a Prospective Observational Study with Adalimumab.

Marc Schmalzing1, Frank Behrens2, Eva C. Scharbatke3, Michaela Koehm3, Bianca Wittig4, Gerd Greger 5, Harald Burkhardt2, and Hans-Peter Tony1.

1University of Würzburg, Würzburg, Germany, 2Goethe-University Frankfurt, Frankfurt, Germany, 3Fraunhofer Institute for Molecular Biology and Applied Ecology IML, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, 4Abbvie Deutschland GmbH & Co. KG, Wiesbaden, Germany, 5AbbVie GmbH & Co KG, Wiesbaden, Germany.

Background/Purpose: Methotrexate (MTX) is currently the most frequently used drug in the treatment of rheumatoid arthritis (RA). MTX co-medication can improve the therapeutic benefit of adalimumab (ADA) in biologic-naive RA patients. However, the impact of concomitant MTX has not been fully characterized in patients pretreated with biologics. Similarly, the influence of adding MTX to established ADA monotherapy has not been fully characterized.

Methods: We analyzed data from a large German multicenter, prospective, observational study of patients with active RA who are treated with ADA during routine clinical care. The effect of therapy on mean DAS28 scores was evaluated at baseline (month 0) and at months 3, 6, and 12 for patients receiving continuous ADA monotherapy, continuous ADA + MTX combination therapy, and MTX added to ADA therapy at 6 months (ADA monotherapy for the first 6 months and ADA + MTX combination therapy for months 6–12). Subgroup analyses for ADA monotherapy vs ADA + MTX were performed on biologic-naive versus biologic-experienced patients. Stepwise forward and backward regression analyses were performed for identifying significant predictors.

Results: Combination therapy with ADA + MTX resulted in lower mean DAS28 scores at month 12 and a significant reduction in ADA scores from baseline than ADA monotherapy (Table). DAS28 improvements in patients who began the observation period on ADA monotherapy and added MTX at month 6 were similar to those receiving ADA + MTX continuously for 12 months. Subgroup analysis by prior biologic therapy indicated that both biologic-naive and biologic-experienced patients achieved lower mean DAS28 scores with ADA + MTX than with ADA monotherapy (p < 0.0001). However, patients treated previously with biologics did not show as much improvement in DAS28 scores as biologic-naive patients, irrespective of MTX use.

Conclusion: Adding MTX to ADA monotherapy at month 6 resulted in DAS28 decreases similar to those observed with continuous ADA + MTX therapy, although patient numbers were small. Both biologic-naive and biologic-experienced patients achieved lower DAS28 scores with ADA + MTX than with ADA monotherapy. These findings support the addition of MTX to ADA therapy for all patient populations.

Table 1. Effect of concomitant MTX on therapeutic response during ADA-therapy.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Therapy*</th>
<th>n</th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Mean DAS28 change at month 12^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Continuous ADA monotherapy</td>
<td>438</td>
<td>5.98</td>
<td>4.31</td>
<td>4.09</td>
<td>4.14</td>
<td>-1.85</td>
</tr>
<tr>
<td></td>
<td>Continuous ADA + MTX</td>
<td>858</td>
<td>5.87</td>
<td>4.14</td>
<td>3.82</td>
<td>3.78</td>
<td>-2.08</td>
</tr>
<tr>
<td></td>
<td>MTX added to ADA monotherapy at 6 months</td>
<td>51</td>
<td>5.84</td>
<td>4.31</td>
<td>3.83</td>
<td>3.70</td>
<td>-2.14</td>
</tr>
<tr>
<td>Biologic-naive patients</td>
<td>Continuous ADA monotherapy</td>
<td>300</td>
<td>5.91</td>
<td>4.10</td>
<td>3.88</td>
<td>3.98</td>
<td>-1.93</td>
</tr>
<tr>
<td></td>
<td>Continuous ADA + MTX</td>
<td>593</td>
<td>5.85</td>
<td>3.98</td>
<td>3.64</td>
<td>3.64</td>
<td>-2.21</td>
</tr>
</tbody>
</table>

aPatients were considered to receive continuous therapy if they were recorded as receiving the stated therapy at each visit during the first 12 months of the observational study.

bMean value calculated from the difference between DAS28 at month 12 and DAS28 at month 0 for each individual patient.

Disclosure: M. Schmalzing, AbbVie, 5; Roche Pharmaceuticals, 5; Actelion Pharmaceuticals US, 5; BMS, 5; Chugai, 5; UCB, 5; Pfizer Inc, 5; F. Behrens, AbbVie, 5; Chugai, 5; Chugai, 5; Roche Pharmaceuticals, 5; Janssen Pharmaceuticals, 5; Sanofi, 5; Astellas Pharma, 5; MSD, 5; Pfizer Inc, 5; Abbott, 5; E. C. Scharbatke, AbbVie, 5; Chugai, 5; Roche Pharmaceuticals, 5; M. Koehm, AbbVie, 2; Pfizer Inc, 2; B. Wittig, AbbVie, 3; G. Greger, AbbVie, 3; H. Burkhardt, Pfizer Inc, 2; Pfizer Inc, 5; AbbVie, 5; UCB, 5; BMS, 5; Chugai, 5; H. P. Tony, None.

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Effects of Exercise on Body Composition, Cardiovascular Fitness, Muscle Strength, and Cognition in Patients with Rheumatoid Arthritis: A Randomised Controlled Trial of a Patient-Specific Exercise Programme.

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1St James’s Hospital and Trinity College Dublin, Dublin, Ireland; 2Trinity College Dublin, Dublin, Ireland.

Background/Purpose: Rheumatoid Arthritis (RA) patients have lower levels of physical activity compared to their non-RA counterparts. Large proportions of patients with RA are overweight or obese, and exhibit poor cardio-respiratory fitness and reduced muscle strength. These factors have been associated with poor function and increased mortality. A less well studied but important co-morbidity that affects RA patients is cognitive impairment, which can have a negative impact on patients’ ability to manage their disease. We aimed to investigate the effects of a specifically designed exercise programme on body composition, aerobic capacity, muscle strength and cognition in RA patients.

Methods: Sixty-six patients with RA were randomised on a 1:1 case:control ratio. A assessments included body composition (waist circumference), fitness (VO2 max), muscle strength (hand-grip) and cognitive testing (Montreal Cognitive Assessment), in addition to disease related measures. Patients in the intervention group were enrolled for a three-month exercise programme. The control group received standard care.

Results: Twenty-eight cases and 24 controls attended for baseline testing. Seven patients were subsequently lost to follow up (4 cases and 3 controls). There were significant improvements in several measured outcomes in the intervention group compared to controls after three months. Median waist circumference was significantly reduced in cases, with median value 94.0 cm (range 67.3–124.5) at 0 months, compared to 91.4 cm (range 66.0–124.5) at 3 months, (2.8% reduction, p < 0.0001). A aerobic capacity, as measured by VO2max, for cases was 23.2 ml/kg/min at 0 months compared to 27.6 ml/kg/min at 3 months (19% increase, p = 0.002). Median right grip strength was 12kg (0–23) at 0 months, compared to 13kg (0–30) at 3 months (8.3% increase, p = 0.025). For left grip strength, the median value was 8kg (0–20) at 0 months, compared to 10kg (0–32) at 3 months (25% increase, p = 0.005). There was a significant improvement in cognitive function for cases, with median Montreal Cognitive Assessment value 25.5 (20–30) at 0 months compared to 28.0 (22–30) at 3 months (10% increase, p = 0.001). There was also a significant reduction in C-reactive protein (median 2.8, range 1.0–27.4 at 0 months compared to 1.9, 1.0–18.4, at 3 months, equating to a reduction of 32.1%, p = 0.025). Fatigue scores, measured by Global Fatigue Index were reduced from median 13.2 (range 6.4–34.1) at 0 months, to 10.9 (6.5–37.5) at 3 months (p = 0.047). There was a significant reduction in trunk fat at 3 months (median 37.3, range 16.3–56.9) compared to 36.2, range 16.3–56.5 (p = 0.004). For all above measures, there was no significant difference in median control values at 3 months.

Conclusion: There are significant benefits associated with physical activity for both general health and RA-related parameters, as evidenced by the current data. This study has demonstrated for the first time that exercise has a significant impact on cognitive function in RA. We can conclude that physical activity is safe and effective in RA patients and should be a vital component of management protocols.

Disclosure: M. Azeem, None; C. Clancy, None; T. O’Dwyer, None; F. Wilson, None; G. Cunname, None.
Inhibition of PADA4 Activity and the Formation of Neutrophil Extracellular Traps Via PTPN22, but Not Its Rheumatoid Arthritis-Prone W620 Variant. I-Cheng Ho1, Hui-Hsin Chang1, Nishant Dwivedi1, Hsiao-Wei Tsa2 and Anthony Nicholas2. 1Brigham and Women's Hospital, Boston, MA; 2University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: One unique feature of rheumatoid arthritis (RA) is the presence of anti-citrullinated protein antibodies (ACPAs). Protein citrullination, a process mediated by peptidyl arginine deiminases, such as PADA4, not only yields antigens recognized by ACPAs but also contributes to RA through several other mechanisms including promotion of neutrophil extracellular traps (NET) formation. A C-to-T single nucleotide polymorphism (SNP) located at position 1856 of human PTPN22, a protein tyrosine phosphatase, carries an odds ratio of 2–3 and, together with HLA alleles, contributes to RA independently of its phosphatase activity. Conversion of the R620 to tryptophan increases the risk of ACPA – a key feature of RA. Here we postulate a role for PTPN22 in the formation of neutrophil extracellular traps.

Methods: We quantified the amount of citrullinated proteins in wild type and PTPN22-deficient cells, as well as PBMC from healthy donors carrying or not carrying the risk T allele was examined with Western blotting using F95 antibody and anti-citrullinated histone H3. Co-immunoprecipitation was used to examine the physical interaction between PTPN22 and PADA4. The formation of neutrophil extracellular traps was analyzed with Sy-tox uptake and immunocytochemistry.

Results: Impaired expression of PTPN22 resulted in hypercitrullination in mouse and human immune cells. This effect was partly mediated by PADA4. PTPN22 did not regulate the expression or tyrosine phosphorylation of PADA4. Instead, PTPN22 physically interacted with and suppressed the activity of PADA4 independently of its phosphatase activity. Conversion of the R620 to a tryptophan disrupted the interaction between PTPN22 and PADA4, and completely ablated the ability of PTPN22 to suppress protein citrullination. Accordingly, the risk T allele is associated with hypercitrullination in PBMC and heightened propensity to form NET in healthy donors.

Conclusion: PTPN22 is a natural inhibitor of PADA4, and the R620 is critical for this non-phosphatase function of PTPN22. The C1858T-mediated conversion of R620 to tryptophan increases the risk of ACPA in RA through hypercitrullination and heightened propensity to form NET. Our data also identify a novel pathway regulating PAD activity and establish a molecular connection between the two RA risk genes PTPN22 and PADA4.

Disclosure: I. C. Ho; None; H. H. Chang; None; N. Dwivedi; None; H. W. Tsa; None; A. Nicholas; None.
heart development (LBH). LBH is a conserved putative protein with largely unknown functions. 

Methods: FLS cultures were established from RA and OA synovial tissues from joint replacement surgery. Gene expression was measured by qPCR. LBH gene expression was silenced using siRNA (mean 91% decrease) or over-expressed (mean 13 fold increase) using an LBH expression vector. Differentially expressed genes of 4 RA FLS lines with modified LBH expression were determined by microarray. The affected pathways were identified using Ingenuity Pathway Analysis. Expression of modified (silenced or over-expressed) gene expression was assessed by cell migration (scratch-wound assay), cell growth (MTT), apoptosis (caspase 3/7 activity) and TNF-stimulated gene expression.

Results: LBH is constitutively expressed in RA FLS as determined by qPCR. LBH gene expression was significantly increased LBH mRNA by 5.0 ± 1.0 fold (P = 0.02) and PDGF-BB (0.1 ng/ml, 12 hr) significantly decreased LBH mRNA expression by 5.7 ± 1.7 fold (P = 0.04). Stimulating FLS with TNF, Wnt3a or Wnt 5a had no effect on LBH gene expression. LBH was then knocked down using siRNA, with no effects on cell migration or TNF-induced MMP3 or IL-6 expression. To determine potential functions, microarrays were performed using LBH-deficient FLS. Pathway analysis of gene expression profiles in LBH low compared to control FLS identified "Cellular growth and proliferation" as the most significantly enriched pathway. Therefore, we performed cell growth assays. LBH deficiency increased FLS proliferation by 92 ± 13% (P = 0.018). LBH did not alter apoptosis. 

Conclusion: We identified LBH as a candidate gene for RA by integrating multiple omics datasets. Microarray experiments focused our attention on cell growth as a potential LBH-regulated function, and this was confirmed using functional assays. Furthermore, the gene is highly regulated by growth factors that modulate the cell cycle. The data suggest that LBH contributes to synovial intimal hyperplasia and joint damage in RA.

Disclosure: A. K. Ekwall, None; D. Hammaker, None; J. W. Whitaker, None; W. Bugbee, None; W. Wang, None; G. S. Firestein, None.

2920 WITHDRAWN

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Contraceptive Factors Are Associated with Serum Antibodies to Citrullinated Protein Antigens in Women at Elevated Risk for Future Rheumatoid Arthritis. Sonia K. Khatte1, Mark C. Parish2, Maria L. Eser3, Jason R. Kollenbach4, Ryan W. Gan5, Michael H. Weisman6, James R. O’Dell7, Ted R. M. Kik2, Richard M. Keating8, Peter K. Gregersen9, Jane H. Buckner9, V. Michael Holers10, Kevin D. Deane11, Jill M. Norris12 and M. Kristen Demoruelle13. 1University of Colorado School of Medicine, Aurora, CO, 2Colorado School of Public Health, Aurora, CO, 3Cedars-Sinai Medical Center, Los Angeles, CA, 4Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, 5Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, 6Scripps Clinic, La Jolla, CA, 7Feinstein Institute for Medical Research, Manhasset, NY, 8Benaroya Research Institute at Virginia Mason, Seattle, WA.

Background/Purpose: The preclinical period of rheumatoid arthritis (RA) development is characterized by elevations of serum RA-related autoantibodies (Abs) including Abs to citrullinated protein antigens (ACPA) and rheumatoid factor (RF). Serum ACPAs are highly predictive of future inflammatory arthritis (IA) classifiable as RA, and recent data suggesting that ACPAs are directly pathogenic in joint disease highlight the need to understand the etiology of ACPA development. In addition, it remains unknown why RA disproportionately impacts women compared to men, and data suggest hormonal factors may influence the risk of developing RA. Importantly, prior data from our group identified that oral contraceptive pill (OCP) use was associated with a decreased risk for RF positivity in the absence of IA (Bhatia 2007). Therefore, we hypothesize that contraceptive factors will be associated with serum ACPA positivity among arthritis-free women at increased risk for RA.

Methods: In the Studies of the Etiology of RA (SERA) project, 1243 first degree relatives (FDR) of probands with RA were enrolled who are women. Of these FDRs, we studied women who at their baseline visit had serum ELISA testing for ACPA using anti-CCP3.1 (IgG/IgA, INOVA) and a detailed prior contraceptive and pregnancy history obtained using a standardized questionnaire (N = 336). To avoid familial correlation, we also randomly selected only one subject per family; therefore, our final analyses included 297 FDRs. All subjects were without clinical IA at the time of serum testing. In cross-section, associations of ACPA and subject factors were analyzed using chi-squared and logistic regression.

Results: In multivariate analyses, prior use of OCPs was associated with a decreased risk of serum ACPA positivity (OR = 0.34; 95% CI 0.15–0.79; adjusted for age, race and smoking). In addition, there was an increased risk of ACPA positivity in women who had a history of intrauterine device (IUD) use (OR = 2.68; 95% CI 1.11–6.47; adjusted for age, race and smoking). ACPA(+) FDRs were slightly older than ACPA(−) FDRs, but were similar in race, smoking and shared epitope status (Table). No significant association was seen between ACPA positivity and pregnancy or breastfeeding.

Conclusion: Prior OCP use was associated with a decreased risk of ACPA positivity in these FDRs, and these results are in line with our prior findings. OCP use associated with a decreased risk of RF positivity. Of interest was the association of an increased risk of ACPA positivity with IUD use. While the mechanisms that link contraceptive factors to ACPA generation are unknown, unlike OCPs, IUDs have been shown to generate endometrial inflammatory responses. Therefore, the association of IUD use and ACPA suggest that IUD-induced endometrial inflammation may be a potential mucosal trigger of RA-related Abs. Mechanisms by which OCPs could protect and IUDs could increase risk for RA-related autoimmunity need further study.

Table. Contraceptive and Other Risk Factors for ACPA Positivity in Women at Elevated Risk for Future RA

<table>
<thead>
<tr>
<th>ACPA(+)</th>
<th>ACPA(−)</th>
<th>p-value</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=92)</td>
<td>(N=205)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of OCP use (%)</td>
<td>51.7 (33.0)</td>
<td>48.3 (32.3)</td>
<td>&lt;0.01</td>
<td>0.29 (0.16–0.52)</td>
</tr>
<tr>
<td>History of IUD use (%)</td>
<td>52.2 (38.6)</td>
<td>46.0 (31.8)</td>
<td>0.23</td>
<td>1.27 (0.83–1.95)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>51.2 (6.8)</td>
<td>49.5 (7.2)</td>
<td>0.07</td>
<td>1.02 (0.93–1.12)</td>
</tr>
<tr>
<td>Race, white non-Hispanic (%)</td>
<td>75.7 (75.7)</td>
<td>72.0 (72.0)</td>
<td>0.63</td>
<td>0.92 (0.74–1.15)</td>
</tr>
<tr>
<td>History of ever smoking (%)</td>
<td>29.4 (35.7)</td>
<td>26.1 (32.9)</td>
<td>0.21</td>
<td>1.16 (0.85–1.58)</td>
</tr>
<tr>
<td>≥1 shared epitope allele (%)</td>
<td>50.0 (54.3)</td>
<td>44.6 (49.6)</td>
<td>0.36</td>
<td>0.84 (0.61–1.17)</td>
</tr>
<tr>
<td>History of pregnancy (%)</td>
<td>73.5 (75.3)</td>
<td>71.6 (72.3)</td>
<td>0.43</td>
<td>0.91 (0.60–1.38)</td>
</tr>
<tr>
<td>Number of pregnancies, mean (SD)</td>
<td>2.0 (1.7)</td>
<td>1.9 (1.4)</td>
<td>0.06</td>
<td>1.15 (0.77–1.73)</td>
</tr>
<tr>
<td>History of breastfeeding (%)</td>
<td>44.1 (46.6)</td>
<td>48.4 (50.1)</td>
<td>0.03</td>
<td>0.93 (0.49–1.83)</td>
</tr>
<tr>
<td>Total duration breastfeeding, mean (SD)</td>
<td>6.8 (14.5)</td>
<td>7.3 (15.5)</td>
<td>0.60</td>
<td>1.01 (0.98–1.03)</td>
</tr>
<tr>
<td>Age of menses onset, mean (SD)</td>
<td>13 (1.5)</td>
<td>13 (1.3)</td>
<td>0.05</td>
<td>0.98 (0.77–1.25)</td>
</tr>
</tbody>
</table>

* Calculated comparing ACPA(+) versus ACPA(−) subjects, chi-squared and t-test used as appropriate.

**Odds ratios were adjusted for age, race and history of smoking.

Table: Association of Single Nucleotide Polymorphisms of PADI4 Gene with Susceptibility to Rheumatoid Arthritis-Related Lung Disease. Seoong-Wook Kang, Seung-Taek Song, Song Soo Kim, Ji Youn Kim, So Yoon Lee, Si-Jin Yoo, In-Seol Yoo, Jinhyun Kim and Seung-Cheol Shim. Chungnam National University School of Medicine, Daejeon, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) causes a myriad of pulmonary complications, including bronchiolitis and bronchiectasis, pleuritis, and interstitial lung disease (ILD). Recently, several studies have shown the association of rheumatoid arthritis-related lung disease (RA-LD) with the high titers of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) which are the most specific serologic marker for RA. Single nucleotide polymorphisms (SNPs) in a citrullinating (or deiminating) enzyme, peptidyl arginine deiminase type IV (PADI4) have been reproducibly associated with RA susceptibility in several populations.

The aim of the present study is to investigate if the SNPs in PADI4 gene are associated with RA-LD.

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studies are warranted to clarify the mechanisms by which SNPs in the PADI4 gene are associated with susceptibility to RA-LD. Further, statistical differences were seen between RA patients with and those without LD with respect to sex, smoking history, anti-Ro antibody, and those without LD with respect to sex, smoking history, anti-Ro antibody, and use of DMARDs.

Conclusion: Our results suggest that SNPs and genotypes in exon-3 (padi4_92) of PADI4 are associated with susceptibility to RA-LD. Further studies are warranted to clarify the mechanisms by which SNPs in the PADI4 gene affect the development of RA-LD.

Table 1: Clinical characteristics of RA patients with or without lung disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RA-no LD</th>
<th>RA-LD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51.77±9.25</td>
<td>58.10±8.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>62 (89.9)</td>
<td>30 (88.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>RA duration (y)</td>
<td>10.49±7.84</td>
<td>7.11±7.34</td>
<td>0.037</td>
</tr>
<tr>
<td>Smoking history</td>
<td>6 (9.1)</td>
<td>1 (1.3)</td>
<td>0.421</td>
</tr>
<tr>
<td>Positive ACPA</td>
<td>33 (47.9)</td>
<td>30 (88.2)</td>
<td>0.208</td>
</tr>
<tr>
<td>Positive RF</td>
<td>30 (42.6)</td>
<td>28 (76.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Positive RF lav</td>
<td>30 (42.6)</td>
<td>28 (76.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Positive anti-Ro</td>
<td>12 (18.8)</td>
<td>4 (11.8)</td>
<td>0.567</td>
</tr>
<tr>
<td>Positive anti-ff</td>
<td>0.71±1.39</td>
<td>0.53±1.27</td>
<td>0.520</td>
</tr>
<tr>
<td>Use of DMARDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologic agents</td>
<td>17 (24.6)</td>
<td>11 (32.4)</td>
<td>0.408</td>
</tr>
<tr>
<td>Miotrotreated</td>
<td>65 (95.7)</td>
<td>27 (79.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Lethomide</td>
<td>7 (10.1)</td>
<td>4 (11.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hydroxychloroquin</td>
<td>17 (24.6)</td>
<td>11 (32.4)</td>
<td>0.408</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>5 (7.2)</td>
<td>2.5 (19.4)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are the number (%), †; (mean ± standard deviation). A total of 103 consecutive RA patients, who satisfied the 1987 American College of Rheumatology classification criteria, were genotyped for two nonsynonymous (padi4_89 and padi4_92) and one synonymous (padi4_104) SNPs in PADI4. RA-LD was diagnosed using high-resolution computed tomography of the chest. The following data were collected from medical records: Age, sex, disease duration, smoking history, use of disease-modifying anti-rheumatic drugs (DMARDs), RF, and ACPA. We used the t-test for continuous variables and the chi-square or Fisher’s exact test for categorical variables. Multivariate logistic regression analysis was performed to assess the relationship between the SNPs in the PADI4 gene and RA-LD. Results: Of the 103 RA patients, 8 (7.8%) had interstitial lung disease (ILD) and 33 (32.0%) had small airway disease (AD). Higher titers of ACPA (≥80 U/mL; p = 0.022) and RF (≥ULN × 3; p = 0.008) were significantly associated with susceptibility to RA-LD (Table 1). SNPs and genotypes in exon-3 (padi4_92) of PADI4 showed significant association with susceptibility to RA-LD (p = 0.004, respectively) (Table 2). No statistically significant differences were seen between RA patients with LD and those without LD with respect to sex, smoking history, anti-Ro antibody, and use of DMARDs.

Conclusion: Our results suggest that SNPs and genotypes in exon-3 (padi4_92) of PADI4 are associated with susceptibility to RA-LD. Further studies are warranted to clarify the mechanisms by which SNPs in the PADI4 gene affect the development of RA-LD.

Table 2: Association of the alleles of PADI4 SNPs with RA-LD susceptibility

<table>
<thead>
<tr>
<th>SNP Allele</th>
<th>RA-no LD</th>
<th>RA-LD</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>padi4_89 A</td>
<td>0.52</td>
<td>0.61</td>
<td>1</td>
<td>0.418</td>
</tr>
<tr>
<td>G</td>
<td>0.48</td>
<td>0.39</td>
<td>0.749</td>
<td></td>
</tr>
<tr>
<td>padi4_92 C</td>
<td>0.18</td>
<td>0.41</td>
<td>1</td>
<td>0.004</td>
</tr>
<tr>
<td>G</td>
<td>0.82</td>
<td>0.59</td>
<td>0.319</td>
<td>(0.147–0.692)</td>
</tr>
<tr>
<td>padi4_104 C</td>
<td>0.61</td>
<td>0.67</td>
<td>1</td>
<td>0.809</td>
</tr>
<tr>
<td>T</td>
<td>0.39</td>
<td>0.33</td>
<td>0.914</td>
<td>(0.441–1.896)</td>
</tr>
</tbody>
</table>

Values are frequency. Age, sex, adjusted odds ratios (ORs) and p-values for carriers of minor susceptibility alleles versus noncarriers were calculated by multivariate logistic regression. SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; 95% CI, 95% confidence interval.

Table 3: Association of PADI4 SNP genotypes with RA-LD susceptibility

<table>
<thead>
<tr>
<th>SNP Allele</th>
<th>RA-no LD</th>
<th>RA-LD</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>padi4_89 AA</td>
<td>0.25</td>
<td>0.39</td>
<td>1</td>
<td>0.087</td>
</tr>
<tr>
<td>A/G/GG</td>
<td>0.75</td>
<td>0.61</td>
<td>0.429</td>
<td>(0.162–1.132)</td>
</tr>
<tr>
<td>padi4_92 CC</td>
<td>0.14</td>
<td>0.39</td>
<td>1</td>
<td>0.004</td>
</tr>
<tr>
<td>G/G/GG</td>
<td>0.06</td>
<td>0.61</td>
<td>0.195</td>
<td>(0.056–0.589)</td>
</tr>
<tr>
<td>padi4_104 CC</td>
<td>0.32</td>
<td>0.46</td>
<td>1</td>
<td>0.081</td>
</tr>
<tr>
<td>C/T/TT</td>
<td>0.68</td>
<td>0.54</td>
<td>0.429</td>
<td>(0.166–1.130)</td>
</tr>
</tbody>
</table>

Values are frequency. Age, sex, adjusted odds ratios (ORs) and p-values for carriers of minor susceptibility alleles versus noncarriers were calculated by multivariate logistic regression. SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; 95% CI, 95% confidence interval.
Clinical Utility of Random Anti-TNF Drug Level Testing and Measurement of Anti-Drug Antibodies on Long-Term Treatment Response in Rheumatoid Arthritis. M. Eghna\textsuperscript{1} Jani, H. Chinyo\textsuperscript{1}, R. B. Warren\textsuperscript{1}, C. M. Griffiths\textsuperscript{1}, A. W. Morgan\textsuperscript{1}, A. G. Wilson\textsuperscript{2}, K. M. Hyrich\textsuperscript{1}, J. Isaacs\textsuperscript{1}, D. Plant\textsuperscript{1} and A. Barton\textsuperscript{1}.\textsuperscript{1} Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, \textsuperscript{2}Dermatology Centre, University of Manchester, Manchester, United Kingdom, \textsuperscript{3}University of Leeds, Leeds, United Kingdom, \textsuperscript{4}University College Dublin, Dublin, Ireland, \textsuperscript{5}Institute of Cellular Medicine, University of Newcastle, Newcastle, United Kingdom, \textsuperscript{6}NHRI Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/ Purpose: Up to 40% of RA patients on anti-TNF treatment fail to respond either due to primary inefficacy or loss of response. One explanation is immunogenicity leading to the development of anti-drug antibodies (ADA) and low drug levels, however the clinical utility of pharmacological monitoring is debated. One challenge is the practicality of obtaining trough drug levels in patients and the impact that would have on service delivery. Our aim was to evaluate whether the presence of ADA and/or non-trough drug levels may predict treatment response in patients with RA treated with anti-TNF drugs.

Methods: 391 patients were selected from the Biologics in RA Genetics and Genomics Study Syndicate prospective cohort (n=160 adalimumab (ADL); n=171 etanercept (ETA)). Serum samples were collected at 3, 6 and 12 months following initiation of therapy. ADAs were measured using RIA and drug levels using ELISA assays at 3, 6 and 12 months. Disease activity (DAS28) scores were measured at each visit. Multiple linear regression, logistic regression, generalised estimating equation and ROC curves were used to test the association and predictive value of ADA and/or non-trough drug levels on treatment response as assessed by the change in DAS28 score between pre-treatment and 12 months post-treatment (DAS28).

Results: 835 serial samples were suitable for pharmacological testing (n=414 ADL; n=421 ETA). Mean age: 56 ± 13 years; 75% female; baseline DAS28 score 5.9 ± 3.8; median BMI 27.5 (IQR 23.6–32.3). 85% were on a DMARD (56% MTX). ADAs to ADL were detected in 24.8% (31/125 patients at ≥1 time points by 12 months) and in none of the ETA patients. The presence of ADAs was significantly associated with lower ADL drug levels (ADAb titres > 100 AU p = 0.0041; Spearman’s rho = 0.06). At 3 months, ADAb formation and low ADL levels were a significant predictor of no EULAR response at 12 months (ROC curve analysis, area under curve (AUC) 0.71, 95% confidence intervals (CI) 0.57–0.85). Patients who developed ADAs received lower median doses of concomitant MTX therapy (15mg/week [IQR 10–20]) and had longer disease duration (14.0 years [6.7–19.4]) vs. patients who did not (20mg/week [15–20] p = 0.01; [7.7 years [3.6–16.0]] p = 0.03). ADL drug level was the most significant independent predictor of DAS28 at all time points after adjusting for confounders (p = 0.003, regression coefficient (RC) 0.12; CI: 0.06–0.18). Patients on ETA with higher drug levels (≥15µg/ml) were more likely to achieve a good EULAR response than patients with sub-therapeutic levels (<10µg/ml; p = 0.01). However low ETA levels at 3 months were not a significant predictor of no EULAR response at 12 months (AUC 0.51; CI: 0.41–0.61). BMI was the strongest predictor of low drug levels (ETA, p < 0.001, RC = 5.97; CI = 0.32 to 3.19; ADL, p = 0.001, RC = 3.86; CI = 0.57 to 2.00). Patients with a BMI ≥ 30 had significantly lower drug levels compared to those with a BMI < 30 in both ADL and ETA cohorts (p < 0.01).

Conclusion: Pharmacological testing in anti-TNF initiated patients is clinically useful even in the absence of trough levels. At 3 months ADAb formation and low ADL drug levels are a significant predictor for poor treatment response at 12 months. Patients with a BMI ≤ 30 were less likely to have therapeutic drug levels.

Disclosure: M. Jani, None; H. Chinyo, Abbvie, 8; Pfizer Inc, 8; R. B. Warren, Abbvie, 8; Pfizer Inc, 8; C. M. Griffiths, Abbvie, 8; Pfizer Inc, 8; A. W. Morgan, None; A. G. Wilson, Abbvie, 8; Pfizer Inc, 8; K. M. Hyrich, Pfizer Inc, 9; A. Barton, Abbvie, 9; Pfizer Inc, 9; J. Isaacs, None; D. Plant, None; A. Barton, None.

Serum MMP-3 Predicts a Subgroup with No Radiographic Progression in Rheumatoid Arthritis Patients with Low-Dose Methotrexate (MTX) M onotherapy. Kazuko Shiozawa\textsuperscript{1}, Takashi Yamasu\textsuperscript{1}, Miki Mura\textsuperscript{1}, T. Nakagawa\textsuperscript{2}, Norikai Yoko\textsuperscript{1}, Ryo Yokusuke\textsuperscript{1}, Yasushi Tanaka\textsuperscript{1}, Ken Tsumiyama\textsuperscript{2} and Shunichi Shiozawa\textsuperscript{1}.

1Kohnan Kakogawa Hospital, Kakogawa, Japan, 2Kyushu University Beppu Hospital, Beppu, Japan.

Background/ Purpose: Studies have shown that treating rheumatoid patients with methotrexate (MTX) monotherapy initially and later providing an option to step up to combination therapy produces outcomes similar to those seen with combination therapies of conventional drugs and/or biologics provided immediately (O’Dell \textit{et al.} Arthritis Rheum 65:1985, 2013). In their study, approximately 30% of patients treated with MTX monotherapy did not require subsequent combination therapy. However, this subgroup was clinically and radiographically indistinguishable from those who required it.

The purpose of the present study was to assess the efficacy of low-dose MTX monotherapy, a regimen which is commonly prescribed in Japan, and to identify a subgroup of patients whose radiographic progression is halted in response to MTX monotherapy. In the present study, 161 rheumatoid patients were treated continuously with low-dose MTX monotherapy continuously for 3 yrs until significant adverse events or radiographic progression were suspected.

Methods: Rheumatoid patients treated with low-dose MTX monotherapy (n=161) were followed prospectively for 3 yrs. Their disease activity and radiographic progression were evaluated with reference to disease activity score (DAS28), modified health assessment questionnaire (mHAQ) and others and by the change in van der Heijde-modified total Sharp score per year (fTSST), by classifying patients into subgroups showing structural remission (REM; fTSST<0.5), radiographic progression (fTSST>3) or rapid radiographic progression (RRP; fTSST>5).

Results: Disease activity was improved yearly, from baseline to 3 yrs: DAS28-ESR (3) improved from 3.2 ± 1.1 to 3.9 ± 1.4 (p < 0.0001), %DAS28 remission from 1% to 19%, mHAQ from 0.54 ± 0.47 to 0.18 ± 0.32 (p < 0.0001), mHAQ remission rate (fTSST<0.5) from 16% to 60%, and Boolean remission from 0.8% to 24.0%. During the 3-yr's MTX monotherapy, the ratio of the patients classified into the REM group increased from 38.5% to 50.4% (p = 0.0466), those in ΔTSS ≥ 3 decreased from 34.2% to 20.4% (p = 0.0095), and those in RRP decreased from 21.7% to 10.9% (p = 0.0190). In particular, the patients with active disease who required biologics arose mostly from the RRP group, followed by the CRRP group. This was, however, not the case when the patients were classified according to disease activity, i.e., DAS28. Receiver operating characteristic (ROC) curve analyses showed that serum matrix metalloproteinase-3 (MMP-3) levels of below 103.7 ng/ml at baseline predict a patient subgroup with no radiographic progression.

Conclusion: Approximately half of the patients given low-dose MTX monotherapy showed no radiographic progression over 3 yrs. A subgroup with no radiographic progression was predicted at outset by lower serum MMP-3.

Disclosure: K. Shiozawa, None; T. Yamane, None; M. Murata, None; C. Tanaka, None; N. Ya, None; R. Yoshihara, None; Y. Tanaka, None; K. Taumiya, None; S. Shiozawa, None.

Calprotectin Serum Levels Reflect Residual Inflammatory Activity in Patients with Rheumatoid Arthritis and Psoriatic Arthritis on Clinical Remission or Low Disease Activity Undergoing TNF-Antagonists Ther-apy. Jose Inclande-Mundo\textsuperscript{1}, M. Vicoria Hernandez\textsuperscript{2}, Sonia Cabrera-Villalba\textsuperscript{3}, Julio Ramirez\textsuperscript{4}, Andrea Cuervo\textsuperscript{1}, Virginia Ruiz-Esquide\textsuperscript{1}, A. Gonzalez Navarro\textsuperscript{1}, J. Ordag\textsuperscript{1}, Juan D. Cañete\textsuperscript{1} and Ramon Sanmarti\textsuperscript{1}.

1Hospital Clinic of Barcelona, Barcelona, Spain, 2Hospital Clinic Barcelona, Barcelona, Spain, 3Hospital Clinic Barcelona, Barcelona, Spain.
Background/Purpose: Calprotectin is a major S100 leucocyte protein, is associated to disease activity in rheumatoid arthritis (RA) and Psoriatic Arthritis (PsA) patients. Calprotectin is a potentially biomarker more sensitive of disease activity than conventional acute-phase proteins.

Objective: To analyze the relationship between calprotectin serum levels and inflammatory disease activity in patients with RA and PsA patients in clinical remission or low disease activity treated with TNF-antagonists. To correlate calprotectin levels with serum trough levels of TNF-antagonists.

Methods: Prospective study of patients diagnosed with RA (ACR 1987 criteria) or PsA (CASPAR criteria) treated with adalimumab (ADA), etanercept (ETN) or infliximab (IFX) for 3–12 months in clinical remission or with low disease activity measured by DAS28-ESR in ≥2 consecutive visits. Clinical and laboratory data were analyzed. Calprotectin serum levels (using kits from Promonitor®, Progenika SA) were determined at 0, 4, 8 and 12 months of follow-up. We present the results at study entry (visit 0).

Results: 103 patients (47 RA, 56 PsA) were included. 61% female, mean age 59 ±8 years, mean DAS28-ESR 2.1 ± 0.58, 76% were in clinical remission and 24% in low disease activity, 48% on monotherapy, 44% receiving reduced dosage of biologic (ADA 16 patients, ETN 22 patients and IFX 5 patients). Calprotectin levels were significantly lower in PsA than in RA patients (1.4 vs 2.2 ±1, p = 0.006). Patient on clinical remission (DAS28<2.6) showed lower calprotectin levels to those observed in those patients with low disease activity (1.2 ±1 vs. 3.4 ±1, p = 0.0001), even when distributed by the most stringent remission criteria (patients with SDAI 3.3 1.9 ±2, p = 0.005). Calprotectin strongly correlates with DAS28-ESR and SDAI in both RA (r = 0.774, p = 0.0001 and r = 0.328, p = 0.025 respectively) and PsA (r = 0.777, p = 0.0001 and r = 0.419, p = 0.001 respectively), whereas no correlation was found between CRP serum levels or ESR with DAS28-ESR and SDAI in both populations. A trend for higher calprotectin levels in patients with low serum trough levels of ADA was showed (n = 17, r = 0.413, p = 0.09), that was statistically significant in those patients with RA treated with adalimumab at standard dose (r = 0.767, p = 0.026). No correlations between calprotectin and serum trough levels ETN or IFX were observed.

Conclusion: Calprotectin was found to have high accuracy to discriminate RA or PsA patients in remission from those in low disease activity undergoing TNF-antagonist therapy, reflecting ongoing inflammatory activity. A strong correlation between disease activity measured by DAS28 and SDAI and calprotectin, but not with CRP or ESR, was found. No clear correlation between calprotectin levels and TNF-antagonists serum trough levels was observed. Calprotectin emerges as a very useful biomarker to detect residual inflammatory activity in these patients.

Disclosure: J. Inciarte-Mundo, Premi Fi de Residencia “Emili Letang,” 2, Beca M SD Societat Catalana de Reumatologia, 2, M. V. Hernandez, None; S. Cabrera-Villalba, None; J. Yagie, None; J. D. Canete, None; R. Sanmarti, unrestricted educational grant from Pfizer, 2.

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Baseline Serum Interferon Beta/Alpha Ratio Predicts Response to Tu

mer Necrosis Factor Alpha Inhibition in Rheumatoid Arthritis.

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Background/Purpose: Response to tumor necrosis factor alpha (TNF-α) inhibition is variable in rheumatoid arthritis (RA). Previous studies have suggested that circulating type I interferon (IFN) levels may predict treatment response to TNF-α inhibitors and other biological agents in RA. Prediction of likely responders prior to initiating therapy would represent a major advance in biological treatment strategies for RA.

Methods: We used ELISA to quantify serum IL-33 level and assessed B-cell-activation biomarkers (rheumatoid factor [RF], anti-CCP antibodies, free light chains, IgG, IgA, IgM, and BAFF levels), serum CXCL12, CXCL13 and CCL19 levels (all log transformed for analysis) in 205 RA patients before receiving a 1st course of RTX (Ig on days 1 and 15) in the SMART trial and 63 controls (CT). Uni and multivariate analyses were performed to identify factors associated with a EULAR response 24 weeks after RTX.

Results: Serum IL-33 level was higher in patients with RA than in CT (median [interquartile range]: 238 [75;1545] vs 35 [22;664] pg/mL, p = 0.001) as well as in anti-CCP positive compared with anti-CCP negative patients (359 [87;1619] vs 102 [39;368] pg/mL, p = 0.001). A similar result was observed for RF status (p = 0.001). Serum IL-33 level was uncorrelated neither with DAS28 nor with CRP level. Unexpectedly, serum IL-33 level was highly correlated with CCL19 (r = 0.7; p = 0.0001) and CXCL13 levels (r = 0.15 p = 0.003). There were 146 (71%) responders (i.e. 44 good and 102 moderate) according to EULAR criteria at 12 weeks (p = 0.02), as well as the presence of anti-CCP antibodies or RF (OR: 2.76 [1.24;6.15]; p = 0.01), with a similar trend for IgG level (OR: 2.00...
IFN activity were evident, these patients were indistinguishable in regards to key SS phenotypic features, except focus score which was highest in type II-predominant patients (p = 0.024). Stratification of SS patients by high vs low IFN activity revealed associations of high IFN activity with high titer ANA (p = 0.0016) and SSA (p = 0.0161) antibodies, hyperglobulinemia (IgG >1445 mg/dl, p = 0.0005; IgA >400 mg/dl, p = 0.0355) and higher focus scores (p = 0.0001). Additionally IFN high patients demonstrated greater evidence of glandular dysfunction as determined by decreased ability to produce saliva (UWS: 0.164 vs 0.549 ml/5min, p = 0.0003) and tears (Schirmer 4 vs 6.5 mm/5min, p = 0.0368).

Conclusion: Our data indicate that the parent phenotype in SS (chronic exocrine gland dysfunction, inflammatory infiltration and autoimmunity) includes distinct molecular subtypes, segregated by magnitude and pattern of IFN responses. While the resulting disease subtypes are clinically similar, therapies targeting type I and type II IFN may need to be selected based on prior analyses of which specific IFN pathway(ies) are active in individual patients.

Disclosure: J. C. Hall, None; A. N. Baer, None; M. Y. Lam, None; L. A. Criswell, None; A. Rosen, None; L. Casciola Rosen, None.

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Precisely Quantified Fibrosis in Labial Salivary Glands Predicts Sjogren’s Syndrome Classification in a Multiple Regression Model.

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1University of Oklahoma Health Sciences Center, Oklahoma City, OK, 2Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Primary Sjögren’s Syndrome (pSS) is a systemic, progressive autoimmune exocrinopathy that presents diagnostic challenges. Focal lymphocytic infiltrates in labial salivary gland (SG) biopsies, serum autoantibodies, objective measures of dryness, and patient-reported symptoms are used to classify pSS. Because focus score (FS) may vary with course of disease, we asked whether precisely quantified SG fibrosis can distinguish pSS from non-SG sicca.

Methods: Formalin-fixed biopsy sections (4-6 glandular cross-sections per subject) collected from symptomatically dry individuals attending the Oklahoma Sjögren’s Syndrome Center of Research Translation clinic were stained with hematoxylin/eosin, imaged and digitally reconstructed. A metric European Consensus Group (AECG) classification status (n=50 pSS; n=28 non-SS) was blinded in order to eliminate bias by the scorers. AECG pSS exclusions were applied to all subjects. Fibrosis was quantified using a digital grid overlay; sections were scored and reported as average percent area

Results: Fibrosis was significantly increased (p=0.0004, Mann-Whitney U) in pSS salivary glands (median 25.39%, range 1.788%-70.45%) compared to non SS sicca subjects (median 15.52%, range 8.876%-31.38%). Among pSS subjects, fibrosis correlated with age (p=0.029, r=0.307), lip biopsy focus score (p=0.03, r=0.360) and van Bijsterveld Score (vBS, p=0.02, r=0.310). No significant correlation between fibrosis and salivary flow or Schirmer’s score was observed. In a predictive model including fibrosis and age, degree of labial salivary gland fibrosis predicted disease classification with 68% accuracy irrespective of age of fibrosis (p=3.91x10⁻³; age, p=0.63).

Conclusion: Although age is associated with salivary gland fibrosis, multiple regression analysis suggests that labial salivary gland fibrosis is a significant feature of primary Sjögren’s syndrome regardless of age.

Disclosure: K. M. Leehan, None; M. Brown, None; C. Montgomery, None; A. Benjamin, None; D. M. Lewis, None; L. Radfar, None; D. U. Stone, None; S. Young, None; R. H. Scofield, None; K. L. Moser Sivils, None; A. Darise Farris, None.

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Longitudinal Examination with Salivary Gland Ultrasonography (SGUS) of Patients with Primary Sjogren’s Syndrome: A Single Center Experience.

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Molecular Diagnostics for Patient Subsetting in Sjögren’s Syndrome.

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Background/Purpose: Sjögren’s syndrome (SS) is a chronic autoimmune disease which targets exocrine glands, particularly salivary and lacrimal glands. While all SS patients have abnormal secretory function and inflammatory infiltration of their salivary glands, there is significant heterogeneity in terms of disease features, pathology and clinical course. Elucidating the inflammatory pathways which are active in pathologic tissues has important implications for defining disease subsets and monitoring disease activity. With the increasing availability of therapies which target specific gene/enzyme in the inflammatory pathways which are active in pathologic tissues has important implications for defining disease subsets and monitoring disease activity. With the increasing availability of therapies which target specific gene/enzyme pathways, defining the activity of distinct molecular pathways in target tissues will be important for selecting therapy. The type I and type II IFNs, which are implicated in SS pathogenesis, are particularly relevant in this regard.

Methods: Clinical data and a frozen labial salivary gland was obtained from each of 82 participants enrolled in the Sjögren’s International Collaborative Alliance Registry (NIH/NIDCR contract HHSN265201300057C) with the following characteristics: (i) 53 individuals meeting ACR criteria for primary SS; (ii) 26 age and sex-matched controls lacking serologic and pathologic evidence of SS, of which 14 exhibited evidence of dry eye disease (OSS = 3 for either eye). Protein lysates were generated from SS and control labial salivary glands proteins were separated by SDS-PAGE and immunoblotted with specific markers of type I or type II IFN activity. Protein expression was normalized to the level of a loading control within the same sample and subject to hierarchical clustering to define patterns of IFN activity (high vs low). Correlations between IFN activity and categorical SS phenotypic features were analyzed using Fisher’s exact test. Continuous phenotypic characteristics were compared between groups using a Wilcoxon rank sum test.

Results: IFN activity was low or absent in controls and detected at high levels in 31 of 53 (59%) SS patients. While patterns consistent with type I-predominant (n=9), type II-predominant (n=11) and mixed I/II (n=11)
Background/Purpose: Recently, convincing data have been published on the diagnostic value of salivary gland ultrasonography (SGUS) in primary Sjögren’s syndrome (pSS). However, a limited number of information are available on the contribution of SGUS in the patients’ prognostic assessment and in the monitoring of the response to therapy during the follow-up. A aim of the study was to prospectively evaluate if SGUS might have a role in the prognostic stratification and in the monitoring of the disease activity in patients with pSS over the follow-up.

Methods: The study population consisted of consecutive patients with a diagnosis of pSS (AECG 2002) who prospectively underwent clinical laboratory and SGUS assessment at baseline, at 12 and at 24 months. An experienced rheumatologist scored the EULAR Sjögren’s Syndrome Activity Index (ESSDAI) at each follow-up time point. Patients received the “best available-therapy” according to the clinical practice. SGUS was performed by the same radiologist blinded to the rheumatologist clinical assessment. The parotid and submandibular glands were scanned on both sides by using a real-time US scanner (Esaote Technos MPX) with a 7.5–12.5 MHz transducer and the following US parameters were recorded: size, parenchymal echogenicity and inhomogeneity in the parotid and submandibular glands on both sides. A previously reported ultrasound scoring system (De Vita 1992) was used to grade the echostructure alterations of the salivary glands. Baseline, 12 months and 24 months SGUS results were compared using the non-parametric Friedman test for multiple comparisons. Correlation between SGUS and ESSDAI changes throughout the follow-up period was assessed using the Spearman linear correlation coefficient. Statistical significance was accepted at p<0.05.

Results: From January 2012 and January 2014, 68 pSS patients were enrolled in this study (median (IQR) age: 53 (45–64) years). At the baseline 28/68 (41.2%) patients had a SGUS score ≥2. These patients, when compared to the group of patients with a SGUS score <2, presented more frequently low C4 levels (p=0.04), positivity for anti-Ro/SSA (p=0.0001) and higher mean ESSDAI scores, with the ESSDAI positively correlating with the SGUS score (r=0.571, p<0.0001). Over the follow-up we still observed a positive correlation between the changes in the ESSDAI and the changes in the SGUS score (r=-0.490, p=0.0001). However, no statistically significant differences were detected over the follow-up in the SGUS score across the multiple test performed and at the end of the study patients with grossly inhomogeneous glands still presented evident inhomogeneities.

Conclusion: This study highlighted the positive correlation between SGUS score and pSS disease activity. However, further research is needed before a conclusion can be made regarding the possibility of using SGUS in the assessment of the response to therapy in pSS.

Disclosure: C. Baldini, None; N. Luciano, None; F. Sernissi, None; D. Martin, None; F. Ferro, None; M. Mosca, None; S. Bombardiere, None.

2932

Marko Yurkovich1, Hyon K Choi2, Eric C. Sayre3, Kamran Shojania1 and J. Antonio Pereira1, Cleonice Bueno 1, Vilma S. T. Viana 3 and Sandra G. Pasoto 1.

Background/Purpose: Recently, convincing data have been published on the diagnostic value of salivary gland ultrasonography (SGUS) in primary Sjögren’s syndrome (pSS). We estimated the population-based risk of newly recorded DVT and PE among incident cases with pSS compared to controls from the general population using physician-billing and hospitalization databases that cover the entire population of the province of British Columbia, Canada (~4.4 million).

Patients and Methods: Our data include all visits to health professionals and all hospital admissions from Jan 1, 1995 to Dec 31, 2010 for all individuals. We conducted a retrospective matched cohort study among patients satisfying at least one of the following criteria: a) diagnosis of pSS in adults on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; b) diagnosis of pSS on at least one visit by a rheumatologist or from hospitalization. To increase specificity we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point. pSS cases that were matched by birth year, sex and calendar year of follow-up were selected from the general population for each outcome. Cases involved PE, DVT, and PE or DVT events based on hospitalization records (for PE and DVT), outpatient visits (DVT) or death certificates (all outcomes). For non-fatal outcomes, we also required the use of anticoagulant medication within six-months of the event as part of all outcome definitions. We estimated relative risks (RRs) comparing pSS with age-, sex- and entry-time-matched comparison cohorts, adjusting for potential risk factors for PE and DVT. Sensitivity analyses were conducted to assess for unmeasured confounders.

Results: Among 1175 incident SjS cases, 14, 10 and 19 developed a first time PE, DVT, and PE or DVT event, respectively (incidence rates = 3.8, 2.7 and 5.2 per 1,000 person years, respectively) (see table). Compared with the age, sex, and entry-time-matched controls, the RR were 4.1 (95% CI: 2.0 – 7.7), 3.0 (95% CI: 1.3 – 6.1) and 3.1 (95% CI: 1.8 – 5.3) for PE, DVT, and DVT or PE, respectively. After adjusting for covariates the results remained similar (see table). The risk of developing DVT, PE or either event was highest within the first year following diagnosis of SjS, decreasing over time to become not significantly increased after 5 years. Our results remained statistically significant after adjusting for the potential impact of an unmeasured confounder (adjusted RR ranging between 1.58 – 1.98 in all sensitivity analyses).

Conclusion: This large population-based study indicates an increased risk of DVT and PE in patients with SjS. Our results support the need for increased monitoring for these complications in SjS patients.

| Table: Risk of Incident PE, DVT or PE or DVT according to SjS Status |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | PE              | DVT             | PE or DVT       |
| Sample size, n   | 1,175           | 11,958          | 1,175           | 11,958          |
| RRs (95% CI)     |                 |                 |                 |
| Time After Initial Diagnosis: |                 |                 |                 |
| < 1 year         | 8.9 (2.7 – 28.0) | 5.0 (1.4 – 16.3) | 5.7 (2.3 – 12.9) |
| < 2 years        | 6.2 (2.4 – 15.0) | 5.1 (1.8 – 13.6) | 4.6 (2.1 – 9.4) |
| < 3 years        | 4.7 (2.0 – 10.4) | 4.4 (1.7 – 10.5) | 4.0 (2.0 – 7.5) |
| < 4 years        | 5.0 (2.3 – 10.5) | 4.3 (1.8 – 9.8)  | 4.0 (2.0 – 7.1) |
| < 5 years        | 4.8 (2.2 – 9.7)  | 4.0 (1.6 – 9.0)  | 3.7 (1.9 – 6.6) |
| ≥ 5 years        | 2.3 (1.0 – 5.6)  | 1.0 (0.0 – 6.5)  | 1.9 (0.4 – 6.5) |
| Multivariate RRs*| 3.2 (1.6 – 6.5)  | 2.8 (1.2 – 6.4)  | 2.4 (1.3 – 4.4) |

*adjusted for alcoholism, liver disease, hypertension, varicose veins, trauma, fractures, surgery, glucocorticoids, hormone replacement therapy, COX-2 inhibitors, Charlson comorbidity score, number of hospitalizations, and number of outpatient visits.

Disclosure: M. Yurkovich, None; H. K. Choi, None; E. C. Sayre, None; K. Shojania, None; J. A. Avina-Zubieta, None.

2933
Metabolic Syndrome, Adipocytokines and Inflammation in Sjögren’s Syndrome.


Faculty of Medicine of the University of São Paulo, São Paulo, Brazil, 2University of São Paulo, São Paulo, Brazil, 3Faculty of Medicine of the University of São Paulo, São Paulo, Brazil.

Background/Purpose: Systemic inflammation has been linked to increased frequency of metabolic syndrome (MetS) in autoimmune diseases. However, there are no studies concerning the frequency of this complication and adipocytokine sera profile in Primary Sjögren’s syndrome (SS).

Methods: Seventy-one female SS patients (American-European Consensus Group Criteria), aged 18–65 years and 71 healthy women matched for age and race were enrolled in this case-control study. Clinical data were collected by a standardized questionnaire and physical examination at inclusion. Serum levels of glucose, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, interleukin-1 beta (IL-1b), IL-6, BAFF, insulin, leptin, adiponectin, visfatin, resistin, ghrelin and plasminogen activator inhibitor-1 (PAI-1) were determined for all patients and controls. MetS (International Diabetes Federation) and disease activity (EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI)) were also determined.

Results: Patients and controls were comparable regarding mean age (47.6 ± 10.3 years vs. 47.2 ± 10.3 years, p=0.833), ethnicity (white: 77.5 vs. 77.5 %, p=1.00), body mass index (BMI) (27.6 ± 6.4 vs. 26.7 ± 3.6 kg/m², p=0.783), smoking (p=0.538), sedentary lifestyle (p=0.847) and menopause...
Background/Purpose: In an open-label proof of concept study, Abatacept is under investigation.

Methods: Fifteen patients with pSS, diagnosed according to the revised American-European Consensus Group criteria, were treated with Abatacept on days 1, 15, 29 and every four weeks thereafter for five months (~10 mg/kg of body weight i.v.). Absolute numbers and frequencies of circulating Th-cell subsets (CD3+CD4+) were examined in fresh blood samples by flow cytometry at baseline and week 1, 2, 4, 12, 16, 24, 36 and 48 weeks after the first dose. Expression patterns of chemokine receptors CCR7 and CD45RO were used for distinction between naive, central memory, effector memory and terminally differentiated Th-cells. Generalized estimating equations (GEE) were used to analyze the presence of different subsets over time in subjects, as well as their association with arthritis activity (ESSDAI). For distinction between naive, central memory, effector memory and terminal differentiated Th-cells, GEE analysis with adjustment for age, ethnicity, current and cumulative prednisone doses and usage time revealed that MTS group had higher values of hypertension (p < 0.001), HOMA-IR (p < 0.001), LDL (p < 0.014), VLDL (p < 0.001), triglycerides (p < 0.001), glucose (p < 0.014), lipoprotein (p < 0.006), leptin (p < 0.008) and IL-1β (p < 0.008).

Conclusion: This study identified a high frequency of MTS and an abnormal adipocytokine profile in pSS patients. The interesting association of MTS with elevated IL-1β suggests that inflammation plays an important role in its pathogenesis in SS.

Disclosure: K. L. Augusto, None; E. Bonfá, None; R. M. R. Pereira, None; C. Bueno, None; V. S. T. Viana, None; S. G. Pasto, None.

**2934**

Abatacept reduces Circulating Efferent Memory T-Helper Cells in Patients with Primary Sjögren’s Syndrome (pSS).

Gwenn Verstappen1, Wjeyl H. Abdulahad2, Petra M. Meiners1, Suzanne Arends1, Silvia Beijer-Liefers1, Arian J Visink1, Frans G. M. Kroese2 and Hendrika Bootma2.

1University Medical Center Groningen, University of Groningen, Groningen, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: In an open-label proof of concept study, Abatacept is a fully human fusion molecule of IgG-Fc and CTLA-4 that modulates the costimulatory interaction between APCs and T-lymphocytes, thereby inhibiting full T-cell activation. Modifying T-helper (Th) cell homeostasis may contribute to the therapeutic effect of Abatacept as Th-cell subset imbalances are involved in the emergence of autoimmunity and arthritis.

Methods: Fifteen patients with pSS, diagnosed according to the revised American-European Consensus Group criteria, were treated with Abatacept on days 1, 15, 29 and every four weeks thereafter for five months (~10 mg/kg of body weight i.v.). Absolute numbers and frequencies of circulating Th-cell subsets (CD3+CD4+) were examined in fresh blood samples by flow cytometry at baseline and week 1, 2, 4, 12, 16, 24, 36 and 48 weeks after the first dose. Expression patterns of chemokine receptors CCR7 and CD45RO were used for distinction between naive, central memory, effector memory and terminally differentiated Th-cells. Generalized estimating equations (GEE) were used to analyze the presence of different subsets over time in subjects, as well as their association with arthritis activity (ESSDAI).

Results: On Abatacept treatment, numbers of peripheral blood CD4+ T-cells did not significantly differ from baseline values. However, absolute numbers and frequencies of total memory Th-cells decreased significantly over time on treatment (p = 0.001 and p = 0.001, resp.). This was mainly a result of a decrease in effector memory Th-cells. On treatment, both absolute numbers and frequencies of effector memory Th-cells decreased significantly over time (p = 0.011 and p = 0.001, resp.), with the largest decrease seen at week 24. On the contrary, frequencies of naive Th-cells increased over time on treatment (p < 0.001). From week 24 to week 48 (off treatment), a trend towards increased absolute numbers and frequencies of effector memory Th-cells was observed. Decrease and repopulation of Th-cell subset correspond to changes in disease activity as assessed with ESSDAI.

Conclusion: CTLA-4Ig treatment with Abatacept decreases the presence of circulating effector memory Th-cells of pSS patients. The observation that decrease and repopulation of effector memory Th-cells correspond to changes in disease activity suggests that these cells are -at least partially- responsible for the effects of Abatacept treatment seen in pSS patients.

Disclosure: G. Verstappen, None; W. H. Abdulahad, None; P. M. Meiners, None; S. Arends, None; S. Beijer-Liefers, None; A. Visink, None; F. G. M. Kroese, None; H. Bootma, BMS, 2.

**2935**

Attainment of Minimal Disease Activity Using Methotrexate in Psoriatic Arthritis.

Barry J. Sheane, Arane Thavaneswaran, Dafna D. Gladman and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Methotrexate (MTX) is used as first-line treatment in psoriatic arthritis (PsA); however, the extent of the disease-modifying effect of MTX on PsA, if any, is not established. Randomized controlled trials examining the efficacy of MTX have been either under-powered or have used dosages that may be sub-optimal. While TNF inhibitors (TNF-I) are used as second-line therapies in PsA, they have proven efficacy and disease-modifying effect. Minimal disease activity (MDA) is achieved at 24 weeks in 39% and 52% of patients treated with adalimumab and infliximab, respectively. There is a need to establish the treatment effect of MTX.

Methods: All patients attending a large, tertiary referral centre for PsA who initiated MTX and were naive to biologic medication on or after January 2004 up until April 2014 were assessed for inclusion. The primary outcome was the achievement of MDA after 6 months of MTX. MDA is defined as: the presence of at least 5 out of the following 7 domains: tender joint count ≤ 1, swollen joint count ≤ 1, Spondylarthritis Assessment Questionnaire score ≤ 0.5, patient global assessment of disease activity Visual Analogue Scale (VAS) score ≤ 20 and patient pain VAS ≤ 15.

Results: Of 204 patients identified, 29 had insufficient duration on MTX to accurately assess outcome. These were excluded, leaving 175 for analysis. Of these, 167 patients had sufficient data for analysis at 6 months.

Conclusion: These findings suggest that MTX is efficacious in the treatment of PsA and should be further evaluated in future studies.

Disclosure: G. Verstappen, None; A. Thavaneswaran, None; D. D. Gladman, None; V. Chandran, None.

**2936**

Is AnaKlyosing Spondylitis a Risk Factor for Cardiovascular Diseases, and How Does This Risk Compare to Those in Rheumatoid Arthritis?

Johan Aaskling1, Lennart Jacobsson2 and Jonas Eriksson3.

1Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; 2 Sahlienska academy, Gothenburg, Sweden.
Performance of the models was evaluated (sensitivity, specificity, positive predictive value, positive likelihood ratio) using classification by ASAS axSpA criteria as external standard. For pts not fulfilling the ASAS criteria who are referred, post-test probability for axSpA was calculated based on the LR product for presence of SpA features. A LR product $\geq 78$ equals a post-test probability $\geq 80\%$ and was used as cut-off for probable axSpA. Pts who were incorrectly not referred met the ASAS axSpA criteria by fulfilling the clinical arm only or the imaging arm (imaging arm only or both arms). [table 2]

Table 2. Performance of referral models. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; LR+, positive likelihood ratio; PTP, post-test probability

Results: In total, 74/192 pts fulfilled ASAS axSpA criteria; 48 with positive imaging (n=15 radiographic sacroiliitis). Most models performed well regarding sensitivity/specificity. Braun alt. model has the most balanced sensitivity/specificity and highest LR+. All models that include HLA-B27 miss axSpA pts with positive imaging, 14–23% with radiographic sacroiliitis (depending on the model). PPV of the models is low, indicating that many pts are referred despite not fulfilling ASAS axSpA criteria. However, 6–16% (depending on the model) of these pts have a post-test probability $\geq 80\%$ for axSpA. This reflects that these pts are rightly referred, despite not fulfilling the axSpA criteria.

Conclusion: Most referral models performed well in the SPACE cohort. However, this cohort includes pts already referred from primary care, probably causing overestimation of performance of all models. All models miss pts fulfilling the ASAS imaging arm, 14–23% of which have radiographic sacroiliitis, which is highly undesirable. Moreover, large numbers of pts referred unnecessarily might lead to a burden for health care systems. Further studies should be conducted in primary care to evaluate these models in their target population.

References:
5. Weel AC&R 2013–09–19

Disclosures: O. Abawi, None; R. van den Berg, None; D. van der Heijde, None; F. van Gaalen, None.

2937

Evaluation of Referral Models for Axial Spondyloarthritis in Primary Care in the Spondyloarthritis Caught Early Cohort. Ozair Abawi, Rosaline van den Berg, Désirée van der Heijde and Floris van Gaalen, Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Several models have been proposed to refer patients (pts) with possible axial spondyloarthritis (axSpA) from primary care to the rheumatologist. Aims of the study was to evaluate performance of referral models for axSpA in the SPondsYoArthitis Caught Early (SPACE) cohort.

Methods: Ten referral models were found in literature and tested in the Leiden SPACE cohort, including pts with back pain ($\geq 3$ months, $\geq 2$ years, onset $< 45$ years; n=192) referred to the rheumatology outpatient clinic of the LUMC. Imaging was omitted from all models if included as a referral parameter, as it is useless for screening in primary care. [table 1]

Table 1. Characteristics of referral models. IBP, inflammatory back pain; IBD, inflammatory bowel disease

Results: Total, 74/192 pts fulfilled ASAS axSpA criteria; 48 with positive imaging (n=15 radiographic sacroiliitis). Most models performed well regarding sensitivity/specificity. Braun alt. model has the most balanced sensitivity/specificity and highest LR+. All models that include HLA-B27 miss axSpA pts with positive imaging, 14–23% with radiographic sacroiliitis (depending on the model). PPV of the models is low, indicating that many pts are referred despite not fulfilling ASAS axSpA criteria. However, 6–16% (depending on the model) of these pts have a post-test probability $\geq 80\%$ for axSpA. This reflects that these pts are rightly referred, despite not fulfilling the axSpA criteria.

Conclusion: Most referral models performed well in the SPACE cohort. However, this cohort includes pts already referred from primary care, probably causing overestimation of performance of all models. All models miss pts fulfilling the ASAS imaging arm, 14–23% of which have radiographic sacroiliitis, which is highly undesirable. Moreover, large numbers of pts referred unnecessarily might lead to a burden for health care systems. Further studies should be conducted in primary care to evaluate these models in their target population.

References:
5. Weel AC&R 2013–09–19

Disclosures: O. Abawi, None; R. van den Berg, None; D. van der Heijde, None; F. van Gaalen, None.

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Disclosures: O. Abawi, None; R. van den Berg, None; D. van der Heijde, None; F. van Gaalen, None.

S1283

Tuesday, November 18
Background/Purpose: Axial spondyloarthritis (axSpA), including ankylosing spondylitis and nonradiographic axial SpA (nr-axSpA), is an chronic inflammatory disease marked by back pain and progressive spinal stiffness. The goal of GO-AHEAD was to determine if golimumab (GLM) is superior to placebo (PBO) in patients with nr-axSpA.

Methods: GO-AHEAD was a Phase 3b, double-blind, randomized, PBO-controlled trial that evaluated subcutaneous (SC) GLM 50 mg vs PBO in patients aged 18–45 years with active nr-axSpA (A assessment of Spondyloarthritis International Society (ASAS) criteria and centrally-read SI joint X-rays; disease duration <5 years; chronic back pain; high disease activity [total back pain ≥40 mm on a 0–100 mm VAS] and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 mm); and inadequate response or intolerance to NSAIDs). Patients were randomized 1:1 to GLM or PBO SC injections every 4 weeks. The primary endpoint was BASDAI 20 attainment at week 16. Key secondary endpoints were ASAS 40, ASAS partial remission, and BASDAI 50 attainment; and Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) sacroiliac (SI) joint score change. AS Disease Activity Score based on C-reactive protein (ASDAS) was assessed. Treatment group differences for all patients-as-treated and the target populations (signs of inflammation by MRI or elevated CRP at baseline) were compared using the stratified Miettinen and Nurminen method for responder endpoints and the Mann-Whitney test for MRI SI joint score.

Results: Of 198 patients enrolled, 197 were treated (GLM=97; PBO=100). Mean age was 31 years; 57% were male. At baseline, mean BASDAI was 6.5 cm (SD=1.5), SPARCC MRI SI was 11.3 (SD=14.0), and ASDAS was 3.5 (SD=0.9). The primary endpoint was achieved by significantly more GLM patients than PBO patients (40.0%; table). Significantly more GLM patients also attained ASAS 40, ASAS partial remission, and BASDAI 50 (table). Mean ASDAS improvements were greater with GLM than PBO (−1.7 vs −0.6, respectively; P<0.0001). Mean SPARCC MRI SI joint score improvements from baseline to week 16 were greater with GLM than PBO (−5.3 vs −0.9, respectively; P<0.0001; improvements for the target population were −6.4 vs −1.2, respectively (P<0.0001).

Conclusion: More GLM patients than PBO patients met the primary endpoint of BASDAI 20 attainment; and GLM also met key ASAS 40, BASDAI 50, and SPARCC MRI SI joint score secondary endpoints. GLM improved disease activity and MRI SI joint scores in patients with nr-axSpA.

Disclosure: J. Sieper, AbbVie, Eli-Lilly, Janssen Biologicals, Merck, Novartis, Pfizer, Roche, and UCB; S. van der Heijde, AbbVie, Amgen, AstraZeneca, Ayuguer, BMS, Celgene, Centocor, Chugai, Covagen, Daichi, Eli-Lilly, Galapagos, GSK, Jansen Biologicals, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, and Vetter; S. Dougdas, AbbVie, Eli-Lilly, Novartis, Pfizer, Roche, Sanofi, and UCB; W. Makowsmowycz, AbbVie, Jansen, and Pfizer; S. Hwang, AbbVie, UCB, Pfizer, Merck, Jansen, Eli-Lilly, Celgene, and Synarc; S. Boice, Merck & Co., Inc.; S. Bergman, Merck & Co., Inc.; S. Curtis, Merck & Co., Inc.; S. Tzontcheva, Merck & Co., Inc.; S. Huyck, Merck & Co., Inc.; S. H. Weng, Merck & Co., Inc., 3.

Table. Primary and Key Secondary Outcomes, Week 16

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>( n=97 )</th>
<th>( n=100 )</th>
<th>( \text{Difference vs PBO} )</th>
<th>( % )</th>
<th>( \text{Difference vs PBO} )</th>
<th>( % )</th>
<th>( \text{Difference vs PBO} )</th>
<th>( % )</th>
</tr>
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<tbody>
<tr>
<td>ASAS 20</td>
<td>69</td>
<td>60</td>
<td>97</td>
<td>100</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>ASAS 40</td>
<td>55</td>
<td>55</td>
<td>110</td>
<td>100</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>BASDAI 50</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Differences derived from the statistical model.

Adverse events (AEs) occurred in 41% of GLM and 47% of PBO patients. Serious AEs occurred in 1 GLM (female partner reported fetal death) and 2 PBO patients (cholelithiasis, back pain). There were no serious infections, serious opportunistic infections, active tuberculosis, malignancies, serious drug-induced hepatotoxicity, or deaths, but without classic X-ray changes of AS. The second was the introduction of a new entity called non-radiographic axial Spondyloarthritides (nr-axSpA), defined based on the presence of MRI changes and HLA-B27, but without classic X-ray changes of AS. We studied the changes in incidence and prevalence of spondyloarthropathies (SpA) over time in Ontario, Canada.

Methods: We performed a population-based, retrospective cohort study on patients with SpA, age 15 or above, living in Ontario between 1995 and 2010. We used a stringent SpA definition of 2 outpatient claims within 2 years with at least one inpatient or rheumatologist claim. Incidence rates, prevalence rates and confidence intervals were calculated using Poisson regression. The incidence of SpA in men and women were compared in the pre-biologic era (1995–2000), early biologic era (2000–2005) and late biologic era (2005–2010).

Results: A total of 21,878 SpA patients were identified. The age, sex and local health integration network (LHIN) standardized prevalence rates (per 100,000) for SpA were 79 in 1995, 132 in year 2000, 175 in 2005 and 213 in 2010. The male:female ratio dropped from 1.25 to 1.08 to 1.03 in 2005–2010. The incidence rates rose uniformly in all age groups (15–44 years, 45–64 years and above 65 years) with time.

Conclusion: In this large population-based study, the period specific adjusted prevalence of SpA progressively increased. More female patients were diagnosed with SpA from 2000 onwards which correlates with the introduction of TNFi therapy in AS. Thus the trend of increasing female SpA patients predate the introduction of MRI and the new ASAS classification criteria for axial SpA.

Disclosure: N. Nigil Haroon, None; P. Li, None; M. Paterson, None; N. Haroon, None.
Physical Function Is Independently Associated with Mortality Among Individuals with Knee and/or Hip OA: The Johnston County Osteoarthrits Project. Rebecca Cleveland, Todd Schwartz, Jordan B. Renner, Joanne M. Jordan and Leigh F. Callahan.

**Background/Purpose:** Declining physical function (PF) is a common consequence of osteoarthritis (OA), and poor PF is associated with death. It is possible that the resulting reduction in physical activity may increase an individual’s risk of development or progression of life-threatening chronic diseases such as CVD and diabetes; however, we previously found that individual knee and/or hip OA was independent of comorbidities. We therefore sought to examine whether poorer PF among those with OA was associated with death at subsequent follow-up, independent of comorbidities associated with reduced PF.

**Methods:** Data were from 1,525 individuals aged 45 or older with radiographically confirmed (KL grade ≥2) knee and/or hip OA (ROA) who entered the cohort during the original study enrollment (1990–1997) and newly enrolled individuals recruited during the cohort enrichment (2003–2004). Vital status was assessed at first follow-up period (1999–2004 for original participants; 2007–2010 for new enrols). Severe ROA was defined as a KL grade ≥3; symptomatic OA (sOA) was a subset of those with ROA and symptoms in the same joint. PF assessment was the 8-ft (2.4-m) walk test. A average number of steps needed to complete the walk and average times to the nearest tenth of a second across two trials were computed. Dichotomous variables based on medians were used for walk time (<3.4 sec and ≥3.4 sec) and number of steps (<5.5 steps and ≥5.5 steps). Multilevel logistic regression models controlling for the primary sampling unit (PSU) were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between each PF measure at baseline and whether death occurred by the first follow-up evaluation. All models were adjusted for age, race, sex, BMI, smoking, depression, stroke, diabetes and CVD.

**Results:** Our sample was mostly women (63%), Caucasian (67%) and had a mean age of 65 years. At first follow-up, 18% of our sample had died. Walking time and number of steps above their medians were associated with a doubling in the odds of death among those with knee and/or hip ROA (Table 1). Similar associations were observed when restricted to individuals with sOA, and slightly attenuated ORs among those with severe disease that failed to reach statistical significance, possibly due to a smaller sample size. The highest odds of death with greater walking times were seen among individuals who had knee ROA whether with knee ROA (OR = 2.33; 95% CI = 1.20–4.51) or without knee ROA (OR = 2.40; 95% CI = 1.25–4.61).

**Conclusion:** Our findings suggest that poor PF among a cohort of individuals with knee and/or ROA is associated with death, findings which are independent of comorbidities linked to increased mortality. We observed associations with death were particularly strong for individuals with hip ROA, therefore suggesting a potential survival benefit through intervention among those individuals.

Table 1. A adjusted odds ratios (95% CI) for death at first follow-up according to 8-foot walking test measures assessed at baseline among those with knee and/or hip ROA (n = 1,525).

<table>
<thead>
<tr>
<th>Walking Time</th>
<th>Knee and/or Hip ROA</th>
<th>Symptomatic Knee and/or Hip ROA</th>
<th>Only Knee ROA</th>
<th>Only Hip ROA</th>
<th>Both Knee and Hip ROA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time &lt; 3.4 sec</td>
<td>85/676</td>
<td>Referent</td>
<td>36/283</td>
<td>Referent</td>
<td>25/134</td>
</tr>
<tr>
<td>Time ≥ 3.4 sec</td>
<td>138/567</td>
<td>1.94 (1.38–2.71)</td>
<td>114/555</td>
<td>2.15 (1.32–3.49)</td>
<td>92/297</td>
</tr>
<tr>
<td>Number of Steps</td>
<td>Stairs &lt; 5.5</td>
<td>121/766</td>
<td>Referent</td>
<td>59/325</td>
<td>Referent</td>
</tr>
<tr>
<td>Stairs ≥ 5.5</td>
<td>154/604</td>
<td>2.23 (1.69–3.03)</td>
<td>90/318</td>
<td>2.77 (1.86–2.87)</td>
<td>68/175</td>
</tr>
</tbody>
</table>

**References:**

BG (18.5–24.9) and current smokers vs non-smokers (OR: 1.62; 95% CI: 1.42 – 1.88). Physical activity was not significantly associated with arthritis. Further analysis showed that the population-level effects of increasing education and income on reducing the arthritis prevalence were almost count-balanced by effects of increasing BMI (obesity).

Conclusion: The findings suggest that the cohort effect of more arthritis in younger cohorts is explained by period effects such that the potential benefits of increased education and income in reducing the prevalence of arthritis may have been partly offset by increases in BMI over time. Our understanding of the impact of BMI on arthritis is therefore likely to be an underestimate. The cohort effect of increased arthritis in younger cohorts also suggests that previous population projections may be underestimated.

Disclosure: E. M. Badley, None; M. Canizares, None; A. V. Perruccio, None; S. Hogg-Johnson, None; M. A. M. Gignac, None.

2943

Severity of Foot Pain Is Linked to the Prevalence of Depressive Symptoms: The Framingham Foot Study.


Background/Purpose: The Framingham Foot Study. Severity of foot pain with depressive symptoms in a population-based study was studied. The purpose of this study was to examine the associations of foot pain (yes or no) and severity of foot pain with depressive symptoms in older adults.

Methods: A validated foot assessment and the 20-item CES-D questionnaire were administered to Framingham Foot Study (2002–08) participants. Age, sex, race/ethnicity, education and income on reducing the arthritis prevalence were almost significantly associated with 44% decreased risk of disability (HR = 0.56 [95% CI, 0.37–0.81], P = 0.003). From further analyses using an isotemporal model, replacing one hour sedentary time with one hour light activity (e.g. walking) was associated with 53% decrease in risk of disability onset for those in the most sedentary quartile, independent of potential confounders and time spent in other activities (HR = 0.49 [95% CI, 0.29–0.85], P = 0.01; not shown in Figure).

Conclusion: Sedentary time appears to be a separate and distinct risk factor for incident disability among adults at elevated risk for disability. In addition to increasing MVPA physical activity, these findings suggest decreasing sedentary time may be an additional strategy to prevent disability onset.

Disclosures: A. Awale, None; A. B. Dufour, None; P. P. Katz, None; V. A. Casey, None; M. T. Hannan, None.

2944

Sedentary Time Is an Independent Risk Factor for Disability Onset Among Adults at Elevated Risk: Prospective Cohort Study.

Jungwha Lee, Jing Song, Barbara Airdworth, Rowland W. Chang, Linda S. Ehrlich-Jones, Christine Pfeiffer, Dr. Pamela Silverman and Dr. Sushama Vohra. Northwestern University Feinberg School of Medicine, Chicago, IL, 2Arizona State University, Phoenix, AZ, 3Rehabilitation Institute of Chicago, Chicago, IL, 4Rush University, Chicago, IL, 5Northwestern University, Chicago, IL.

Background/Purpose: Disability threatens personal independence and is a major driver of health care costs. Physical activity has been shown to prevent disability. Sedentary behavior, already associated with poor health outcomes, may have a unique relationship to the development of disability or simply reflect limited recommended moderate/vigorous physical activity (MVPA). If a separate and distinct risk factor, reducing sedentary behavior may provide an additional strategy to reduce disability among older adults.

Methods: Prospective multi-site cohort of 1680 community dwelling adults aged 49 years or older were at elevated risk to develop disability due to knee osteoarthritis or having knee osteoarthritis risk factors. Baseline sedentary and non-sedentary (e.g., light, moderate, vigorous) time were objectively measured using accelerometers. Participants were classified into sedentary time quartiles. Disability was ascertained from limitations in instrumental and basic activity of daily living (IADL/AADL) at baseline and two years. Hazard ratios for disability onset over 2 years follow-up were estimated from discrete time proportional hazards models controlling MVPA time, socioeconomic factors (age, sex, race/ethnicity, education, income), health factors (function, comorbidity, Center for Epidemiological Studies Depression score, body mass index category, current smoking, knee pain, knee OA severity, knee symptoms, knee injury, other lower extremity joint pain, gait speed).

Results: Incident disability was 147 versus 69, 62, and 72 per 1000 person-years over 2-years follow-up in the most sedentary quartile (>=11.5 sedentary hours per day) compared to the three less sedentary quartiles, respectively. Less sedentary time was significantly associated with decreased risk of disability independent of moderate/vigorous minutes and other covariates (hazard ratios comparing three less sedentary quartiles vs. the most sedentary quartile, 0.62, 0.52, 0.57, respectively) (Figure). The average of the three less sedentary quartiles compared to the most sedentary quartile was associated with 44% decreased risk of disability (HR = 0.56 [95% CI, 0.37–0.81], P = 0.003). From further analyses using an isotemporal model, replacing one hour sedentary time with one hour light activity (e.g. walking) was associated with 53% decrease in risk of disability onset for those in the most sedentary quartile, independent of potential confounders and time spent in other activities (HR = 0.49 [95% CI, 0.29–0.85], P = 0.01; not shown in Figure).

Conclusion: Sedentary time appears to be a separate and distinct risk factor for incident disability among adults at elevated risk for disability. In addition to increasing MVPA physical activity, these findings suggest decreasing sedentary time may be an additional strategy to prevent disability onset.

Background/ Purpose: Foot pain is associated with poorer physical function in older adults, but few studies have examined how foot structure (high / low arches) and foot function (supination / pronation) are related to lower extremity physical function. The purpose of this cross-sectional study was to evaluate whether foot structure and function were associated with self-report and performance-based physical function in a community-based study of Caucasian and African American men and women 50+ years old.

Methods: During the 2006-2010 exam of the Johnston County Osteoarthritis Project, foot pressure scans were obtained and physical function of participants was assessed via self-report and performance tests. Physical function measures included: the Foot and Ankle Outcome Score – A-activities of Daily Living subscale (FAOS-ADL, 0-100 [extreme - no limitation]), 5 timed chair stands (unable and quartiles of completion time in seconds [s]), 8-foot walk (unable and quartiles of time in s), and standing balance (unable to stand without assistance, <10 s semi-tandem, semi-tandem 10 s but unable full tandem >2 s, full tandem 3-9 s, and full tandem 10 s). Foot pressure scans were used to determine foot structure (modified arch index) during standing and foot function (center of pressure excursion index) while walking. Based on population data, foot structure was categorized as high arch, low arch, and referent; foot function was categorized as over-pronated, over-supinated, and referent. The most extreme foot structure and function for each participant were used in analyses. Separate linear (continuous outcomes) and logistic (categorical outcomes) regression models were used to estimate the associations between foot type and physical function measures, adjusting for age, body mass index [BMI], sex, and race.

Results: 1571 participants had foot structure data and 1490 had foot function data (mean age 69 years, mean BMI 32 kg/m², 68% women, 30% African American). In standing, 22% had a low arch and 39% had high arch; during walking, 22% had an over-pronated foot and 31% had an over-supinated foot. Compared to the referent foot structure, higher FAOS-ADL scores (better physical function) were associated with a high arch in adjusted models, while a low arch was associated with worse physical performance on the chair stand and 8-foot walk tasks and with poorer balance (Table); these results were attenuated after controlling for age, BMI, sex, and race. Compared to the referent foot function, an over-supinated foot was associated with a faster 8-foot walk speed.

Conclusion: A high arch and an over-supinated foot were related to better lower extremity physical function. Longitudinal studies are needed to determine the effect of foot structure and function on changes in physical function and to assess interventions for modifying foot type (e.g., shoe orthotics) to limit physical decline in populations.

**Table.** Associations of Foot Structure and Foot Function with Physical Function

<table>
<thead>
<tr>
<th>Physical Function</th>
<th>Foot Structure</th>
<th>Foot Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Arch</td>
<td>High Arch</td>
</tr>
<tr>
<td>FAOS-ADL mean (SD)</td>
<td>58.6 (28.2)</td>
<td>106.1 (28.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>61.8 (24.9)</td>
<td>109.8 (28.5)</td>
</tr>
<tr>
<td>Adjusted beta (SE)</td>
<td>-1.7 (1.1)</td>
<td>0.3 (1.0)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-4.5 (-1.1)</td>
<td>1.9 (-1.0)</td>
</tr>
<tr>
<td>Adjusted beta (SE)</td>
<td>-1.9 (1.4)</td>
<td>-0.2 (1.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-4.2 (-1.4)</td>
<td>0.6 (-1.2)</td>
</tr>
<tr>
<td>Unadjusted beta (SE)</td>
<td>0.7 (1.0)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-2.4 (-1.7)</td>
<td>2.6 (-1.7)</td>
</tr>
<tr>
<td>Chair Stand Unable</td>
<td>116 (15.4)</td>
<td>345 (15.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>86 (12.4)</td>
<td>375 (12.4)</td>
</tr>
<tr>
<td>Unadjusted beta (SE)</td>
<td>0.7 (1.2)</td>
<td>0.1 (1.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.8 (-1.4)</td>
<td>2.6 (-1.4)</td>
</tr>
<tr>
<td>8-foot walk Unable</td>
<td>126 (19.3)</td>
<td>321 (19.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>94 (16.4)</td>
<td>257 (16.4)</td>
</tr>
<tr>
<td>Unadjusted beta (SE)</td>
<td>0.7 (1.2)</td>
<td>0.1 (1.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.8 (-1.4)</td>
<td>2.6 (-1.4)</td>
</tr>
</tbody>
</table>

**Figure.** Change in gait function over two years, adjusting for baseline gait speed and PM monitoring time.
Adenosine A2A Receptor as a Potential New Therapeutic Target for the Prevention/Treatment of Osteoarthritis. Carmen Corcillo1, Anzazu Mediero2, Tuere Wider3 and Bruce N. Cronstein1. 1NYU School of Medicine, New York, NY; 2NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Osteoarthritis results from trauma, mechanical factors or metabolic changes in bone and cartilage. Adenosine, acting via the A2A R, inhibits inflammation and plays a critical role in regulating bone factors or metabolic changes in bone and cartilage. Adenosine, acting via the A2A R, has chondroprotective effects in mice. A2AKO mice experience difficulty in movement, taking food and walking. We determined whether changes in their bone or joint structure or function could explain these changes.

Methods: Bone volume/total volume was determined with microCT analysis. Immunostaining for MMP-13 and Collagen-X was carried out. MicroCT analysis of knees was performed on the distal femur below the growth plate. Immunostaining for MMP-13 and Collagen-X showed an increase in Collagen-X and MMP-13 expression and release, with an increase in b-catenin expression. These effects are reversed by the A2A R antagonist, ZM241385.

Conclusion: Deficiency in adenosine A2A R leads to spontaneous osteoarthritis and stimulation of A2A Rs on chondrocytes diminishes changes associated with osteoarthritis, findings that suggest that A2A R may be novel targets for development of therapies to ameliorate or prevent osteoarthritis.

Disclosure: M. H. van den Bosch, None; A. B. Blom, None; R. P. Hoek, None; R. F. Schelbergen, None; S. W. Suen, None; A. E. van Erp, None; W. B. van den Berg, None; P. M. van der Kraan, None; P. L. van Lent, None.
stained with safranin-O and fast green for histologic scoring of the entire articular surface, using the OARSI grading system. Some knee sections also were analyzed by immunohistochemistry (IHC) for expression and -phosphorylation of AMPKα and appearance of NITEGE neoepitope of aggrecanase activity.

**Results:** After DM M surgery, non-treated mice developed OA in the knee medial compartment, with a mean score of 3.72, indicated by loss of cartilage. In contrast, berberine significantly reduced spontaneous OA development, and particularly so in 24 months-old mice. The mean total joint scores for the berberine treated mice were 0.38 and 2.2 (p = 0.008), compared to non-treated mice at 24 months, 95% CI of difference: 0.84 to 7.97) at 18 and 24 months, respectively. Moreover, IHC analysis demonstrated that berberine inhibited both loss of phosphorylation of AMPKα and the appearance of NITEGE neoepitope in articular cartilage.

**Conclusion:** Maintenance of articular chondrocyte AMPK activity by berberine is therapeutically chondroprotective in vivo in mouse knee biomechanical injury and aging models. Targeted activation of AMPK by pharmacologic means, studied here using berberine, provides a novel approach to limiting OA development and progression in mice in vivo, and merits investigation in human OA.

**Disclosure:** W. de Munter, None; P. M. van der Kraan, None; W. B. van den Berg, None; P. L. van Lent, None.

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**2951**

**Syndecan-4 Regulates Chondrocyte Phenotype and Cartilage Homeostasis Via the WNT Signaling Pathway.** Charlotte Kimberley Clarke, Annelena Held, Richard Stange, Uwe Hansen, Lars Godmann, Jessica Bertrand, Thomas Pah, Giovanna Nalesso, Frank Echtenberger, Francesco Dell’Accio, Joanna Sherwood, Institute of Experimental Musculoskeletal Research, Barts and the London Queen Mary’s School of Medicine and Dentistry, London, United Kingdom.

**Background/Purpose:** Syndecan-4 (Sdc4), family member of type I transmembrane heparan sulfate proteoglycans (HSPGs), is a regulator of various cartilage-related processes including osteoarthritis (OA). Blockade of Sdc4 signaling protects mice from cartilage degradation in experimentally induced OA. OA is characterized by hypertrophic differentiation of chondrocytes and matrix remodeling. Various signaling pathways including the WNT signaling pathway may trigger this induction of chondrocyte differentiation. Experiments investigating the effect of different WNT3a concentrations on WT and Sdc4 deficient chondrocytes have emphasized a complex dialogue between canonical and non-canonical WNT pathways. We hypothesize that Sdc4 controls the chondrocyte phenotype by specific modulation of WNT signaling pathways.

**Methods:** In vitro analyses were performed using neonatal wild type (wt) and Sdc4-/- chondrocytes, or blocking antibodies against Sdc4. The influence of WNT3a on glycosaminoglycan (GAG) production was analyzed using alcian blue staining of micromass cultures. Expression of marker genes (e.g. aggrecan, collagen2, MMP13) was measured by quantitative RT-PCR. Effects of WNT3a on canonical and non-canonical WNT signaling were analyzed using Western Blot and luciferase reporter assay (AP-1, NFAT, TCF/Lef). The influence of WNT3a on the remodeling of the ECM was investigated by electron microscopy. Basal calcium concentrations without and upon WNT3a stimulation were examined using the Fura-2 method. In vivo relevance was investigated upon induction of OA using the DMM model.

**Results:** Micromass cultures revealed a higher basal GAG production in Sdc4-/- chondrocytes. WNT3a stimulation led to a decrease in GAG production in wt cells, which was absent in Sdc4-/- chondrocytes. qRT-PCR showed a 10X higher basal production of aggrecan and collagen2 in Sdc4-/- chondrocytes. WNT3a increased the expression of both genes in Sdc4-/- chondrocytes, MMP13 was significantly less expressed in Sdc4-/- chondrocytes and, unlike in wt cells, was not upregulated upon WNT3a stimulation. Western blot showed that β-catenin is strongly reduced and not upregulated upon stimulation with WNT3a in Sdc4-/- chondrocytes. LRPF was less phosphorylated and TCFα of promoter was less activated upon WNT3a stimulation in Sdc4-/- chondrocytes. pCamKII was increased under basal conditions, but decreased upon WNT3a stimulation in Sdc4-/- cells. The same effects on canonical and non-canonical WNT signaling upon WNT stimulation were obtained by using a blocking anti-Sdc4 antibody. Upon WNT3a stimulation, Sdc4-/- cells displayed a finer, more condensed and disorganized ECM structure compared

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**2950**

**Synovial Macrophages Promote TGF-β Activation after Intra-Articular Injections of Oxidized LDL in Naïve Murine Knee Joints, Preventing Production of Pro-Inflammatory Factors (IL-1β, IL-6) and Promoting Chondroprotection.** Annelena Held, Richard Stange, Uwe Hansen, Lars Godmann, Jessica Bertrand, Thomas Pah, Giovanna Nalesso, Frank Echtenberger, Francesco Dell’Accio, Joanna Sherwood, William Harvey Research Institute, Barts and the London Queen Mary’s School of Medicine and Dentistry, London, United Kingdom.

**Background:** Macrophages regulate joint pathology during experimental osteoarthritis (OA). Blockade of synovial macrophage-depleted joints. NITEGE expression was markedly increased (fold increase 1.92) in the synovial-cartilage contact areas after oxLDL injection (p<0.05).

**Conclusion:** Synovial macrophages promote anabolic effects after ox-LDL injections in knee joints, supporting earlier studies which show increased ectopic bone formation during LDL-rich conditions in experimental osteoarthritis. In absence of synovial macrophages, however, ox-LDL induces cell influx, production of pro-inflammatory mediators and aggrecanase activity.

**Disclosure:** W. de Munter, None; P. M. van der Kraan, None; W. B. van den Berg, None; P. L. van Lent, None.

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**S1289**

**2030**

**Cartilage Degrading Enzymes, Cartilage Matrix Remodeling, and the Wnt-Frizzled Signaling Pathway.** Philip Balnave, Anna C. Lee, Ophelie Delacourt, Charles Kimberley Clarke, Annelena Held, Richard Stange, Uwe Hansen, Lars Godmann, Jessica Bertrand, Townes Pah, Giovanna Nalesso, Frank Echtenberger, Francesco Dell’Accio, Joanna Sherwood. William Harvey Research Institute, Barts and the London Queen Mary’s School of Medicine and Dentistry, London, United Kingdom.
to wt. Sdc4−/− chondrocytes had increased intracellular Ca2+ levels, which were reduced after 24h incubation with WNT3a. In vivo stainings confirmed in vitro results.

**Conclusion:** Sdc4 is a major regulator of the chondrocyte cellular response to WNT signalling through facilitating the induction of the canonical WNT signalling pathway. The blockade of Sdc4 protects from OA induced changes in chondrocyte phenotype by inhibiting WNT induced differentiation of chondrocytes.

**Disclosure:** C. K. Clarke, None; A. Held, None; R. Stange, None; U. Hansen, None; L. Godmann, None; J. Bertrand, None; T. Pap, None; G. Nalesso, None; F. Echtermeyer, None; F. Dell’Aciocco, None; J. Sherwood, None.

### 2952

**S100A9 Inhibitor Paquinimod (ABR-215757) reduces joint Destruction in Experimental Osteoarthritis and Blocks Activating Effects of S100A9 in OA Synovium.**

Peter L. van Lent1, Rik Schelbergen1, Arjen B. Blom1, Tomas Leandersson2, Helena Eriksson2 and Wim B. van den Berg3.

**Background/Purpose:** Synovial activation is present in more than 50% of osteoarthritic (OA) patients and it is thought to be involved in the development of OA pathology. Previously, we found that S100A8 and S100A9 are elevated in synovium of OA patients and that high S100A8/A9 serum levels correlate with 2-year progression of the disease. Furthermore, in experimental OA, S100A8/A9 proteins regulate cartilage degradation and synovial activation. Paquinimod is a quinoline-3-carboxamide compound with immune modulatory properties that is currently in clinical development for treatment of systemic sclerosis. It targets the carboxytail of the cytokine receptor-like Ig domain of the immune modulatory Tyro3, Axl, and MERTK (IIM) receptors (IIMRs). In this study we investigated the effect of paquinimod in two experimental osteoarthritis models differing in synovial activation and its effect on S100A9 stimulated OA synovium.

**Methods:** Collagenase induced OA (CIOA) was induced by two times intra-articular injection of 1U collagenase and DMM was induced by transection of the medial anterior meniscotibial ligament leading to destabilization of the medial meniscus (DM M), both in C57Bl16 mice. Paquinimod (3,75 mg/kg) was administered in the drinking water which was refreshed twice a week. Treatment started 4 days before induction of OA in both CIOA and DMM. Synovial thickening and cellularity was measured using an arbitrary score from 0–3. OA-like cartilage pathology was scored using a modified Prizker OARSI score. Osteophyte size was assessed by a blinded observer using imaging software. Human OA synovium was anonymously obtained from patients undergoing arthroplasty and stimulated with S100A9 and/or paquinimod. Proteins released by synovium were measured with Luminex.

**Results:** Paquinimod treatment of CIOA expressing high synovial activation resulted in significantly reduced synovial thickening (57%), osteophyte size at the medial femur (66%) and cruciate ligament formation (67%). Moreover, cartilage damage was reduced by paquinimod in CIOA at the medial tibia (47%) and femur (75%). In contrast, paquinimod did not reduce cartilage damage and reduced osteophyte size only slightly (only at the medial femur) in DMM, in which synovial activation is scant. In addition, human OA synovium comprising lining macrophages, was incubated with human S100A9 and/or paquinimod. S100A9 significantly upregulated pro-inflammatory IL-6, IL-8 and TNFα (9-fold, 12-fold and 20 fold increase respectively) and catabolic factors MMP1/1a, 3/1 (up to 2.5 fold). Adding paquinimod significantly inhibited S100A9-induced levels of IL-6 (35% reduction) and IL-8 (38% reduction) but not TNFα whereas MMP1 and MMP3 were reduced by 39% and 64% respectively.

**Conclusion:** Paquinimod reduces synovial activation, osteophyte formation and OA-like cartilage pathology in experimental OA with high synovial activation and ex vivo blocks pathological effects of S100A9 in OA synovium. Paquinimod could prove a very promising treatment for osteoarthritis patients expressing high synovial activation.

**Disclosure:** P. L. van Lent, None; R. Schelbergen, None; A. B. Blom, None; T. Leandersson, None; H. Eriksson, None; W. B. van den Berg, None.
The Impact of Northern European Ancestry and Susceptibility Loci on the Risk of Lupus Nephritis.


University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA; Johns Hopkins University School of Medicine, Baltimore, MD; Feinstein Institute for Medical Research, Manhasset, NY; Genentech, Inc., South San Francisco, CA; Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA; University of California, Davis, CA.

Background/Purpose: Lupus nephritis (LN) has a higher prevalence among African Americans, Hispanics, and Asians compared to Caucasians. Significant differences in SLE severity also exist within continental groups, with northern European genetic ancestry conferring protection against autoantibody production and renal disease, which we have previously shown to be independent of socioeconomic status (SES). The goal of our study was to test whether the effect of northern European ancestry is mediated by known SLE risk alleles or recently identified LN susceptibility loci.

Methods: We studied 1142 SLE patients from four independent case collections with genotype data obtained from a previous genome-wide association study (GWAS). A set of continental and intra-European ancestry informative markers (AIMs) was analyzed using the program STRUCTURE to define the percent European and northern European ancestry for each subject. Subjects with <90% European ancestry were excluded. Multivariate logistic regression of LN risk was performed including percent northern European and other covariates (Table 1). Susceptibility loci were incorporated as potential mediators of the effect of genetic ancestry on the risk of LN. Forty-nine independent SLE risk alleles and 12 renal GWAS SNPs were included in the model of LN risk. A polygenic risk score (PRS), a statistical method for calculating the effect of many common variants in aggregate, was generated from a random 2/3 of individuals using the program PLINK to select 12,935 SNPs with evidence of cumulative association with LN (p < 0.05).

Results: The overall rate of LN in the study population was 27.3%. A 25% increase in the proportion of northern European ancestry was associated with a 16% reduction in the odds of having renal disease, after adjustment for disease duration and gender (OR 0.84, 95% CI 0.72-0.99, p = 0.04). Two previously reported SLE susceptibility loci (BANK1, HLA-DR3) and 7 of 12 LN risk SNPs were significantly associated with LN in our dataset. Adjustment for all 9 putative LN susceptibility loci did not substantially alter the association between northern European ancestry and LN (Table 1). Exploratory analyses incorporating the PRS were underpowered in our study but suggested that a more comprehensive set of genetic variants, as captured by the PRS, may explain more of the effect of Northern European ancestry on the risk of LN.

Conclusion: Northern European ancestry has a significant protective effect for renal disease among SLE patients of European ancestry; this effect is not fully explained by known SLE risk alleles.
appears to be independent of currently known SLE risk alleles and LN susceptibility loci, but may be partially explained by a PRS.

Disclosure: S. French, None; K. E. Taylor, None; S. A. Chung, None; J. Nitham, None; M. Petri, None; P. K. Gregersen, None; W. Ortmann, Genentech Inc., 3; A. T. Lee, None; T. W. Behrens, Genentech Inc., 3; S. Manzi, None; F. Y. Demirci, None; M. I. Kanbour, None; R. G. Graham, Genentech Inc., 3; M. F. Seddin, None; L. A. Criswell, None.

2956

Identification of Autoimmune Functional Variants Under Positive Selection in the Gullah African American Population from South Carolina. Paula S. Ramos1, Satria Sajuthi2, Jasmin Divers2, Yiqi Huang2, Ume Nayak2, Wei-Min Chen2, Kelly J. Hunt2, Diane L. Kamen2, Gary S. Gilkeson3, Jyotika K. Fernandes4, Ida J. Spruill5, W. Timothy Garvey1, Michelé M. Sale1, and Carl D. Lange4. 1Medical University of South Carolina, Charleston, SC; 2Wake Forest School of Medicine, Winston-Salem, NC; 3University of Virginia, Charlottesville, VA; 4University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The reasons for the ethnic disparities in rheumatologic and autoimmune diseases (ADs) are largely unknown. We posit that population-specific selection influencing the allele frequencies at some loci contribute to ethnic disparities. Relative to other African Americans (AA), the Gullah population has lower European admixture and higher ancestral homogeneity from the Sierra Leone (SL) area in Far-West Africa. The shorter Gullah population has lower European admixture and higher ancestral contribute to ethnic disparities. Relative to other African-Americans (AA), the population-specific selection influencing the allele frequencies at some loci has the potential to elucidate AD risks in AA and help explain the ethnic disparity.

Methods: We computed the cross population extended haplotype homozygosity test (XP-EHH) to identify alleles with higher than expected frequency relative to their haplotype length in Gullah population controls (n=277) relative to SL population controls (n=400), to HapMap Phase II Africans (YRI, n = 203), and Caucasians (CEU; n=165). In total 679,513 SNPs met standard GWAS quality control criteria. Variants that met suggestive significance (XP-EHH > 4, P < E-04) were annotated and prioritized based on the potential impact of amino acid changes and regulatory functions using RegulomeDB and HaploReg, as well as overlap with immune/autoimmune-related genes and regions associated with ADs.

Results: Near the same number of loci showed suggestive evidence for selection between the Gullah and YRI (0.15%) of all SNPs, and Gullah and SL (0.14%), although only 106 SNPs in 12 regions showed evidence for selection in both comparisons. Fewer loci showed evidence for selection between Gullah and CEU (0.06%). This is reflected in the enrichment of different pathways in each comparison. Enhancer enrichment analysis of all suggestive SNPs revealed a significant enrichment of strongest enhancers in different pathways in each comparison. Enhancer enrichment analysis of all suggestive SNPs revealed a significant enrichment of strongest enhancers in different pathways in each comparison.

Conclusion: These results reveal several autoimmune-related genes harboring multiple SNPs with high regulatory scores based on the simultaneous presence of QTTLs, transcription factor binding and DNAse sites, including those showing evidence of selection between Gullah and YRI (CCR2, ADCY2, HLA, CD36, CAV1, GLG1, FXR2), Gullah and SL (CCR2, ADCY2), and Gullah and CEU (TET3).

2957

The Rheumatoid Arthritis -Risk Locus CCR6 and Its SNP-Dependent Response to Estrogen: A Possible Genomic Link Between Sex Hormones and the IL-17 Inflammatory Pathway. Ming-Fen Ho, None; R. M. Weinshilboum, None; L. Wang, None; T. Bongartz, None.

Background/Purpose: The CCR6-CCL20 mediated migration of Th17 cells to inflamed tissues may represent an important mechanism in the etiology of rheumatoid arthritis (RA). The CCR6 SNP rs3093023 is associated with RA disease risk. Variation in the CCR6 locus has been found to affect CCR6 expression and influence the IL17 serum concentration in RA patients (1). Importantly, an analysis of disease risk stratified by gender revealed opposing effects in Asian subjects: Specifically a CCR6SNP (rs3093024), which is in almost complete linkage disequilibrium with rs3093023, was associated with an increased risk of RA in women, but appeared to have a protective effect in men (2). We set out to determine whether variation in estrogen levels might influence the expression of CCR6 and other IL-17 pathway related genes. Furthermore, we aimed to clarify if such estrogen dependent regulation might be influenced by the presence of the variant CCR6genotype that is associated with RA disease risk in Europeans.

Methods: We genome-wide genotyped human lymphoblastoid cells using the Illumina 550K and 510S SNP beadchip and the Affymetrix SNP array 6.0. We then cultured eight LCLs homozygous for the wild-type (WT) SNP rs3093023 sequence and eight LCLs homozygous for the variant (V) allele with increasing concentrations of estradiol (E2). Expression of CCR6, CCL20, IL17A and IL17RA mRNA was measured by qPCR. We then performed siRNA knockdown experiments for CCR6 to explore the downstream effects. To predict putative estrogen receptor binding sites in the CCR6gene, we queried the TRANSFEC database. The functional relevance of putative binding sites was confirmed using ChIP assays.

Results: The basal expression levels of CCR6, CCL20, IL17A and IL17RA showed no differences when comparing cell lines with CCR6 WT versus V genotypes. Knockdown of CCR6 resulted in upregulation of CCL20 and IL-17A, but downregulation of IL-17RA expression. Treatment with E2 for 24 hours resulted in a significant increase in CCR6 expression in a dose-dependent manner, but only in cells with the V allele. CCL20, IL-17A and IL-17RA expression was also SNP-dependent in cells with the variant genotype. E2 treatment resulted in higher IL-17RA expression. Conversely, CCL20 and IL-17A expression decreased with estrogen treatment only in cells homozygous for the V allele. The TRANSFEC database predicted the presence of two estrogen response elements in the CCR6intronic region flanking the rs3093023 SNP. Chip assays demonstrated increased binding of estrogen receptor alpha when the V allele was present.

Conclusion: Our results indicate that a CCR6variant, which is associated with RA disease risk, can modulate the CCR6/CCL20/IL-17 axis in an estrogen-dependent manner. Enhanced binding of estrogen receptor alpha to the variant CCR6 genotype may contribute to the mechanism underlying this observation. Such a genomic link between variation in sex hormone levels and variation in cytokine/chemokine expression may provide new insights into the gender differences in RA prevalence and prognosis.

References:

Disclosure: M. F. Ho, None; R. M. Weinshilboum, None; L. Wang, None; T. Bongartz, None.
ments were defined by SNPs in proximity (−50 kb) to genes involved in 1. Urate transport: ABCG and SLC family members of urate-associated transporters and their direct connections in Inweb and String network databases\(^2\) (348 genes), 2. Urate metabolism: purine metabolism and glycolysis KEGG pathways (256 genes), 3. Immune-related: genes targeted by the Immunochip array (184 genes), 4. All other genomic regions, and 5. Intergenic regions. Polygenic scores based on GWAS P-value thresholds\(^3\) were calculated in Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) samples, with incident gout cases having met ACR criteria for diagnosis, and were tested in multivariate analysis with sex, age, BMI and a 31 SNP urate genetic risk score as covariates.

**Results:** Polygenic scores were significantly associated with gout in metabolic genes (n=797 SNPs with \(P_{\text{GWAS}} < 10^{-8}\); \(P = 0.005\)) and other genomic regions (n=570,599 SNPs with \(P_{\text{GWAS}} < 0.5\); \(P = 0.001\)), with similar results for association with serum urate (\(P = 0.0025\) and \(P = 0.007\) for metabolic and other genes respectively). The immune gene compartment was not significant in gout (\(P>0.12\)) but was significant outside of the defined compartments also contributing. Excluding known loci, we found no additional evidence for polygenic variation in urate transport or immune-related functions contributing to serum urate or gout. Genomic compartments defined on function can provide additional discoveries and further biological insights into the etiologies of urate and gout.

**Conclusion:** Our results demonstrate an important role for metabolism in both serum urate and risk of gout, with genes outside of the defined compartments also contributing. Excluding known loci, we found no additional evidence for polygenic variation in urate transport or immune-related functions contributing to serum urate or gout. Genomic compartments defined on function can provide additional discoveries and further biological insights into the etiologies of urate and gout.
Methods: The Health Professionals Follow-up Study (HPFS) and Nurses’ Health Study (NHS) have systematically collected a wide range of exposures and health outcome data, including incident cases of gout, regularly for several decades. We ascertained incident gout cases using the American College of Rheumatology survey criteria. Using GWAS data from the two cohorts (4223 men from the HPFS and 6850 women from the NHS), we calculated a weighted genetic risk score (GRS) based on GUGC urate loci (possible range 0 to 58). Cox proportional hazards models were used to examine the association of GRS with GUGC urate loci and the risk of incident gout in these cohorts separately and together.

Results: Over a total of 262,805 person years, we documented 1081 confirmed cases of incident gout (727 in the HPFS and 354 in the NHS). The GRS ranged from 12.2 to 44.5 among our study participants. Increasing GRS scores were associated with an increasing risk of incident gout in both cohorts (P for heterogeneity < 0.17), and the pooled relative risks (RRs) for incident gout according to increasing GRS categories were 0.34, 0.66, 1.00 (referent), 1.37, 2.01, and 3.48 (P trend < 0.001 (Table 1)). Our analyses for individual loci (Table 2) showed that SLC2A9, ABCG2, and GCKR were significantly associated with the risk of incident gout in each cohort as well as in the pooled cohort. TME171, SLC1A7, INHBC, VEGFA, and UBE2Q2 were moderately associated only in men (HPFS), and PRKAG2, B4GALT1, MAF, and HLF were modestly associated only in women (NHS). Heterogeneity between the sexes of these loci was significant for INHBC, PRKAG2, B4GALT1, and HLF.

Conclusion: These two large prospective cohort studies confirm that the urate GRS scores are strongly associated with the risk of incident cases of gout among men as well as among women. SLC2A9, ABCG2, and GCKR were most strongly associated with the risk of incident gout, and nine additional urate loci are more modestly associated with the risk as well.

Table 1. Relative risks (RRs) of Incident Gout According to Genetic Risk Score

<table>
<thead>
<tr>
<th>Genes</th>
<th>HPFS (Men)</th>
<th>NHS (Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk allele</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.76 (0.59–1.02)</td>
<td>0.73 (0.49–1.09)</td>
</tr>
<tr>
<td></td>
<td>1.25 (1.06–1.46)</td>
<td>1.04 (0.58–1.87)</td>
</tr>
<tr>
<td></td>
<td>0.82 (0.25–2.88)</td>
<td>0.80 (0.03–21.51)</td>
</tr>
<tr>
<td></td>
<td>0.50 (0.27–0.92)</td>
<td>0.63 (0.28–1.41)</td>
</tr>
<tr>
<td></td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
</tbody>
</table>

Table 2. RR of Incident Gout According to Individual Urate Loci (Limited to 12 Loci with Significance in at Least One or the Pooled Cohort)

<table>
<thead>
<tr>
<th>SNP Gene</th>
<th>Risk allele</th>
<th>HPFS (Men)</th>
<th>NHS (Women)</th>
<th>P</th>
<th>P pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2943466</td>
<td>SLC2A9</td>
<td>A</td>
<td>0.76 (0.59–1.02)</td>
<td>0.73 (0.49–1.09)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1250660</td>
<td>GCKR</td>
<td>T</td>
<td>1.25 (1.06–1.46)</td>
<td>1.04 (0.58–1.87)</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1394125</td>
<td>UBE2Q2</td>
<td>A</td>
<td>0.50 (0.27–0.92)</td>
<td>0.63 (0.28–1.41)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1766419</td>
<td>SLC1A7</td>
<td>T</td>
<td>0.82 (0.25–2.88)</td>
<td>0.80 (0.03–21.51)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Methods: Summary level statistics from the Kottgen et al. GWAS were used in collaboration with the Global Urate Genetics Consortium. The Genome-Wide Complex Trait Analysis (GCTA) package was used to test for association conditional on the lead single nucleotide polymorphism (SNP). A total of 9713 HapM ap2 genome-wide imputed genotypes from European participants of the Atherosclerosis Risk in Communities study were used as a reference. An independent effect at each locus was defined as an association signal, after conditional analysis, of P < 0.05 divided by the number of SNPs analyzed. Further rounds of analyses were conducted if SNPs remained significant after conditioning. The percent variance explained for each SNP was calculated by the formula b^2*(var(X)/var(Y)).

Conclusion: The independent effects provide evidence for multiple etiological variants at the serum urate loci in Europeans, emphasizing the complex genetic control of serum urate levels. These results are an important initial step in fine-mapping the causal variants. For example, one of the independent effects at SLC2A9 (rs3775948) was the lead SNP in a urine GWAS in East Asian individuals, indicating both shared and unique genetic effects between East Asians and Europeans. The use of multiple ancestral groups will be important in future fine-mapping.
Background/Purpose: Gout results from innate immune response to monosodium urate (MSU) crystals that form in the context of supersaturation of urate. Identification of genetic risk factors for hyperuricemia and the MSU immune response is therefore important for insight into the etiology of gout. Genome-wide association analyses have provided significant insights into the causes of hyperuricemia, however there are no confirmed loci for normouricemia. In addition, including MSU crystals. To replicate, we tested rs2149356 for association with gout in 2,501 European and Polynesian cases and 9,105 controls.

Methods: All gout cases were clinically ascertained according to the American Rheumatism Association criteria. European cases (n = 1614) were recruited from New Zealand (n = 647), by the Epiqgroup consortium within the American Crystal Network (n = 779) and by the Arthritis Genomics Recruitment Initiative in Australia (AGRA; n = 1188). European normouricemia (n = 8017) were recruited from NZ (n = 875) and sourced from the Atherosclerosis Risk in Communities (n = 4143) and Framingham Heart (n = 2999) studies. There were 872 New Zealand Māori and Pacific Island (Polynesian) cases and 1088 controls.

Genotyping of rs2149356 was done by Taqman in the New Zealand samples and imputed in A RIC and FH5 from a Affymetrix genome-wide data. Association analysis was done by STATA and adjusted by age, sex and (as appropriate) estimate of Polynesian ancestry.

Results: Using controls unstratified for urate status, there was no evidence for allelic or genotypic association in the European sample sets (Table). However the TT genotype was associated with gout in Polynesians (OR TT genotype = 0.68, P = 0.012). Comparison of cases to hyperuricemic controls revealed evidence for association with gout in Europeans (OR G allele = 1.26, P = 0.005; OR T allele = 1.63, P = 0.009), but weakened evidence for association in Polynesians (OR G allele = 0.88, P = 0.25; OR T genotype = 0.77, P = 0.21).

Conclusion: The previous report of association of TL4 with gout in Chinese 2 was replicated in Europeans with the T allele of rs2149356 conferring risk in both populations. Evidence for association was weaker in Polynesians, with the G-allele conferring risk. The strengthening of association in Europeans using hyperuricemic controls is consistent with a role for this locus in gouty inflammation in the presence of hyperuricemia. Subject to further replication, TL4 represents the first replicated non-urate serum genetic risk locus identified in gout, and provides support for a role of TL4 in the etiology of gout.


2594 Association Analysis of Apolipoprotein B and Very Low-Density Lipoprotein with Hyperuricemia and Gout. Humaira Rasheed1, Angela Hsu1, Nicola Dal'beth2, Lisa K. Stamp3, Sally McCormick1 and Tony R. Merriman1.

1University of Otago, Dunedin, New Zealand, 2University of Auckland, Auckland, New Zealand, 3University of Otago, Christchurch, New Zealand.

Background/Purpose: Gout results from innate immune response to monosodium urate (MSU) crystals deposited in joints. Increased very low-density lipoprotein (VLDL) has been associated with gout. Apolipoprotein B (apoB), present on VLDL, regulates neopterin response to MSU crystals. ApoB has been positively associated with gout and the apoB mRNA-editing gene, AICF, is associated with urate levels. However the relationship of apoB and VLDL with gout in the presence of hyperuricemia has not previously been tested. Therefore we tested the association of VLDL and apoB with gout in the presence of hyperuricemia (HU).

Methods: New Zealand European (n = 90) and Māori and Pacific Island (Polynesian) (n = 90) male gout case and control sample sets were divided into normouricemia (NU: serum urate <411 mmol/L), asymptomatic hyperuricemia (HU: serum urate =411 mmol/L) and gout groups. Gout was classified using the 1997 American Rheumatism Association criteria. Size exclusion chromatography and enzyme-linked immunosorbant assay were used to measure VLDL and apoB. Multivariable linear regression was used to assess the risk of gout and HU per unit change in VLDL and apoB.

Results: Increased levels of VLDL triglycerides (Tg) were observed in the gout sample set compared to NU and HU in European (P = 0.02 and 2×10−4, respectively) and Polynesian subjects (P = 0.042 and 0.019, respectively). This increase was driven by overproduction of VLDL particles in the European subjects and by the Tg-enrichment of existing VLDL particles in the Polynesian subjects. Each mmol/L increase in VLDL Tg was significantly associated with gout in the presence of HU in Europeans, with a similar trend
in Polynesians (OR = 6.82, P = 0.017 and 2.85, P = 0.066, respectively). Each 
μmol/L increase in ap08 was associated with a decreased risk of HU (OR = 0.47; P = 0.046) and, conversely, with increased risk of gout in the presence of HU (OR = 4.79; P = 0.005: Table 1) in combined sample set.

**Conclusion:** Increased VLDL Tg is associated with the risk of gout in the presence of HU. If genetic approaches indicate evidence for causality of VLDL in gout, this would provide further support for clinical trials examining the effects of fibrates as a treatment option in gout.

**Table 1:** A analysis of association of VLDL Tg and apo B associated traits with hypertriglyceridemia

<table>
<thead>
<tr>
<th>Association with VLDL Tg</th>
<th>Association with Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>VLDL Tg</td>
<td></td>
</tr>
<tr>
<td>Europese</td>
<td>3.51 [0.94–13.18]</td>
</tr>
<tr>
<td>Polynesians</td>
<td>1.05 [0.37–2.97]</td>
</tr>
<tr>
<td>Combined apo B</td>
<td>1.92 [0.95–3.86]</td>
</tr>
<tr>
<td>Total apo B</td>
<td>1.24 [0.32–4.87]</td>
</tr>
<tr>
<td>Polynesians</td>
<td>0.23 [0.04–1.34]</td>
</tr>
<tr>
<td>Combined</td>
<td>0.85 [0.37–1.97]</td>
</tr>
</tbody>
</table>

**Disclosure H. Raduced, None; A. Hsu, None; N. Dalbeth, None; L. K. Stamp, None; S. McCormick, None; T. R. Merriman, None.**

**ACR Concurrent Abstract Session**

**Pain: Basic and Clinical Aspects II/Orthopedics, Low Back Pain and Rehabilitation**

**Wednesday, November 19, 2014, 9:00 AM–10:30 AM**

**2966**

**Genome-Wide Association Analysis of Pain Reduction in Rheumatoid Arthritis Patients Treated with TNF Inhibitors.** M. A. van de Laar1, M. A. Umicevic-Mirkov2, Sophie B. Krintel3, Julia Johansen4, Corinne Michel-Richard5, Henrik Kalberg6, Hans Schefler7, Wieske Kiewit1, Maartje van de Laar1, Piet L. C. M. van Riel1, X. Mariette8, Saediddin Saevardsdottir9, Marieke J. H. Coenen1, Piet L. C. M. van Riel, J. H. Mariette, K. Etterw, S. Vermeulen8, I. Albers1. 1Radboud university medical center, Nijmegen, Netherlands, 2Copenhagen University Hospital, Glostrup, Glostrup, Denmark, 3University of Copenhagen, Frederiksberg, Denmark, 4Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France, 5Karolinska University Hospital, Stockholm, Sweden, 6University Twente & Medisch Spectrum Twente, Enschede, Netherlands, 7Paris-Sud University, Paris, France, 8Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, 9DANTIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark.

**Background/Purpose:** Gout is a common inflammatory arthropathy with a high prevalence in rheumatoid arthritis (RA) patients treated with TNF inhibitors (TNFi). Due to the high frequency of concomitant osteoarthritis (OA), therapeutic options are limited. We aimed to identify and replicate genetic factors predicting pain reduction upon TNFi treatment in patients with RA using genome-wide association approach.

**Methods:** We included 508 TNFi treated RA patients. Association analysis of change of visual analogue scale of pain (VAS-pain) after 14 weeks of treatment was performed on imputed genome-wide genotyping data under additive genetic model with adjustment for baseline VAS-pain. We also conducted a meta-analysis including 1287 RA patients. Gene-based analysis was performed using VEGAS.

**Results:** No findings reached the threshold for genome-wide significance (P-value<1×10^-8) in the discovery cohort. Meta-analysis revealed 213 SNPs suggestively associated (P<10^-4) with change in VAS-pain after fourteen weeks of TNFi treatment. The most significant SNP rs2295739 (p=2.21×10^-6), located ~35kb upstream from the KCNK19 gene. Which belongs to a family of genes involved in sensory perception. The top hit in the gene-based analysis was RET, known to regulate ion channels and receptors participating in detection and transduction of sensory stimuli. Besides Ret-deficient mice show elevated pain responses.

**Conclusion:** We have identified several suggestive genomic regions, further studies are required to validate if these regions play a role in pain reduction upon TNFi treatment.

**Disclosure:** M. A. van de Laar, None; M. A. Umicevic-Mirkov, None; S. B. Krintel, None; J. H. Mariette, None; S. Saevardsdottir, None; M. L. Hetland, None; S. Vermeulen, None; M. A. Albers, None; W. Kievit, None; P. L. C. M. van Riel, None; X. Mariette, None; S. Saevardsdottir, None; M. L. Hetland, None; S. Vermeulen, None; C. A. Albers, None.
Patient Reported Pain By the PainDetect Questionnaire Reveals Multimodal Elements to Pain Perception in Rheumatoid Arthritis. Saja Ahmed1, Tejal Magan2, Mário Vargas3, Abiola Harrison3 and Nidhi Sofat4. 1St George’s, University of London, London, United Kingdom, 2St George’s University of London, London, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory autoimmune condition typified by systemic inflammation targeted towards synovial joints. Inhibition of pro-inflammatory networks by disease-modifying anti-rheumatic drugs e.g. methotrexate and biologic therapies including TNFα inhibitors, often leads to suppression of disease activity. However, despite the era of widespread use of disease-modifying treatments, there remain significant groups of patients who continue to experience pain.

Methods: Our study formulated a pain assessment tool to be used in the arthritis clinic to assess feasibility of measurements including the visual analogue scale (VAS) for pain (range 0–100 mm) and painDETECT questionnaires (range 0–38) to evaluate neuropathic features of pain in people with established RA (n=100). Clinical measures of disease activity (DAS28), disease-modifying medication use, body mass index (BMI) and worst pain ever were also recorded. Continuous data was described and analysed using parametric statistics, with ANOVA and Chi-squared tests for groups with 3 or more categories.

Results: We found that participants with RA reported relatively high pain levels, despite widespread use of disease-modifying drugs (Table 1). The majority, 54%, reported ‘severe pain’ on the visual analogue scale (VAS), which identifies people with a VAS of ≥41–100 mm as having the highest severity of pain. The mean DAS28 in the group was 2.09 ± 0.96. The majority of subjects had duration of diagnosis greater than or equal to 5 years (84%), suggesting that pain was a persisting symptom despite sustained use of disease-modifying agents and a DAS28 score suggesting clinical remission. All participants evaluated had been stable on DMARD therapy for at least 3 months prior to completing the study and had not required a change in their treatment, or addition of corticosteroid therapy during that time. The majority of participants were being treated with disease-modifying drugs, including the commonest agent, methotrexate (82%). Using the painDETECT questionnaire, 67% of patients had unlikely neuropathic pain. A significantly high proportion of 28% subjects had possible neuropathic pain and 5% had features of likely neuropathic pain by painDETECT scoring. We found a positive correlation between VAS and painDETECT (r² = 0.757). Of note, the group who had likely or probable neuropathic pain also showed significantly increased pain perception by VAS (p < 0.01). Subjects who were clinically obese (BMI > 30) had statistically higher proportions of pain reporting (VAS 89.0 ± 0.7) compared with subjects who had a normal BMI (VAS 45.2 ± 21.8), p < 0.05.

Conclusion: Our findings suggest that multimodal features of pain perception exist in RA, including neuropathic and sensitisation elements, perhaps explaining why a subgroup of people with RA continue to experience ongoing pain, despite their apparent suppression of inflammation.

Disclosure: S. Ahmed, None; T. Magan, None; M. Vargas, None; A. Harrison, None; N. Sofat, None.

Improvement Following Total Knee Replacement (TKR) Surgery: Exploring Preoperative Symptoms and Change in Preoperative Symptoms. Ernest R. Vina1, Michael J. Hannon2 and C. Kent Kwoh3. 1University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, 2University of Pittsburgh School of Medicine, Pittsburgh, PA, 3University of Arizona, Tucson, AZ.

Background/Purpose: Few have examined the trajectories of preoperative health-related quality of life (HRQOL) measures in osteoarthritis (OA) patients who undergo TKR. Yet, the type and rate of preoperative decline may predict the outcomes of TKR. The objectives of the study are to determine whether changes in preoperative HRQOL measures are associated with improvement after TKR and to identify important predictors of clinically significant improvement.

Methods: Data from people who underwent TKR were obtained from the Osteoarthritis Initiative (OAI), a study which annually assessed participants. T0 was the assessment prior to TKR while T-1 was the assessment prior to that. T+2 was the second assessment after TKR. We compiled data on OA-related symptoms (i.e. pain/aching/stiffness most days of the month in the last year), the WOMAC, activities, and radiographic severity (i.e. Kelgren-Lawrence grade, KLG). We defined clinically significant improvement as improvement in WOMAC total score ≥ the minimal important difference (0.5 standard deviation of mean change in the study data) between T0 and T+2. After conducting bivariate tests for differences, logistic regression models were performed to evaluate the relationship between improvement and preoperative measures. Only variables associated with improvement at p ≤ 0.2 in a series of stepwise regressions were included.

Results: Our sample consists of 211 improved & 58 unimproved patients. Improved, compared to unimproved, patients had higher preoperative (T0) WOMAC pain (39.31 ± 17.86 vs. 22.73 ± 17.92, p < 0.001), disability (39.17 ± 15.08 vs. 18.23 ± 16.86, p < 0.001) and stiffness (46.45 ± 20.21 vs. 27.37 ± 20.47, p < 0.001) scores in the index knee (i.e. TKR knee). Those who had improvement were more likely to report OA-related symptoms in the index knee (96.68% vs. 77.59%, p < 0.001). They also had greater worsening of their WOMAC pain (9.65 ± 19.53 vs. 2.48 ± 13.19, p < 0.002), disability (9.87 ± 17.22 vs. 0.16 ± 13.38, p < 0.001) and stiffness (9.11 ± 23.23 vs. -0.24 ± 20.34, p = 0.009) scores from T-1 to T0 in the index knee.

Conclusion: Pain measures as predictors of improvement in our multivariate model included: Higher WOMAC disability (OR 1.09, 95% CI [1.05–1.13], p < 0.001), presence of OA-related symptoms in the index (OR 7.13, 95% CI [1.77–28.67], p = 0.006) but absence in the contralateral (OR 8.07, 95% CI [2.75–23.74], p < 0.001) knee, exposure to frequent knee bending (OR 3.01, 95% CI [1.02–8.87], p = 0.045), having a KLG of 4 (vs. 0, 1, 2 or 3) in the contralateral (OR 4.40, 95% CI [1.24–15.56], p = 0.022) and index knee (p = 0.124), and worse SF-12 Mental Health score (p = 0.209).

Disclosure: E. R. Vina, None; M. J. Hannon, None; C. K. Kwoh, None.

Mortality after Knee Replacement Surgery for Osteoarthritis in a Population-Based Propensity-Score Matched Cohort. Devyani Misra1, Tuhina Neogi1, Na Lu1, David T. Felson2, Thomas Einhorn1, Hyon Choi2, Jessica Maxwell3 and Yuqing Zhang4. 1Boston University School of Medicine, Boston, MA, 2Harvard Medical School, Boston, MA, 3Boston University, Boston, MA.

Background/Purpose: Knee replacement (KR) surgery for osteoarthritis (OA) provides improvement in symptoms and function. Whether these improvements translate into survival benefit has been unclear, likely related to selection of healthier patients for surgery, exclusion of the post-operative immune response, and inadequate length of follow-up in prior studies. The purpose of this study was to determine risk of mortality related to KR by comprehensive adjustment for confounders using a propensity-score (PS) matched cohort approach and long follow-up.

Methods: Participants ages 50–89 years with a diagnosis of knee OA (from Read Codes) were included from The Health Improvement Network....
(THIN), an electronic medical records database representative of the UK general population. High risk subjects who are less likely to be surgical candidates (BMI > 40, history of joint infection, high risk cancers (pancreatic, esophageal, gastric or other metastatic), end-stage renal disease on dialysis, use of nasal cannula oxygen, or DMARD therapy) were excluded. PS for KR was calculated using logistic regression with KR as the dependent variable and the confounders listed in the table as independent variables, that reflect indications for KR and risk for poor outcomes. One year cohort-accrual blocks were matched within each KR subject and a random date within the cohort accrual block for non-KR subjects, and continued until death or censoring. We examined the association of KR with mortality by calculating crude incidence rates (IR) and Hazard ratios (HR) using Cox proportional hazard regression. We also examined the association stratified by age category (<70 years, 70–80 years, 80+ years) and within percentile categories of the PS.

Results: There were 14,675 pairs of subjects with knee OA (mean age 71.8 years; mean BMI 29.0 kg/m²) in the PS-matched cohort. The follow-up years were 63,669 and 60,582 for matched KR and non-KR subjects, respectively. Overall there was a 31% lower risk of mortality among subjects with KR (HR 0.69, 95% CI 0.64–0.75). The lower risk remained in subjects <70 years but no such relation was noted in subjects ≥70 years (table). The crude IR for mortality among KR subjects decreased as PS percentile category increased, while no such trend was noted for the non-KR subjects. Mortality risk was lowest (HR 0.29, 95% CI 0.13–0.63) in the highest PS percentile (>98%) category (table).

Conclusion: We found KR to be protective for mortality risk among subjects <70 years and among those with the highest propensity for KR. Although a protective effect of KR cannot be ruled out, there likely remains confounding by indication despite comprehensive adjustment of covariates. Patients, physicians, and surgeons consider additional factors in performing KR that are not adequately captured within administrative databases.

Table: A association of Knee Replacement Surgery and Mortality Risk, stratified by age and by percentiles of propensity scores, in a propensity-score matched cohort of men and women with knee osteoarthritis.

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
<th>Non-KR Follow-up</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
<th>KR Follow-up</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>14675</td>
<td>1225</td>
<td>6538.3</td>
<td>0.030</td>
<td>2048</td>
<td>8082.7</td>
<td>0.027</td>
<td>0.64 (0.61–0.67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–80%</td>
<td>6538.3</td>
<td>0.030</td>
<td>0.64 (0.61–0.67)</td>
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<td>80–90%</td>
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<td>&gt;90%</td>
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Propensity-score percentile

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<tr>
<th>Score</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
<th>Non-KR Follow-up</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
<th>KR Follow-up</th>
<th>No. of Subjects</th>
<th>Death</th>
<th>IR Death</th>
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<td>&lt;70%</td>
<td>14675</td>
<td>1225</td>
<td>6538.3</td>
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<td>2048</td>
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<tr>
<td>70–80%</td>
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<td>0.030</td>
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Propensity-score percentile

Table 1. Incidence of heterotopic ossification

<table>
<thead>
<tr>
<th>Brooker Classification Criteria for</th>
<th>HO</th>
<th>N</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
<th>p-value (Fisher's Exact Test)</th>
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<tbody>
<tr>
<td>OA</td>
<td>N</td>
<td>341</td>
<td>62</td>
<td>59</td>
<td>18</td>
<td>4</td>
<td>484</td>
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<td>PsA</td>
<td>N</td>
<td>140</td>
<td>44</td>
<td>47</td>
<td>19</td>
<td>4</td>
<td>242</td>
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</table>

OA = Osteoarthritis; PsA = Psoriatic Arthritis

Discussion: M. Cedillo, None; A. Fein, None; S. M. Goodman, None; R. Zhu, None; M. P. Figgie, None; M. Alexiades, None; J. C. Burket, None; L. A. Mandl, None.

2971

Patient's Self-Monitoring Via Smartphone: The Compass Study Correlation Between Patient Self-Assessment of Rheumatoid Arthritis Disease Activity Via Smartphone Technology and Physicians' Validated Scores, Ruediger Mueller1, Ulrich Walker2, Diego Kyzurz3, Robert Theiler4, Adriaan Forster5, Fabiana Ganz6 and Patrick Dufner7. 1Kantonspital St. Gallen, St. Gallen, Switzerland, 2Department of Rheumatology, Basel University, Basel, Switzerland, 3Universitats Hospital, Basel, Switzerland, 4Tirrelli spital, Zurich, Switzerland, 5Spital Thurgau AG, Diessenhofen, Switzerland, 6Abov not, Baar, Switzerland.

Background/Purpose: In clinical practice, patients with RA are usually seen every 3 to 6 months1. Although desirable, monthly visits with assessments of disease activity are often not possible due to limited physician resources2. However, patients increasingly wish to be actively involved in treatment decisions. Therefore, the development of an internet-based tool for disease activity score assessments by patients could represent an innovative solution. The CoMPASS study aims to demonstrate a correlation between the patient assessments of RA disease activity via smartphone and the disease activity done by the physician using traditional scores.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Clinical Aspects VII: New Aspects of Monitoring Disease Wednesday, November 19, 2014, 9:00 AM–10:30 AM

S1298
Methods: Adult RA patients under current non-intravenous DMARD treatment were included in the prospective, single-arm, multicentre study. Patients were equipped with smartphones and educated to use a web application (WebApp) for self-assessment. Patients were assessed clinically by the treating physician at baseline. The assessment included joint counts, global assessment, laboratory values, along with simultaneous WebApp questionnaires (RAPID3/4) that were filled in by the patient. During the subsequent 3 months, patients were asked to fill in the WebApp questionnaire at least once a week. Descriptive statistics for RA disease activity according to the WebApp and rheumatologist evaluation at the baseline visit were analysed with the Pearson Correlation. Sensitivity analysis was performed.

Results: Ninety patients were recruited in five Swiss clinics (mean: SD); RA duration: 7.1 years (8.6); age: 54.7 years (13.5); 60% male. The data showed a strong correlation between patient and rheumatologist assessment of disease activity when comparing RAPID3 with DAS44 at baseline (Fig 1, R = 0.60; 95% CI 0.43 - 0.73), CDAI (R = 0.53; 95% CI 0.34-0.68) and SDAI (R = 0.49; 95% CI 0.28 - 0.65). The sensitivity analysis demonstrated that this correlation was independent of disease characteristics, treatment type, demographics, and centre effects, as well as unaffected by a delay of the smartphone data entries up to 7 days after baseline assessment by the rheumatologist. A similar correlation was seen for RAPID4 and DAS44 (R = 0.61; 95% CI 0.45 - 0.74), CDAI (R = 0.55; 95% CI 0.37 - 0.70) and SDAI (R = 0.50; 95% CI 0.30 - 0.66).

Conclusion: In this multicentre study patients’ self-assessment of disease activity (RAPID3 and 4) correlated strongly with that of rheumatologists (DAS44, CDAI, SDAI), indicating that patients are able to self-assess their disease activity. This provides a rationale to further explore the use of smartphone technology for tight disease monitoring in order to help the rheumatologist to optimize RA management. Whether or not the use of a WebApp for self-assessment will lead to better treatment outcomes will have to be shown in future studies.

Figure 1: Pearson Correlation at Baseline - RAPID3 and DAS44 at baseline as primary endpoint.

Disclosure: R. Winchester, None; J. T. Giles, None; S. Nativ, None; H. Z. Zhang, None; K. Downner, None; J. Bathon, None.

2972

Elevations of Certain Memory-Effecter T Cell and Inflammatory Monocyte Subpopulations in Rheumatoid Arthritis Are Associated with the Presence of Subclinical Coronary Artery Atherosclerosis. Robert Winch-ester, Jon T. Giles, Simona Nativ, Hui-Zhu Zhang, Kendall Downer and Joan Balthazard Columbia University, New York, NY, “Morristown Medical Center, Morristown, NJ.

Background/Purpose: Factors that identify cardiovascular disease (CVD) fully in RA are lacking. Peripheral blood mononuclear cell (PBMC) subsets in RA patients differ markedly, on average, from non-RA controls with respect to memory T cell subset differentiation to memory effector status and in the degree of circulating PBMCs reflecting differentiation to memory effector status/acquisition of NK receptors and higher levels of intermediate (inflammatory) monocytes. We hypothesized that elevations in these subpopulations would distinguish those with subclinical atherosclerosis.

Methods: Patients with RA and no clinical CVD underwent cardiac computed tomography (CT). Coronary arterial calcium (CAC) was quantified by the Agatston method. PBMC subsets were assessed by multiparameter flow cytometry. Multivariable linear and logistic regression were used to assess the associations between PBMC subpopulations and CAC, adjusting for relevant confounders associated both with PBMC subsets of interest and CAC. The area under the receiver operator curve (AUC) was used to estimate the contribution of covariates on the prediction of any CAC.

Results: 72 RA patients [mean age 54±14 years; 64% female; shared epitope positive 64%, median RA duration 6.6 years; median DAS28-3.9; current biologic use in 31%] were studied. Any CAC [CAC >0] was observed in 34%. In univariate analyses, compared with patients with no CAC, those with CAC had significantly higher percentages of circulating CD4 T cell subsets denoting activation (CD4+HLA-DR+, CD4+CD28+HLA-DR-), differentiation to memory effector (CD4+CD28+HLA-DR+CD4+CD56+CD57+), and acquisition of NK receptors (CD4+CD56+CD57+) and similar increases of analogous CD8 T cell subsets, along with increases in the proportion of intermediate CD14+CD16 monocytes. The CD4 and CD8 subsets were highly correlated, while the CD14+CD16+ monocyte subset was independent of the CD4 and CD8 subsets. In multivariable models including all non-collinear PBMC subsets of interest, only levels of CD4+CD56+CD57+ T cells and CD14+CD16+ monocytes remained significantly associated with the presence of CAC after adjusting for relevant RA and CVD risk factors (Figure). CRP, serum IL-6 and DA528 were not associated with CAC. The AUC for any CAC for the model containing only the two PBMC subsets of interest was 0.76 (95% CI: 0.64 - 0.87), this increased to 0.89 (95% CI: 0.82 - 0.96) with the addition of age and systolic blood pressure to the model. Neither PBMC subset of interest was associated with the extent of CAC within those with a positive CAC score.

Conclusion: Subclinical atherosclerosis was robustly associated with levels of circulating PBMCs reflecting differentiation to memory effector status/acquisition of NK receptors and higher levels of intermediate (inflammatory) monocytes, independent of demographics, CVD risk factors, and, importantly, RA disease activity and severity. These factors may account for a portion of the unexplained contributors to enhanced atherogenesis in RA.

Disclosure: R. Winchester, None; J. T. Giles, None; S. Nativ, None; H. Z. Zhang, None; K. Downner, None; J. Bathon, None.

2973

The Multi-Biomarker Disease Activity Score As a Predictor of Radiographic Progression in a Registry of Patients with Rheumatoid Arthritis. Eric H. Sasso1, George Wu2, CC Hwang3, Michael E. Weinblatt2, Nancy A. Shadick2, Claire Alexander1 and Oscar Segurado1. 1Crescendo Bioscience Inc., South San Francisco, CA, 2Brigham and Women’s Hospital, Boston, MA.

Background/Purpose: This study evaluated the association between baseline disease activity, as assessed with the multi-biomarker disease activity (M BDA) blood test, CRP or clinical measures, and the rate of radiographic progression over 2 years for patients with rheumatoid arthritis (RA) receiving stable therapy in the Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS) Registry.

Methods: M BDA scores, CRP, DAS28-CRP, CDAI, RAPID3, and radiographic progression were analyzed at baseline (defined as the initial visit in the BRASS registry), for 143 patients with RA who had received a stable treatment, i.e., with no addition or removal of DMARDs and irrespective of dosing, over 2 years. Radiographs of hands and wrists only, taken within 3 months of baseline in BRASS and 2 years later, were evaluated to determine the change per year in total Sharp score (ΔTSS). Radiographic progression (RP) was defined as ΔTSS > 3 per year over 2 years. Predictive performance was assessed using AUROC. Associations with RP were evaluated using univariate and multivariate logistic regression adjusted for potential founders.

Results: For 143 patients, mean age and disease duration were 59 and 18 years, respectively, with 84% female, 80% seropositive (RF+ and/or anti-CCP+), and 52% receiving MTX/non-biologic DMARD monotherapy, 19% a TNF inhibitor alone, 27% both in combination, and 2% not on any DMARD therapy. Mean baseline values were MBDA score = 39, CRP = 0.86 mg/dL.
DAS28-CRP = 4.1, CDAI = 24.8, RAPID3 = 8.1 and TSS = 6.8. RP was observed in 18% (26/143) of patients. Better predictive accuracy for RP was observed for baseline MBD A score (AUROC = 0.75), compared with baseline clinical CRP (AUROC = 0.71), DAS28-CRP (AUROC = 0.62), CDAI (AUROC = 0.50) or RAPID3 (AUROC = 0.50). Adjusting for BMI and baseline TSS, the significant independent predictors for RP were MBD A score (OR 0.99, 95% CI 1.54–3.6, r = 0.28–0.35), DAS28 (AUROC = 0.71, 95% CI 1.46–3.62), and DAS28-CRP (AUROC = 0.74, 95% CI 1.04–3.94), but not DAS2 (OR = 0.46, 95% CI 0.2–2.41) and RAPID3 (OR = 0.49, 95% CI 0.61–3.55). For patients with low CRP (≤1 mg/dL), at baseline, RP was observed in 34.8% (8/23) with high MBD A score (>44) versus 8.1% (7/86) with low/moderate MBD A score (<44) (p = 0.003).

Conclusion: Baseline MBD A score was a better predictor of radiographic progression over 2 years than CRP, DAS28-CRP, CDAI or RAPID3 in patients with RA on stable therapy from the BRAS5 registry.


2974 Multi-Biomarker Disease Activity Score Is Associated with Power Doppler Ultrasound in Patients with Rheumatoid Arthritis in Low Disease Activity State.

M argaret H. Ma,1, Toby Garrood,1, Wanying Li,1, Nadine A. Defranoux,2, Gabrielle H. Kingsley,1, Andrew P. Cope1 and David L. Scott1.

1King’s College Hospital, London, United Kingdom, 2Guy’s and St. Thomas’ Foundation Hospital NHS Trust, London, United Kingdom, 3Crescendo Bioscience Inc., South San Francisco, CA, 4King’s College London, London, United Kingdom, 5King’s College London, Department of Rheumatology, London, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) patients increasingly achieve clinical remission with intensive treatment regimens. However, ultrasound (US) subclinical synovitis has been reported in remission states. The multi-biomarker disease activity (MBDA) blood test assesses overall RA disease activity.

The purpose of this study was to evaluate associations between US signals, MBD A score and its component biomarkers in the REMIRA cohort, a 1-year prospective observational study of patients with RA in low disease activity.

Methods: We studied 95 patients with RA on stable therapy for ≥6 months with DAS28 = 3.2 for ≥1 month. Clinical measurements and serum samples were collected every 3 months for 1 year and US were conducted at baseline (BL) and 1 year. MBD A scores (range 1–100) were calculated from the serum concentrations of VCAM-1, EGF, VEGF-A, IL-6, TNF-R1, YKL-40, MMP-1, MMP-3, IL-1, leptin, resistin, SAA and CRP using the validated Vectra® DA algorithm. MBD A disease activity thresholds have been defined as remission (≤2.6), low (2.6–29), moderate (30–44), and high (>44). Power doppler (PD) and synovial hypertrophy (SH) of bilateral MCP joints and wrists were assessed by the same sonographer on the same machine and with MCP and PIP joints rarely involved (both 2% respectively). A higher frequency of signal, no intra-articular flow to 3+ (44) was counted. Of the 101 patients included, median (IQR) age was 54 (48, 63) years old. Clinical characteristics such as age, sex and seropositivity were observed. Patients with low disease activity had high PDUS-DAS28 (p = 0.001), ESR (p = 0.002) and were more likely to receive combination triple therapy (DMARDs) (p = 0.008). Residual large joint involvement was significantly associated with mHAQ > 0.5 (p = 0.03), lower SF12 physical component scores (p = 0.02) and higher RAID score (p = 0.001).

Conclusion: Ultrasound PD and SH signals could be detected in most RA patients of the REMIRA cohort. After applying a modified, more stringent, scoring system, 21% to 31% had detectable US signals. We have shown, for the first time, significant correlations with PD and mPD scores for MBD A scores and some of its component biomarkers. Correlations were also found with DAS28 and SJC28. Remission by MBD A score was significantly associated with mPD = 0. These results suggest that MBD A score detect low grade inflammation and subclinical synovitis in patients with RA in clinical remission or low disease activity.

Disclosure M. H. M. None; T. Garrood, None; W. Li, None; A. Cope, None; D. L. Scott, None.

2975 Residual Large Joint Synovitis By Power Doppler Ultrasound Is Associated with Higher Disease Activity and Significant Impact of Disease in Multi-Ethnic Asian Patients with Established Rheumatoid Arthritis.

Y. Xiao Guo1, Manjari Lahiri2 and Peter Chevron1.

1Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, 2Division of Rheumatology, National University Hospital, Singapore, Singapore.

Background/Purpose: Regular monitoring of disease activity with appropriate modification of disease-modifying anti-rheumatic drug (DMARD) therapy results in improved radiographic and functional outcomes in patients with rheumatoid arthritis (RA). Large joint involvement has been shown to impact significantly on both disease activity and disability. Power Doppler ultrasound (PDUS) can effectively detect subclinical active synovitis not appreciated by clinical examination. The objective is to evaluate the presence of residual large joint disease in established RA patients in a multi-ethnic Asian cohort using PDUS as the reference standard, and whether there is increased impact and disability.

Methods: Patients with established RA (ACR 1987 criteria) and stable disease were recruited as part of a randomized controlled single centre study, evaluating the use of ultrasonography feedback as training tool for patient self-assessment of synovitis. At baseline, 28 joints (2 shoulders, 2 elbows, 2 wrists, 10 MCP, 10 PIP, 2 knees) of each patient were assessed for synovitis in B-mode (from 0 = absence of synovial thickening to 3 = marked synovial thickening) and PDUS (from 0 = absence of signal, no intra-articular flow to 3 = marked signal in more than half of the synovial area). Semi-quantitative grade ≥1 on PDUS was considered as active synovitis. Patients with residual large joint disease (shoulders, elbows, knees) on PDUS were evaluated for differences in baseline demographics, disease activity, physical function (modified Health Assessment Questionnaire, mHAQ) and SF12-physical component score) and impact of disease (Rheumatoid Arthritis Impact of Disease Score, RAID) with patients that did not have large joint involvement. Measures of association were evaluated using logistic regression.

Results: Of the 101 patients included, median (IQR) age was 54 (48, 63) years old. Clinical characteristics such as age, sex and seropositivity were observed. Patients with low disease activity had high PDUS-DAS28 (p < 0.001), ESR (p = 0.002) and were more likely to receive combination triple therapy (DMARDs) (p = 0.008). Residual large joint involvement was significantly associated with mHAQ > 0.5 (p = 0.03), lower SF12 physical component scores (p = 0.02) and higher RAID score (p = 0.001).

Conclusion: Multi-ethnic Asian RA patients with relatively stable established disease have a high proportion of residual PDUS large joint activity that significantly impacts on patients. Physicians should aggressively treat this subset of patients with either systemic/local therapies to prevent further disability.

Disclosure Y. X. Guo, None; M. Lahiri, None; P. Cheung, None.
Lung Ultrasonography for Interstitial Lung Disease in Rheumatoid Arthritis. Comparison with Usual Detection Algorithms in Clinical Practice. Marco Antivallie, Michele Chevallard, Michele Battelino, Maria Chiara Ditto, Valentina Varisco, Federica Rigamonti, Alessandra Mutili, Fabiola Atzeni, Alberto Batticciotto and Piercarlo Sarzi-Puttini. L. Sacco University Hospital, Milan, Italy.

Background/Purpose: Interstitial lung disease (RA-ILD) is one of the most serious extrarticular complications of rheumatoid arthritis (RA). Presently, it is not clear which is the best strategy for the detection of RA-ILD. We have previously reported on the feasibility and accuracy of lung ultrasound (LUS) in the detection of RA-ILD (1). Aim of the present study was to assess the performance of LUS in the detection of RA-ILD in clinical practice, and to compare its accuracy with the detection algorithms usually adopted.

Methods: 147 unselected RA patients (114 F and 33 M) were studied. In all patients, LUS was performed as previously described (1) by an expert physician (MC), blinded to clinical and HRCT data, using a standard commercially available US equipment (Esaote MyLabfive) with a 7.5–12 MHz probe. By LUS, RA-ILD was defined by a B-lines score >10. The results of the LUS study were compared to clinical, pulmonary function tests, chest X-ray, and lung CT (HRCT) data, as available from clinical records. Four clinical algorithms (ALG) were identified: ALG 1: presence of dyspnea (NYHA class >2), fever and bibasilar crackles; ALG 2: as ALG 1 + FVC < 80%; ALG 3: as ALG 1 + DLCO < 80%; ALG 4: as ALG 1 + evidence of ILD at chest X-ray. Sensitivity, specificity, and predictive values of LUS and clinical algorithms with reference to HRCT were calculated, and compared by McNemar test.

Results: RA-ILD was detected by LUS in 41/146 (28.1%) patients. Clinical data, FVC, DLCO, X-ray, and CT were available in 146(100%), 63(43%), 61(42%), 102(70%), and 67(46%) cases respectively. LUS showed a significantly higher accuracy in the detection of RA-ILD than clinical algorithms (Table 1). 33/64 (52%) asymptomatic patients, and 31/82 (38%) patients with clinical suspicion of RA-ILD, were not further evaluated by neither PFTs nor by HRCT. Overall, LUS detected unsuspected signs of RA-ILD in 9/146(6%) patients (Fig 1).

Conclusion: LUS is more accurate than usual clinical algorithms in the evaluation of RA-ILD, and allows the detection of a substantial number of unsuspected cases.

Table 1 - Sensitivity, specificity, and predictive power of LUS and clinical algorithms in the detection of RA-ILD. HRCT is the gold standard.

<table>
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<tr>
<th>LUS</th>
<th>ALG 1</th>
<th>ALG 2</th>
<th>ALG 3</th>
<th>ALG 4</th>
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</thead>
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<tr>
<td>Sensitivity (%)</td>
<td>87.0 (79.6–93.6)</td>
<td>78.1 (62.0–92.8)</td>
<td>9.1 (3.3–22.1)</td>
<td>7.5 (2.9–42.7)</td>
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<tr>
<td>Specificity (%)</td>
<td>72.7 (63.3–82.4)</td>
<td>43.2 (31.3–55.8)</td>
<td>58.6 (48.4–68.8)</td>
<td>53.5 (41.7–65.1)</td>
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<tr>
<td>PPV % (IC 95%)</td>
<td>41.9 (30.1–54.5)</td>
<td>66.7 (51.1–79.4)</td>
<td>45.5 (31.0–60.7)</td>
<td>62.5 (45.8–76.8)</td>
</tr>
<tr>
<td>NPV % (IC 95%)</td>
<td>62.5 (49.8–73.8)</td>
<td>41.9 (30.1–54.5)</td>
<td>66.7 (51.1–79.4)</td>
<td>45.5 (31.0–60.7)</td>
</tr>
</tbody>
</table>

McNemar test * = p<0.05 by the comparison of LUS with clinical algorithms.

Fig. 1: LUS RA-ILD in the population (LUS+). Orange-filled boxes show LUS-positive patients which were unsuspected on clinical ground.

References:

Disclosure: M. Antivallie, None; M. Chevallard, None; M. Battelino, None; M. Ditto, None; V. Varisco, None; F. Rigamonti, None; A. Mutti, None; F. Atzeni, None; A. Batticciotto, None; P. Sarzi-Puttini, None.

ACR Concurrent Abstract Session
Sjögren’s Syndrome: November 12, 2014; 9:00 AM–10:30 AM

Distinct Serum Protein Signature and Novel Biomarkers of primary Sjögren’s Syndrome Revealed by comprehensive High-Throughput Proteomic Analysis. A yumi Nishikawa1, Katsuya Suzuki2, Yoshiaki Kassai2, Y. yumi Got01, Takahiro Miyazi2, Maiko Takiguchi2, Masaru Takeshita1, Atsuko Murota3, Rimppei Morita3, Akihiko Yoshimura2, and Tsutomu Takeuchi21. Keio University School of Medicine, Tokyo, Japan, 2Takeda Pharmaceutical Company Limited, Kanagawa, Japan, 3Takeda Pharmaceutical Company Limited, Tokyo, Japan, *Department of Medical and Immunology, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The EULAR SS Disease Activity Index (ESSDAI) is currently used as an objective evaluation method of clinical disease activity in clinical research into primary Sjögren’s syndrome (pSS). This comprehensive indicator reflects patient signs and symptoms and organ involvement. However, a useful substitute serum biomarker of disease activity has not been established. Although several proteomic investigations of small and large salivary and lachrymal glands have been recently reported, information on serum protein is insufficient. Here, we aimed to reveal a distinct serum protein signature of pSS and identify novel biomarkers of disease activity.

Methods: We studied 90 serum samples from 30 pSS patients, 30 untreated rheumatoid arthritis (RA) patients as non-SS autoimmune disease controls, and 30 healthy control (HC) subjects. 1128 serum proteins, including inflammatory cytokines and chemokines, were quantitatively measured by comprehensive high-throughput proteomics assay using nuclear acid aptamers (SOMAscan Assay; Somalogic Inc, CO, USA). Associations between serum protein concentrations, clinical indicators and laboratory test results were statistically analyzed.

Results: A total of 58 proteins for statistical reasons, 1100 of 1128 proteins in 90 subjects were analyzed. We first screened differentially up- and down-regulated proteins among the three groups, by which 195 proteins, including some overlap (83; pSS vs HC, 124; RA vs HC, 81; pSS vs RA), were statistically extracted (p<0.05 in the t-test and U-test, and fold change ≥ 1.2 or ≤ 0.83). Sixty proteins were up-regulated in pSS compared with HC, including BAPF (pSS patients/healthy control subjects: 9.4-fold), TAL (1.82-fold), VWF (1.57-fold), p2-microglobulin (1.47-fold), while 25 were down-regulated, including Immunoglobulin (lg) D (0.21-fold), CTAP-III (0.79-fold), and GP1% (0.83-fold). Enrichment analysis for characterization of up-regulated genes identified these as cytokines and chemokines including TNF-associated molecules and coagulation factors, indicating a serum protein signature in pSS. Multivariate analysis of these 60 proteins and ESSDAI identified 15 proteins with a statistically positive correlation, including TNF-associated molecules (BAPF, sCD163, TRAIL-R4 and others), LAG-3, p2-microglobulin, and others.

Conclusion: This comprehensive proteomics analysis highlighted a dysregulated immunity and coagulation signature in patients with pSS. Fifteen up-regulated proteins were found to be correlated with disease activity. These proteins are candidate serum biomarkers for use in the clinical prediction of disease activity of pSS.


None; None; None; None; None; None; None; None; None; None.
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Characterization of the Sjögren’s Syndrome Intergenic Non-Coding RNA 1 (SSINCR1). John A. Ice1, He Li2, Indra Adrianto3, Mikhail G. Dzomorov4, A Astrid Rasmussen5, Graham B. Wiley6, Jennifer A. Kelly1, Kimberly S. Hefer7, Donald U. Stone1, Raj Gopalakrishnan8, David R. Stone9, Young Powers Thompson2, Juan-Matias Anaya4, Swamy Venuturupalli6, Barbara M. Segal7, Nelson L. Rodus8, Lida Radfar9, Michael H. Weisman10, Judith A. James1, Courtney G. Montgomery11, R. Hal Scofield12, Patrick M. Gaffney7, Linda F. Thompson1, A. Darise Farris10, Susan Kovats5, Jonathan D. Wren1, Kathy L. Silvis1, and Christopher J. Lessard1. 1Oklahoma Medical Research Foundation, Oklahoma City, OK, 2Hefner Eye Care and Optical Center, Oklahoma City, OK, 3University of Oklahoma Health Sciences Center, Oklahoma City, OK, 4University of Minnesota, Minneapolis, MN, 5Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogota, Colombia, 6Cedars-Sinaí Medical Center, West Hollywood, CA, 7Hennepin County Medical Center, Minneapolis, MN, 8Cedars-Sinaí Medical Center, Los Angeles, CA, 9US Department of Veterans Affairs Medical Center, Oklahoma City, OK, 10Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Sjogren’s syndrome (SS) is a common autoimmune disorder characterized by immune-mediated exocrine gland destruction and systemic inflammatory responses that contribute to clinical heterogeneity. Widespread dysregulation of transcribed RNAs in SS, including coding and non-coding elements, has been identified, but the complex regulatory mechanisms governing these responses are poorly understood. We performed an RNA-sequencing (RNA-seq) study that identified over 2,600 differentially expressed (DE) transcripts associated with SS, including 969 long non-coding RNAs (lncRNAs). This study sought to validate, replicate, and functionally characterize one upregulated IncRNA mapped to chromosome 2p25.1, SSINCR1, to better understand its role in SS pathogenesis.

Methods: Whole blood RNA from 27 healthy controls and 57 SS patients was sequenced, and 2,632 statistically significant DE transcripts were identified. Technical validation and replication of SSINCR1 upregulation was assessed by qRT-PCR in an independent set of 36 SS patients and 21 controls. Bioinformatic analyses using GAMMA-seq and the IncRNA database were performed to identify co-expression patterns of SSINCR1 with other coding and non-coding transcripts and to identify candidate protein binding partners. To determine cellular expression patterns of SSINCR1, we employed fluorescence-assisted cell sorting (FACS) staining for 10 distinct immune cell subsets in a healthy control followed by RNA isolation and assessed SSINCR1 expression by qRT-PCR. Statistical comparisons were made using t-tests and Pearson correlations.

Results: RNA-seq showed significant upregulation of SSINCR1 when comparing healthy controls and SS patients (P_value=3.69×10^-5; Fold Change=-2.4). Technical validation by qRT-PCR using the RNA-seq cDNA library confirmed this finding (P=0.0096), and correlation with RNA-seq results was observed (r=0.869). Transcript expression in an independent sample set replicated and confirmed SSINCR1 upregulation (P=0.0183). Co-expression patterns by GAMMA-seq showed T, NK, and dendritic cell activation, development, and proliferation, and assessment of SSINCR1 using IncRNA tor suggested protein binding with cyclin T1 and FIP1L1. FACS analysis showed that SSINCR1 expression levels were highest in the CD3+CD56+ compartment (containing NK cells; relative units [RU]=8.25), followed by CD8+ T cells (RU=3.34), CD56+ NK cells (RU=2.08), CD56hi NK cells (RU=0.83), and CD4+ T cells (RU=0.81). Expression was not detected in CD14+ and CD1c+CD1c+ myeloid DCs, monocytes, B cells, or pDCs.

Conclusion: We have identified, technically validated, and independently replicated the upregulation of a novel SS IncRNA, SSINCR1. We show that transcript expression is highly enriched in CD4+ and CD8+ T cells, NK cells, and NK cells. Ongoing studies are assessing potential protein binding partners and SSINCR1 expression in refined T and NK subsets and in expanded groups of affected and healthy individuals to determine subset-specific DE. This study establishes SSINCR1 as the first IncRNA associated with SS and lays the groundwork for further functional characterization in the pathogenesis of this complex disorder.

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Nucleic Acid Sensing Receptors TL7R, RIG-I and MDA5 Collaborate in Driving the Systemic IFN Signature and Amplify the Pathogenic Loop: Potential New Targets for Therapy in Primary Sjögren’s Syndrome. Naomi I. Maria1, Cornelia G. van Helden-Meeuwsen2, Eline C. Steenwijk3, Arne S. J. Ijms4, Wouter Beumer5, Zana Brkic5, Virgil A. Dalm4, Paul L. van Dael6, Pi M. Martin van Hagen6, Peter J. van der Spek6, Hemmo A. Drexhage6, and Marjan A. Versnel7. 1Erasmus Medical Center, Immunology, Rotterdam, Netherlands, 2Erasmus Medical Center, Bioinformatics, Rotterdam, Netherlands.

Background/ Purpose: Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disease characterized by autoantibodies targeting RNA-associated antigens, anti-SSA/SSB. The IFN signature is present in over 50% of pSS patients, and is associated with higher disease-activity and autoimmune presence. Endosomal Toll-like receptor-like, RLR7 and TL9, are crucial for both the generation of auto-antibodies by B-cells and immune-complex-mediated production by plasmacytoid dendritic cells (pDCs) in autoimmunity. Recently opposing effects were described for RLR7 and TL9 in murine lupus-molds, where TL9-deletion limited autoimmunity and TL9-deletion paradoxically exacerbated disease. Interestingly, we recently found the TL9-pathway upregulated in IFN-positive pDCs of pSS patients, whereas TL9 was not. Here we set out to further investigate this imbalanced endosomal TL9-signaling in IFN-driven pSS.

Methods: Blood samples were obtained from 58 healthy controls (HC) and 58 pSS patients, diagnosed according to the 2002 American-European criteria, and stratified according to their IFN signature. Fluorescence-activated cell sorting was used to isolate CD123+BDCA4+ pDCs, CD14+ monocytes, CD3+ T-cells and CD19+ B-cells >98% purity, from peripheral blood mononuclear cells (PBMCs). Genome-wide Microarray analysis conducted on sorted pDCs and monocytes revealed increased expression of cytoplasmic and endosomal pattern recognition receptors: TLR7, retinoic acid inducible gene-1 (RIG-I/DDX58), melanoma differentiation associated gene 5 (MAF-5/IFIH1), and further downstream MYD88-dependent signaling, confined to IFN-positive patients. mRNA expression of the resulting differentially expressed genes (DEGs), as assessed by Ingenuity pathway analysis (IPA), was validated in sorted cell-suspensions and whole blood (Paxgene) using real-time quantitative PCR. To further clarify the possible TL9-driven activation of the IFN signature, PBMCs of HC were stimulated in vitro with imiquimod, a TLR7 agonist, and inhibited with the TLR7 antagonist IRS661. RNA-sensing receptors RIG-I and MDA-5 (p<0.001) were specifically downregulated, as assessed by Ingenuity pathway analysis (IPA), was validated in sorted cell-suspensions and whole blood (Paxgene) using real-time quantitative PCR. To further clarify the possible TL9-driven activation of the IFN signature, PBMCs of HC were stimulated in vitro with imiquimod, a TLR7 agonist, and inhibited with the TLR7 antagonist IRS661.

Results: Confirming our microarray results, we found an upregulation of TLR7 (p<0.05), but not TL9, in IFN positive pDCs, monocytes, B-cells and in whole blood (p<0.0001) as well as further downstream MYD88, RAS2 D2 and IRF7 (p<0.001). We also observed the upregulation of intracellular RNA-sensing receptors RIG-1 and MDA-5 (p<0.01), recently described to collectively initiate effective IFN signaling. This widespread upregulation of TLR7 and its downstream signaling pathway is confined to IFN-positive pSS patients. In vitro studies with HC-PBMCs reveal that triggering of the TL9-pathway by Imiquimod causes further upregulation of the other RNA-sensing receptors RIG-1 and MDA-5, inflammatory cytokines, IFN-inducible genes and also BAFF. Specific TLR7-inhibition subsequently showed a dose-dependent decrease.

Conclusion: Taken together, these RNA-sensing receptors — TLR7, RIG-I and MDA-5 — seem to collaborate in amplifying the pathogenic IFN-driven loop in pSS. A better understanding of this unrestrained and potentially auto-reactive loop reveals novel targets for therapeutic interventions in pSS.

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**Genome-Wide DNA Methylation Analysis of CD19+ B Cells in Primary Sjögren’s Syndrome.** Gunnel Nordmark1, Juliana Irgemgen-Kreuz2, Jonas Carlson Aalmof2, Jessica Nordlund1, Roald Omdal1, Katriine H. Norheim2, Maija-Leena Etoransa1, Lars Rönnblom2 and Johanna K. Sandling1.1Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, 2Molecular Medicine and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden. 

**Background/Purpose:** Increasing evidence suggests an epigenetic contribution to the pathogenesis of autoimmune diseases, including primary Sjögren’s Syndrome (pSS) (1). A genome-wide DNA methylation study in T cells from patients with pSS and controls identified a large number of differentially methylated genes (2). B cells play an important role in pSS with production of autoantibodies and the potential development of B cell lymphomas. The aim of this study was to investigate DNA methylation profiles in purified CD19+ B cells from patients with pSS and healthy controls.

**Methods:** Seventeen female patients with pSS, mean age 53.2 years and 28 healthy blood donors, 11 females/17 males, mean age 46.7 years were included. All patients fulfilled the AECG criteria for pSS, 94.1% were anti-SSA and/or -SSB positive and none of the patients had lymphoma. DNA was prepared from CD19+ B cells positively selected from fresh blood samples. Genome-wide DNA methylation profiles were generated on the Illumina HumanMethylation450 BeadChip array. After quality control and normalization, 383,258 CpG sites remained. A threshold of 10% difference between cases and controls in average methylation level per CpG site was applied. Age and sex were included as covariates and a Bonferroni corrected p-value of <1·10^-7 was considered significant.

**Results:** We identified 482 differentially methylated CpG sites, 91 hypomethylated annotated to 63 genes and 391 hypermethylated annotated to 316 genes. Pathway analysis of genes with hypomethylated sites showed over-representation in Interferon signalling genes, and for genes with hypermethylated sites Syndecan-1-mediated signalling events and the EGF receptor signalling pathway. Disease association of genes with differentially methylated sites showed enrichment for genes implicated in cancer, viral infections and B cell and follicular lymphomas. The most distinct difference in average methylation was observed in the interferon-induced gene IFI44L with 31% decreased methylation in pSS CD19+ B cells compared to control B cells.

**Conclusion:** Our results demonstrate that DNA methylation is altered in CD19+ B cells from patients with pSS, which underscores the importance of these cells in the pathogenesis of the disease. The significance of genes in the interferon system is highlighted and the enrichment of genes involved in B cell lymphoma is intriguing and warrants further investigation.

**References:**

Disclosure: G. Nordmark, None; J. Irgemgen-Kreuz, None; J. Carlson Aalmof, None; J. Nordlund, None; R. Omdal, None; K. H. Norheim, None; M. L. Etoransa, None; L. Rönnblom, None; J. K. Sandling, None.

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**Prognostic Value of the Complex P2X7 Receptor-Inflammasome in Patients with Primary Sjögren’s Syndrome at Lymphoma Risk.** Chiara Baldini1, Eleonora Santini2, Chiara Rossi3, Francesca Sernisci1, Daniela Martini1, Alessia Gallo3, Valentina Donati3, Nicoletta Luciano3, Francesco Ferro4, Illias Alevizos3, Anna Solini2 and Stefano Bombardieri3.1Rheumatology Unit, Pisa, Italy, 2Rheumatology Unit, University of Pisa, Pisa, Italy, 3NIDCR, Bethesda, M.D.

**Background/Purpose:** Pro-inflammatory P2X7 receptor has been recently implicated in the pathogenesis of primary Sjögren’s syndrome (pSS), suggesting that it may be involved in the initiation and amplification of the innate immune response in salivary glands. In particular, previous studies have shown that the expression of P2X7 receptor in minor salivary glands was significantly higher in patients with positive anti-Ro-SSA and that it correlated with the minor salivary gland biopsy focus score. To date, however, no data are available on the role of the complex P2X7 receptor-inflammasome in the prognostic stratification of patients with pSS, specifically concerning their risk for lymphoma. The aim of this study was, therefore, to explore any eventual association or correlation between P2X7 mRNA levels in pSS minor salivary glands and in blood peripheral lymphocytes and traditional histological and serological risk factors for lymphoma in pSS.

**Methods:** Consecutive, unselected patients with a diagnosis of pSS made according to the AECG 2002 were enrolled in this study. All subjects had a standardized evaluation for pSS which included oral and ophthalmologic examinations, laboratory testing and a rheumatologic evaluation. Mononuclear cells were isolated from fresh blood by density gradient centrifugation. Total RNA was extracted from the frozen salivary gland tissue and from the frozen pellet of lymphocytes and expression of the P2X7 7R mRNA was determined by real-time PCR. Minor salivary gland biopsies were re-evaluated by light microscopy in order to identify GC-like structures. For statistical comparisons, non parametric Mann-Whitney test and Spearman’s rank correlation coefficient were employed.

**Results:** Twenty pSS subjects were enrolled in the study. At diagnosis, 20% of pSS patients had GC-like structures in their salivary glands. P2X7 mRNA expression was significantly higher in the salivary glands of pSS with GC-like structures than in those without GC-like structures and correlated significantly with minor salivary gland focus score (r = 0.688, p = 0.000), beta-2 microglobulin levels (r = 0.538, p = 0.02) and IgG levels (r = 0.452, p = 0.02). Moreover, P2X7 7R mRNA expression levels were significantly higher in patients with clinically evident major salivary glands enlargement and/or disease specific parenchyma dyshomogenization documented by salivary gland ultrasound. No significant correlations were found between P2X7 7R expression in peripheral lymphocytes and all the histological and laboratory risk factors for lymphoma examined in the study.

**Conclusion:** The results of this proof of concept study reinforce the potential involvement of the salivary P2X7 7R in pSS chronic salivary inflammation which have consistently been associated with an increased risk of malignant lymphomas. Further investigation are mandatory to clarify whether salivary P2X7 7R expression might be useful to identify pSS patients at lymphoma risk.

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**Identification of Whole Blood Gene Expression Signature in Primary Sjögren’s Syndrome Associated Lymphoma.** Shereen Al-Ali1, Simon Cockell1, Andrew Skelton1, Katherine James1, Jessica Tarn2, David Young3, Bridget Griffiths4, Simon Bowman5, James Locke6 and Wan-Fai Ng7.1University of Basrah, Basrah, Iraq, 2Newcastle University, Newcastle upon Tyne, United Kingdom, 3Newcastle University, Newcastle Upon Tyne, United Kingdom, 4Freeman Hospital, Newcastle Upon Tyne, United Kingdom, 5University Hospital Birmingham, Birmingham, United Kingdom.

**Background/Purpose:** Primary Sjögren’s syndrome (pSS) is associated with a substantially increased risk of lymphoma development. The aim of our study is to identify a whole blood gene expression signature of pSS-associated lymphoma and to explore the potential biological significance of such signature using pathway and network analysis.

**Methods:** Whole blood RNA samples (n=144) from pSS patients and healthy controls taken part in the UK primary Sjögren’s syndrome registry (UKPSSR). All patients fulfilled the AECG criteria and were stratified into five clinical subsets (pSS = 61, pSS with lymphoma = 16, pSS with other cancers = 21, pSS with paraproteinemia = 23 and healthy controls = 23).

**Results:** Distinct gene expression profiles and similar differentially expressed genes were observed when comparing each clinical subset with healthy controls. Comparison between the “Lymphoma” group and those without lymphoma revealed 25 upregulated genes and 43 downregulated genes. When compared with pSS patients with other cancers, only one gene was differentially expressed and it was
Fatty lesions of the bone marrow in the axial skeleton (sacroiliac joints - SIJ, and spine) on magnetic resonance imaging (MRI) are considered nowadays as earliest post-inflammatory changes preceding new bone formation in axial spondyloarthritides (axSpA). It has been shown in several trials with tumour necrosis factor (TNF) α inhibitors that resolution of inflammation under anti-TNF therapy is associated with an increase of a fatty lesion score. This raised concerns that TNF blockers might therefore promote the process of new bone formation in axSpA. The aim of the current analysis was to investigate the difference in fatty lesions formation rates in patients treated with the TNF inhibitor infliximab (IFX) added to naproxen (NPX) as compared to NPX alone given over 28 weeks in patients with early axSpA.

Methods: Part I of the INFAST study was a double-blind, randomized controlled trial of IFX in biologic-naive patients 18–48 years of age with early (<3 years symptom duration), active axSpA with signs of active sacroiliac on MRI. A total of 158 patients were randomized (2:1) to receive 28 weeks of treatment with either intravenous IFX 5 mg/kg (weeks 2, 6, 12, 18, and 24) + NPX 1000 mg/d (n=106) or intravenous PBO+NPX 1000 mg/d (n=52). MRI’s of the SIJ and of the spine were performed at baseline and week 28 and were scored according to the Berlin scoring system for active inflammation and for fatty lesions, including a detailed fatty degeneration score for the SIJ by a reader who was blinded for clinical data including treatment allocation.

Results: Complete MRI sets (baseline and week 28, both STIR and T1-weighted sequences) were available in 147 patients for the spine (n=99 IFX + NPX, n=48 NPX alone) and in 143 patients for the SIJ (n=97 IFX + NPX, n=46 NPX alone). At baseline there were no meaningful differences between treatment group neither in osteitis nor in fatty lesion scores. In both treatment groups there was a significant reduction of inflammation in the spine and in the SIJ at week 28 as compared to baseline. In table, which was however more prominent in the combined treatment group since after 28 weeks patients in the IFX + NPX group had significantly lower osteitis scores in the SIJ (p<0.001) and in the spine (p<0.001). Similarly, in both groups there was a significant and comparable increase in the fatty lesion score (table) in the spine and in the SIJ at week 28 as compared to baseline, but no statistically significant difference between treatment groups was observed in the fatty lesion status score at week 28.

Conclusion: Effective anti-inflammatory treatment of axSpA in this study was associated with an increase in the fatty lesion score in the SIJ and in the spine that was independent of the treatment arm. The results suggest that fatty lesion formation after resolution of inflammation is possibly a universal pathogenetic mechanism in axSpA and not a direct effect of anti-TNF therapy.

Table 1. Changes in MRI scores over 28 weeks in patients with active axSpA in the INFAST study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>IFX + NPX Week 28</th>
<th>p-value*</th>
<th>Baseline</th>
<th>NPX Week 28</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine osteitis score (0–24)</td>
<td>3.7 ± 5.4</td>
<td>0.8 ± 1.9</td>
<td>&lt;0.001</td>
<td>4.7 ± 5.7</td>
<td>2.7 ± 4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Spine fatty lesion score (0–24)</td>
<td>4.9 ± 7.4</td>
<td>3.7 ± 8.2</td>
<td>&lt;0.001</td>
<td>6.2 ± 8.0</td>
<td>7.2 ± 8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIJ osteitis score (0–24)</td>
<td>5.3 ± 5.3</td>
<td>3.0 ± 1.9</td>
<td>&lt;0.001</td>
<td>6.1 ± 4.0</td>
<td>2.2 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIJ fatty lesion score (0–24)</td>
<td>9.2 ± 7.6</td>
<td>10.8 ± 7.3</td>
<td>&lt;0.001</td>
<td>11.2 ± 8.6</td>
<td>12.5 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*SWilcoxon Test, Week 28 vs Baseline
healthy controls were screened against ten 14-3-3 with inflammation and have diagnostic and prognostic properties. Were generated in AS and which specific autoantibody might be associated groove. We aimed to determine whether autoantibodies to the native protein inflammatory cascades that result in expression of inflammatory factors and 51 (44%) received TNF blocker therapy. Mean (SD) baseline mSASSS assessed by CRP and MRI of the sacroiliac joint (SIJ) and spine, which was performed by two central readers and an adjudicator using the modified Stoke AS Spine Score (mSASSS). Patients had mean age of 39.7 years, 73% male, mean symptom duration 16.9 years, and S1 (44%) received TNF blocker therapy. Mean (SD) baseline mSASSS was 13.6 (17.6), mean change in mSASSS was 1.8 (2.7), and 52.5% had mSASSS change > 0. Mann-Whitney U test was used to determine group differences and ROC analysis (AUC) was used to assess diagnostic utility. Potential associations were assessed by Pearson correlation. Multivariate regression analyses were used to examine associations significant in univariate analyses.

Results: Discrimination by AUC ranged from 0.81–0.89 for all 10 autoantibodies (p<0.0001 for all). For example, median (SD) expression of the Pan-3 14-3-3 autoantibody was significantly higher in SpA than in healthy controls (838 U/ml (605–1287) vs. 456 U/ml (346–566), p=0.0001) and area under the ROC curve was 0.86, 95%CI (0.82–0.91). A cut-off of 803 U/ml delivered 95% specificity and 53% sensitivity (LR + = 11.2, LR - = 0.5). For inflammation parameters, Pan-1 and Pan-5 correlated significantly with CRP (r=0.23, p=0.02; r=0.27, p=0.005) and Pan-1 correlated with SPARCC SIJ MRI score (r=0.21, p=0.04). For radiographic progression measured by change in mSASSS, significant correlations were observed with all 10 Pan specificities, notably, Pan-2 (r=0.39, p<0.0001), Pan-3 (r=0.34, p=0.0004), and Pan-10 (r=0.35, p<0.0003). Independent predictors of MRI inflammation were sex (p=0.006) and Pan 1 autoantibody (p=0.008) (adjusted for age, sex, symptom duration, CRP). Controlling for baseline mSASSS CRP, age, sex, symptom duration, and treatment, Pan antibodies were the only significant predictors of the change in mSASSS at 2 years in multivariate regression analysis. Pan composite score (p=0.001), Pan-1 (p=0.008), Pan-2 (p=0.001), Pan-3 (0.005), Pan-10 (p=0.0004).

Conclusion: 14-3-3 autoantibodies are novel serum markers that are differentially expressed in AS versus healthy controls. They are significantly associated with MRI inflammation and baseline expression of several autoantibody specificities predicts radiographic progression.

Disclosure: W. Maksymowych, Augurex Life Sciences Corp, 5; S. Wichuk, None; R. Lambert, None; M. Murphy, Augurex Life Sciences Corp, 3; A. Marotta, Augurex Life Sciences Corp, 3.

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Fat Metaplasia on MRI of the Sacroiliac Joints Is a Lead Indicator of Radiographic Progression in the Spine of Patients with Ankylosing Spondylitis. WP Maksymowych1, Stephanie Wichuk1, RG Lambert2, MA Reed Murdoch1 and ANTHONY MAROTTA2. 1University of Alberta, Edmonton, AB, 2Molding, University of Alberta, Edmonton, AB.

Background/Purpose: Fat metaplasia in the SIJ on MRI is an early feature of sacroiliitis and occurs both in subchondral bone marrow and also in the excavated area caused by erosion, when it is called backfill. Recent data has shown that these lesions are key intermediaries in the development of SIJ ankylosis. We aimed to test the hypothesis that these lesions may also be lead indicators of new bone formation in the spine of patients with axial SpA. This could provide an important target for therapeutic intervention.

Methods: Bone marrow fat metaplasia and backfill were scored using the SPARCC MRI SIJ structural score (SSS) by two readers and an adjudicator using pre-specified rules for adjudication. 137 pairs of MRI scans blinded to time point (baseline, 2 years) were assessed from a prospective cohort of AS patients (mean age 40.5 years, mean symptom duration 16.9 years, 53% on anti-TNF) followed for mean 2.3 years. Two readers and an adjudicator independently scored pairs of radiographs (baseline, 2 years) from the same patients using the mSASSS. Radiographic progression was compared in patients with and without positive SIJ MRI for fat metaplasia (SSS score ≥ 2 or <2) and the degree of SIJ fat metaplasia at baseline (absolute SSS score) was compared in patients with and without radiographic progression (mSASSS > 0 or =0) using Mann-Whitney and cumulative probability. Multivariate regression analyses included variables significant in univariate analyses (age, sex, symptom duration, CRP, baseline mSASSS) and treatment.

Results: Radiographic progression was significantly greater in those with positive SIJ fat metaplasia (p=0.015) (figure), and especially in patients who only received non-biologic therapy (p=0.023). Baseline SSS SIJ fat metaplasia scores were significantly higher in those who developed radiographic progression compared to those without (1.58 vs 0.65, p=0.008). Both positive SIJ MRI for fat metaplasia and the degree of fat metaplasia were significantly associated with radiographic progression in multivariate analyses (β=0.38 (p=0.005) and β=0.06 (p=0.0001) respectively). SSS score for backfill was also significantly associated with radiographic progression in multivariate analysis (β=0.04 (p=0.199)).

Disclosure: F. de Bruin, None; M. O. Treyvaud, None; A. Feydy, None; M. Dougdos, None; L. Gossec, None; J. L. Bloem, None; D. van der Heijde, None; M. Rajniere, None.

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Autoantibodies to 14-3-3γ Are Novel Biomarkers Associated with Inflammation and Radiographic Progression in Ankylosing Spondylitis. WP Maksymowych1, Stephanie Wichuk1, RG Lambert1, M. Reed Murdoch1 and Anthony Marotta2. 1University of Alberta, Edmonton, AB, 2Augurex Life Sciences Corp, North Vancouver, BC.

Background/Purpose: 14-3-3γ is a ubiquitous intracellular chaperone protein that is expressed extracellularly in rheumatoid arthritis and mediates inflammatory cascades that result in expression of inflammatory factors and metalloproteinas. An autoantibody response (AAb) is elicited to a range of epitopes on the native protein both within and outside the ligand-binding groove. We aimed to determine whether autoantibodies to the native protein were generated in AS and which specific autoantibody might be associated with inflammation and have diagnostic and prognostic properties.

Methods: Sera from 116 patients with AS followed prospectively and 106 healthy controls were screened against ten 14-3-3γ peptides (Pan 1–10) using an electrochemiluminescent multiplex assay platform. Inflammation was assessed by CRP and MRI of the sacroiliac joint (SIJ) and spine, which was performed by two central readers and an adjudicator using the Spondyloarthitis Research Consortium of Canada (SPARCC) score. Radiographic progression over 2 years was assessed by two central readers and an adjudicator using the modified Stoke AS Spine Score (mSASSS). Patients had mean age of 39.7 years, 73% male, mean symptom duration 16.9 years, and S1 (44%) received TNF blocker therapy. Mean (SD) baseline mSASSS was 13.6 (17.6), mean change in mSASSS was 1.8 (2.7), and 52.5% had mSASSS change > 0. Mann-Whitney U test was used to determine group differences and ROC analysis (AUC) was used to assess diagnostic utility. Potential associations were assessed by Pearson correlation. Multivariate regression analyses were used to examine associations significant in univariate analyses.

Results: Discrimination by AUC ranged from 0.81–0.89 for all 10 autoantibodies (p<0.0001 for all). For example, median (SD) expression of the Pan-1 14-3-3γ autoantibody was significantly higher in SpA than in healthy controls (838 U/ml (605–1287) vs. 456 U/ml (346–566), p=0.0001) and area under the ROC curve was 0.86, 95%CI (0.82–0.91). A cut-off of 803 U/ml delivered 95% specificity and 53% sensitivity (LR + = 11.2, LR - = 0.5). For inflammation parameters, Pan-1 and Pan-5 correlated significantly with CRP
Conclusion: The appearance of fat metaplasia in SIJ subchondral bone marrow and/or at sites of erosion in the SIJ may identify AS patients at increased risk of radiographic progression in the spine.

Disclosure: W. Maksymowych, None; S. Wichuk, None; P. Chiochwansawiat, None; R. Lambert, None; S. Pederen, None.

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Value of Color Doppler Ultrasound Assessment of Sacroiliac Joints in Patients with Inflammatory Chronic Low Back Pain. Maximiliano Bravo1, Leandro Ferreyra Garrott2, David A. Navarta3, Emmanuel Bertiller4, Ricardo Garcia-M Onaco5, Santiago Ruta6, Javier Rosa6 and Enrique Soriano1.

1Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 2Radiology and Imagingology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, 3Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: The utility of ultrasound in the evaluation of sacroilitis has not been extensively studied yet. To evaluate the diagnostic value of color Doppler ultrasound (US) for the detection of sacroiliac (SI) active inflammatory lesions in patients with inflammatory chronic low back pain (LBP).

Methods: Consecutive patients older than 18 years, with chronic inflammatory low back pain, defined as LBP with more than 3 months of continuous duration, of insidious onset, with improvement with exercise, no improvement with rest, and pain at night (with improvement upon getting up), without a definitive diagnosis (patients at risk of having undetected spondyloarthritides (SpA)), were included. Patients with Ankylosing spondylitis (AS) according to modified New York criteria, were included as control group.

Clinical assessment included BASDAI, BASFI, and HAQ. Ultrasound evaluation was performed by a blinded rheumatologist experienced in this technique with a My lab 70 machine (Esaote) with a multi-frequency convex array transducer (1-8 MHz). Standardized scanning method was used to investigate increased local perfusion with color Doppler US. When color Doppler signal was found in or around the SI joints, spectral Doppler was used and the resistive index (RI) was measured. Color Doppler US sacroiliac joints was defined as a positive color Doppler signal with a RI < 0.75 at any of the SI joints.

The following sequences were used on the MRI assessment: T1-weighted spin echo (SE) and short-tau inversion recovery (STIR). MRI sacroiliac joints was defined according to ASAS definition of active sacroiliac inflammatory lesions.

Sensitivity, specificity, positive and negative predictive values for the diagnosis of sacroiliitis by color Doppler US features were calculated, using MRI as the gold standard.

Results: Forty-four patients were included. Twenty-four (54%) were males. Mean age was: 40 years (SD: 11 yrs). Median disease duration was 2 years (IQR: 0.5–10 yrs). Mean BASDAI was 4.8 (SD: 2.4), mean BASFI: 3.6 (SD: 2.7), and mean HAQ was 0.6 (SD: 0.5). Ten patients had AS. Among all patients observed values were: sensitivity 59 % (95% CI: 42–75%), specificity: 94% (95% CI: 83–99.6%). Positive predictive value (PPV) was 87% (95% CI: 77–100%) and negative predictive value (NPV) was: 83% (95% CI: 72–94%). Among AS patients observed values were: sensitivity 83% (95% CI: 60–99), PPV: 75% (95% CI: 48–100) and NPV: 83% (95% CI: 60–99%) and among inflammatory LBP patients diagnostic test values were: sensitivity 59 % (95% CI:42–75%), specificity: 94% (95% CI:86–100%), PPV: 91% (95% CI:81–100) and NPV: 70% (95% CI: 54–89%).

Conclusion: color Doppler US seems to be a practical and useful tool for the diagnosis of active sacroiliitis. Larger studies would be needed to confirm these results.

Disclosure: M. Bravo, UCB, 2; L. Ferreyra Garrott, UCB, 2; D. A. Navarta, UCB, 2; E. Bertiller, UCB, 2; R. Garcia-M Onaco, UCB, 2; S. Ruta, UCB, 2; J. Rosa, UCB, 2; E. Soriano, UCB, 2.

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1Department of Rheumatology Ghent University Hospital, Ghent, Belgium, 2Institute of Immunology University of Muenster, Muenster, Germany, 3Department of Pathology Ghent University Hospital, Ghent, Belgium, 4University Children’s Hospital Muenster, Muenster, Germany.

Background/Purpose: Microscopic gut inflammation is present in about 50% of spondyloarthritides (SpA) patients. Two types can be distinguished: an acute type resembling infectious enterocolitis, and a chronic type similar to early Crohn’s disease. Although subclinical, microscopic gut inflammation appears to be a prognostic factor in SpA, linked with more extensive disease and a less favorable outcome. At this moment, however, reliable biomarkers are missing. The calgranulins S100A8/S100A9 and S100A12 are very sensitive markers of innate immune activation. They are released from monocytes and granulocytes in the early phase of the immune response and exert important pro-inflammatory effects via Toll-like receptor 4 dependent mechanisms. Calgranulins can be measured in serum and stool. Moreover, the S100A8/S100A9 heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease. Our aim was to assess whether calgranulins can be used as biomarkers for microscopic gut inflammation in SpA.

Methods: Serum levels of calgranulins were measured in 103 newly diagnosed SpA patients and 24 healthy controls. Ninety seven SpA patients underwent an ileocolonoscopy to assess the presence of microscopic gut inflammation. Ileal and colonic biopsies were histologically scored and subsequently immuno-stained for S100A8 and S100A9.

Results and Conclusion: Serum levels of S100A8/S100A9 and S100A12 were significantly higher in SpA patients versus healthy controls (p = 0.035 and p = 0.024). Levels correlated moderately with CRP, but not with ASDAS, BASDAI or swollen joint count. SpA patients with the acute type of microscopic gut inflammation (N = 17) had significantly higher calgranulin levels compared to those with normal gut histology (N = 56) (p = 0.021 for S100A8/S100A9 and p = 0.05 for S100A12). Furthermore, immunohistology showed high staining of S100A8 and S100A9 on acutely inflamed gut biopsies, compared to absent/minimal staining on normal biopsies. Chronically inflamed biopsies (N = 24) stained positive only when they had high inflammatory activity (in ~ 50% of cases). Importantly, NSAID intake had neither influence on immunohistology stainings nor on serum levels of calgranulins. To conclude, we found that calgranulin levels, both systemically and locally, marked the presence of acute microscopic gut inflammation in SpA. These results illustrate their high sensitivity as they reflected inflammation present only on a subclinical level. Therefore we anticipate that they may be of particular value in detecting (or excluding) latent (systemic) disease.

Acknowledgements: The research leading to these results has received funding from the European Union’s 7th Framework Program under EC GA No. 305266 “MIAIM”.

Disclosure: H. Cyppers, None; G. Varkas, None; L. Van Praet, None; J. Roth, None; T. Vogl, None; C. Cuvelier, None; D. Föll, None; M. Ilaicri, None; F. van Den Bosch, None; D. Elewaat, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Central Nervous System and Other Clinical Aspects

Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Lupus Impact Tracker Is Responsive to Changes in Disease Activity in Lupus. David Giangreco1, Hevè Devillers2, Nandreer Amanappedry3, Joel A. Block1 and M enakshi jolly3.

1Department of Rheumatology Ghent University Hospital, Ghent, Belgium, 2Department of Rheumatology Ghent University Hospital, Ghent, Belgium, 3Department of Internal Medicine and Systemic diseases, Dijon, France.

Background/Purpose: Patient reported outcomes (PRO) are important to understand, educate, manage and follow patients with systemic lupus erythematosus (SLE). Lupus Impact Tracker (LIT) is a ten-item tool developed to facilitate patient-physician communication. Herein, we present its responsiveness to physician and patient assessed changes in disease status from data obtained during routine SLE patient care visits.

Disclosure: M. Bravo, UCB, 2; L. Ferreyra Garrott, UCB, 2; D. A. Navarta, UCB, 2; E. Bertiller, UCB, 2; R. García-M Onaco, UCB, 2; S. Ruta, UCB, 2; J. Rosa, UCB, 2; E. Soriano, UCB, 2.
Methods: Longitudinal data on LupusPRO, physician assessed disease activity assessment, and patient reported changes in SLE health status was collected during 182 SLE patient routine clinical visits. LIT score was derived from PRO data. Disease activity assessments used as anchors for testing responsiveness were the SLEDAI physician global assessment (PGA), Total SELENA-SLEDAI score, SELENA-Flare Index (SFI), and Patient reported changes in SLE health status. Cut-offs used to determine change in disease activity were as follows: PGA (change of 0,3), Total SELENA-SLEDAI (change of 4), SFI (remitting of 4), and Flaring) and Patient reported changed in SLE health status (7 to 7). For patient reported change in SLE health status, we categorized −2 to 2 as unchanged, −3 to −7 as worsening and 3 to 7 as improvement. Mixed model regression analysis was used to compare changes in LIT against disease activity and patient reported changes in SLE health status anchors.

Results: There were 658 visit data available for 182 SLE patients. Consecutive visits were 2-5 months apart with a median number of visits per patient of 7. PGA was available for 630 visits; Total SLEDAI was available for 249 visits; SFI was available for 610 visits; Patient reported change in SLE health status was available for 449 visits. Mean (SD) age and SLE-SELENA-SLEDAI were 43.3 (13.2) years and 6.4 (7.3), respectively. PGA changed significantly for 269 visit data (increased in 125, decreased in 144) while 361 visit data had unchanged PGA. Total SELENA-SLEDAI changed significantly among 66 visits (29 increased, 37 decreased) and remained stable among 183 visits. Significant changes in SFI were observed in 194 visit data (80 remitting, 69 flaring) while 461 visit data was unchanged. Patient reported change in SLE health status changed significantly for 221 (150 improved, 71 worsened) and remained stable for 228 visits. LIT scores responded significantly and in the appropriate direction for changes in PGA (p<0.05), Total SLEDAI (p<0.001), and SFI (p<0.05) and patient reported changes in SLE health status (p=0.001).

Conclusion: LIT is responsive to physician- and patient-assessed changes in disease status in SLE. In addition to being used in clinical trials, LIT is an effective tool that may be used by patients and physicians in facilitating communication and tracking disease impact in SLE.

Disclosure: D. Giangreco, None; H. DeWilliers, None; N. Annapureddy, None; J. A. Block, None; M. J. Ottley, None.

2990


Background/Purpose: Posterior reversible encephalopathy syndrome (PRES) is a well-known but rare complication in systemic lupus erythematosus (SLE) patients (<1%). However, current epidemiologic data is quite scant. The aim of the present study was to describe potentially unrecognized risk factors for PRES.

Methods: We performed a single-center retrospective case-control study in a tertiary care center in Mexico City between 1999 and 2014. We included 48 patients (cases) with SLE diagnosis (≥4 ACR criteria) who presented with reversible neurological manifestations (seizures, visual abnormalities, acute confusional state, among others) associated with changes by magnetic resonance (MRI) (iso or hypointensity in T1 and hyperintensity in T2/FLAIR). Controls (n=96) were patients with SLE without evidence of PRES that were hospitalized during the same period as cases (≥3 months) and matched by gender. Association between variables was calculated by χ2 test and OR (95% CI). Multivariate analysis was performed by logistic regression.

Results: SLE patients with PRES were younger (27.9±1.05 vs 36.2±3.16 years, p<0.001). Ninety percent of the cases occurred in women. PRES occurred in 28/48 patients (40%) after 24 hours of admission (2-30 days). The vast majority (80.2%) of cases presented with seizures, and up to 18% showed “atypical” MRI images. Decrease or resolution of MRI images in the first 12 weeks after the event occurred in 88.8% of cases. Variables associated with the development of PRES, three months prior to hospitalization and at the time of the event are summarized in Table 1. A multivariate analysis, hypertension at admission (OR 16.3, 95% CI 4.03-65.85, p<0.001) and low C3 levels (OR 0.38, 95% CI 0.14-0.98, p=0.039) were independent risk factors for the development of PRES in SLE. Length of hospital stay was similar between groups (17.2±2.07 vs 14.60±1.11 days, p=0.26) and none of the cases died during hospitalization.

Conclusion: Our data is in agreement with prior studies that link end-stage renal disease, hypertension and high SLEDAI scores to the development of PRES in SLE. Furthermore, we found that persistent lymphopenia is a novel independent risk factor for PRES in SLE, which could be related to endothelial dysfunction in these patients.

Table 1. Variables associated with development of PRES in SLE patients (univariate analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI ≥6 points</td>
<td>4.41</td>
<td>1.87-10.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.50</td>
<td>1.68-7.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3.36</td>
<td>1.36-8.29</td>
<td>0.006</td>
</tr>
<tr>
<td>Low C3 levels</td>
<td>2.71</td>
<td>1.21-6.07</td>
<td>0.013</td>
</tr>
<tr>
<td>History of renal replacement therapy</td>
<td>2.66</td>
<td>1.15-6.12</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Disclosure: J. Merayo-Chalico, None; E. Apodaca, None; A. Barrera-Vargas, None; J. Alcocer-Varela, None; D. Gomez-Martin, None.

2991

Anti-Ribosomal P Antibody Is a Key Autoantibody Associated with Complications of NP-SLE with High Levels of CSF IL-8. Hidenagako Kawasumi1, Takahisa Gono1, Yasushi Kawaguchi1, Yasushi Kasumata2, Hisae Ichida1, Aiko Tochimoto1, Masaomi Hanaka1, Yuko Okamoto2, Sayuri Katoaka1 and Hisashi Yamanaka2. 1Tokyo Women’s Medical University, Tokyo, Japan, 2Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan.

Background/ Purpose: Complications of neuropsychiatric systemic lupus erythematosus (NP-SLE) are associated with the morbidity and mortality of patients with SLE. Although the detailed pathophysiology of NP-SLE remains unknown, complements, autoantibodies, and cytokines are involved in the inflammation of the central nervous system (CNS) or the peripheral nervous system (PNS) in SLE. Previous studies have demonstrated that anti-phospholipid (PL), anti-ribosomal P, anti-N-methyl-D-aspartate receptor subunit 2 (NR2), and anti-U1-RNP antibodies are associated with the development of NP-SLE. In addition, cerebrospinal fluid (CSF) proinflammatory cytokines, such as IL-6, are increased in NP-SLE. In this study, we evaluated the associations between several serum autoantibodies and CSF proinflammatory cytokines in NP-SLE.

Methods: In the present study, seventy patients with SLE who had been admitted to our hospital from 2001 to 2013 were enrolled. SLE was diagnosed according to the 1997 ACR revised criteria for the classification of SLE. Disease activity was measured using the SLE disease activity index 2000 (SLEDAI-2k). NP-SLE manifestations were classified according to the 1999 ACR nomenclature and case definitions for NP-SLE syndromes. Serum and CSF samples were obtained from all enrolled patients with SLE. We measured serum autoantibodies, including anti-PL, anti-ribosomal P, anti-NR2, anti-U1-RNP and anti-Sm antibodies, and CSF cytokines (IL-6, IL-8, and IFN-α).

Results: Of the 70 patients with SLE, all patients were female, and their median age was 32 years. The median score on the SLEDAI-2k was 12. NP-SLE was diagnosed in 24 patients. Serum anti-PL, anti-ribosomal P, anti-NR2, anti-U1-RNP, and anti-Sm antibodies were detected in 15, 23, 23, 24, and 13 patients, respectively. The CSF levels of IL-8 were significantly higher in the NP-SLE subset compared with the non-NP-SLE subset (p<0.05). There were no significant differences in the CSF levels of IL-6, IFN-α, total protein, or IgG index between the two subsets. High levels of CSF IL-8 (>30 pg/ml) were significantly (p<0.001) associated with the complications of NP-SLE. No patient was diagnosed with NP-SLE when the CSF levels of IL-8 were less than 30 pg/ml. To identify the specific autoantibodies associated with high levels of CSF IL-8, a multivariate analysis was conducted. Anti-ribosomal P was the most significant autoantibody involved in the high levels of CSF IL-8.
Conclusion: High levels of CSF IL-8 are associated with the complications of NP-SLE. Anti-ribosomal P is a key autoantibody associated with NP-SLE with high levels of CSF IL-8.

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Usefulness of Diagnostic Biomarker for Neuropsychiatric Systemic Lupus Erythematosus By Anti-Microtubule Associated Protein 2 Antibody in Cerebrospinal Fluid. Yusuke Yamada, Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan.

Background/Purpose: Microtubule associated protein-2 (MAP-2) is found exclusively in nerve cells. MAP-2 has been shown to stabilize microtubules by binding to the outer surface and participate in determining the structure of nerve cells. Interestingly, a previous report has shown that an autoantibody against MAP-2 has been reported to be found in sera with SLE patients especially having neuropsychiatric manifestations. However, there are no additional reports concerning anti-MAP-2 antibody. NPSLE involves a wide range of focal and diffuse central and peripheral nervous system disorders. The diagnosis of NPSLE is often clinically difficult because discrimination of secondary causes such as infection, medication side-effects, and metabolic abnormalities was required. The diagnostic inference of NPSLE can be made only after these secondary causes have been excluded. There is no one single diagnostic tool specific to NPSLE so far. Multiple diagnostic examinations such as IL-6 measurement in cerebrospinal fluid or Magnetic Resonance Imaging (MRI) have been used for diagnosis with NPSLE. However, the findings from these examinations are not specific for NPSLE. Therefore, novel diagnostic biomarkers have been expected to be established. Herein, we conducted this study to clarify that anti-MAP-2 antibody in cerebrospinal fluid can be used for a diagnostic biomarker of NPSLE.

Methods: Anti-MAP-2 antibody, anti-ribosomal P antibody, and IL-6 was measured by ELISA in cerebrospinal fluid from NPSLE patients (n=24) or non NPSLE controls (n=18). The diagnosis with NPSLE was made by the nomenclature system proposed by American College of Rheumatology (ACR, 1999). Non NPSLE controls consisted of SLE patients with CNS disorders caused by the secondary causes such as steroid psychosis, and other tissue connective diseases with CNS disorder.

Results: Titer of anti-MAP-2 antibody in cerebrospinal fluid was significantly higher in NPSLE patients compared to non NPSLE controls. When the cutoff value was designed as average + 3SD of the controls, the prevalence of anti-MAP-2 antibody in NPSLE patients was 33.3% (8/24), and none of patients with non NPSLE controls (0/18) had an anti-MAP-2 antibody. Furthermore, titer of anti-ribosomal P antibody and IL-6 concentration in cerebrospinal fluid, which are other diagnostic biomarker for NPSLE, were significantly higher in NPSLE patients with anti-MAP-2 antibody compared to NPSLE patients without anti-MAP-2 antibody or non NPSLE controls.

Conclusion: Anti-MAP-2 antibody in cerebrospinal fluid was recognized in 33.3% patients with NPSLE and the appearance was highly specific for NPSLE. We propose that anti-MAP-2 antibody in cerebrospinal fluid is a novel diagnostic biomarker for NPSLE.

Disclosure: Y. Yamada, None.

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MRI in Neuropsychiatric Lupus: Correlations with the 1999 ACR Case Definitions. Minyoung Her1, Dongyook Kim1, Na young Park1, Seong-Kyu Kim2, Lee Sung Won2 and Lee sang Yeo2. 1Inje University, Pusan Paik Hospital, Busan, South Korea, Busan, South Korea, 2Catholic University of Daegu, Daegu, South Korea, Daegu, South Korea, 3Dong-A University, Busan, South Korea, Busan, South Korea.

Background/Purpose: Neurological manifestations in SLE are diverse. Because of its varied manifestations and low prevalence, the ACR has developed nomenclature and case definitions for neuropsychiatric SLE (NP-SLE) to facilitate clinical research. Brain MRI has been used for the evaluation of neurological symptoms. The purpose of this study was to identify characteristic brain MRI findings in NP-SLE and to investigate the association between brain MRI findings and NP-SLE manifestations.

Methods: All brain MRI cases that received the diagnosis of SLE at three tertiary university-based hospitals from August 2002 to August 2013 were screened. 219 brain MRIs with diagnosis of SLE were screened. All clinical manifestations found by brain MRI were retrospectively assessed and were classified as NP-SLE according to the 1999 NPSLE ACR nomenclature and case definitions. In total, 139 brain MRIs in 121 patients with NP-SLE from 2002 to 2013 were retrospectively reviewed. The images were evaluated for the presence of white matter hyperintensity (WMH), gray matter hyperintensity (GMH), parenchymal defects, atrophy, enhancement, and the abnormalities in diffusion-weighted image (DWI). The number, side, and location of WMH, GMH and parenchymal defects were evaluated. The NP-SLE manifestations of each patient were classified according to the 1999 ACR case definitions for NP SLE syndromes. The associations between MRI findings and manifestations of NP-SLE were examined.

Results: In total, 97 MRIs (69.8%) demonstrated abnormalities among the 139 brain MRIs reviewed. There were 164 NP events that encompassed 16 of 19 NP syndromes. The most common NP abnormalities were WMHs. One or more WMHs were found in 78 MRIs (56.1%) among the total 139 MRIs. GMHs were observed in 42 MRIs (32.0%). GMHs tended to involve much larger areas than WMHs. Patients with cerebrovascular disease or seizures were more likely to have GMHs than patients with other NP manifestations. 33 MRIs among 42 GMHs which had GMHs also exhibited WMHs. Parenchymal defects were found in 34 MRIs (24.5%). A trophic was detected in 20 MRIs (14.4%). Brain MRIs were enhanced in 21 of the 122 cases that had undergone enhancement. Patients who had seizures were more likely to demonstrate MRI enhancement than patients with other NP manifestations. DWIs were obtained in 97 MRIs and abnormal DWIs were obtained in 17 MRIs cases. Patients with cerebrovascular disease were more likely to have GMH, parenchymal defects and abnormal DWI than patients with other NP manifestations.

Discussion: M. Her, None; D. Kim, None; N. Y. Park, None; S. K. Kim, None; L. Sung Won, None; L. sang Yeo, None.

2994

Blood Brain Barrier and Anti-NR2 Antibody in SLE Patients with Cognitive Impairment. Gaurav Gulati1, Philip Iliffand, Vikram Puvenna2, Damir Janigro2 and Michael Luggen3. 1University of Cincinnati College of Medicine, Cincinnati, OH, 2Cleveland Clinic Lerner College of Medicine, Cleveland, OH.

Background/Purpose: Cognitive Impairment (CI) is one of the most common manifestations of neuropsychiatric SLE (NP-SLE) and one of the most devastating. The pathogenesis of CI in SLE is not known, but in animal models, antibody to the NR2 subunit of the N-methyl D-aspartate receptor (NR2) can cause memory impairment. However, this effect can only be demonstrated if the blood brain barrier (BBB) has been disrupted or if the antibody is introduced intracereally. Several studies in SLE patients have failed to find an association of NR2 with CI. None, however, has assessed the integrity of the BBB as a potential pathogenic cofactor. S100B protein is an astrocyte specific protein that has been used as biomarker of BBB disruption in traumatic brain injury and some neurodegenerative disorders. An antibody to this protein may indicate previous exposure to this immunologically privileged protein and might be used as an indicator of preceding BBB disruption. We hypothesized that NR2 antibody is pathogenic in SLE patients only if there evidence of previous or ongoing BBB disruption as indicated by increased levels of S100B or anti-S100B.

Disclosure: M. Her, None; D. Kim, None; N. Y. Park, None; S. K. Kim, None; L. Sung Won, None; L. sang Yeo, None.

2995

Disclosures: None.
Methods: Patients who fulfilled the revised American College of Rheumatology (ACR) criteria for SLE and were stable for at least 4 weeks were recruited from three different settings. Basic demographic, clinical and laboratory data was collected. The Automated Neuropsychological Assessment Metrics (ANAM), a computerized and validated tool, was utilized to measure cognitive function. The Total Troughscore (TTS = number of correct responses/time) was used as the primary outcome measure. CI was defined as a score of less than 1.5 SD below the age, sex, and race matched RA population mean. Patients also had assessment of fatigue, depression, SLE activity and SLE damage using the FACTI fatique score, Becks Depression Inventory (BDI), SLEDAI 2K, and SLICC respectively. Serum was analyzed by established ELISA techniques for anR2 antibody, anti-S100B antibody and intact serum S100B protein.

Results: A total of 57 patients were evaluated. Demographic and clinical data is summarized in Table 1. The age, ethnicity, and family income were significantly different between the two groups (p<0.05). In a multiple regression model using the above independent variables together with simple reaction time and opioid use, no significant effects of aNR2, S100B, or aS100B on decreasing TTS were found. However, aNR2 antibodies significantly decreased TTS at higher, but not lower, levels of S100B (p<0.01, model R² of 0.657, p<0.0001).

Conclusion: Antibody to NR2 may play a role in the pathogenesis of CI in SLE patients, but it does so only if there is disruption of the blood brain barrier as has been previously suggested. Confirmation of these findings and further investigation of the causes of BBB damage in these patients may improve our understanding of this important problem.

Table 1. Clinical and Demographic Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALL SUBJECTS</th>
<th>CD (n=22)</th>
<th>NO CD (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>49.9 (11.2)</td>
<td>54.9 (8.8)</td>
<td>46.5 (13.3)</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>13.1 (10.5)</td>
<td>17.5 (13.9)</td>
<td>12.0 (8.6)</td>
</tr>
<tr>
<td>Family income (% &lt; $20K)</td>
<td>45.6</td>
<td>75.0</td>
<td>37.7</td>
</tr>
<tr>
<td>Education (% &lt; 12 yrs)</td>
<td>36.8</td>
<td>50.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>36.8</td>
<td>8.3</td>
<td>44.4</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>3.6 (3.4)</td>
<td>3.2 (4.3)</td>
<td>3.8 (3.3)</td>
</tr>
<tr>
<td>SLICC</td>
<td>2.75 (2.4)</td>
<td>3.4 (2.1)</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>Pain (100 mm VAS)</td>
<td>40.1 (28.2)</td>
<td>49.6 (29.3)</td>
<td>36.2 (27.7)</td>
</tr>
<tr>
<td>Patient global Assessment (100 mm)</td>
<td>53.7 (22.6)</td>
<td>58.8 (22.6)</td>
<td>52.3 (22.7)</td>
</tr>
</tbody>
</table>

Disclosures: G. Gulati, None; P. Iffland, None; V. Puvvuna, None; D. Janigro, None; M. Luggen, None.

ACR Concurrent Abstract Session

Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics III: Updates in Predictors and Outcomes in Systemic Sclerosis

Wednesday, November 19, 2014, 9:00 AM - 10:30 AM

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Surrogate Measures of Extent of Intersitial Lung Disease As Measured By Quantitative Radiographic Analysis in Patients with Systemic Sclerosis. Elizabeth Volkman1, Donald Tashkin2, Chi-hong Tseang3, Kim Hyun1, Jonathan Goldin5, Philip J. Clements4, Daniel E. Furst3, Dinesh Kanna, Eric Kleerep1, Michael Roth1 and Robert Elashoff2. 1University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, 2University of California at Los Angeles, Los Angeles, CA, 3University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 4University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 5University of Michigan Health System, Ann Arbor, MI, 6University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: Extent of systemic sclerosis (SSc)-related interstitial lung disease (ILD) predicts disease course, mortality and treatment response. While quantitative analyses of total extent of ILD (QILD) are more sensitive and reproducible than visual assessments of SSc-ILD, these analyses are not widely available. This study evaluates the relationship between disease parameters and QILD scores to identify potential surrogate measures of QILD.

Methods: Using baseline data from the Scleroderma Lung Study I (SLS I) (N=158), multivariate regression analyses were performed using the best subset selection method to identify 1 to 5 variable-models that best predict QILD scores in both whole lung (WL) and the zone of maximal involvement (ZM). These models were subsequently validated using baseline data from SLS II (N=142). SLS I&II did not include patients with clinically significant pulmonary hypertension (PH).

Results: Diffusing capacity for carbon monoxide (DLCO) was the single best predictor of QILD in the WL and ZM in all of the best subset models (Tables 1, 2). Adding other disease parameters to the models did not substantially improve model performance. Forced vital capacity (FVC) did not predict QILD scores in any of the models.

Conclusion: In the absence of PH, DLCO provides the best overall estimate of HRCT-measured QILD in patients from 2 large SSc cohorts. FVC, which is commonly used to monitor disease course in SSc-ILD, may not be the best surrogate measure of extent of QILD.

Table 1. Multivariate regression analyses of the best 1 to 5 variable-models that predict extent of quantitative interstitial lung disease (QILD) in the zone of maximal involvement (ZM).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>p value</th>
<th>Adjusted r² for SLS I</th>
<th>Correlation SLS I</th>
<th>Correlation SLS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>From best 1-variable model</td>
<td>DLCO% predicted</td>
<td>0.87</td>
<td>0.13</td>
<td>&lt;0.0001</td>
<td>0.29*</td>
<td>0.44*</td>
</tr>
<tr>
<td>From best 2-variable model</td>
<td>Diffuse disease</td>
<td>6.70</td>
<td>3.23</td>
<td>0.04</td>
<td>0.39*</td>
<td>0.57*</td>
</tr>
<tr>
<td>From best 3-variable model</td>
<td>Diffuse disease</td>
<td>6.72</td>
<td>3.21</td>
<td>0.039</td>
<td>0.39*</td>
<td>0.59*</td>
</tr>
<tr>
<td>From best 4-variable model</td>
<td>Diffuse disease</td>
<td>6.22</td>
<td>3.23</td>
<td>0.057</td>
<td>0.33*</td>
<td>0.60*</td>
</tr>
<tr>
<td>From best 5-variable model</td>
<td>Diffuse disease</td>
<td>6.16</td>
<td>4.51</td>
<td>0.021</td>
<td>0.33*</td>
<td>0.60*</td>
</tr>
</tbody>
</table>

* p<0.0001. Visual analog scale for breathing (Range of scores 0–100). aModified Rodman Skin Score (Range of scores 0–5). bDisease duration = Number of years since diagnosis of first non-Raynaud’s symptom to randomization.

Table 2. Multivariate regression analyses of the best 1 to 5 variable models that predict extent of quantitative interstitial lung disease (QILD) in the whole lung (WL).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>p value</th>
<th>Adjusted r² for SLS I</th>
<th>Correlation SLS I</th>
<th>Correlation SLS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>From best 1-variable model</td>
<td>DLCO% predicted</td>
<td>0.59</td>
<td>0.12</td>
<td>&lt;0.0001</td>
<td>0.19*</td>
<td>0.44*</td>
</tr>
<tr>
<td>From best 2-variable model</td>
<td>Diffuse disease</td>
<td>-0.49</td>
<td>0.12</td>
<td>0.0001</td>
<td>0.24*</td>
<td>0.50*</td>
</tr>
<tr>
<td>From best 3-variable model</td>
<td>Diffuse disease</td>
<td>-0.51</td>
<td>0.12</td>
<td>&lt;0.0001</td>
<td>0.25*</td>
<td>0.52*</td>
</tr>
<tr>
<td>From best 4-variable model</td>
<td>Diffuse disease</td>
<td>-0.54</td>
<td>0.12</td>
<td>&lt;0.0001</td>
<td>0.25*</td>
<td>0.53*</td>
</tr>
<tr>
<td>From best 5-variable model</td>
<td>Diffuse disease</td>
<td>-0.56</td>
<td>0.12</td>
<td>&lt;0.0001</td>
<td>0.26*</td>
<td>0.54*</td>
</tr>
</tbody>
</table>

* p<0.0001. Visual analog scale for breathing (Range of scores 0–100). aModified Rodman Skin Score (Range of scores 0–51).
**Background/Purpose:** Knowledge of mortality risk and predictors is important in systemic sclerosis (SSc) patient care and clinical trial design. There is no validated 5-year mortality model in early diffuse SSc (dcSSc), a high-risk population. The objective of this study was to derive and externally validate a 5-year mortality risk stratification tool in early dcSSc patients.

**Methods:** The derivation cohort was a prospectively enrolled inception cohort of adult early dcSSc patients first seen between 1980 and 2009 and enrolled in a US Scleroderma Center database. Early dcSSc was defined as <2 years from the first SSc symptom and proximal skin thickening. Predefined candidate predictor variables at the first visit (demographic, history, exam, lab values, organ system objective tests) were placed into a stepwise multivariable logistic regression model. Regression diagnostics were performed. Beta-estimates were rounded to the nearest 1, and then summed for a total score, which was then classified into low, moderate, and high risk mortality categories. The external validation cohort was a large UK Scleroderma Center database, with patients meeting identical inclusion criteria and an initial visit between 2000 and 2008. A re-run under the curve (AUC) was calculated to assess discrimination in the derivation and validation cohorts, and stratum-specific chi-square analysis performed.

**Results:** In the US derivation cohort, 760 early dcSSc patients were identified, of whom 388 were Caucasian and had all objective testing required to assess internal organ involvement at the first visit. The mean age was 50.4 ± 13.3 years, 76% female and median disease duration 0.93 years (IQR 0.55–1.33). The mean skin thickness score was 45.4 ± 11.7. After 5 years, 110 of the 388 (28.4%) had died. 144 patients composed the UK validation cohort, with no significant differences in age, gender or skin score from the US cohort. Median disease duration was longer at 1.02 (0.78,1.45) years (p = 0.03). At 5 years 38/144 (26.4%) had died, which was not different (p = 0.65) from the US cohort.

**Table 1:** Multivariable model and risk point assignment for 5-year mortality

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>β Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
<th>Point Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first visit (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>–0.66</td>
<td>0.56</td>
<td>0.20–1.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35–44</td>
<td>–0.38</td>
<td>0.69</td>
<td>0.31–1.54</td>
<td>0.40</td>
</tr>
<tr>
<td>45–54</td>
<td>0.76</td>
<td>1.96</td>
<td>0.94–4.10</td>
<td>0.017</td>
</tr>
<tr>
<td>55–64</td>
<td>1.4</td>
<td>4.12</td>
<td>1.92–8.85</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>1.3</td>
<td>3.36</td>
<td>1.71–6.59</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

| GI involvement* | 0.93 | 2.42 | 1.39–4.21 | 0.002 | 2 |
| RNA polymerase III antibody | –0.86 | 0.41 | 0.23–0.72 | 0.002 | 2 |
| Anemia (hemoglobin < 12 mg/dL) | 0.62 | 2.17 | 1.25–3.76 | 0.0006 | 2 |

**Total Sum Score**

*defined as any one of: heartburn, pharyngeal pain, abnormal esophagram or manometry, antibiotics for or documented small bowel bacterial overgrowth, small bowel dysmotility by radiographic imaging, pseudo-obstruction, malabsorption or necessity for hyperalimentation. Tnote that RNA polymerase III is protective.

Significant independent predictors of 5-year mortality at first visit were age, gender, tenderness, fibrinogen, GI involvement, RNA polymerase III antibody and anemia (Table 1). The AUC in the US derivation cohort was 0.79 (95% CI 0.74–0.84) for the overall model and 0.74 (0.65–0.82) in the UK cohort. Using the total sum score, risk stratification was defined as low (≤3), moderate (4–7) and high (≥8) risk. The AUC for the 3-level risk stratification in the US derivation cohort was 0.76 (0.72–0.81) compared to 0.68 (0.60–0.76) in the UK validation cohort (p = 0.24). There were no significant differences in mortality rate between each strata of the risk stratification model in the US and UK cohorts.

**Conclusion:** We have developed and externally validated an easy-to-use 3-level risk stratification tool for 5-year mortality in early dcSSc patients. This tool requires only history, exam and bloodwork.

**Disclosure:** R. T. Domsic, None; S. I. Nihtyanova, None; M. Lucas, None; S. R. Wisniewski, None; M. J. Fine, None; C. K. Kwoh, None; C. P. Denton, None; T. A. Medsger Jr., None.
Screening for Interstitial Lung Disease in Systemic Sclerosis: Performance of High-Resolution Computed Tomography with Limited Number of Slices - a Prospective Study. Thomas Frauenfelder, Anna Winkelthner, Thi Dan Linh Nguyen, Rucscandra Dobrota, Stephan Baumberl, Britta Maurer and Oliver Distler.

**Background/Purpose:** Early diagnosis of interstitial lung disease (ILD), currently the main cause of death in systemic sclerosis (SSc), is needed. We performed a prospective validation of a dedicated, 9-slice HRCT protocol with reduced radiation dose for the detection of ILD in patients with SSc.

**Methods:** We analysed 170/205 consecutive patients with SSc. Whole chest HRCT, serving as standard of reference, and the reduced HRCT with 9 slices allocated according to a basal-apical gradient were obtained. ILD presence, extent (>20% vs. <20%), and diagnostic confidence were assessed. The reduced CT was independently analysed by 2 blinded radiologists, who also evaluated image quality. The effective radiation doses and the test performance parameters of the reduced HRCT were calculated.

**Results:** The study cohort included early (n=66), limited cutaneous SSc (n=34) patients, with a median disease duration of 60 months (Q1:Q3 28,120). Standard chest HRCT showed ILD in 77/170 patients. With the reduced HRCT, 68/77 cases with ILD were identified (sensitivity 88.3%, both readers). The accuracy (91.8%-reader1, 94.7%-reader2), diagnostic confidence (98.8%-reader1, 95.3%-reader2) and image quality rates were high (Table 1). Missed cases were exclusively identified (sensitivity 88.3%, both readers). The accuracy (91.8%-reader1, 94.7%-reader2), diagnostic confidence (98.8%-reader1, 95.3%-reader2) and image quality rates were high (Table 1). Missed cases were exclusively identified (sensitivity 88.3%, both readers). The accuracy (91.8%-reader1, 94.7%-reader2), diagnostic confidence (98.8%-reader1, 95.3%-reader2) and image quality rates were high (Table 1).

**Table 1. Estimated accuracy and diagnostic certainty in detecting ILD on reduced CT scans**

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Accuracy</th>
<th>NPV (95% CI)</th>
<th>High diagnostic confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>88.3% (78.5%-94.2%)</td>
<td>94.6% (87.3%-98.0%)</td>
<td>91.8%</td>
<td>90.7% (82.7%-95.4%)</td>
<td>98.8%</td>
</tr>
<tr>
<td>Reader 2</td>
<td>88.3% (78.5%-94.2%)</td>
<td>100% (95.1%-100%)</td>
<td>94.7%</td>
<td>91.2% (83.5%-95.6%)</td>
<td>95.3%</td>
</tr>
</tbody>
</table>

* degree of confidence score 1 or 2 (i.e. 1 = fully confident; 2 = probably confident); CI = Confidence interval (in parenthesis); NPV = Negative predictive value

**Table 2. Estimated extent of ILD in standard CT and reduced CT scans**

<table>
<thead>
<tr>
<th>Lung involvement in standard CT</th>
<th>No ILD</th>
<th>Minimal (20%)</th>
<th>Moderate (30%)</th>
<th>Extensive (40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>Reader 1/2</td>
<td>Reader 1/2</td>
<td>Reader 1/2</td>
<td>Reader 1/2</td>
</tr>
<tr>
<td>Minimal (20%)</td>
<td>n=99</td>
<td>n=38/37*</td>
<td>n=5/6</td>
<td>n=0/0</td>
</tr>
<tr>
<td>Moderate (30%)</td>
<td>n=0/0</td>
<td>n=0</td>
<td>n=22/26*</td>
<td>n=0/0</td>
</tr>
</tbody>
</table>

*ILD was present in 77 patients in standard CT. Correctly estimated extent in reduced CT as compared to standard CT.

**Conclusion:** The above-described reduced chest HRCT protocol reliably detects even mild SSc-ILD in clinical practice, with the advantage of a much lower radiation dose compared to standard whole chest HRCT. This makes it an attractive protocol for periodical screening for ILD in SSc.

**Disclosure:** T. Frauenfelder, None; A. Winkelthner, None; T. D. L. Nguyen, None; R. Dobrota, Pfizer Inc; S. Baumberl, None; B. Maurer, None; O. Distler, Aetion, Pfizer, Ergonex, BMS, Bayer, United BioSource Corporation, RocheGenentech, medac, Biointivium, Boehringer Ingelheim Pharma, Novartis, 4D Science, Aetion, Novartis, Sanofi-Aventis, Serodapham, GSK, Epipharm, 5. Aetion, Pfizer, Ergonex, Sanofi-Aventis, 2.
trial, 58% of M TX group vs. 19% in placebo group were considered improved.

Conclusion: We’ve developed a feasible composite response index with strong ability to discriminate patients who have improved vs. those who have not. The CRISS is currently being validated in RCTs of dcSSc.

Disclosure: D. Khanna, NIH Scleroderma Foundation, Pulmonary Hypertension Association, 2, University of Michigan, 3, Actelion, Bayer, Boehringer-Ingelheim, 5, Actelion Pharmaceuticals US, 5; Sigma Tau, 5, InterMune, 5, Boehringer Ingelheim, 5; Aries, 5, EMD Serono, 5, Gilead, 5, United Therapeutics, 5, United Therapeutics, 8, None; O. Distler, None; V. Berrocal, None; E. Giuliani, None; M. Hayes, None, P. A. Merker, None; J. Siegel, Genentech and Biogen IDEC Inc., 3; J. R. Seibold, Bayer, 5; A. Aries, 5, EMD Sereno, 5, Gilead, 5, United Therapeutics, 5, United Therapeutics, 8, Sigma Tau, 5, InterMune, 5, Boehringer Ingelheim, 5; M. Baron, None; P. J. Clements, None; Y. Allanore, None; V. D. Steen, Actelion Pharmaceuticals US, 5, United Therapeutics, 5, Pulmonary Hypertension Science, 2, Sanofi-Aventis, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Behring, 2, InterMune, 2, Bayer, 5; S. C. P. Denton, Actelion Pharmaceuticals US, 5; O. Distler, None; S. R. Johnson, None; M. Matucci-Cerinic, Actelion Pharmaceuticals US, 5; L. Czirjak, None; J. E. Pope, None; S. Proudman, None; W. K. Wong, None; A. U. Wells, None; D. E. Furst, None.

3000

Comparison of Systemic Sclerosis Subsets As Predictors of Mortality and Morbidity. Hebah Alhajeri1, Marie Hudson1, Canadian Scleroderma Research Group CSRG1 and Murray Baron2, 1McGill University, Montreal, QC, 2Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC.

Background/Purpose: Identifying systemic sclerosis (SSc) subsets that predict mortality and morbidity could provide useful prognostic information. We undertook this study to compare the predictive ability of different approaches to subsetting SSc.

Methods: SSc subjects from the Canadian Scleroderma Research Group cohort were studied. Three approaches to subsetting were used: Leroy subsets based on skin involvement (limited (lcSSc) and diffuse cutaneous (dcSSc) subsets), serological subsets (anti-centromere (ACA) and anti-topoisomerase I (ATA) antibody subsets) and unsupervised clustering (but not Leroy classification) predicted mortality, with ACA having better survival than RNAP and ATA 1 having better survival than the 2 other clusters. All three approaches to subsetting predicted FVC < 70% development of ILD: dcSSc was worse than lcSSc, ACA was better than ATA and RNAP, and cluster 1 was better than the other clusters. None of the 3 approaches to subsetting predicted time to PH. Subsetting based on Leroy classification and autoantibodies, but not clusters, predicted time to SF-36 PCS < 40, with ACA worse than ATA.

Conclusion: Different approaches to subsetting provide different prognostic information. Subsetting based on clinical and serological profiles remains a challenge in SSc. In the future, subsetting based on molecular profiles may improve the predictive ability of SSc subsets.

3001

Targeting IL-6 By Both Passive or Active Immunization Strategies Prevents Inflammation-Driven Skin Fibrosis. Jerome Avouac1, Lucille Desalais2, Maxime Frechét1, Mourad Elhai3, Jean François Zagury2 and Yannick Allanore2, 1Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, 2Chaire de Bioinformatique, Laboratoire Génomique, Bioinformatique et Applications, EA 4627, Conservatoire National des Arts et Métiers, Paris, France, 3INSERM U1016, Cochin Institute, Paris, France.

Background/Purpose: Interleukin 6 (IL-6) is a pleiotropic cytokine involved in inflammatory and autoimmune processes. Preliminary data have suggested that IL-6 might contribute to systemic sclerosis (SSc). Our aims are to evaluate the efficacy of both passive and active immunization against IL-6 to reduce skin fibrosis in complementary mouse models of SSc.

Methods: Human serum levels and skin expression of IL-6 were determined by ELISA and immunohistochemistry, respectively. We evaluated the monoclonal IL-6R antibody MR16-1 in the mouse model of bleomycin-induced dermal fibrosis, reflecting early and inflammatory stages of SSc. Six-week-old DBA/2 mice received in parallel subcutaneous injections of bleomycin (0.5 mg/ml) and intraperitoneal (ip.) injection of MR16-1 or control antibody at a dose of 2 mg at day 0 followed by one ip. injection of 1 mg at day 7 and 14. Then, we assessed the merit of MR-16 in the tight skin (Tsk-1) mice, an inflammation-independent mouse model of skin fibrosis. Tsk-1 mice received a first ip. injection of 2 mg of MR16-1 or control antibody at the age of 5 weeks followed by one ip. injection of 1 mg once a week for 5 weeks. Thereafter, because of the drawbacks of anti-cytokine monoclonal antibodies, we developed an innovative strategy using active immunization against a small peptide derived from murine IL-6, which was performed in the mouse model of bleomycin-induced dermal fibrosis. Infiltrating leukocytes, T cells and B cells were quantified, and IL-6 levels were measured in the serum and lesional skin of mice after passive or active immunization.

Results: Serum and skin levels of IL-6 were significantly increased in patients with early SSc. Passive immunization with MR16-1 exerted antifibrotic effects in the mouse model of bleomycin-induced dermal fibrosis; reflecting early and inflammatory stages of SSc. Six-week-old DBA/2 mice received in parallel subcutaneous injections of bleomycin (0.5 mg/ml) and intraperitoneal (ip.) injection of MR16-1 or control antibody at a dose of 2 mg at day 0 followed by one ip. injection of 1 mg at day 7 and 14. Then, we assessed the merit of MR-16 in the tight skin (Tsk-1) mice, an inflammation-independent mouse model of skin fibrosis. Tsk-1 mice received a first ip. injection of 2 mg of MR16-1 or control antibody at the age of 5 weeks followed by one ip. injection of 1 mg once a week for 5 weeks. Thereafter, because of the drawbacks of anti-cytokine monoclonal antibodies, we developed an innovative strategy using active immunization against a small peptide derived from murine IL-6, which was performed in the mouse model of bleomycin-induced dermal fibrosis. Infiltrating leukocytes, T cells and B cells were quantified, and IL-6 levels were measured in the serum and lesional skin of mice after passive or active immunization.

Conclusion: Our results support the relevance of targeting IL-6 in patients with early SSc since IL-6 is overexpressed in early stages of the disease. Targeting IL-6 by both passive or active immunization strategies prevented the development of bleomycin-induced dermal fibrosis in mice. Our results highlight the therapeutic potential of active immunization against IL-6, which is a seductive alternative to passive immunization.

Disclosure: J. Avouac, None; L. Desalais, None; M. Fréchet, None; M. Elhai, None; J. F. Zagury, None; Y. Allanore, None.

ACR Concurrent Abstract Session

Systemic Sclerosis, Fibrosing Syndromes and Raynaud’s - Pathogenesis, Animal Models and Genes II

Wednesday, November 19, 2014, 9:00 AM – 10:30 AM

S1312
Anti-Fibrotic Effects of a Newly Discovered HGF Receptor Carboxy-Terminal Fragment in Systemic Sclerosis. Yuchiro Shirai1, Ilia Aanelishvili2, Tanjina Akte3, Richard Silver4 and Galina Bogatkevich1. 1Medical University of South Carolina, Charleston, SC, 2Medical University of South Carolina, Charleston, USA, 3Medical University of South Carolina, Charleston, SC.

Background/Purpose: Systemic sclerosis (SSc) is an irreversible fibrotic disorder with interstitial lung disease (ILD) being a major complication and leading cause of mortality. African American SSc patients exhibit higher prevalence of ILD and worse outcomes than those of other races. We previously reported that a cell-protective and antifibrotic factor, hepatocyte growth factor (HGF), is downregulated in bronchoalveolar lavage fluid and plasma from African American SSc-ILD patients compared with white SSc-ILD patients. Here we report a newly identified C-terminal fragment of the HGF receptor, designated as “M10”, as a peptide with robust antifibrotic properties that is lacking in certain African American SSc-ILD patients.

Methods: Lung tissue was collected postmortem from SSc patients with ILD and RNA was extracted from lung fibroblasts. The coding exons of the HGF receptor, MET (mesenchymal-epithelial transition factor), were amplified by PCR, and sequences were analyzed. A denovourises carrying wild type MET gene or the D1398G mutant observed in African American patients were generated. Lung fibroblasts were infected by either type of adenovirus and treated with HGF, transforming growth factor-β (TGF-β), and the M10 peptide. MET phosphorylation, connective tissue growth factor (CTGF), CCN2 and collagen expression was examined by immunoblotting. Potential peptide-protein interactions were modulated in silico.

Results: We have identified the D1398G mutation in a African American SSc-ILD patients whose MET signaling is impaired. When we compared MET phosphorylation following HGF treatment between normal lung fibroblasts expressing wild type or the D1398G MET, we found that the D1398G mutant showed reduced MET phosphorylation. Additionally, normal fibroblasts expressing the D1398G mutant exhibited a diminished reduction in CTGF and collagen expression following HGF treatment compared with wild type. Sequence analysis revealed that the D1398G mutation is located at the terminal amino acid sequence of “DEVD” which is a Caspase-3 cleavage motif, suggesting that the D1398G MET mutant is incapable of generating the terminal 10-amino-acid-fragment of MET, M10. We found that synthetic M10 peptide effectively reduces, in a dose-dependent manner, collagen and CTGF in SSc fibroblasts. Computational molecular modeling based on the peptide-binding sites from protein surfaces predicts that M10 may negatively regulate MET phosphorylation following HGF treatment between normal lung fibroblasts expressing the D1398G mutant and shifted macrophages from M2 phenotype to M1 phenotype. Furthermore, a M10 directly reversed the pro-fibrotic phenotype of normal dermal fibroblasts treated with TGF-β1 and SSc dermal fibroblasts via suppressing the transcription and reducing the mRNA stability of COL1A2 gene, increasing mRNA levels of M MP-1 gene, and decreasing mRNA levels of CTGF gene.

Conclusion: These results suggest that A m10 inhibits the development of experimental dermal fibrosis via reversing the pro-fibrotic phenotype of fibroblasts, dermat microvascular endothelial cells, and immune cells and would be a candidate of new therapeutic drugs against dermal fibrosis of SSc.

Disclosure: T. Toyama, None; Y. Asano, None; T. Takahashi,None; R. Saigusa, None; Y. Ichimura, None; T. Taniguchi, None; S. Noda, None; K. Akamata, None; S. Sato, None; T. Kadono, None; K. Shudo, None.

3004

Autoantibody-Mediated Raynaud’s Phenomenon: Animal Model and Human Disease. Dana P. Ascherman1, Y unjuan Zang1, Laisel Martinez1, Judith Pignac-Kobinger2, Irene Fernandez2 and Eric L. Greindl2. 1Miami VAMC, Miami, FL, University of Miami, Miami, FL.

Background/ Purpose: Raynaud’s Phenomenon (RP) is frequently seen in autoimmune conditions, but a autoimmune basis for RP has not been established.

Methods: Sera derived from anti-RNP+ individuals were screened for antibodies associated with RP by immunoprecipitation, western blot, and ELISA. Autoantigens targets were then identified by mass spectrometry. Biological effects of antigen-specific monoclonal antibodies as well as human and murine antisera were assessed in in vitro and in vivo models of experimental dermal fibrosis via reversing the pro-fibrotic phenotype of fibroblasts, dermal microvascular endothelial cells, and immune cells and would be a candidate of new therapeutic drugs against dermal fibrosis of SSc.

Conclusion: A m10 inhibits the development of experimental dermal fibrosis via reversing the pro-fibrotic phenotype of fibroblasts, dermat microvascular endothelial cells, and immune cells and would be a candidate of new therapeutic drugs against dermal fibrosis of SSc.

Disclosure: T. Toyama, None; Y. Asano, None; T. Takahashi, None; R. Saigusa, None; Y. Ichimura, None; T. Taniguchi, None; S. Noda, None; K. Akamata, None; S. Sato, None; T. Kadono, None; K. Shudo, None.

3003

Am80 Ameliorates Bleomycin-Induced Dermal Fibrosis By Suppressing the Pro-Fibrotic Phenotype of Fibroblasts, Endothelial Cells, and Immune Cells. Tetsuo Toyama1, Y oshhide Asano2, Takuro Takahashi3, RyosukeSaigusa3, Y oheichimura4, Takashi Taniguchi5, Shinji Noda5, Kaname Akama3, Shinichi Sato3, Takaumi Kadono6 and Koichi Shudo7. 1University of Tokyo Graduate School of Medicine, Tokyo, Japan, 2Research Foundation ITSUU Laboratory, Tokyo, Japan.

Background/Purpose: A m80 is a synthetic retinoid serving as an agonist for retinoic acid receptor α/β with chemical and pharmacological advantages over all-trans retinoic acid, such as higher chemical stability, a lower affinity for cellular retinoic acid-binding protein, and a lack of affinity for retinoid acid receptor-γ. A m80 has been shown to modulate the pathological processes of various autoimmune and inflammatory diseases and their animal models. The primary objective of the study was to investigate the effect of A m80 on dermal fibrosis of a bleomycin (BLM)-induced murine model of systemic autoimmune disease (SSc), normal dermal fibroblasts treated with TGF-β1 and SSc dermal fibroblasts.

Methods: A BLM-induced murine model of SSc was generated with wild type C57BL/6 mice in the presence or absence of oral administration of A m80. The mRNA and protein levels of target molecules were determined by quantitative reverse transcription-PCR, immunostaining, and immunoblotting in the skin and cultured cells. Th1/Th2/Th17 polarization of immune response and macrophages polarization were evaluated by flow cytometry.

Results: A m80 significantly decreased tissue fibrosis and mRNA levels of the Tgfb and Cgfl genes in the lesional skin of BLM-treated mice. In response to A m80, the expression levels of cytokines and chemokines, including IL-4, IL-10, IL-13, IL-17A, TNF-α, IFN-γ, and MCP-1, in the lesional skin were decreased and the differentiation of naïve T cells into cytokine producing effector T cells, such as Th1/Th2/Th17 cells, and regulatory T cells were suppressed in BLM-treated mice. In addition, the infiltration of macrophages, mast cells, and T cells was attenuated by A m80 in BLM-treated mice. A m80 also exerted on dermal microvascular endothelial cells through attenuating the induction of endothelial-to-mesenchymal transition and the expression of intercellular adhesion molecule-1, and shifted macrophages from M2 phenotype to M1 phenotype. Furthermore, A m80 directly reversed the pro-fibrotic phenotype of normal dermal fibroblasts treated with TGF-β1 and SSc dermal fibroblasts via suppressing the transcription and reducing the mRNA stability of COL1A2 gene, increasing mRNA levels of M MP-1 gene, and decreasing mRNA levels of CTGF gene.

Conclusion: These results suggest that A m80 inhibits the development of experimental dermal fibrosis via reversing the pro-fibrotic phenotype of fibroblasts, dermal microvascular endothelial cells, and immune cells and would be a candidate of new therapeutic drugs against dermal fibrosis of SSc.

Disclosure: T. Toyama, None; Y. Asano, None; T. Takahashi, None; R. Saigusa, None; Y. Ichimura, None; T. Taniguchi, None; S. Noda, None; K. Akamata, None; S. Sato, None; T. Kadono, None; K. Shudo, None.
**3005**

**Essential Role for Alternately Spliced Tenasin C and TL R4 Signaling in Persistent Organ Fibrosis.** Swati Bhattacharyya1, Wenxia Wang1, Luisa Morales-Nebreda1, Kajita Lakota2, Robert Lafayitis3, Monica E. Hinchcliff3,4, Scott Budinger3,4, Zenshiro Tanaki5 and John Varga1.

**Background/Purpose:** Transforming growth factor-beta stimulates collagen synthesis and myofibroblast differentiation, and is implicated as a key initiating factor in pathological tissue remodeling in scleroderma. However, the mechanistic role for the persistence fibrotic response associated with scleroderma is not well understood. Recent studies provide evidence for activated innate immunity in patients with scleroderma. Many alternately spliced factors that govern normal embryonic and fetal development are currently recognized as being central to postnatal repair and injury responses. We hypothesized that tissue injury in scleroderma leads to generation and accumulation of alternately spliced extracellular matrix molecules such as tenasin C that are recognized by, and serve as endogenous ligands for TLR4 to drive persistent fibrosis.

**Methods:** Tissue expression of tenasin C was investigated in scleroderma skin biopsies by microarray, immunofluorescence and real-time qPCR. Tenasin C was assayed in 3-D human skin equivalents reconstituted with scleroderma fibroblasts and in scleroderma serum. Cellular responses elicited by tenasin C in human and mouse skin fibroblasts and in 3-D organotypic human skin equivalents were examined. The role of tenasin C in scleroderma skin and lung fibrosis was investigated using tenasin C-null mouse.

**Results:** Levels of an alternately spliced full-length tenasin C isoform (TN-FL) were markedly elevated in scleroderma serum and skin biopsies, as well as in fibroblastic and lung tissues from mice. TN-FL mRNA levels correlated with the skin score. The splicing factor serine/arginine-rich (SR)-rich splicing factor SRSF6, implicated in alternate splicing of tenasin C, was elevated in scleroderma fibroblasts as well as in scleroderma fibroblasts populating skin equivalents. Treatment with TGF-β stimulated the expression of both SRSF6 and TN-FL. In vitro, TN-FL stimulated collagen synthesis and myofibroblasts differentiation, and induced dermal sclerosis in skin equivalents. All of these profibrotic responses were abolished by genetic or pharmacological disruption of TLR4 signaling. Importantly, tenasin C-null mice treated with bleomycin were protected from development of skin and lung fibrosis and loss of lung compliance.

**Conclusion:** Increased SRSF6-driven alternate splicing of tenasin C leads to aberrant TN-FL accumulation in scleroderma. TN-FL triggers TLR4-dependent fibroblast activation, contributing to intracatable skin and lung fibrogenesis. Disrupting the tenasin C-TLR4 signaling axis by preventing tenasin C accumulation through SRSF6 blockade, or by blocking TLR4 signaling using selective small molecule inhibitors, represents appealing novel strategies for attenuating progressive fibrosis as treatment for scleroderma.

**Disclosure:** S. Bhattacharyya, None; W. Wang, None; L. Morales-Nebreda, None; K. Lakota, None; R. Lafayitis, None; M. E. Hinchcliff, None; G. S. Budinger, None; Z. Tanaki, None; J. Varga, None.

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**3006**

**Activation of the Thromboxane A2 Receptor By 8-isoprostane Inhibits the Pro-Angiogenic Effect of Vascular Endothelial Growth Factor in Scleroderma.** Pei-Suen Tsou1, George Zakhem2, Beatrix Balogh2, M. Asif Amin3, Phillip Campbell3, Gautam Edhayan4, Ray A. Qhara5, Elena Schiopu5, Dinesh Khanna3,6, Alisa E. Koch7 and David A. Fox3,4.

**Background/Purpose:** Scleroderma (SSc) is a complex disease characterized by inflammation, vasculopathy, and excessive deposition of extracellular matrix. Various studies have demonstrated a paradoxical increase in angiogenic factors and a decrease in the vascular endothelial growth factor (VEGF), in both the skin and serum of patients with SSc. Despite this, angiogenesis does not occur normally. 8-isoprostane is an oxidized lipid created by excessive oxidative stress, and has been shown to be elevated in SSc. The thromboxane A2 receptor (TXAR) and ROCK pathway, which can be activated by 8-isoprostane (8-IP), inhibits VEGF-induced endothelial cell (EC) differentiation and migration. However, its role in SSc has not been examined. In this study we determined whether the TXAR pathway was activated by 8-IP in SSc ECs. Its effect on VEGF-induced angiogenesis was also determined.

**Methods:** Dermal ECs were isolated from punch biopsies from healthy subjects or patients with diffuse cutaneous SSc. Angiogenesis was assessed by chemotaxis and in vitro microtube formation assays. TXAR expression was determined by qPCR and Western blotting. Knockdown studies were performed using TXAR siRNAs.

**Results:** SSc patient had significantly higher 8-IP plasma levels (60.9-8.4 pg/ml) compared to healthy subjects (24.9-5.0 pg/ml, p<0.05). Increased oxidative stress was detected in SSc ECs as increased 8-IP in SSc EC conditioned media and excessive superoxide in SSc ECs were observed. In healthy ECs, 8-IP inhibited VEGF-induced EC migration, and the inactivation of TXAR or ROCK pathways restored VEGF-induced angiogenesis inhibited by 8-IP. In SSc ECs, VEGF did not induce EC migration, however, addition of the TXAR or ROCK inhibitors restored the pro-angiogenic effect of VEGF. This was further confirmed by TXAR siRNA experiments which showed TXAR knockdown led to inhibition of VEGF-induced migration towards VEGF while the SHAM-transfected ECs did not. We then measured ROCK activity in healthy and SSc ECs before and after VEGF or 8-IP stimulation. Basal ROCK activity was significantly higher in SSc ECs compared to healthy ECs. Moreover, 8-IP-induced ROCK activation was significantly higher in SSc ECs while VEGF induced significantly higher ROCK activation in healthy ECs. The expression of key players in this pathway was also examined. The protein expression of TXAR, RhoA, ROCK1/2 were all elevated in SSc ECs compared to healthy ECs.

**Conclusion:** We show that 8-IP inhibits VEGF-induced migration in healthy ECs through the TXAR/ROCK pathway. ECs not only produce high levels of 8-IP, but also show elevated expression of TXAR and RhoA/ROCK levels. This could explain the increased activation of the TXAR pathway in terms of ROCK activity in SSc ECs compared to healthy ECs. This hyper-activation leads to inhibition of VEGF-induced EC migration, as using the TXAR or ROCK inhibitor, as well as specific knockdown of TXAR, results in restoration of VEGF activity. These results suggest that the TXAR pathway plays a crucial role in angiogenesis and that 8-IP is not just a by-product as a result of oxidative stress, but instead plays a significant role in impaired angiogenesis that characterizes SSc.

**Disclosure:** P. S. Tsou, University of Michigan Scleroderma Cure Fund, 9, The Arthritis Foundation, 2, G. Zakhem, None, B. Balogh, None, M. A. Amin, None, P. Campbell, None, G. Edhayan, None, R. A. Qhara, None, E. Schiopu, None, D. Khanna, NIH K24 AR063120-02, 2, University of Michigan Scleroderma Cure Fund, 9, A. E. Koch, Eli Lilly and Company, 3, D. A. Fox, None.

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**ARHP Concurrent Abstract Session Clinical Practice/Patient Care**

Wednesday, November 19, 2014, 9:00 AM-10:30 AM

**3007**

**Can Knee Pain Be Prevented through Diet and Exercise Among Those at High Risk? the Look Ahead Study.** Daniel White1, Tuhiha Negi2, W. Jack, Rejeski3, Michael Wilkup3, Cora E. Lewis4, Michael Nevitt5, Capri experiment6 and David T. Felson7.

**Background/Purpose:** There is accumulating evidence that a low-carbohydrate, higher-protein diet rich in vegetables and fruits is associated with a lower risk of developing knee osteoarthritis (OA). We examined whether changes in diet and physical activity (PA) predicted changes in knee pain in the Look AHEAD study, a multi-center randomized intervention trial of an intensive lifestyle intervention (ILI) vs. diabetes support and education (DSE) comparison group in adults with a BMI >25 kg/m2 and type II diabetes. Participants in the ILI had goals of reducing weight by 7% and participating in >175 minutes/week of physical activity by one year. We included subjects with knee pain at baseline and examined to what extent the ILI reduced weight and increased PA may have prevented the development of knee pain among those at high risk. We examined whether an intensive weight loss and exercise intervention prevented the development of knee pain among obese adults with type II diabetes, a group at risk for knee pain due to excess weight.

**Methods:** We carried out a secondary analysis of the Look AHEAD study, a multi-center randomized intervention trial of an intensive lifestyle intervention (ILI) vs. diabetes support and education (DSE) comparison group in adults with a BMI >25 kg/m2 and type II diabetes. Participants in the ILI had goals of reducing weight by 7% and participating in >175 minutes/week of physical activity by one year. We included subjects with knee pain at baseline and examined to what extent the ILI...
group protected against developing knee pain at year 1 and 4. Knee pain was assessed by asking “Have you had any pain or discomfort in your knees in the past month?” In a second separate analysis, we examined whether meeting treatment goals, i.e., weight loss only, physical activity only, or both weight loss and physical activity, reduced the risk of developing knee pain compared with those not meeting any goal at year 1 and 4. This second analysis was performed in a subset of 989 participants whose clinic sites provided an accelerometer.

**Results:** Of the 2998 participants with no knee pain at baseline (age 58.5 ± 6.7, men 44.9%, BMI 35.1 ± 5.6) 50.1% were assigned to the ILI group and the remainder to the DSE. Subject characteristics were similar between groups at baseline. At year 1, ILI participants were 15% less likely to develop knee pain compared with. At year 4, this decreased to 5% and was not statistically significant. In the second analysis, participants meeting both weight loss and physical activity goals had 47% less risk of developing knee pain at year 1. Only those meeting the weight loss goal at year 1 had less risk that met statistical significance of developing knee pain at year 4.

**Conclusion:** An intensive lifestyle intervention of diet and exercise prevented the development of knee pain among those at high risk in the short-term. Weight loss appears to have the most important preventing for the development of knee pain over four years.

**Table:** (A) Association of an Intensive Lifestyle Intervention vs. Diabetes Support and Education control with developing knee pain (n = 2998). (B) Association of meeting treatment goals at one year with the development of knee pain at one and four years among all participants who were an accelerometer (n = 989).

<table>
<thead>
<tr>
<th>Treatment Goals</th>
<th>Knee Pain at Year 1</th>
<th>Knee Pain at Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Support and Education control</td>
<td>1448 (50.1%)</td>
<td>6.7, men 44.9%, BMI 35.1 ± 5.6</td>
</tr>
<tr>
<td>Intensive Lifestyle Intervention</td>
<td>1441 (49.9%)</td>
<td>5.6) 50.1% were assigned to the ILI group</td>
</tr>
<tr>
<td>Did not meet either treatment goal at year 1</td>
<td>281 (19.4)</td>
<td>0.85 [0.74, 0.98]</td>
</tr>
<tr>
<td>Met only the weight loss goal</td>
<td>22 (12.3)</td>
<td>0.53 [0.31, 0.90]</td>
</tr>
</tbody>
</table>

**Conclusion:** Subclinical joint and enthesal PDUS abnormalities are common in IBD patients, regardless of clinical subtype, subclinical time and intestinal activity. Prospective longitudinal studies are needed to define its predictive value of clinically overt musculoskeletal disease and its association with structural deterioration.

**Disclosure:** E. Vicente None; S. Pérez-Esteban None; M. Chaparro None; F. Rodríguez-Salvanes None; L. Vega None; S. Castañeda None; J. P. Gisbert None.

**3009**

**Stem Cell Augmentation for Cardiovascular Risk in Rheumatoid Arthritis.** Nidhi Garg1, Ashit Synge2 and Pawan Krishan1. 1Punjab University Patala, India, Patala, India, 2Healing Touch City Clinic, Fortis Multispecialty Hospital, Chandigarh, India.

**Background/Purpose:** Bone marrow derived stem cells, endothelial progenitor cells (EPCs), protect against atherosclerotic vascular damage by overcoming endothelial damage. However, EPCs are depleted in RA and contribute to the enhanced cardiovascular (CV) risk. Therapeutic potential of augmenting EPCs to treat the heightened CV risk of RA has not yet been exploited. We aimed to investigate the effect of rosuvastatin on EPCs population, endothelial dysfunction, nitrite, adhesion molecules and on markers of inflammation in RA.

**Methods:** 50 RA patients were randomized to receive 24 weeks of treatment with rosuvastatin (10mg/day, n = 25) or placebo (n = 25) as an adjunct to existing stable antirheumatic drugs. EPCs (CD34+/CD133+) were quantified by Flow Cytometry. Flow mediated dilatation (FMD) was assessed by AngioDefenderTM (Everest Genomic Ann Arbor, United States). Inflammatory measures included DAS28, CRP, ESR and Pro-inflammatory cytokines (TNF-α, IL-6 and IL-1) were measured at baseline and at 12 weeks. Estimation of serum nitrite, Lipids, and adhesion molecules (ICAM-1 and VCAM-1) was done at baseline and after treatment.

**Results:** At baseline, inflammatory measures, pro-inflammatory cytokines, adhesion molecules and nitrite levels were elevated and EPCs and endothelial function were impaired among both groups. At 24 wks: DAS28, ESR, CRP, TNF-α and IL-6 improved significantly (p < 0.05) in the rosuvastatin group. Concentration of serum nitrite (p = 0.02) and ICAM-1 (p = 0.01) was significantly lower in the rosuvastatin group compared with placebo. EPCs increased significantly from (CD34+/CD133+) 0.01 to 0.03 (p = 0.01). ICAM-1 (r = 0.47, p = 0.01) after treatment with rosuvastatin as compared with placebo and after 24 wks percentage change in EPCs was 71.4% and 22.2% in the rosuvastatin and placebo groups respectively (Fig.1). After treatment with rosuvastatin there was significant improvement in FMD (p < 0.01) as compared to placebo. Rosuvastatin exerted positive effect on lipid spectrum by significantly increasing HDL cholesterol levels (p = 0.01) and decreasing LDL cholesterol (p = 0.02). Significant inverse correlation was observed between EPCs and CRP (r = -0.44, p = 0.02) and TNF-α (r = -0.42, p = 0.03). ICAM-1 (r = -0.45, p = 0.03) and FMD (r = 0.47, p = 0.01) after treatment with rosuvastatin.

**Conclusion:** First study to show that rosuvastatin augments EPCs population in RA mediated by lowering of the levels of cytokines, especially IL-6 and TNF-α, which downregulates adhesion molecule, CRP and nitric oxide production. This defines a novel mechanism of rosuvastatin treatment.
in patients with RA: the augmentation of EPCs with improvement in inflammatory disease activity and endothelial dysfunction. The augmentation of EPCs by rosuvastatin represents a fascinating new approach for the management of RA.

Disclosure: N. Garg, None; A. Syngle, None; P. Krishan, None.

3010


Background/Purpose: Patient-initiated services in rheumatology have been found to be cost-saving without compromising the clinical or psychosocial well-being of patients with rheumatoid arthritis. Self-monitoring is a technique used in many other long-term conditions and is associated with reductions in healthcare utilisation and mortality and has been found to be satisfactory from the patient's perspective. The aim of this study was to evaluate the efficacy of a service which integrates self-monitoring into patient-initiated follow-ups for patients with RA or PsA on methotrexate; in terms of healthcare utilisation and clinical outcomes, using a mixed methods approach including a randomised controlled trial (RCT) and qualitative semi-structured interviews.

Methods: One hundred patients with RA or PsA (according to ACR/EULAR/ESPOAR criteria) on methotrexate were randomised to either an intervention group or usual care. All participants were assessed over 6 blood tests. Those in the intervention group attended one training session where they were taught how to monitor their blood test results and which symptoms and side effects they should report. These participants had no scheduled appointments with their rheumatology nurse during the trial period, but continued with their consultant appointments as usual. Blood test results were sent to intervention participants and along with their assessment of symptoms and side effects; patients initiated a review with their nurse, when necessary. If these reviews were required an immediate outpatient appointment was made. Healthcare utilisation was monitored throughout the trial period. Poisson regressions and multi-level modelling were used to explore the impact of the intervention on healthcare usage and clinical outcomes.

Results: There were no significant differences in clinical or demographic variables between the two groups at baseline. A cross the trial period 77% of decisions made by intervention participants were considered to be safe. At the end of the trial period participants in the intervention group had 54.55% fewer hospital appointments with their nurse specialist (p < 0.0001). There were no significant differences in the number of appointments with the rheumatologist or GP. Levels of pain, fatigue, ESR, CRP and disease activity did not differ between groups (p > 0.05). Intervention participants were positive about the new model of care, valuing its efficiency and tailored approach. The service allowed patients to gain new knowledge and use this information along with the skills they obtained to take control of their health and arthritis.

Conclusion: After brief training patients with RA and PsA can successfully understand and interpret their blood test results and use this information along with reports of their symptoms and side effects to initiate appropriate reviews with their rheumatology nurse. Participants in the intervention group had fewer hospital appointments with their nurse specialist with no detrimental effects to their clinical status and with no increase in visits to the rheumatologist or GP. This model of care offers a viable alternative for reducing in healthcare utilisation and mortality and has been found to be cost-saving without compromising the clinical or psychosocial status with patients (52 matched pairs of female patients and controls, age: 44 ± 7 yrs, BMI: 24 ± 4 kg/m²).

DT gait analysis was performed in 80 elderly patients (age 68 ± 14 yrs, BMI 25 ± 5 kg/m²), suffering from gait instability, memory impairment, recurrent falls.

Results: Study 1: In knee osteoarthritis two gait variables are highly significant and relevant: area under the ROC curve (SR: 0.79 ± 0.05, SW: 0.78 ± 0.06).

Study 2: In Parkinson’s disease two gait variables are highly significant and correlated to motor score: SR (r = 0.59, p < 0.01); CCR (p = 0.65, p < 0.003).

Study 3: Fibromyalgia patients ROC curves confirm the utility of SF (0.74 ± 0.04); SR (0.68 ± 0.05) and CCR (0.69 ± 0.05) in the identification of fibromyalgia patients.

SR is correlated to the Fibromyalgia Impact Questionnaire (r = 0.33, p < 0.01).

SR is correlated to cognitive dysfunction measured by the Copping Strategy Questionnaire (r = 0.31, p < 0.003).

CCR is correlated to pain (weekly VAS: r = -0.33, p < 0.01).

Study 4: Gait exhibited no abnormality under ST in 13 patients. Gait abnormalities occurred under DT in each patient, moreover the decrease of one or more of the following gait variables (WS, SR, SF) alerted the clinician to an underlying neurological pathology.

Conclusion: The Single Task Gait Analysis condition is well adapted to knee osteoarthritis (SR and SW: a measurement of shock wave), to Parkinson’s disease (SR, CCR: a measurement of kinesia); to fibromyalgia patients (SR, SF, CCR: a method for the identification of homogenous subgroups). Gait Analysis Test under Dual Task conditions is of major interest in exploring the cognitive reserve and explaining gait instability in the elderly.

Disclosure: B. Auvinet, Centaure Metrix, 1; C. Touzard, None; V. Goëb, None.

3011

Ambulatory Gait Analysis in Clinical Practice: Single or Dual Task Conditions? Bernard Auvinet, Claude Touzard and Vincent Goeb. 1Polyclinic, LAVAL, France; 2Hospital of LAVAL, LAVAL, France; 3Amiens University Hospital, Amiens, France.

Background/Purpose: Interest in ambulatory gait analysis is increasing thanks to validated gait analysis apparatus dedicated to clinical practice. Such methodology has to be reproducible, sensitive, specific and pertinent. Traditionally gait analysis was carried out during a walking test with no additional tasks (called single task [ST]). Recently due to the fact that gait control involves the cognitive domain, gait analysis has additionally been carried out using the dual task paradigm, when a task demanding attention is performed during walking - this type of gait analysis is known as Dual Task (DT). We hypothesise that gait analysis under ST or DT conditions has to be chosen according to the objectives of the clinician, as well as that of the choice of gait variables.

Methods: Locometrix is a validated accelerometric device which allows the measurement of the following gait variables: walking speed (WS, m/s), stride frequency (SF, Hz), stride length (SL, m), step symmetry (SS, dimensionless), stride regularity, an index of similarity of successive strides (SR, dimensionless), crano-caudal power (CCP, W/kg), high frequency energy modulus at heel contact (HFEM, %): a measurement of shock wave (SW).

ST gait analysis was performed in three pathological conditions: 1- knee osteoarthritis compared to a control group (41 patients, age: 65 ± 10 yrs, BMI: 28.4 ± 4 kg/m², mean Lequesne index: 9 ± 4.24); 2- newly diagnosed Parkinson patients with no treatment, compared to a control group (22 patients, age: 69.9 ± 9 yrs, BMI: 26.3 ± 3 kg/m², mean motor score: 23.5 ± 3.0); 3- Fibromyalgia patients (52 matched pairs of female patients and controls, age: 44 ± 7 yrs, BMI: 24 ± 4 kg/m²).

DT gait analysis was performed in 80 elderly patients (age 68 ± 14 yrs, BMI 25 ± 5 kg/m²), suffering from gait instability, memory impairment, recurrent falls.

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Conclusion: The Single Task Gait Analysis condition is well adapted to knee osteoarthritis (SR and SW: a measurement of shock wave), to Parkinson’s disease (SR, CCR: a measurement of kinesia); to fibromyalgia patients (SR, SF, CCP: a method for the identification of homogenous subgroups). Gait Analysis Test under Dual Task conditions is of major interest in exploring the cognitive reserve and explaining gait instability in the elderly.

Disclosure: B. Auvinet, Centaure Metrix, 1; C. Touzard, None; V. Goeb, None.

3012

Needs Assessment Survey - Evaluation of Sexual Dysfunction Among Patients at a Tertiary Rheumatology Clinic. Sharon Wesner Peleg, Ori Patay, Buria Ya'ini and Jacob N. Abin. 1Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 2Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background/Purpose: Sexual function is a major component of well-being and is adversely affected by many disease states. Previous studies have demonstrated various aspects of sexual dysfunction among rheumatological patients. These may include reduced libido, pain upon intercourse (dysparunia) and erectile dysfunction; tenderness, limitations of range of motion and depression may have a compounding negative effect. In a previous study we have demonstrated aspects of sexual dysfunction found among fibromyalgia patients. The aim of the current preliminary study was to evaluate aspects of sexual dysfunction among rheumatological patients. We also wished to evaluate the needs of rheumatological patients in sexological counseling, in order to assess the need for establishing a reproductive health clinic at our rheumatology center and design future interventions in this field. A similar approach has been previously used for evaluation the needs of cancer patients.
Methods: Patients: patients were recruited among those attending the rheumatology clinic at the Tel Aviv Sourasky Medical Center from a broad range of rheumatological diagnoses. Participants filled out the following questionnaires:

1. A demographic questionnaire
2. Self-report Sexual questionnaire which was translated into Hebrew and adapted for the needs of the patients at the rheumatology institute. This questionnaire included questions regarding common domains of sexual dysfunction, including decreased libido, difficulty achieving arousal, difficulty in achieving an erection (males) or vaginal dryness (females) pain during intercourse, difficulty in achieving an orgasm, and feeling unattractiveness sexually.

Results: Forty three patients were recruited, (8 males and 35 females). The most frequent age group of the patients was 41-50.

Diagnoses included Rheumatoid arthritis (50%), Osteoarthritis (32%), Fibromyalgia (13%), Systemic Lupus Erythematosus (3.2%) Psoriatic arthritis (13%). Other: 31% reported being currently active sexually.
41% expressed interest in receiving attention for their sexual issues by the attending rheumatologist and 19% would be interested in receiving specialized sexual consultation with their partner, in the context of the rheumatology follow up.

A mong female patients, 25.7% reported a decrease in libido. 17.1% reported pain during sexual intercourse and 17.1% reported difficulty achieving sexual arousal. 14.3% reported vaginal dryness and a decrease sense of attractiveness respectively. 11.4% reported difficulty in achieving an orgasm.

Conclusion: Sexual dysfunction is highly prevalent among rheumatology patients. While not routinely evaluated in clinical practice, this issue appears to be pertinent for many patients who also express interest in receiving specific advice and treatment, as part of their rheumatological follow up. Rheumatological health care providers should be aware of this important aspect of the quality of life of their patients and should feel comfortable about raising the topic during the course of follow up. Further research is warranted into the specific causes of sexual dysfunction in various rheumatological populations and regarding the optimal treatment of these problems.

Disclosure: S. Nesher Peleg, None; O. Elkayam, None; B. Y. Ahini, None; J. N. Ablin, None.

ARHP Concurrent Abstract Session
Innovations in Rheumatologic Care
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

S1317

3013

The Reserve Capacity Model in Patients with Rheumatoid Arthritis: Understanding the Relationship of Socioeconomic Status, Psychosocial Resources, Mood, and Pain.

Desiree Azizoddin1, Taylor Draper1, Sarah Ormseth1, Perry M. Nicassio2, Michael R. Irwin1, Michael Weisman2 and Hilary Wilson1.
1University of California, Los Angeles, Los Angeles, CA.
2Cedars-Sinai Medical Center, Los Angeles, CA.

The Reserve Capacity Model in Patients with Rheumatoid Arthritis: Understanding the Relationship of Socioeconomic Status, Psychosocial Resources, Mood, and Pain.

Background/Purpose: The reserve capacity model is a framework for understanding how low SES may affect health outcomes through both positive and negative emotions separately and the depletion of psychosocial resources. The purpose of this study was to explore the reserve capacity model in persons with rheumatoid arthritis, using structural equation modeling (SEM; see Figure 1). It was hypothesized that SES would be negatively related to self-reported pain directly and/or indirectly through the potential mediators of positively related psychosocial resources (reserve capacity) and negatively related negative mood.

Methods: Data of 106 participants were drawn from a randomized comparative efficacy trial of psychosocial interventions for RA. In the hypothesized model, SES (years of education and annual income) predicted pain (VAS and Rapid Assessment of Disease Activity in Rheumatology total joint score) through reserve capacity (Personal Mastery Scale, A rthritis Helplessness Index, and Social Provisions Scale), and negative mood (Hamil ton Depression Rating Scale, Perceived Stress Scale and the Positive and Negative Affect Schedule), using EQS 6.1 to evaluate the structural model.

Results: SEM revealed a confirmed the hypothesized relations among model constructs (see Figure 1). Higher SES was positively associated with reserve capacity, which predicted lower levels of negative mood and related directly and positively to pain severity. The indirect effect of SES on pain via reserve capacity and negative mood was significant (β indirect = –.10, p = .027). Evidence supported a partial mediation of reserve capacity and negative mood between SES and pain, as the direct effect of SES on pain remained significant after controlling for the attenuating mediators of reserve capacity and negative mood.

Conclusion: These findings underscore the importance of a multi-dimensional framework in evaluating pain in RA using a structural-equation approach. The mediating variables of reserve capacity and negative mood may play major roles in explaining pain in RA, and represent modifiable factors for targeted interventions.

Disclosure: D. Azizoddin, None; T. Draper, None; S. Ormseth, None; P. M. Nicassio, None; M. R. Irwin, None; M. Weisman, None; H. Wilson, None.

3014

Does the Order or Amount of Risk-Benefit Information Presented Influence Patients' Perceived Value of a Proposed New Medication? Liana Fraenkel1, Richard Street2, Harjinder Chowdary3, Sarah Swift4 and Ellen Peters5.
1Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, 2Texas A & M University, College Station, TX, 3Yale University, New Haven, CT, 4Ohio State University, Columbus, OH.

Background/Purpose: The order and amount of information has been shown to influence risk perceptions related to hazards. In this study we sought to examine whether order and amount of risk and benefit information influences patients' perceived value of a proposed new medication.

Methods: We created 5 videos of a physician describing a new medication. The videos were identical except for the order and number of side effects (SEs) and benefits presented (see Table). Subjects with a systemic inflammatory rheumatic disease were randomly assigned to view one of the videos. Perceived medication value (PMV) was assessed by having subjects choose: the risks outweigh the benefits, the risks and benefits are equally balanced or the benefits outweigh the risks. We subsequently examined whether differences in the order and amount of information was associated with subjects' PMV. This outcome was chosen because one's overall impression more strongly predicts behavior than recall of verbatim information. We also examined the association of demographic characteristics (age, minority status, and difficulty paying for medications), attitudes towards illness and treatment (factor analysis of illness perceptions, patient activation and trust resulting in 4 factors: worry about illness, perceived treatment efficacy, impact of illness, patient activation), and current medications on PMV using bivariate analyses.

Results: Of the 242 patients recruited, 40% minority (African American and/or Hispanic). In bivariate analyses, the order and number of SEs and benefits, current use of prednisone, and minority status and difficulty paying for medications were all significantly associated with PMV. This outcome was chosen because one's overall impression more strongly predicts behavior than recall of verbatim information. We also examined the association of demographic characteristics (age, minority status, and difficulty paying for medications), attitudes towards illness and treatment (factor analysis of illness perceptions, patient activation and trust resulting in 4 factors: worry about illness, perceived treatment efficacy, impact of illness, patient activation), and current medications on PMV using bivariate analyses.

Variables found to be significant (p < .05) were included in a multinomial logistic regression model. Because of the known influence of numeracy on risk perception, all analyses were stratified by high versus low subjective numeracy (dichotomized at the median).

Results: 389 subjects participated; mean (SD) age = 55 (14), 75% female, 40% minority (African American and/or Hispanic). In bivariate analyses, the order and number of SEs and benefits, current use of prednisone, and minority status were associated with PM V in subjects with high numeracy (n = 242). Presenting SEs first or between benefits were both associated with more negative PMV compared to the reference video (3 benefits followed by 6 SEs) (See Table). Among subjects with low numeracy (n = 142), the order and...
number of risk and benefits presented were not associated with PMV. In bivariate analyses, use of a biologic, difficulty paying for medications, perceived treatment efficacy, patient activation, and minority status, were associated with PMV in subjects with low numeracy. Except for current use of a biologic, all remained significant in the multivariate model (see Table).

Conclusion: Order and amount of information matter, but only in patients with high subjective numeracy. Minority patients have a much more negative PMV compared to Caucasian, non-Hispanic patients, regardless of their level of numeracy.

### Table: Multinomial logistic regression model examining association of risk/benefit presentation and patients characteristics on perceived medication value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Perceived Medication Value (Ref: Risks outweigh Benefits)</th>
<th>Adjusted Odd Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Numeracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Video (Ref: 3 benefits → 6 SEs)</td>
<td>Balanced</td>
<td>1.87 (0.59-5.08)</td>
</tr>
<tr>
<td>6 benefits → 6 SEs</td>
<td>Benefits outweigh Risks</td>
<td>0.45 (0.14-1.48)</td>
</tr>
<tr>
<td>6 benefits → 3 SEs</td>
<td>Balanced</td>
<td>0.79 (0.24-2.64)</td>
</tr>
<tr>
<td>6 SEs → 3 benefits</td>
<td>Balanced</td>
<td>0.60 (0.19-1.83)</td>
</tr>
<tr>
<td>3 benefits → 6 SEs → 3 benefits</td>
<td>Balanced</td>
<td>0.47 (0.16-1.40)</td>
</tr>
<tr>
<td>3 benefits</td>
<td>Benefits outweigh Risks</td>
<td>0.20 (0.07-0.58)</td>
</tr>
<tr>
<td>6 SEs</td>
<td>Benefits outweigh Risks</td>
<td>0.34 (0.18-0.66)</td>
</tr>
<tr>
<td>Currently on a biologic</td>
<td>Balanced</td>
<td>0.76 (0.34-1.76)</td>
</tr>
<tr>
<td>Difficulty paying for medications</td>
<td>Balanced</td>
<td>0.95 (0.48-1.95)</td>
</tr>
<tr>
<td>Minority vs Caucasian</td>
<td>Balanced</td>
<td>0.25 (0.11-0.58)</td>
</tr>
</tbody>
</table>

| Low Numeracy | | |
| Perceived treatment efficacy | Balanced | 1.46 (0.90-2.37) |
| Patient activation | Balanced | 2.22 (1.28-3.83) |
| Currently on a biologic | Balanced | 2.75 (1.09-2.81) |
| Difficulty paying for medications | Balanced | 1.05 (0.62-1.78) |
| Minority vs Caucasian | Balanced | 1.13 (0.35-3.66) |

### 3015 Evaluation of the effic Educational Needs Assessment Tool (ENAT) Focused Patient Education on Health Outcomes in Patients with Rheumatoid Arthritis - a Randomised Controlled Trial.

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2. Barnsley Hospital NHS Foundation Trust, Barnsley, United Kingdom
3. Barnsley Hospital NHS Foundation Trust, Barnsley, United Kingdom
4. University of Leeds, Leeds, United Kingdom

Background/Purpose: The Educational Needs Assessment Tool (ENAT) is a quick and simple, self-completed questionnaire that ensures that patient education is relevant, appropriate and timely for people with Rheumatoid Arthritis (RA). It has been validated for use in RA and six other rheumatic diseases and has been cross-culturally adapted into nine European languages. Our aims were (i) to evaluate the effectiveness of ENAT focused patient education on self-efficacy, patient knowledge and health outcomes (physical function, symptoms, role/work, social interaction and psychological status/affect) (ii) to evaluate the usability of the ENAT in clinical practice, from both a practitioner and patient perspective.

Methods: This was a mixed methods (quantitative and qualitative) study conducted in seven rheumatology centres across the United Kingdom. Patients were randomised to either the ENAT group (EG) where patients completed the ENAT which was then used as a template by the Nurse Practitioner (NP) to meet their educational needs; or usual care (UC) by NP without the ENAT. Patients were seen at baseline then at weeks 16 and 32. The outcomes were self-efficacy (ASES), health status (AIM2-SF) and patient knowledge (PKQ). The primary outcome was self-efficacy (ASES) at week 32.

Results: A total of 132 patients were entered into the study of which 70 received ENAT (53%) and 62 usual care (47%). At week 16, there were no significant between-group differences. By week 32, the ASES mean scores, were higher for the ENAT group than the usual care group; ASES-Pain, MD = 4.36 (95%CI: 1.17, 7.55), t = 2.72, p = 0.008; ASES-Other symptoms, MD = 5.84 (95%CI: 2.07, 9.62), t = 3.07, p = 0.003. (Bonferroni-adjusted P-value = 0.025 for significance at the alpha level). Trends over time revealed significant decrease in the overall ENAT score for all domains (managing pain, movement, arthritis process, self-help measures and support) except the feelings domain. The decrease in the total ENAT score by the end of the study, indicates that patients' educational needs were being met effectively.

Conclusion: This is the first study to report the effects of ENAT-focused education in people with RA. The results of the primary outcome (ASES-Pain and ASES-Other symptoms) suggest that the ENAT could be a useful addition to usual care.

Disclosure: A. O. Adebajo, None; D. Johnson, None; H. Bernardette, None; C. Hale, None; M. Ndosi, None.

### 3016 Measuring the Impact of an Early RA Support and Education Program Using a Program Evaluation with Patient Identified Outcomes.


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Background/Purpose: The Early RA Support and Education Program addresses the unique psycho-educational needs of people recently diagnosed (<2yr) with RA. This free monthly program is co-facilitated by an MSW and RN and was developed based on a needs assessment with patient input; it features an RA- focused lecture followed by a support group, aimed at enhancing emotional coping and disease management. In order to measure program impact on concerns most relevant to new RA patients, we developed an evaluation tool incorporating patient identified outcomes (Hewlett, 2003), on which we previously reported. Since that time, we have piloted the evaluation and now report the results.

Methods: Through a multi-level collection of data, we identified patient derived program outcomes and language most relevant to participants. This process yielded 3 key domains: M anaging RA, Connecting with Others with RA and Coping with the Emotional Impact (Wolrich, 2011). From this data we created a 20-item evaluation, using a 6 point Likert scale and open-ended questions, which incorporates patient identified outcomes under each of the domains. This new tool was administered to participants after each of 12 monthly sessions.

Results: 127 evaluations were completed from 180 participants. Demographics: Gender: 93%; M age: 49; Ethnicity: White 59%; African American 19%; Asian American 11%; Latino 11%; Education: College or higher: 92%. Results indicate % of participant agreement (either “completely” or “a great deal”) with the following Likert scale question statements, which represent each of the 3 key domains. I. MANAGING RA: As a result of this program’s value within the 3 domains: M anaging RA, Connecting with Others with RA and Coping with the Emotional Impact (Wolrich, 2011). From this data we created a 20-item evaluation, using a 6 point Likert scale and open-ended questions, which incorporates patient identified outcomes under each of the domains. This new tool was administered to participants after each of 12 monthly sessions.

Results: A total of 132 patients were entered into the study of which 70 received ENAT (53%) and 62 usual care (47%). At week 16, there were no significant between-group differences. By week 32, the ASES mean scores, were higher for the ENAT group than the usual care group; ASES-Pain, MD = 4.36 (95%CI: 1.17, 7.55), t = 2.72, p = 0.008; ASES-Other symptoms, MD = 5.84 (95%CI: 2.07, 9.62), t = 3.07, p = 0.003. (Bonferroni-adjusted P-value = 0.025 for significance at the alpha level). Trends over time revealed significant decrease in the overall ENAT score for all domains (managing pain, movement, arthritis process, self-help measures and support) except the feelings domain. The decrease in the total ENAT score by the end of the study, indicates that patients' educational needs were being met effectively.

Conclusion: This is the first study to report the effects of ENAT-focused education in people with RA. The results of the primary outcome (ASES-Pain and ASES-Other symptoms) suggest that the ENAT could be a useful addition to usual care.

Disclosure: A. O. Adebajo, None; D. Johnson, None; H. Bernardette, None; C. Hale, None; M. Ndosi, None.
about what I learned); Connecting ("I don’t feel so alone"); Emotional Coping ("learned ways to deal with stress of RA").

**Conclusion:** Evaluation results indicate that in domains I and II, and in domain III, "more confident in managing my RA", the program is making a strong positive impact. In domain III, "RA is less disruptive to my daily life", results reflect positive impact, though not as marked as in other questions. Future work is needed to explore how patients define "disruptive" and develop targeted content to address this for future groups. Future research might also follow participants longitudinally, to determine how program participation over time, and other variables, impact this outcome. This tool was administered to measure how effectively the program meets patient-identified needs. Our process can serve as a model for including the patient perspective in evaluating outcomes in other disease-specific support and education programs.

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**3017**

**Program Evaluation of ‘the Joint Clinic’: An Innovative Clinical Service for Patients with Hip or Knee Osteoarthritis.** J. Haxby Abbert,1 Helen Harcombe,2 Chris Crane,3 Liam Hutton,4 Kirsten Stout,5 Cathy Chapple6 and David Gwynne-Jones.1

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**Background/Purpose:** In socialized healthcare systems with free public access to healthcare, there are circumstances wherein patients referred by general medical practitioners (GPs) for specialist consultation may not be offered a first specialist appointment (FSA), when demand exceeds supply. Thus, clinical prioritization is necessary. To address unmet need for FSA in patients with hip or knee osteoarthritis, we initiated and evaluated a physical therapist-led clinic offering non-surgical management of osteoarthritis and outpatient treatment.

**Methods:** We conducted a program evaluation comprising: a proof-of-concept evaluation, an implementation evaluation, a process evaluation, and an outcomes evaluation. Mixed-methods qualitative and quantitative methodology grounded in health services research were used. Patients, GPs, surgeons, and hospital clinical, management and administrative staff were interviewed and/or surveyed. Patient trajectories were analysed and patient-reported outcome measures were assessed.

**Results:** The concept model was supported by best-practice literature, and was implemented in close concordance with the model proposed. Qualitative interviews and survey data indicate the "Joint Clinic" has been well accepted by key stakeholders and end-users, is functioning well within the host organisation, is accessible and operating at close to intended capacity. In the 2-year evaluation period, the clinic served 358 new patients (53% female, mean(sd) age 66(10), BMI 29.9(7.51) in 637 consultations. Unmet need was reduced by 80% compared with pre-implementation for hip/knee OA patients; 30% overall. 31% of patients experienced clinically significant (~20%) improvement on patient-reported outcome measures. 25% of patients were referred for FSA (mean wait 77 days) for fast-track access to joint replacement surgery. 70% of patients were satisfied to be seen by the "Joint Clinic" instead of an orthopaedic surgeon; 98% were satisfied with the knowledge and expertise of the "Joint Clinic" staff; 80% would recommend the clinic to others. Cost-per-patient was NZ$384 (year 2). The host organisation has accepted the service as value-for-money and sustainable.

**Conclusion:** These data indicate successful implementation and functioning of an innovative service. The service is achieving satisfactory outcomes benefiting patients through clinically significant improvement, monitoring on optimal non-surgical management, or fast-tracked referral for joint replacement surgery.

**Disclosure:** J. H. Abbott, None; H. Harcombe, None; C. Crane, None; L. Hutton, None; K. Stout, None; C. Chapple, None; D. Gwynne-Jones, None.

**3018**

**Testing of a Newly Developed Computerized Animated Activity Questionnaire for Assessing Activity Limitations in Patients with Hip and Knee Osteoarthritis.** Wilfred FH Peter1, Mick Loos2, Henrica de Vet1, Maxine Enthoven3, Jaap Harlaar1, Leo D. Roorda1, Rudolf Poolman1, Vanessa Scholtes2, Jan Bogard3, Hilda Buitelaar3, Martin P. M. Steultjens4, Ewa M. Roos5, Anne-Christine Ra6, Francis Guillemin7, Maria Graia Benedetti6, Antonio Escobar Martinez9, Nina Østerås10 and Caroline Terwee1

1VU University Medical Center, Amsterdam, Netherlands, 2Amsterdam Rehabilitation Research Center Reade, Amsterdam, the Netherlands, 3Amsterdam, Amsterdam, 4University of Southern Denmark, Odense, Denmark, 5University of Lorraine, Nancy, France, 6INSERM, Centre d’Investigation Clinique - Epidemiologie Clinique (CIC-EC) CIE6, Nancy, France, 7Istituto Ortopedico Rizzoli, Bologna, Italy, 8Baso University Hospital, Bilbao, Spain, 9Diaconhjemmet Hospital, Oslo, Norway.

**Background/Purpose:** Self-report questionnaires and performance-based tests correlate moderately in measuring activity limitations, indicating that they measure different aspects. Self-reports measure mainly how patients think they perform an activity, and is influenced by pain, fatigue or situations they are referring to. This may lead to cross-cultural differences. Performance-based tests measure an artificial situation, is resource-intensive and burdensome for patients. To overcome these drawbacks we developed and tested a pilot version of an Animated Activity Questionnaire (AAQ), which demonstrated some promising features[1]. The aim of this study was to develop a computerized Animated Activity Questionnaire (AAQ) to assess activity limitations in patients with hip/knee osteoarthritis and preliminary testing of its validity and reliability.

**Methods:** Based on the pilot version, International Classifications of Functioning core set for osteoarthritis, focus groups of patients, and existing measurement instruments, the AAQ was developed. In 482 patients correlations were calculated between the Animated Activity Questionnaire (AAQ) and self-reported Hip disability and Knee Injury Osteoarthritis Outcome physical functioning score. In addition internal consistency was calculated. In 65/482 patients also correlations with performance based tests (Stair Climbing Test, Timed Up and Go test, and the 30 second Chair Stand Test) were calculated. Test-retest reliability was assessed by repeated scoring in 56/482 patients.

**Results:** The Animated Activity Questionnaire (AAQ) includes animated videos of 17 basic daily activities with four levels of increasing difficulty (check the following link for two examples: http://kmin-vumc.nl/_14_0.html). Patients were asked to select the video that best matched their own performance. Cronbach’s alpha was 0.95, Correlation with self-reported physical functioning scores was high (0.72). The AAQ correlated moderately with the performance based tests (0.49, 0.44, and 0.57, respectively). Correlations of the AAQ score with pain was lower (0.51) than the correlation of the self-reported physical functioning score with pain (0.75). For test-retest reliability, a Intraclass Correlation Coefficient of 0.97 (95% Confidence Interval 0.93–0.98) was found.

**Conclusion:** A computerized Animated Activity Questionnaire (AAQ) was developed showing a high internal consistency and excellent test-retest reliability. Content validity was considered good, and construct validity is supported by high correlations with self-reported physical functioning and moderate correlations with performance-based tests. The AAQ seems to be less influenced by pain compared with self-reported physical functioning. Since the AAQ needs no reading ability or translation, it has potential for international use. Continuing research will focus on construct validity and cross-cultural validity.

**Reference**


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2014 ACR/ARHP Abstract

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